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Amaç ve Kapsam / Aims and Scope

Türkiye Romatoloji Derneği'nin (TRD) yayın organı olan Ulusal Romatoloji Dergisi (önceki adı: RAED Dergisi) yılda üç kez, Türkçe ve İngilizce yayımlanan hakemli bir bilimsel dergidir (p-ISSN: 2651-2653; e-ISSN: 2651-2661). Dergi, romatoloji biliminin bütün konularında orijinal deneysel ve klinik araştırmaları, olgu sunumlarını, derlemeleri, tanıtım ve haberleri, yazarlara ve editöre mektupların yanı sıra romatoloji camiasını ilgilendiren duyuruları yayımlar. Bunun dışında romatoloji alanındaki yenilik ve gelişmelere yönelik toplantıların konuşma metinlerini ya da bu gelişmeleri içeren yazıları ek vererek yayımlayabilir. Derleme yazılar genellikle davetli yazı konumunda olduğundan dergiye gönderilmeden önce editör ile iletişime geçilmesi gerekmektedir. Dergi, doğrudan gönderilen derleme türü yazıları kabul etmemektedir.

Ulusal Romatoloji Dergisi **EBSCO, Gale, J-Gate, Türk Medline ve TÜBITAK ULAKBİM TR Dizin** veritabanında İndekslenmektedir.

Ulusal Romatoloji Dergisi'nin amacı ülkemizde romatoloji ile ilgilenen diğer disiplinlerin de katılımıyla romatoloji alanında güncel bir bilimsel tartışma zemini ve arşiv oluşturmaktır. Dergi bu birikimini, saygın bir biyomedikal periyodik olarak uluslararası bilimsel paylaşıma sunmayı ve böylece romatoloji biliminin gelişmesine akademik katkı sağlamayı hedeflemektedir.

Dergide makale yükleme, işlem veya yayınlanma ücreti uygulanmamaktadır. Değerlendirme ve yayın süreci boyunca hiçbir şekilde yazarlardan herhangi bir ücret talep edilmez.Tüm yazılar dergi web sitesinde yer alan online makale sistemi aracılığıyla sisteme yüklenmelidir.

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Dergide açık erişim politikası uygulanmaktadır. Açık erişim politikası Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/ kuralları esas alınarak uygulanmaktadır.

Açık Erişim, "[hakem değerlendirmesinden geçmiş bilimsel literatürün], İnternet aracılığıyla; finansal, yasal ve teknik engeller olmaksızın, serbestçe erişilebilir, okunabilir, indirilebilir, kopyalanabilir, dağıtılabilir, basılabilir, taranabilir, tam metinlere bağlantı verilebilir, dizinlenebilir, yazılıma veri olarak aktarılabilir ve her türlü yasal amaç için kullanılabilir olması"dır. Çoğaltma ve dağıtım üzerindeki tek kısıtlama yetkisi ve bu alandaki tek telif hakkı rolü; kendi çalışmalarının bütünlüğü üzerinde kontrol sahibi olabilmeleri, gerektiği gibi tanınmalarının ve alıntılanmalarının sağlanması için, yazarlara verilmelidir.

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Ulusal Romatoloji Dergisi'nde yayınlanan tüm yazılarda görüş ve raporlar yazar(lar)ın görüşüdür ve editör, editörler kurulu ya da yayıncının görüşü değildir; Editör, editörler kurulu ve yayıncı bu yazılar için herhangi bir sorumluluk kabul etmemektedir.

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Aims and Scope / Amaç ve Kapsam

Journal of Turkish Society for Rheumatology (formerly RAED Journal), the official organ of Turkish Society for Rheumatology, is a peer-reviewed scientific journal published quarterly in Turkish or English (p-ISSN: 2651- 2653). The journal publishes three times in a year original contributions in the form of basic and clinical research articles, case reports, reviews, news, letters to the editor and authors as well as announcements related to all topics of rheumatology. Also, abstracts or full texts of scientific meetings in rheumatology can be published as supplements of the journal. The reviews are usually invited; therefore it is necessary to contact the editor before sending them to the journal. The journal does not accept unsolicited reviews.

Journal of Turkish Society for Rheumatology is indexed in **EBSCO, Gale, J-Gate, Turkish MEDLINE and TUBITAK ULAKBIM TR Index.**

Journal of Turkish Society for Rheumatology aims to constitute a current scientific discussion platform and archive in rheumatology with the contribution of the disciplines related to rheumatology together. The journal intends to share its experiences with the international scientific community in a prestigious way and to provide academic contribution to the development of rheumatology science.

Processing and publication are free of charge with Journal of Turkish Society for Rheumatology. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system which is available through the journal's web page.

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Dergide yer alan bölümler aşağıda aşağıdaki gibi sınıflandırılmaktadır:

- Klinik Araştırma
- Deneysel Çalışma
- Olgu Sunumu
- Derleme
- Editöre Mektup
- Öneri
- Yazara Mektup
- Kitap Tanıtımı
- Haberler
- Özetler

ETİK VE HAKEM DEĞERLENDİRMESİ

Ulusal Romatoloji Dergisi bağımsız, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan süreli bir yayın organıdır. Makale baş editöre ulaşınca bilimsel kalitesi değerlendirilir ve ön değerlendirmeyi geçen yazılar yardımcı editöre gönderilir. Bölüm editörü makaleyi 2 hakeme gönderir. Hakemler 21 gün içinde kararlarını belirtmelidirler. Yardımcı editör hakem kararlarına kendi değerlendirme ve önerisini ekleyerek baş editöre gönderir ve son kararı baş editör verir. Hakemlerin kararları çatışıyorsa dergi editörü yeni hakem atayabilir.

Derginin alıntı kontrolü "Crossref Similarity Check" tarafından geliştirilen "iThenticate" programı kullanılarak yapılmaktadır. İntihal raporuna göre makale yazara geri gönderilebilir ya da reddedilebilir.

Yayınlanmak üzere dergiye gönderilen yazılar daha önce başka bir dergide yayınlanmamış veya yayınlanmak üzere eş zamanlı olarak herhangi bir dergiye gönderilmemiş olmalıdır. Bilimsel toplantılarda sunulmuş bildirilerden hazırlanan yazılar, tamamı yayınlanmamış olmak koşuluyla dergiye gönderilebilir. Gelen yazılar Yayın Kurulu tarafından ön incelemeden geçirilir. Derginin yayın amacına uygun olmayan yazılar doğrudan reddedilebilir ya da hakem değerlendirmesine alınmadan yayın amacına ve yayın kurallarına uygun hale getirilmesi amacıyla yazara geri gönderilir. Dergi kapsamına uygun görülen yazılardan klinik araştırma, deneysel çalışma, derleme ve olgu sunumu sınıfı yazılar hakem değerlendirme (eş değerlendirme/*peer review*) sürecine girerler. Yayın Kurulu, hakem yorum ve önerileri doğrultusunda dergiye gönderilen yazıların yayına hazırlanması aşamalarında gerekli gördüğü düzeltme ve değişiklikleri önermeye yetkilidir. Dil birliğini sağlamak amacıyla cümlenin bilimsel anlamını değiştirmeyen kelime değişikliklerini yapabilir. Eş değerlendirme sürecinde gerekli düzelti aşamalarını geçtikten sonra sayfa düzeni yapılıp yayına hazır hale getirilen yazıların provası, son baskı onayı için ilgili (yazışmaların yapıldığı) yazara göndeilir.

Romatoloji bilim toplantılarının özetleri veya tam metinleri, derginin ekleri olarak yayımlanabilir. Yalnızca konferans konusu kapsamındaki bildiri metinleri kabul edilmektedir. Dergiye yapılan tüm başvurular, bir editör tarafından incelenmeden önce eksiksizlik açısından ilk değerlendirmeye tabi tutulur. Ardından, bu makaleler konferansın bilimsel editöryel komitesi tarafından değerlendirilir.

Araştırma Etiği

Yazar(lar), insanlar üzerinde yapılan çalışmalarda katılımcı bireylerden Bilgilendirilmiş Olur alındığını yazılarında belirtmeli ve çalışmanın yapıldığı kurumun Etik Kurulu veya eşdeğeri bir kuruldan alınan onay belgesini yazıyla birlikte göndermelidir(ler). Olgu sunumlarında, her olgunun kendisine ait bilgilerin yayın amacıyla kullanılacağına dair bilgilendirildiğini gösterir bir belgenin sunulması gerekir. Tüm çalışmalar Helsinki Deklarasyonu'nun son değişiklikleri işlenmiş şekline uygun yapılmış olmalıdır. Hasta bilgileri 01.08.1998 tarih ve 23420 sayılı Resmi Gazete'de yayımlanan Hasta Hakları Yönetmeliği'ne uygun olarak alınmış olmalıdır. Hayvanlar üzerindeki sonuçları bildiren deneysel çalışmaların, Hayvan Hakları Evrensel Bildirgesi, Deneysel ve Diğer Bilimsel Amaçlarla Kullanılacak Omurgalı Hayvanların Korunması Hakkındaki Avrupa Konvansiyonu (European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose), T.C. Tarım ve Köy İşleri Bakanlığı'nın Deneysel ve Diğer Bilimsel Amaçlar İçin Kullanılan Deney Hayvanlarının Üretim Yerleri ile Deney Yapacak Olan Laboratuvarın Kuruluş Çalışma Denetleme Usul ve Esaslarına Dair Yönetmelik, Laboratuvar Hayvanları Biliminin Temel İlkeleri (Principles of Laboratory Animal Science), laboratuvar hayvanlarının bakım ve kullanılmasıyla ilgili el kitaplarında yer alan kural ve ilkelere uygun olarak ve çalışmanın yapıldığı kurumda mevcut ise, Deney Hayvanları Etik Kurulu'ndan alacakları onay sonrasında yapılmış olması gerekir. Etik Kurul onayı yazı ile birlikte sunulmalıdır. Yazılarda, insan ve hayvanlarda yapılan çalışmalarda kullanılan ameliyat sonrası ağrı giderici tedavi yöntemleri hakkında da bilgi verilmelidir.

Yayın Etiği ve Kötüye Kullanım Bildirgesi

Ulusal Romatoloji Dergisi yayın etiğini en yüksek standartlarda uygulamayı ve Yayın Etiği ve Kötüye Kullanım Bildirgesinin aşağıdaki ilkelerine uymayı taahhüt eder. Bu bildirge Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) ve International Committee of Medical Journal Editors (ICMJE) adlı birlik ve inisiyatiflerin, dergi editörleri için geliştirdikleri öneri ve kılavuzlar temel alınarak hazırlanmıştır. Yayımlanmak üzere dergiye gönderilen yazılar daha önce başka bir dergide yayımlanmamış (bilimsel toplantılarda sunulmuş ve tam metin yayımlanmış bildiriler dahil) veya yayımlanmak üzere eşzamanlı olarak herhangi bir dergiye gönderilmemiş olmalıdır. Dergiye gönderilen yazılar, bir editör ve en az iki danışman (hakem) tarafından incelenmek suretiyle tek-kör eş değerlendirme *(peer review)* sürecine alınır.

Dergimiz gönderilen yazıların herhangi bir aşamada, amaca yönelik bir yazılım aracılığıyla intihal açısından incelenebileceği hakkını saklı tutar. Bu amaçla intihale yönelik izinsiz alıntı ya da düzmece veriler, sahtecilik (tablo şekil ya da araştırma verilerinin uydurma ya da manipüle edilmiş olması) ve araştırmada uygunsuz insan ya da hayvan denekler kullanımına yönelik incelemeler söz konusu olabilir. Bu standartlara uygun olmayan yazılar dergide yayımlanmaz. Bu standartlara uygun olmayan yazılar dergide yayımlanmaz. Bu kural, yayımlanma sonrası aşamada saptanabilecek bu standartlarla ilgili herhangi bir uyumsuzluk durumunda da geçerlidir ve yazının yayımdan geri çekilmesini gerektirir. Yayın etiği gereği dergimiz intihal ya da duplike yayın şüphesi durumlarını rapor edecektir. Dergimiz, yayın etiğinin kötüye kullanımı ya da ihlali ile ilgili olası durumlarda COPE tarafından geliştirilen Yayın Etiği Akış Şemalarını temel alır.

Yazar Sorumluluğu

Yazarlar gönderdikleri yazıların özgünlüğünü teminat altına almalıdır. Yazının daha önce herhangi bir yerde, herhangi bir dilde yayımlanmadığı ya da yayımlanmak üzere değerlendirmeye alınmış olmadığını beyan etmelidirler. Geçerli telif hakkı sözleşme ve yasalarına uymalıdırlar. Dergimizde tablo, şekil ya da diğer katkı sunan alıntılar gibi telifli materyal ancak geçerli izin ve telif onayı ile yayımlanır. Yazarlar; başka yazarlar, katkı sağlayıcılar ya da kaynaklara uygun bir biçimde atıf yapmalı ve ilgili kaynakları belirtmelidir. Araştırma türü yazıların (kısa raporlar dahil) yazar(lar)ı "çalışmayı tasarlama", "verileri toplama", "verileri inceleme", "yazıyı yazma" ve "verilerin ve analizlerin doğruluğunu onaylama" aşamalarından en az 3 tanesine katılmış olmak ve bu durumu beyan etmek zorundadır. Yazarlar, çalışma ile ilgili bilinmesi gereken ve çalışmanın bulgularını ya da bilimsel sonucunu potansiyel olarak etkileyebilecek bir mali ilişkiyi ya da çıkar çakışması (conflict of interest) veya rekabet (competing interest) alanlarını açıklamakla yükümlüdür. Çalışmaya yapılan tüm mali katkıları, sponsorlukları ya da proje desteklerini açıklıkla bildirmelidirler. Derginin Çıkar Çakışması Politikası ile ilgili ayrıntılı bilgiyi de içeren ve olası çıkar çakışması durumunda kullanılabilecek "Çıkar Çakışması Beyan Formu"na PDF dokümanı olarak erişilebilir. Yazar yayımlanmış yazısında anlamlı bir bilimsel hata ya da uygunsuzluk saptadığında, yazıyı geri çekme ya da hatayı düzeltme amacıyla olabildiğince hızlı bir şekilde editör ile temasa geçme yükümlülüğünü taşır.

Hakem Sorumlulukları

Hakemler gelen yazıları, yazarlarının etnik köken, cinsiyet, cinsiyet tercihi, tabiyet, dini inanış ya da politik felsefelerini dikkate almaksızın bilimsel içerik açısından değerlendirir. Hakemler açısından; araştırma, yazarları ya da destekleyiciler ile ilgili bir çıkar veya rekabet çakışması bulunmamalıdır. Hakem kararları nesnel olmalıdır. Hakemler yazar tarafından atıf yapılmamış yayımlanmış ilintili yayınları belirtmelidir. Gönderilen yazı ile ilgili tüm bilgilerin gizli tutulması ve yazar tarafından yapılan telif hakkı ihlali ve intihal durumlarının farkına vardığında Editöre bildirilmesi ile yükümlüdürler. Hakem, gönderilen bir yazının içeriğinin kendi bilimsel alanı ya da birikimi ile uyumsuz olduğunu düşündüğünde ya da hızlı bir değerlendirme yapamayacağı durumlarda Editörü bilgilendirmeli ve değerlendirme sürecinden affını istemelidir.

Editör Sorumlulukları

Editörler gelen yazıları, yazarlarının etnik köken, cinsiyet, cinsiyet tercihi, tabiyet, dini inanış ya da politik felsefelerini dikkate almaksızın bilimsel içerik açısından değerlendirmelidir. Gönderilen yazıların yayımlanması için adil bir eş değerlendirme süreci sağlamalıdırlar. Gönderilen yazı ile ilgili tüm bilgilerin yayımlanana kadar gizli tutulmasını garanti altına almalıdırlar. Editörler yayının içeriği ve toplam kalitesinden sorumludur. Erratum sayfaları yoluyla gerektiğinde düzeltme yayımlamalıdırlar. Editör; yazarlar, editörler ve hakemler arasında olabilecek herhangi bir çıkar veya rekabet çakışmasına olanak vermemelidir. Ulusal Romatoloji Dergisinde hakem atamasında sadece Editör tam yetkiye sahip olup yazıların yayımlanması ile ilgili sonuç kararından da kendisi sorumludur.

YAYIN POLİTİKASI

Tüm makaleler bilimsel katkıları, özgünlük ve içerikleri açısından bilimsel komite tarafından değerlendirilecektir. Yazarlar verilerinin doğruluğundan sorumludurlar. Dergi gerekli gördüğü yerlerde dil ve uygun değişiklik yapma hakkını saklı tutar. Gereğinde makale revizyon için yazara gönderilir. Daha önce herhangi bir dilde yayınlanmış makaleler dergide yayınlanmak üzere kabul edilmeyecektir. Yazarlar bir başka dergide yayınlanmak üzere olan makaleyi teslim edemez. Tüm değişiklikler, yazar ve yayıncının yazılı izin alındıktan sonra yapılacaktır. Tüm makalelerin tam metinleri derginin www.manuscriptmodule.com/raed web sitesinden indirilebilir.

Yayın Politikası ve Makale Yazım Kuralları aşağıda belirtilen maddeler "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2013, http://www.icmje.org/) temel alınarak hazırlanmıştır.

Araştırma makalelerinin hazırlığı, sistematik derleme, meta-analizleri ve sunumu ise uluslararası kılavuzlara uygun olmalıdır:

Randomize çalışmalar için; CONSORT (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/).

Sistematik derleme ve meta-analizlerin raporlamaları için; PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097) (http://www.prisma-statement.org/).

Tanısal değerli çalışmalar için; STARD (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/).

Gözlemsel çalışmalar için; STROBE (http://www.strobe-statement.org/).

Meta-analizleri ve gözlemsel çalışmaların sistematik derlemeleri için; MOOSE (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting

"Meta-analysis of observational Studies in Epidemiology" (MOOSE) group. JAMA 2000; 283: 2008-12).

GENEL KURALLAR

Aşağıda belirtilen özelliklerin dışında yazılarla ilgili ilkeler açısından "International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts" dokümanları (www.icmje.org) esas alınmalıdır.

Dergiye gönderilecek yazılarda bulunması gereken bölümler sırası ile şunlardır ve her biri ayrı sayfada başlayacak şekilde sunulmalıdır:

Sayfa 1: Başlık sayfası

Sayfa 2: Türkçe Başlık, Özet ve Anahtar Sözcükler

Sayfa 3: İngilizce Başlık (Title), Özet (Abstract) ve Anahtar Sözcükler (Key words)

Sayfa 4 ve sonrası: Temel Metin

Sonraki sayfa: Kaynaklar

Sonraki sayfa: Tablo Açıklama Yazısı ve Tablo (her tablo ayrı sayfada belirtilmelidir)

Sonraki sayfa: Şekil ve Resim Alt Yazıları ve Resim/Şekiller (her şekil ayrı sayfada belirtilmelidir)

Başlık Sayfası

Başlık sayfasında aşağıdaki sıralama gözetilmelidir:

1- Yazının gönderildiği kategori (klinik araştırma, deneysel çalışma, derleme, olgu sunumu vb)

2- Yazının başlığı (başlık 80 karakteri geçmemeli ve standart dışı kısaltmalar içermemelidir)

3- Yazarların ad, soyad, iletişim adresleri ve araştırmanın yapıldığı sırada çalıştıkları kurum

4- Yazının, dergide yayınlandığında devam sayfalarının üst tarafında görünmesi arzu edilen ve 40 karakteri geçmeyen kısaltılmış başlığı

5- Varsa destekleyen kurum ve kuruluşlar

6- Yazı daha önce sunulmuşsa, sunulduğu toplantının ayrıntıları

7- İletişim kurulacak yazarın haberleşme bilgileri

8- Eğer varsa yazının içeriğiyle ilgili maddi desteğin belirtilmesi

Türkçe Özet

Araştırma yazılarında Amaç, Yöntem, Bulgular ve Sonuç bölümlerinden oluşmalı ve 250 kelimeyi geçmemelidir. Derleme ve olgu bildirilerinde yapılandırılmamış özet verilmelidir. Olgu sunumlarının özeti 100 kelimeyi geçmemelidir. Türkçe özet sayfasında en az 3 en fazla 6 anahtar kelime belirtilmelidir.

İngilizce Özet

Araştırma yazılarında "Objectives", "Methods", "Results", and "Conclusions" bölümlerinden oluşmalıdır ve 250 kelimeyi geçmemelidir. İngilizce Özet sayfasında en az 3 en fazla 6 İngilizce anahtar sözcük belirlenmeli, yazının İngilizce başlığı eklenmelidir.

Temel Metin

Giriş, Hastalar/Gereç ve Yöntem, Bulgular, Tartışma ve Kaynaklar bölümlerinden oluşmalıdır. Kısaltmalar standart olmalı ve ilk kullanıldığında parantez içinde açıklanmalıdır. Ölçümlerde uluslararası kabul edilmiş birimler kullanılmalıdır.

Tablo, Şekil ve Resimler

Metinde kullanılış sırasına göre numaralandırılmalı ve gereksiz kullanımdan kaçınılmalıdır. Olgularda kullanılan fotoğraflarda izin alınmalı ve tanınmayı önlemek için gerekli tedbirler uygulanmalıdır. Fotoğraf ve varsa çizim kalitesine özen gösterilmelidir. Yayın Kurulu yeterli kalitede olmadığı gerekçesiyle tablo, şekil ve resimlerde düzeltme veya yenileme isteğinde bulunabilir. Şekil ve resimlerin orijinal olmaları gerekir. Başka bir yayın içinde kullanılmış bulunan resim, şekil ve grafiklerin dergimizde yayımlanabilmesi için, gerekli izinler yazarlar tarafından ve makale başvurusu yapılmadan önce alınmalıdır. İznin alındığını gösterir belgenin kopyası yazıyla birlikte dergiye gönderilmelidir.

Kaynaklar

Kaynaklar güncel ve yazı için gerekli olanlardan seçilmelidir. Yazı metninde kaynaklar parantez içinde gösterilmeli ve kullanılış sırasına göre numaralandırılmalıdır. Süreli yayın adları PubMed kurallarına uygun olarak kısaltılmalı, burada yer almayan dergilerin adlarında kısaltma kullanılmamalıdır. Bildiri özetlerinin kaynak gösterilmesinden kaçınılmalıdır. Bir dergi tarafından kabul edilmiş fakat henüz yayımlanmamış olan yazılar gerektiği şekilde belgelendirilerek kaynak olarak kullanılabilir. Kabul edilmemiş yazılar da dahil olmak üzere bunun dışındaki bilgi, yazı içinde "yayınlanmamış gözlem" olduğu belirtilerek kullanılabilir. Kaynaklar aşağıdaki örneklere göre yazılmalı ve 6 yazara kadar olan kaynaklarda yazarların tamamı sunulmalı, daha fazla yazarı olan kaynak künyeleri, ilk 3 yazar ve sonuna ve ark. (yabancı dildeki kaynakların künyelerinde et al.) kısaltması gelecek şekilde düzenlenmelidir. Kaynakların doğruluğu açısından sorumluluk yazarlara aittir.

Örnekler

Türkçe süreli yayın örneği:

Göksedef D, Ömeroğlu NÖ, Denli Ş, Üreyen C, Sayılgan C, İpek G. Sistemik lupus eritematozuslu bir olguda aort yetmezliği nedeniyle aort kapak replasmanı. Cerrahpaşa Tıp Dergisi 2008;39:73-5.

Yabancı dilde süreli yayın örneği:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arhritis: a 14-year prospective evaluatin of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Elektronik dergide yayımlanan süreli yayın örneği:

Yurdakul S. Is there really a higher risk for infection with anti TNF-alpha agents or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Kitap bölümü örneği:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-8.

Hazırlanan yazıların dergiye gönderilmeden önce aşağıdaki kontrol listesine göre gözden geçirilmesi önerilir:

1- Başlık sayfası

2- Özetler (Türkçe ve İngilizce; olgu sunumlarında en fazla 100 sözcük, diğerlerinde en fazla 250 sözcük; araştırma yazılarında yapılandırılmış)

3- Anahtar sözcükler (en az 3'er adet)

4- Temel metin (alt başlıklar)

5- Kaynaklar (ICMJE kurallarına uygunluk)

6- Şekil, tablo ve resimler (numaralandırma; alt yazılar; özgünlük/izin yazısı)

7- Başvuru mektubu

8- Telif Hakkı Devir Formu (tüm yazarlar tarafından imzalanmış)

9- Çıkar Çakışması Beyan Formu (gereğinde)

Journal of Turkish Society for Rheumatology (formerly RAED Journal), the official organ of Turkish Society for Rheumatology, is a peer-reviewed scientific journal published three times in a year in Turkish or English (p-ISSN: 2651- 2653). The journal publishes original contributions in the form of experimental and clinical research articles, case reports, reviews, news, letters to the editor and authors as well as announcements related to all topics of rheumatology. Also, abstracts or full texts of scientific meetings in rheumatology can be published as supplements of the journal. The reviews are usually invited; therefore it is necessary to contact the editor before sending them to the journal. The journal does not accept reviews which are directly submitted.

The article types in the journal are classified as below:

- Clinical Research Article
- Experimental Study
- Case Report
- Review
- Letter to the Editor
- Recommendation
- Letter to the Author
- Book Review
- News
- Abstracts

ETHICS & PEER-REVIEW

Journal of Turkish Society for Rheumatology is an independent journal based on double-blind peer-review principles. The manuscript is assigned to the Editor-in-Chief, who reviews the manuscript and makes an initial decision based on manuscript quality and editorial priorities. Manuscripts that pass initial evaluation are sent to an Associate Editor. The Associate Editor assigns the manuscript to two reviewers (internal and/or external reviewers). The reviewers must review the manuscript within 21 days. The Associate Editor recommends a decision based on the reviewers' recommendations and sends the manuscript to the Editor-in-Chief. The Editor-in-Chief makes a final decision based on editorial priorities, manuscript quality, and Associate Editor's and reviewers' recommendations. If there are any conflicting recommendations from reviewers, the Editor-in-Chief can assign a new reviewer.

All manuscripts submitted are screened for plagiarism using Crossref Similarity Check powered by "iThenticate" software. Results indicating plagiarism may cause manuscripts being returned or rejected.

Manuscripts sent to the journal for publication should not have been previously published in another journal or sent to any journal simultaneously to be published. Manuscripts prepared from papers presented at scientific meetings can be sent to the journal, provided that they are not fully published. Incoming articles are pre-examined by Editorial Board. Manuscripts that are not suitable for publication purposes may be rejected directly or sent back to the author for publication and publication rules without being evaluated by the reviewer. Among the articles deemed appropriate for the scope of the journal, clinical research, experimental study, review and case report class articles enter the peer-review process. The Editorial Board is empowered to propose the corrections and changes it deems necessary during the preparation of the articles sent to the journal in line with the comments and suggestions of the reviewers. In order to ensure language unity, he/she can make word changes that do not change the scientific meaning of the sentence. After the necessary correction steps have passed in the peer evaluation process, the proof of the articles that are made ready for publication and the page layout is sent to the relevant author (for whom correspondence is made) for the final print approval.

Abstracts or full texts of scientific meetings in rheumatology can be published as supplements of the journal. Only proceeding papers within the scope of the conference topic are accepted. All submissions to the journal undergo an initial assessment for completeness before being reviewed by an editor. Then, these articles are reviewed by the scientific editorial committee of the conference.

Research Ethics

The author(s) should indicate in their articles that Informed Consent was received from the participating individuals in the studies conducted on people and send the approval document(s) received from the Ethics Committee or equivalent board of the institution where the study was conducted. In case reports, a document must be presented, indicating that each case is informed that their information will be used for publication. All work must have been done in accordance with the final amendments to the Helsinki Declaration. Patient information should be obtained in accordance with the Patient Rights Regulation published in the Official Gazette dated 01.08.1998 and numbered 23420. The European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose, by the Universal Declaration of Animal Rights, which reports results on animals, for the Protection of Vertebrates to be Used for Experimental and Other Scientific Purposes, T.C. The Regulation of the Ministry of Agriculture and Rural Affairs on the Production Areas of the Experimental Animals Used for Experimental and Other Scientific Purposes and the Regulation on the Establishment Operation Control Procedures and Principles of the Laboratory to Experiment, the Principles of Laboratory Animal Science, by the care and use of laboratory animals. If it is available in accordance with the rules and principles contained in the relevant manuals and in the institution where the study is carried out, it should be made after approval from the Experimental Animals Ethics Committee. Ethics Committee approval must be submitted with the letter. In the articles, the information should be given about post-operative pain-relieving treatment methods used in human and animal studies.

Publication Ethics and Malpractice Statement

Journal of Turkish Society for Rheumatology undertakes to apply the publication ethics to the highest standards and to comply with the following principles of the Publication Ethics and Abuse Declaration. This declaration is prepared based on the suggestions and guidelines developed by the journal on editors of the Committee

on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) and International Committee of Medical Journal Editors (ICMJE). Manuscripts sent to the journal for publication should not have been previously published in another journal (including papers presented at scientific meetings and published in full text) or simultaneously not sent to any journal for publication. Manuscripts sent to the journal are taken into the peer review process by an Editor and at least two consultants (reviewers). Our journal reserves the right to examine the submitted articles at any stage in terms of plagiarism through a purposeful software. For this purpose, unauthorized quotations or fraudulent data regarding plagiarism, fraudulence (made up or manipulated in the form or research data of the table) and investigations may be subject to inappropriate human or animal subjects. Manuscripts that do not comply with these standards are not published in the journal. This rule also applies in case of any incompatibility with these standards which can be determined at the post-publishing stage and requires the withdrawal of the article from the publication. Due to publication ethics, our journal will report cases of plagiarism or duplicate publication. Our journal is based on Publication Ethics Flowcharts developed by COPE in possible situations related to malpractice or violation of publication ethics.

Author Responsibility

Authors should ensure the authenticity of the articles they send. They must declare that the manuscript has not been published in any language, or has been evaluated for publication. They must comply with applicable copyright contracts and laws. In our journal, copyrighted material such as tables, figures or other contributory citations is published only with valid permission and copyright approval. Authors; other authors, contributors or sources should cite appropriately and indicate relevant sources. Participating in at least three stages of research type articles (including short reports) "designing the study", "collecting data", "reviewing data", "writing the article" and "confirming the accuracy of data and analysis" must declare. The authors are responsible for disclosing a financial relationship or areas of conflict of interest or competing for interest that should be known about the study and potentially affect the findings or scientific outcome of the study. They must explicitly report all financial contributions, sponsorships or project supports to the study. The "Conflict of Interest Conflict Declaration Form", which contains detailed information about the journal's Conflict of Interest Policy and can be used in case of potential conflict of interest, is available as a PDF document. When the author detects a meaningful scientific error or incompliance in his published article, he has an obligation to contact the Editor as quickly as possible for the purpose of withdrawing or correcting the article.

Reviewer Responsibilities

Reviewers evaluate incoming articles in terms of scientific content, regardless of their authors' ethnicity, gender, gender preference, nationality, religious belief, or political philosophy. For the reviewers; there should be no conflict of interest or competition regarding research, authors or promoters. Reviewer decisions must be objective. The Reviewers should indicate the related publications that have not been cited by the author. They are obliged to keep all information regarding the submitted article confidential and inform the Editor when they become aware of copyright infringement and plagiarism by the author. The reviewer should inform the Editor and ask for forgiveness from the evaluation process when he considers that the content of a sent article is incompatible with his or her scientific field or knowledge, or when he cannot make a quick evaluation.

Editor Responsibilities

Editors should evaluate incoming articles in terms of scientific content, regardless of their authors' ethnicity, gender, gender preference, nationality, religious belief, or political philosophy. They must provide a fair peer-review process for the publication of the submitted articles. They must ensure that all information regarding the submitted letter is kept confidential until it is published. Editors are responsible for the content and overall quality of the publication. If necessary, they should publish a correction through the Erratum pages. The Editor should not allow any conflicts of interest or competition between authors, editors and reviewers. Only the Editor has full authority in the assignment of the reviewers in the Journal of Turkish Society for Rheumatology and is also responsible for the final decision on the publication of the articles.

PUBLICATION POLICY

All articles will be evaluated by the scientific committee in terms of their scientific contributions, originality and content. Authors are responsible for the accuracy of their data. The journal reserves the right to change the language and appropriate changes where it deems necessary. If necessary, the article is sent to the author for revision. Articles previously published in any language will not be accepted for publication in the journal. Authors cannot submit an article that is about to be published in another journal. All changes will be made after the written permission of the author and publisher. The full text of all articles can be downloaded from the journal's website, www.manuscriptmodule.com/raed.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

GENERAL RULES

Apart from the features mentioned below, "International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts" documents (www.icmje.org) should be taken as a basis.

The sections that should be included in the articles to be sent to the journal are as follows and should be presented in a way that each starts on a separate page:

Page 1: Title page

Page 2: Turkish Title, Abstract and Keywords

Page 3: Title, Abstract and Key Words in English

Page 4 and afterwards: Main Text

Next page: Resources

Next page: Table Explanation and Table (each table should be specified on a separate page)

Next page: Figure and Image Subtitles and Image / Shapes (each shape must be specified on a separate page)

Title Page

The title page should be considered in the following order:

1- The category in which the article was sent (clinical research, experimental study, review, case report, etc.)

2- Title of the article (the title should not exceed 80 characters and should not contain non-standard abbreviations)

3- Name, surname, contact addresses of the authors and the institution they work at the time of the research

4- The abbreviated title of the article, which is desired to appear at the top of the continuation pages when published in the journal and does not exceed 40 characters.

5- Supporting institutions and organizations, if any

6- If the article has been submitted before, details of the meeting it was presented

7- Communication information of the author to be contacted

8- Indicating the financial support regarding the content of the article, if any

Turkish Abstract

The research articles should consist of the "Objectives", "Methods", "Results", and "Conclusions" sections and should not exceed 250 words. An unstructured abstract should be provided in reviews and case reports. The abstract of case reports should not exceed 100 words. A minimum of 3 and a maximum of 6 keywords should be specified in the Turkish abstract page.

English Abstract

The research articles should consist of "Objectives", "Methods", "Results", and "Conclusions" sections and should not exceed 250 words. At least 3, maximum of 6 English keywords should be determined in the English Abstract page, and English title of the article should be added.

Main Text

The introduction should consist of the Patients / Materials and Methods, Results, Discussion and References sections. Abbreviations should be standard and should be explained in parentheses when they are used first. Internationally accepted units should be used in the measurements.

Tables, Figures and Images

It should be numbered in the order of use in the text, and unnecessary use should be avoided. In the photographs used in the cases, permission should be obtained, and necessary measures should be applied to prevent recognition. Attention should be paid to the quality of photographs and drawings if any. Editorial Board may request correction or renewal in tables, figures and pictures on the grounds that it is not of sufficient quality. Figures and pictures must be original. In order for the pictures, figures and graphics used in another publication to be published in our journal, the necessary permissions must be obtained by the authors and before applying for an article. A copy of the document indicating that the permit has been obtained must be sent to the journal with the article.

References

References should be selected from the ones that are up to date and necessary for the article. References in the text should be indicated in parentheses and numbered according to the order of use. Name of the journals should be abbreviated in accordance with PubMed rules, and abbreviations should not be used in the names of journals which are not included here. Citation of proceedings should be avoided. Manuscripts accepted by a journal but not yet published can be documented as required and used as a source. Information other than this, including unaccepted articles, can be used by stating that there is "unpublished observation" in the article. References should be written according to the examples below, and all the authors should be presented in references up to 6 authors, references which have more authors should be arranged in a way that ''et al.'' abbreviation will be placed at the end of the first three authors. The responsibility for the accuracy of the references belongs to the authors.

Examples

Periodical publication example in Turkish:

Göksedef D, Ömeroğlu NÖ, Denli Ş, Üreyen C, Sayılgan C, İpek G. Sistemik lupus eritematozuslu bir olguda aort yetmezliği nedeniyle aort kapak replasmanı. Cerrahpaşa Tıp Dergisi 2008;39:73-5.

Periodical publication example in a foreign language:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow-acting antirheumatic therapy in rheumatoid arhritis: a 14-year prospective evaluatin of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Example of periodical publication published in an online journal:

Yurdakul S. Is there really a higher risk for infection with anti TNF-alpha agents or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Example of book section:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-8.

It is recommended that the prepared articles are reviewed according to the following checklist before being sent to the journal:

1- Title page

2- Abstracts (Turkish and English; maximum 100 words in case reports, maximum 250 words in others; structured in research papers)

3- Keywords (at least three each)

4- Main text (subheadings)

5- Resources (Compliance with ICMJE rules)

6- Figures, tables and pictures (numbering; subtitles; originality/ permission letter)

7- Application letter

8- Copyright Transfer Form (signed by all authors)

9- Conflict of Interest Declaration Form (if required)

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Original Article / Orijinal Araştırma

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Ulus Romatol Derg 2023;15(3):106-112

Hypovitaminosis D in patients with systemic sclerosis: Evaluating the role of skin involvement

Sistemik skleroz hastalarında D hipovitaminozu: Deri tutulumunun rolünün değerlendirilmesi

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Abstract

Objective: Systemic sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis of internal organs and the skin. In SSc, skin involvement may be responsible for vitamin D deficiency/insufficiency. We aim to evaluate the frequency of hypovitaminosis D (deficiency/insufficiency) in SSc and to investigate its relationship with skin involvement in this study.

Methods: In this cross-sectional study, 59 SSc (88% female) patients were included. Modified Rodnan Skin Score (mRSS) was used to assess skin involvement. Pulmonary arterial hypertension (PH) and pulmonary involvement were recorded. Spearman correlation analysis and logistic regression analysis were performed.

Results: Fifty-nine SSc patients were enrolled in this study. 50.8% of patients were limited cutaneous SSc and 49.2% were diffuse cutaneous SSc. The frequency of hypovitaminosis D (≤30 ng/mL) was 76.3%. There was no significant correlation between mRSS and hypovitaminosis D in SSc patients. Hypovitaminosis D was highly prevalent in SSc patients with darker skin tone compared to patients with lighter skin tone (p=0.035). SSc patients with PH had low levels of vitamin D than those without PH (p=0.016). Similarly, SSc patients with cardiac involvement had also low levels of vitamin D than those without cardiac involvement (p=0.037). In binary logistic regression analysis, the odds of hypovitaminosis D were almost 4 times higher (odds ratio=3.740 95% confidence interval 1.124-12.443, p=0.031) in patients with darker skin tone.

Conclusion: Skin color, PH, and cardiac involvement are found to be associated with low levels of vitamin D. On the other hand, no significant relationship is observed between mRSS and vitamin D levels in SSc patients.

Keywords: Systemic sclerosis, vitamin D level, modified Rodnan skin score, pulmonary arterial involvement, systemic involvement

Öz

Amaç: Sistemik skleroz (SSc) deri ve iç organların fibrozisi ile karakterize nadir otoimmün bir hastalıktır. SSc'de deri tututlumu D vitamin eksikliği/yetersizliğine neden olabilir. Bu çalışmada SSc'de D hipovitaminoz (eksikliği/yetersizliğine) sıklığının ve bunun deri tutulumu ile ilişkisinin değerlendirilmesi amaçlandı.

Yöntem: Bu kesitsel çalışmaya, 59 SSc'li (%88'i kadın) hasta dahil edildi. Deri tutumu modifiye Rodnan deri skoru (mRSS) ile değerlendirildi. Pulmoner arteriyel hipertansiyon (PH) ve pulmoner tutulumları kaydedildi. Spearman korelasyon analizi ve lojistik regresyon analizi uygulandı.

Bulgular: Çalışmaya 59 SSc hastası dahil edildi. Hastaların %50,8 limited kutanöz SSc ve %49,2'si diffüz kutanöz SSc idi. D hipovitaminoz (≤30 ng/mL) sıklığı %76,3'tü. SSc hastalarında mRSS ile D hipovitaminoz arasında anlamlı ilişki saptanmadı. Koyu tenli SSc hastalarında D hipovitaminozu açık tenlilere göre daha sıktı (p=0,035). PH'li SSc hastalarında D vitamini değerleri PH olmayanlara göre daha düşüktü (p=0,016). Benzer şekilde, kardiyak tutulumu olan SSc hastalarında da D vitamini değerleri kardiyak tutulumu olmayanlara göre daha düşük bulundu (p=0,037). İkili lojistik regresyon analizinde, D hipovitaminoz olasılığı koyu tenli hastalarda yaklaşık 4 kat daha yüksekti (risk oranı=3,740 %95 güven aralığı 1,124-12,443, p=0,031).

Sonuç: Deri rengi, PH ve kardiyak tutulum düşük D vitamin değerleri ile ilişkili bulundu. Diğer yandan SSc'li hastalarda mRSS ve D vitamin değerleri arasında anlamlı ilişki gözlenmedi.

Anahtar Kelimeler: Sistemik skleroz, D vitamini değeri, modifiye Rodnan deri skoru, pulmoner arteriyel tutulum, sistemik tutulum

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Introduction

Systemic sclerosis (SSc) is a rare and chronic progressive connective tissue disease characterized by heterogeneous clinical symptoms with progressive skin fibrosis and multisystemic involvement, playing an important role in morbidity and mortality. In general, SSc patients have been classified as limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the degree of skin involvement.[1] The Modified Rodnan Skin Score (mRSS) is a widely used semi-quantitative method to describe the degree and severity of skin involvement in SSc. Higher scores are associated with the disease severity and mortality, especially in patients with dcSSc.[2]

Vitamin D has a hormone-like function and its major natural source is the synthesis in the skin. The most important effect of vitamin D is on calcium homeostasis and bone health. In the literature, vitamin D deficiency/insufficiency, which is a common health problem, is closely related to many chronic diseases. Accordingly, low vitamin D level has been shown as a risk factor for many autoimmune diseases by modulating the immune system. In addition, vitamin D deficiency can contribute to fibrosis in diseases such as SSc, in which fibrosis is involved in the pathogenesis.[3-5] In line with this, numerous studies have proven that vitamin D deficiency is prevalent in SSc.[6-10] The underlying reasons for vitamin D deficiency have been defined as increased 25 (OH) D antibodies in the blood, decreased vitamin D synthesis in the epidermis due to capillary damaged dermal fibrosis, skin hyperpigmentation, low sunlight exposure, insufficient intake with diet or vitamin D malabsorption due to gastrointestinal involvement. Among these factors, cutaneous fibrosis, characteristic feature of SSc, is of utmost importance to cause hypovitaminosis.[7,11,12] Accordingly, the relationship between skin involvement and hypovitaminosis D in SSc may be described as "a chicken and egg dilemma".

In accordance with the abovementioned studies, we aimed to assess the frequency of hypovitaminosis D in SSc patients and to evaluate its relationship with the skin thickness.

Materials and Methods

Study Population

The present study was designed as a cross-sectional study. Accordingly, 70 SSc patients were screened for eligibility. Exclusion criteria were as follows: i) patients aged <18 years, ii) patients aged >85 years, iii) presence of extremity amputation, iv) history of more than one rheumatological disease or overlap syndrome, v) presence of renal failure, vi) patients with postinflammatory hyperpigmentation in the two skin areas assessed for skin color and vii) history of diseases that affect vitamin D metabolism, such as liver disease and endocrinological disease were excluded. Accordingly, 59 SSc patients who fulfilled 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[13] were enrolled in the study.

Evaluations

Medical records of SSc patients were used to extract the data on demographic information, clinical and laboratory findings. Vitamin D, calcium and bisphosphonate supplements, smoking, the menopausal status of female patients and dressing style were questioned. Laboratory outcomes such as calcium (Ca), phosphorus, alkaline phosphatase, parathormone and 25 (OH) D levels, which were studied between May and August, were noted. Similar to previous studies, vitamin D level above 30 ng/mL is defined as normal, between 21 and 30 ng/mL as insufficiency and below 20 ng/mL as deficiency of vitamin D. Hypovitaminosis D is regarded as deficiency/insufficiency of vitamin D.[14]

The findings of pulmonary involvement in chest computed tomography were screened. The presence of pulmonary fibrosis on computed tomography scan were noted. The findings of cardiac involvements (myocarditis and arrythmia) diagnosed by electrocardiography, echocardiography (ECHO), and cardiac magnetic resonance imaging were recorded. Patients with pulmonary hipertension (PH) were defined as having a pulmonary artery pressure greater than 45 mmHg as measured by the Doppler flow of the tricuspid regurgitant jet on ECHO. ECHO is accepted as an important non-invasive technique that gives results close to right heart catheterization results. Therefore, right heart catheterization, which is the gold method for evaluating the pulmonary hemodynamics, was not performed.[15]

mRSS was performed to measure skin thickness of 17 different areas (fingers, hands, forearms, upper arms, face, chest, abdomen, upper legs, lower legs and feet) under appropriate conditions. This evaluation was made by two different rheumatologists who had previously been trained with the repetitive teaching method. Each area was scored according to the degree of thickness as; 0= normal, 1= mild thickening, 2= moderate thickening and 3= severe thickening, and total score was noted (the total maximum score is 51).[2]

Evaluator (E.S.) decided on the skin color and categorized SSc patients into two groups as darker skin tone and lighter skin tone. The color was assessed in two skin sites, the back of the hand and the face. Patients with postinflammatory

hyperpigmentation in these two skin sites were not enrolled in the study.

The study was approved by Ethics Committee of Kocaeli University (ethics approval number: KU GOKAEK-2019/12.03). Written informed consent form was obtained from each patient.

Statistical Analysis

IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program was used to assess the data. The Kolmogorov-Smirnov test was performed to evaluate the distribution of variables. The Independent Sample t-test and Mann-Whitney U test were used to compare parametric and non-parametric continuous variables, respectively. Categorical variables were compared using chi-square test and Fisher exact test. Spearman correlation analysis was performed to find the relationships between variables. Logistic regression analysis was used to to examine the association of mRSS, skin involvement, and organ involvement with hypovitaminosis D. For the testing of two-sided hypotheses, $p<0.05$ was considered as sufficient for statistical significance.

Results

Of 59 patients included in our study, 30 (50.8%) were lcSSc and 29 (49.2%) were dcSSc. According to chest computed tomography findings, pulmonary involvement was in 45.8% of patients; PH in ECHO was in 16.9%, and cardiac involvement was in 15.3%. The demographic and laboratory characteristics of the patients are given in Table 1. There was no difference between dcSSc and lcSSc group in terms of demographic, clinical and laboratory findings, except for pulmonary involvement (Table 1). Hypovitaminosis D (≤30 ng/mL) was found in 76.3% of SSc patients. There was no difference between lcSSc and dcSSc subgroups in terms of vitamin D levels (Table 1 and Table 2).

In Spearman correlation analysis, we did not find any correlation between vitamin D level and age, gender, SSc subgroups, disease duration, and skin color. When hypovitaminosis D and demographic findings were compared, a significant difference was observed only between hypovitaminosis D and skin color. Deficiency/insufficiency of vitamin D was found to be significantly higher in patients with darker skin tone ($p=0.035$) (Table 3).

When SSc patients were divided two subgroups according to the systemic involvement, patients with PH (15.1±10.2 vs 23.6±11.2 ng/mL; $p=0.016$) and patients with cardiac involvement (18.6±19.5 vs 22.8±9.5 ng/mL; $p=0.037$) were associated with low level of vitamin D.

In binary logistic regression analysis, no associations were found between vitamin D insufficiency and MRSS and organ involvement. However, the odds of hypovitaminosis D were almost 4 times higher [odds ratio (OR)=3.740 95% confidence interval (CI) 1.124-12.443, $p=0.031$] in patients with darker skin tone. After adjusting for age, mRSS, organ involvement, the odds of hypovitaminosis D were 6.4 times higher (OR=6.431 95% CI 1.502-27.531, $p=0.012$) in patients with darker skin tone (Table 4).

Discussion

In the present study, higher frequency of hypovitaminosis D was observed in patients with SSc. Even though skin thickness was not associated with the level of vitamin D, darker skin color was related to low vitamin D levels. Moreover, some clinical findings such as PH and cardiac involvement were found in SSc patients with vitamin D deficiency/insufficiency.

Vitamin D deficiency is quite common in the general population (30-50%).[16] In SSc patients, vitamin D deficiency has been reported between 29.2% and 86%.[6,8-11] In a study conducted by Hax et al.[17], the prevalence of low vitamin D levels was found higher in patients with SSc than healthy controls, despite taking more vitamin D supplements. Many factors such as antibodies against vitamin D, decline in vitamin D synthesis due to the skin fibrosis, skin hyperpigmentation, insufficient intake, vitamin D malabsorption, and low sunlight exposure play a role in hypovitaminosis D in SSc. The last one is closely associated with latitudinal gradient. While the highest hypovitaminosis rates have been shown in China, northern France and Italy,[10] lower rates have been reported from India, Israel and Italy.[8,11,18] Interestingly, the countries reporting these low rates are those with enough sunlight at right angles. In our study, low vitamin D level was found in 76.3% of SSc patients. This result was similar to the rates reported from regions of similar latitude. Skin fibrosis plays an important role in hypovitaminosis D in patients with SSc. Therefore, unsurprisingly, higher skin thickness may be correlated with lower vitamin D levels. A meta-analysis evaluating the level of vitamin D in SSc showed that patients with diffuse type SSc were more likely to have lower vitamin D status.[19] However, in the current study, we could not be able to demonstrate this difference between two SSc subgroups.

In the present study, we evaluated the laboratory outcomes of our patients between May and August to eliminate the effect of seasonal variations. Recently published review article showed that seasonal vitamin D changes may impact on clinical symptoms of SSc.[20] Accordingly, only one study presented their large data included 2.480 Thai-

Table 1. Demographic, clinical and laboratory findings, and the comparison of lcSSc and dcSSc patients

n (%)	All patients (n=59)	lcSSc (n=30)	dcSSc (n=29)	p[a]
Age (year)[&]	55.02±11.55	54.30±10.92	55.76±12.31	0.632[T]
Disease duration (month)[&]	104.24±59.97	87.80±87.80	121.24±69.78	**0.031***[T]
Gender (Women)	52 (88.1)	27 (90)	25 (86.2)	0.706
Smoking				
Smoker	4 (6.8)	2 (6.7)	2 (6.9)	0.893
Smoked and quit	10 (16.9)	6 (20)	4 (13.8)	
Non smoker	45 (76.3)	22 (73.3)	23 (79.3)	
Skin color				
Dark skin	39 (66.1)	20 (66.7)	19 (65.5)	1.000
Veiled clothing (Only women)	44/52 (84.6)	21/27 (77.8)	23/25 (92)	0.252
Menopause (Only women)	39/52 (75)	19/27 (70.4)	20/25 (80)	0.631
Systemic involvement				
Pulmonary involvement	27 (45.8)	9 (30)	18 (62.1)	**0.027***
Pulmonary hypertension	10 (16.9)	6 (20)	4 (13.8)	0.731
Cardiac involvement	9 (15.3)	4 (13.3)	5 (17.2)	0.731
GIS involvement	18 (30.5)	10 (33.3)	8 (27.6)	0.844
Kidney involvement	1 (1.7)	1 (3.3)	0	1.000[F]
Joint-tendon involvement	18 (30.5)	9 (30)	9 (31)	1.000
Myositis	1 (1.7)	0	1 (3.4)	0.492[F]
Use of replacement				
Only Ca	8 (13.6)	3 (10)	5 (17.2)	0.122
Only vitamin D	9 (15.3)	7 (23.3)	2 (6.9)	
Bisphosphonate	6 (10.2)	2 (6.7)	4 (13.8)	
Ca + vitamin D	3 (5.1)	0	3 (10.3)	
Osteoporosis	15 (25.4)	6 (20)	9 (31)	0.500
Low Ca	2 (3.4)	1 (3.3)	1 (3.4)	1.000[F]
Low P	1 (1.7)	1 (3.3)	0	1.000[F]
ALP elevation	4 (6.8)	4 (13.3)	0	0.112[F]
PTH elevation	13 (22)	6 (20)	7 (24.1)	0.945
25(OH)D (ng/mL)[&]	22.1±11.4	22.1±11.4	23.0±10.2	0.693[T]
Low Serum 25 (OH) D[a]	45 (76.3)	22 (73.3)	23 (79.3)	0.590
Otoantikorlar				
Anti-Scl 70	19 (32.2)	2 (6.7)	17 (58.6)	0.000
Anti-centromer	16 (27.1)	15 (50)	1 (3.4)	
CENP-B	26 (44.1)	22 (73.3)	4 (13.8)	
mRSS [median (25-75 pers.)]		5 (4-8.5)	9 (6-14.5)	**0.005***[M]

**p<0.05 statistically significant; [&]: mean ± SD, [a]: the comparison results of lcSSc and dcSSc; [T]: was used Student t-test; [M]: was used Mann-Whitney U test, [F]: was used Fisher exact test; [a]: serum 25 (OH) D was <30 ng/mL.*

ALP: Alkaline phosphatase, Ca: Calcium, dcSSc: Diffuse cutaneous systemic sclerosis, GIS: Gastrointestinal system, lcSSc: Limited cutaneous systemic sclerosis, mRSS: Modified Rodnan Skin score, P: Phosphorus, PTH: Parathormone

Table 2. Vitamin D levels in two subsets of SSc

n (%)	lcSSc (n=30)	dcSSc (n=29)	p
25(OH)D <20 ng/mL	14 (46.7)	13 (44.8)	0.887
25(OH)D 21-30 ng/mL	8 (26.7)	10 (37.9)	0.514
25(OH)D >30 ng/mL	8 (26.7)	6 (17.2)	0.589

dcSSc: Diffuse cutaneous systemic sclerosis, lcSSc: Limited cutaneous systemic sclerosis, SSc: Systemic sclerosis

Table 3. Demographic features according to vitamin D levels in patients with systemic sclerosis

n (%)	Hypovitaminosis D (n=45)	Normal vitamin D (n=14)	p
Gender			
Woman	40 (76.9)	12 (23.1)	0.748
Skin color			
Light skin (n=20)	12 (60)	8 (40)	**0.035***
Dark skin (n=39)	33 (84.6)	6 (15.4)	
Clothing Style (only women)			
Nonveiling clothing	5 (62.5)	3 (37.5)	0.293
Veiling clothing	35 (79.5)	9 (20.5)	
Smoking			
Smoker	4 (100)	0 (0)	
Smoked and quit	5 (50)	5 (50)	0.067
Non smoker	36 (80)	9 (20)	
mRSS [median (25-75 pers.)]	7 (7.3-11.5)	7 (5.5-11.1)	0.993^{M}

**p<0.05 statistically significant, ^{M}: was used Mann-Whitney U*

Table 4. Logistic regression analysis for factors associated with hypovitaminosis D in patients with systemic sclerosis

	Unadjusted			Adjusted		
	OR	95% CI	p	OR	95% CI	p
Age (years)	0.973	0.923-1.025	0.302	0.947	0.885-1.013	0.113
mRSS	1.028	0.931-1.136	0.582	1.020	0.902-1.054	0.749
Pulmonary involvement	0.560	0.176-1.784	0.327	0.314	0.073-1.352	0.120
Pulmonary hypertension	3.971	0.461-34.205	0.209	4.209	0.198-89.470	0.357
Cardiac involvement	3.429	0.393-29.880	0.265	4.499	0.185-109.118	0.355
Skin color	3.740	1.124-12.443	**0.031**	6.431	1.502-27.531	**0.012**

CI: Confidence interval, mRSS: Modified Rodnan Skin score, OR: Odds ratio

SSc patients and showed that the highest acceptance rate into the healthcare system was observed in rainy season (from mid-May to mid-October). Even though the authors did not clarify the exact reason for this increased admission, the study pointed out the seasonal variations.[21]

Although exposed to the similar rate of sunlight, dark-skinned individuals produce less 25(OH)D than light-skinned individuals. In a single study, the rate of vitamin D deficiency according to skin color has been reported as 68% in dark-skinned and 17% in light-skinned patients.[22] In our study, vitamin D deficiency/insufficiency was found to be higher only in SSc patients with darker skin tone (84.6% vs 60%, p=0.035). In addition, vitamin D deficiency was more common in SSc patients with darker skin color than SSc patients with lighter skin color.

Individuals who use excessive amounts of sunscreens or wear clothes that cover most of their body have minimal exposure to sunlight. Even in the sunny regions of the world such as Beirut and Lebanon, it has been reported that there is a relationship between the veiled clothing style and the frequency of vitamin D deficiency in the healthy population.[23] In the present study, we could not show any significant difference between the groups in terms of veiled clothing style. In addition, veiled clothing was not found to be a significant risk factor for vitamin D deficiency/insufficiency in SSc. However, the reason for the inconsistent results between the aforementioned study and the present study may be due to the different study population and latitudinal gradient.

Vitamin D plays an anti-fibrotic role by decreasing the production of collagen I and collagen III as a result of TGF-β (a profibrotic cytokine) reduction, and it also increases the production of antifibrotic factors such as metalloproteinase-8.[20,24] It is suggested that the most important reason for vitamin D deficiency in SSc is skin fibrosis, which affects active vitamin D synthesis steps.[12] While some studies have reported an inverse relationship between skin fibrosis and low vitamin D levels,[25,26] other studies have not shown this relationship.[7,9,27,28] In the present study, as expected, we found higher skin scores in dsSSc patients. However, no significant relationship was observed between mRSS and vitamin D deficiency/insufficiency in the study population, regardless of subtypes (dcSSc and lcSSc).

According to the recently published systematic literature review article, vitamin D deficiency is likely to be linked with various clinical and serological characteristics of SSc.[29] For instance, in two independent studies, vitamin D deficiency was closely related to the higher pulmonary artery pressure and lower diffusing lung capacity.[8,10] As far as we know, there is no other study on this subject in literature. In our study, no significant relationship was found between vitamin D deficiency/insufficiency and clinical findings, except PH (p=0.016) and cardiac involvement (p=0.037). The study conducted by Clements et al.[30] presented the significant relationship between baseline mRSS (≥20) and baseline cardiac and joint involvement (for cardiac involvement p=0.025; for joint involvement p=0.035) in dSSc patients.

Moreover, this baseline skin score was an important predictor for mortality and scleroderma renal crisis. In our study, no significant relationship was found between mRSS and organ involvement, except pulmonary involvement (p=0.024). The reason why we could not find any association between mRSS and systemic involvement in our study population may be due to the long disease duration (>5 years) leading to atrophic skin characterized by low mRSS. In addition, we may not have found any link between skin involvement and vitamin D level due to low mRSS. Therefore, comprehensive studies are needed to reach a more definite conclusion on this issue.

Study Limitations

There are some limitations in this study. First, we did not exclude the patients having long disease duration (>5 years) leading to atrophic skin. Second, we did not enroll the patients according to the information about vitamin D replacement therapy use. However, studies reported that there was no difference between the patients who received the replacement therapies and those who did not. Third, sample size was not enough to show more accurate results. On the other hand, the study population is generally small due to its rarity in studies evaluating SSc. Fourth, we did not use any validated and/or reliable method to measure the skin color. Last, we did not design this study as a case-control study. Thus, healthy age-matched subjects were not included in this study.

Conclusion

In conclusion, the frequency of hypovitaminosis D in patients with SSc is found to be 76.3%. Darker skin, PH, and cardiac involvement are closely associated with low vitamin D levels. Multicentered studies with a larger sample size are needed to show the exact link between vitamin D level and systemic involvement.

Ethics

Ethics Committee Approval: The study was approved by Ethics Committee of Kocaeli University (ethics approval number: KU GOKAEK-2019/12.03).

Informed Consent: Written informed consent form was obtained from each patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Design: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Data Collection or Processing: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Analysis or Interpretation: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Literature Search: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Writing: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y.

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Secukinumab experience in patients with axial spondyloarthritis: A 3-year real life data of a single centre

Aksiyel spondiloartrtit hastalarında secukinumab deneyimi: Tek merkez 3 yıllık gerçek yaşam verileri

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Abstract

Objective: Secukinumab is a fully human immunoglobulin G1 kappa monoclonal antibody which binds to interleukin-17A. We aimed to assess the demographic, clinical and laboratory features of axial spondyloarthritis (axSpA) patients using secukinumab and to evaluate drug adherence and adverse effects.

Methods: The study is a retrospective analysis of secukinumab-treated axSpA patients who presented to our center between May 2018 and March 2022.

Results: Of 52 patients, 20 (38.5%) were male, and the mean age at diagnosis of axSpA was 36.5±12.1. The median follow-up period was 89.3 (Q1-Q3: 65.0-160.9) months. Sixteen patients (30.8%) were on tumor necrosis factor-α (TNF-α) inhibitor (TNFi) naive. The overall cumulative secukinumab drug survival rates observed at 12 and 24 months were 96% and 93%, respectively. The duration of drug survival was not significantly different between the TNFi-naive and TNFi- nonresponder (TNF-IR) groups (p=0.18). After starting secukinumab, only 1 patient experienced uveitis for the first time. No exacerbation of inflammatory bowel disease was observed.

Conclusion: Our study presents the real-life experience of secukinumab from Turkey. The treatment response does not change in TNFi-naive and TNF-IR patients which indicates that secukinumab is almost equally efficacious both in TNFi-naive and TNF-IR patients. To conclude, secukinumab is a safe and effective treatment option for patients with axSpA.

Keywords: Secukinumab, axial spondyloarthritis, IL-17A antibody

Öz

Amaç: Secukinumab, interlökin-17A'ya bağlanan insan immünoglobülin G1 kappa monoklonal antikorudur. Secukinumab kullanan aksiyal spondiloartrit (aksSpA) hastalarının demografik, klinik ve laboratuvar özelliklerini ve ilaç uyumunu ve ilaç yan etkilerini değerlendirmeyi amaçladık.

Yöntem: Mayıs 2018-Mart 2022 tarihleri arasında merkezimize başvuran secukinumab ile tedavi edilen aksSpa'lı hastaların retrospektif analizi yapılmıştır.

Bulgular: Elli iki hastanın, 20'si (%38,5) erkek idi. Ortalama aksiyel spondiloartrit tanı yaşı 36,5±12,1 idi. Ortalama takip süresi 89,3 (Q1-Q3: 65,0-160,9) ay idi. Hastaların 16'sı (%30,8) tümör nekroz faktörü-α (TNF-α) ihibitörü (TNFi) kullanmamıştı. On ikinci ve 24. ayda gözlemlenen secukinumab ilacı sağkalım oranları sırasıyla %96 ve %93 idi. İlaç kalma süresi, TNFi-naif ve TNFi yanıtsız (TNF-IR) grupları arasında anlamlı bir fark göstermedi (p=0,18). Secukinumab tedavisine başlandıktan sonra sadece 1 hasta ilk kez üveit atağı geçirdi. enflamatuvar barsak hastalığı alevlenmesi görülmedi.

Sonuç: Çalışmamız Türkiye'den secukinumabın gerçek yaşam deneyimini sunmaktadır. TNFi-naif ve TNF-IR hastalarda tedavi yanıtının değişmemesi, secukinumabın hem TNFi-naif hem de TNF-IR hastalarında neredeyse eşit derecede etkili olduğunu göstermektedir. Sonuç olarak secukinumab, aksSpA'lı hastalar için güvenli ve etkili bir tedavi seçeneği olacaktır.

Anahtar Kelimeler: Sekukinumab, aksiyel spondiloartrit, IL-17A antikoru

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition which mainly affects the spine and sacroiliac joints. AxSpA is divided into 2 different types according to the X-ray imaging of sacroiliac joints, radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA).[1] Patients with axSpA may also experience dactylitis, enthesitis, and peripheral arthritis. Furthermore, extra-articular findings

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such as psoriasis, inflammatory bowel disease (IBD), and uveitis may be observed.[1-3]

The exact etiopathogenesis of axSpA is not completely understood. Numerous immune system components and cytokines including interleukin (IL)-17, IL-23, and tumor necrosis factor-α (TNF-α) play a part in the pathophysiology of the disease.[4,5] Non-steroidal anti-inflammatory drugs are the first line therapeutic agents in the treatment of axSpA. In resistant cases, further treatment options, such as TNF-α inhibitors (TNFi), IL-17 inhibitors and JAK/STAT pathway inhibitors, are required.[6]

Secukinumab, a fully human IgG1 kappa monoclonal antibody which binds to IL-17A, has been approved for axSpA treatment. Secukinumab was shown to be rapidly effective in axSpA patients in a phase 3 study.[7] Likewise, in the MEASURE studies, secukinumab treatment was shown to be effective and demonstrated low rates of radiographic progression rate in patients with r-axSpA.[8-10] In the MEASURE 2 study, the patients who received secukinumab showed substantial improvements in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores and Assessment of spondyloarthritis international society.[11] 40 response criteria in both the TNFi-naive and TNFi-nonresponder (TNF-IR) groups.[12] In the PREVENT study, the use of secukinumab improved the symptoms in patients with nr-axSpA.[13] In a real-life study called as CORRONA study, it was shown that patients receiving secukinumab had a decrease in disease activity at a similar rate compared to patients receiving other biologic drugs.[14] However, there are some concerns about its use in patients with IBD and uveitis.[15-18]

In this retrospective observational study, we aimed to assess the demographic, clinical and laboratory features of r-axSpA patients using secukinumab and to evaluate drug adherence and adverse effects.

Materials and Methods

The records of 86 spondyloarthritis (SpA) patients who were seen at the biologic treatment outpatient clinic of the Ankara University Faculty of Medicine between May 2018 and March 2022 and used secukinumab were retrospectively evaluated. Fourteen patients who did not fulfill the ASAS classification criteria and 6 patients who did not have axial involvement were excluded.[19] Among 66 patients with axSpA, 52 who had a follow-up period of 16 weeks, or more were included in the final analyses. Patients' demographic data, extra-articular findings, therapies, BASDAI scores at the beginning of secukinumab treatment, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values were recorded.[19-21] The patients were also screened for the presence of accompanying fibromyalgia syndrome (FMS) according to 2010 ACR fibromyalgia diagnostic criteria.[22]

Patients who did not receive TNFi prior to secukinumab were considered TNFi-naive, patients who received one or more TNFi, and developed ineffectiveness before secukinumab initiation were considered as TNFi non-responder (TNF-IR). Patients who did not respond or were intolerant to secukinumab at the 12th week of treatment were called primary non-responders, and patients who did not respond to treatment beyond the 6th month were called secondary non-responders.

Drug adherence was defined as the condition in which patients continued to take their medication without discontinuing for any reason, including inefficacy, difficulty in using medication, side effects and loss to follow-up.

This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles and was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: İ11-697-22, date: 10.01.2023).

Statistical Analysis

Data are shown as total numbers and percentages for categorical variables. Chi-square and Fisher exact test (in case of an expected count <5) was used to investigate the relationship between two categorical variables. Continuous variables were compared by either Student's t test or Mann-Whitney test according to normality distribution and given as mean ± standard deviation (SD) or as the median and 25th and 75th percentiles (Q1-Q3). To demonstrate the differences between in the initial and the last and acute phase reactant levels, Wilcoxon rank test was performed. Paired sample t-test was done to compare baseline and the last BASDAI scores. Statistical significance was defined as a two-sided p-value <0.05. All statistical analyses were conducted with SPSS software version 26.

Results

Of the 52 patients, 20 (38.5%) were male, and the mean age at diagnosis of axSpA and onset of secukinumab were 36.5±12.1 and 44.9±10.6, respectively (Table 1). Of 52 patients, 16 patients (30.8%) were TNFi naive (Table 1). There was no significant difference in the baseline BASDAI scores between TNFi-naive and TNF-IR groups (p=0.16). The characteristic features of TNFi naive patients and TNF-IR patients are given in Table 2. There was no significant difference in last BASDAI scores between

Table 1. Demographic characterisctics of patients

	All patients n=52	Secukinumab discontinied n=5 (9.6%)	Drug continuing n=47 (90.4%)	p
Age of diagnosis, year (SD)	36.5 (12.1)	39.7 (16.6)	36.2 (11.7)	0.54
Age at drug onset, year (SD)	44.9 (10.6)	44.1 (14.4)	44.9 (10.3)	0.86
Gender, male, n (%)	20 (38.5)	1 (20.0)	19 (40.4)	0.64
Radiographic SpA, n (%)	39 (75.0)	4 (80.0)	35 (74.5)	>0.99
Smoker, n (%)	20 (47.6)	4 (80.0)	16 (43.2)	0.17
Family history, n (%)	16 (34.8)	0 (0.0)	16 (39.0)	0.15
Inflammatory back pain, n (%)	51 (98.1)	5 (100.0)	46 (47.9)	>0.99
Peripheral arthritis, n (%)	21 (40.4)	0 (0.0)	21 (44.7)	0.073
HLA-B27 positivity	16 (44.4)	1 (33.3)	15 (45.5)	>0.99
Psoriasis, n (%)	7 (13.5)	0 (0.0)	7 (14.9)	>0.99
Inflammatory bowel disease, n (%)	2 (3.8)	1 (20.0)	1 (2.1)	0.19
Uveitis, n (%)	7 (13.5)	1 (20.0)	6 (12.8)	0.53
Enthesitis, n (%)	17 (32.7)	1 (20.0)	16 (34.0)	>0.99
Secukinumab concomitant therapies				
NSAID, n (%)	29 (55.8)	2 (40.0)	27 (57.4)	0.64
Glucocorticoids, n (%)	5 (9.6)	0 (0.0)	5 (10.6)	>0.99
Methothrexate, n (%)	4 (7.7)	0 (0.0)	4 (8.5)	>0.99
Leflunomide, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Sulfasalasine, n (%)	14 (26.9)	0 (0.0)	14 (29.8)	0.31
Biological agent before sec				
Certolizumab, n (%)	8 (15.4)	2 (40.0)	6 (12.8)	0.16
Golimumab, n (%)	7 (13.5)	1 (20.0)	6 (12.8)	0.53
Infliximab, n (%)	11 (21.2)	2 (40.0)	9 (19.1)	0.28
Adalimumab, n (%)	22 (42.3)	2 (40.0)	20 (42.6)	>0.99
Etanercept, n (%)	19 (36.5)	2 (40.0)	17 (36.2)	>0.99
TNFi naive, n (%)	16 (30.8)	0 (0.0)	16 (34.0)	0.31
Taking 1 TNFi, n (%)	13 (25.0)	2 (40.0)	11 (23.4)	
2 TNFi, n (%)	18 (34.6)	2 (40.0)	16 (34.0)	
3 TNFi, n (%)	2 (3.8)	1 (20.0)	1 (2.1)	
4 TNFi, n (%)	3 (5.8)	0 (0.0)	3 (6.4)	
5 TNFi, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Ustekinumab, n (%)	1 (1.9)	0 (0.0)	1 (2.1)	>0.99
First CRP-before secukinumab, (mg/dL)	10.3 (4.9-30.4)	6.5 (4.7)	12.1 (8.8)	0.17
First ESH-before secukinumab, (mm/hours)	19 (11-46)	13 (11-28)	19.5 (10.5-48)	0.52
First BASDAI	5.6 (1.8)	4.9 (1.8)	5.7 (1.8)	0.37
The last CRP, (mg/dL), median	6.4 (2.1-13.8)	6.1 (2.2-17.7)	6.5 (2.1-14.3)	>0.99
The Last ESH, (mm/hours)	16.5 (5.3-21.8)	15 (12-22.5)	17 (5-22)	0.77
The Last BASDAI	2.9 (1.9)	3.2 (2.8)	2.8 (1.9)	0.65

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IBD: Inflammatory bowel disease, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation, TNFi: Tumour necrosis factor alpha inhibitors

Table 2. BASDAI scores of TNFi naive and TNF

	TNFi naive n=16 (31.0%)	TNFi-IR n=36 (69.0%)	p-value
First BASDAI score, mean (SD)	5.2 (2.1)	5.8 (1.6)	0.29
Final BASDAI score, mean (SD)	3.2 (2.1)	2.7 (1.9)	0.47

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, SD: Standard deviation, TNFi: Tumour necrosis factor alpha inhibitors, TNFi-IR: TNFi non-responder

TNFi naive and TNF-IR (p=0.44). There was a significant difference between baseline and final follow-up BASDAI of 16 TNFi-naive patients (p=0.011), the mean difference was -2.0 [95% confidence interval (CI) -0.5-(-3.5)]. There was a significant difference between baseline and final follow-up BASDAIs in 36 TNFi-IR patients (p<0.001), the mean difference was -3.1 [95% CI -2.3-(-3.8)] (Table 2). While the median initial CRP value of our patients was 10.3 (Q1-Q3: 4.9-30.4) mg/L, the final median CRP value was 6.4 (Q1-Q3: 2.1-13.8) (p<0.001). The median initial ESR was 19 (Q1-Q3: 11-46) mm/h, while the final post-treatment ESR was 16.5 (Q1-Q3: 5.3-21.8) mm/h (p<0.001).

Of the 52 patients, 11 (21.2%) had FMS. When we excluded patients with FMS for possible bias, the median duration of secukinumab use in 41 patients was 24.9 (Q1-Q3: 11.5-38.3) months. One-year drug retention was 94% and, both 2 and 3-year drug retention rates were 91%. When baseline and final follow-up BASDAI scores of 41 patients were compared, there was a shift of -2.9 [95% CI -3.6-(-2.3)] (p<0.001).

The median follow-up period of 52 patients from axSpA diagnosis to the last follow-up was 89.3 (Q1-Q3: 65.0-160.9) months). Secukinumab was discontinued in 5 (9.6%) individuals during a median follow-up time of 27.4 (Q1-Q3: 11.9-37.7) months. Secukinumab treatment was terminated due to secondary non-response in 2 patients, pregnancy planning in 1 patient, hypertensive attack in 1 patient, and long-term SpA remission in 1 patient. The overall cumulative secukinumab drug survival rates observed at 12 and 24 months were 96% and 93%, respectively. The duration of drug survival was not significantly different between the TNFi-naive and TNF-IR groups [33.2 months (Q1-Q3: 19.5-39.7) and 24.3 months (Q1-Q3: 10.9-37.1), respectively; p=0.18].

After starting secukinumab medication, no uveitis attack was seen while receiving secukinumab medication, even though 7 patients had a history of uveitis before the initiation of secukinumab. Only 1 patient experienced uveitis episode for the first time, and any attacks did not occur again in this patient over the 39-month follow-up period. In addition, during the follow-up of 2 (3.9%) individuals who had been previously diagnosed with IBD, no exacerbation was detected. Overall, no malignancy was detected, and no patient died during the follow-up period of these 52 patients.

Discussion

Our study is a real-life experience of a single centre that demonstrates the efficacy of secukinumab treatment and the duration of drug survival in axSpA patients.

In terms of treatment response, a previous study showed a change in BASDAI score as -2.6 in the TNFi-naive group and -1.6 in the TNF-IR groups from baseline to week 16.[12] Even though the evaluation period is not identical, in our study, it was found to be -2.0 in the TNFi-naive group and -3.1 in the TNF-IR group, which was not statistically different (Table 3). Similar to the studies such as MEASURE and BIOBADASER, patients who received secukinumab in our study showed a decrease in CRP values, regardless of prior TNFi use.[12,23]

In many studies in the literature, including the ASTURias and EuroSpA studies, the duration of drug retention rate in the TNFi-naive group was higher than that of TNF-IR group.[24-27] Contrary to these studies, in a real-life study of Bektaş et al.,[28] previous use of TNFi did not affect the drug retention rate. In our study the duration of drug survival was not significantly different between the TNFi-naive and TNF-IR groups as in Beştaş et al.'s[28] study (p=0.18). The small sample size of our patients may have resulted in differing conclusions in this regard.

In literature, the rate of drug retention during the first year ranged from 55 to 86%.[24-29] In our study, the 1-year drug retention rate for patients receiving secukinumab was 96%, which is greater than what has been reported in the literature. In this instance, the selection of the appropriate patient may have had a role, and the low number of our patients may have contributed to this outcome.

Secukinumab does not increase the risk of uveitis, according to published Phase 3 studies.[15] In the study by Bektaş et al.,[28] patients receiving secukinumab did not develop a new case of uveitis. However, uveitis attacks have been reported in some case reports following secukinumab treatment.[17] In our study, uveitis attack under treatment was observed only in one patient. The attack did not recur in the following period. Seven patients with a history of uveitis did not experience a new attack during the secukinumab use. This could also suggest that secukinumab does not increase the risk of uveitis. However, long-term, and largely populated studies are required.

Furthermore, there are some studies and case reports demonstrating that secukinumab treatment exacerbates IBD.[30,31] On the contrary, there are studies showing that it does not increase the risk of IBD.[32,33] In our study, neither a new occurrence of IBD in the entire cohort nor an exacerbation of the disease in the 2 individuals who had previously been diagnosed with IBD was seen. However, our case number and duration of follow-up might be insufficient to make firm conclusions.

Table 3. TNFi naive and TNFi-IR patients characteristics

	TNFi-naive	TNFi-nonresponder
Age at daiagnosis, year (SD)	38.7 (13.9)	35.6 (11.3)
Age at drug onset, year (SD)	44.7 (10.6)	44.9 (10.8)
Gender, male, n (%)	5 (31.3)	15 (41.7)
Radyographic SpA, n (%)	13 (81.3)	26 (72.2)
Smoker, n (%)	3 (30.0)	17 (53.1)
Family history, n (%)	3 (25.0)	13 (38.2)
Inflammatory back pain, n (%)	16 (100)	35 (97.2)
Peripheral arthritis, n (%)	5 (31.3)	16 (44.4)
HLA b27 positivity, n (%)	4 (33.3)	12 (50.0)
Psoriasis, n (%)	1 (6.3)	6 (16.7)
Inflammatory bowel diseae, n (%)	0 (34)	2 (5.6)
Uveitis, n (%)	1 (6.3)	6 (16.7)
Enthesitis, n (%)	3 (18.8)	14 (38.9)
Secukinumab concominant therapies		
NSAIDs, n (%)	8 (50.0)	21 (58.3)
Glucocorticoids, n (%)	2 (12.5)	3 (8.3)
Methotrexate, n (%)	0 (34)	4 (11.1)
Leflunomide, n (%)	0 (34)	0 (34)
Sulfasalasine, n (%)	8 (50.0)	6 (16.7)
CRP at secukinumab initiation, mg/dL, median (Q1-Q3)	11.1 (5.1-27.8)	10.2 (4.7-31.8)
ESR at secukinumab initiation, mm/hours, median (Q1-Q3)	19 (11-46)	19 (9-46)
The last CRP, mg/dL, median (Q1-Q3)	4.1 (2.0-9.4)	6.6 (2.3-16.2)
The last ESR, mm/hours, median (Q1-Q3)	16.5 (9.3-21)	16 (5.22.8)

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation

Secukinumab is safe and efficacious in TNFi-naive and TNF-IR axSPA patients.[24] In the MEASURE 2 study, secukinumab treatment was demonstrated to be safe and effective for both TNFi-naive and TNF-IR patients. [12] During a median follow-up period of 27,4 months, no serious infections, malignancies, or mortality were observed in our study. This is in line with the current literature. However, the follow-up period may not be long enough to detect the development of malignancy. There is a need for larger cohort studies with longer follow-up periods.

Study Limitations

The major limitation of our study is the small number of our study cohort. In addition, the duration of follow-up was short to evaluate drug safety. As for strengths of the study, it presents the real-life experience of secukinumab by also including axSpA patients with extra-articular involvement.

Conclusion

Our results suggest that secukinumab is to be safe and effective treatment option for patients with axSpA regardless of previous TNFi exposure. Likewise, the fact that the treatment response does not change in TNFi-naive and TNF-IR patients indicates that secukinumab is almost equally efficacious both in TNFi-naive and TNF-IR patients. The absence of newly formed IBD implies that secukinumab is a viable treatment option for patients who do not respond to TNFi.

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It was presented as an oral presentation at the 15th Anatolian Rheumatology Days meeting.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles and was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: İ11-697-22, date: 10.01.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.U.Y., D.Ş.E., E.G.A.G., A.İ., T.M.T., G.K., A.A., Concept: E.U.Y., D.Ş.E., Design: E.U.Y., D.Ş.E., A.İ., T.M.T., G.K., A.A., Data Collection or Processing: D.Ş.E., E.G.A.G., Analysis

or Interpretation: D.Ş.E., Literature Search: E.U.Y., D.Ş.E., A.İ., Writing: E.U.Y.

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Kadın Behçet hastalarında fertilite, gebelik ve doğum verilerinin değerlendirilmesi

The evaluation of fertility, pregnancy and birth data in female Behçet's patients

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**Klinik çalışmanın özeti "IX. Romatolojide Yaklaşımlar ve Profesörlerle Yuvarlak Masa Toplantıları" adlı bilimsel kongrede bildiri olarak sunulmuştur.*

Öz

Amaç: Behçet hastalığı (BH) mukokutanöz bulgular ile birlikte sistemik organ tutulumları olan, reprodüktif çağdaki kadınları da etkileyen enflamatuvar bir hastalıktır. BH'nin diğer enflamatuvar hastalıklar gibi fertilite üzerine etkilerinin olması muhtemeldir. Bu çalışmanın amacı, BH tanısı alan kadınlarda, BH'nin doğurganlık, gebelik ve doğum süreçleri üzerindeki etkilerini araştırmaktır.

Yöntem: İki yüz yetmiş dört kadın Behçet hastasının evlilik, doğurganlık ve gebelik öyküleri retrospektif olarak değerlendirilmiştir. BH tanısından önce (n=450), sonra (n=113) gerçekleşen toplam 563 gebeliğin verileri analiz edilmiştir.

Bulgular: Çalışmaya dahil edilen hastaların ortalama yaşı 39,8 yıl idi. İnfertilite oranı %2,3 (n=5) saptanmıştır. Yardımcı üreme teknikleri ile gerçekleşen gebelik oranı %1,4 (n=3) idi. BH tanısından sonra 3 ve ≥4 gebelik gerçekleşen hasta sayısı istatiksel olarak anlamlı derecede azdır (p<0,001). BH tanısından önce %24,8 olan düşük oranı, tanıdan sonraki gebeliklerde %17,4 idi, fark istatistiksel olarak anlamlı saptanmamıştır. İntrauterin ölüm (%6,2'ye karşın %2,2, p=0,027) ile düşük doğum ağırlıklı bebek oranı (%8,8'e karşın %3,8, p=0,024) BH tanısından sonraki gebeliklerde istatistiksel olarak anlamlı yüksekti. İntrauterin ölüm ve fetal komplikasyon, gebelik öncesi steroid kullanımı ile ilişkili bulundu. Sezaryen ile doğum oranı tanıdan sonraki gebeliklerde istatistiksel olarak anlamlı derecede daha yüksek bulunmuştur (p<0,001).

Sonuç: BH olan kadınlarda, hastalığın doğurganlık üzerine etkisi olmadığı ancak maternal ve fetal komplikasyon için risk artışı olduğu görülmektedir.

Anahtar Kelimeler: Behçet hastalığı, fertilite, kadın

Abstract

Objective: Behçet's disease (BD) is an inflammatory disease that also affects women of reproductive age, with mucocutaneous findings and systemic organ involvement. Like other inflammatory diseases, BH is likely to have effects on fertility. The aim of this study is to investigate the effects of BH on fertility, pregnancy and birth processes in women diagnosed with BD.

Methods: Marriage, fertility and pregnancy histories of 274 female Behçet's patients were evaluated retrospectively. Data of 563 pregnancies before (n=450) and after (n=113) diagnosis were analyzed.

Results: The mean age of the patients included in the study was 39.8 years. Infertility rate was determined as 2.3% (n=5). The pregnancy rate with assisted reproductive techniques was 1.4% (n=3). The number of patients who had 3 and ≥4 pregnancies after the diagnosis of BD was statistically significantly less (p<0.001). The miscarriage rate, which was 24.8% before the diagnosis of BD, was 17.4% in the pregnancies after the diagnosis, the difference was not statistically significant. Intrauterine death (6.2% vs. 2.2%, p=0.027) and low birth weight infant rate (8.8% vs. 3.8%, p=0.024) were statistically significantly higher in pregnancies after BD diagnosis. Intrauterine death and fetal complications were associated with pre-pregnancy steroid use. The rate of cesarean section was found to be statistically significantly higher in pregnancies after diagnosis (p<0.001).

Conclusion: In women with BD, it seems that the disease has no effect on fertility, but there is an increased risk for maternal and fetal complications.

Keywords: Behçet's disease, fertility, women

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Giriş

Behçet hastalığı (BH) sistemik enflamatuvar bir hastalıktır. Patogenezindeki yolaklar tam olarak bilinmemekle birlikte immünolojik anormallikler rol oynamaktadır. Klinik belirtileri arasında oral aft, genital ülser, papülopüstüler ve nodüler deri lezyonları, eklem tutulumu, kalıcı körlüğe neden olabilen üveit, vasküler olaylar, nörolojik ve gastrointestinal tutulumlar vardır.[1]

BH prevalansının en yüksek olduğu bölge Akdeniz havzasıdır. En yüksek prevalans Türkiye'den bildirilmektedir. İran ve Japonya'da da prevalansı yüksektir. Hastalık genç erişkinleri etkilemekte, özelikle 20-30 yaşlarında tanı konulmaktadır. Hastalığın *HLA-B51* (insan lökosit antijeni-B51) genleri ile ilişkisi ortaya konulmuştur.[2]

Literatürde BH ve fertilite ile ilgili bazı çelişkili bilgiler vardır. Jadaon ve ark.[3] yaptığı bir çalışmada, gebeliğin BH'nin seyri üzerinde negatif bir etkisinin olmadığı ancak düşük riski ve sezaryen doğum oranının yüksek olduğu gösterilmiştir. Gungor ve ark.[4] yaptığı başka bir çalışmada ise sağlıklı kontrol grubu ile kıyasladığında düşük doğum ağırlıklı bebek ve düşük görülme oranın arttığı görülmüştür. Bir başka çalışmada ise gebelik komplikasyonlarının artmadığı sonucuna ulaşılmıştır.[5] BH'nin neonatal ve obstetrik komplikasyonlarını inceleyen bir diğer çalışmada gebelik sürecinde hastalık semptomlarında alevlenme olan gebelerde komplikasyon riskinin daha fazla olduğu görülmüştür.[6] BH'nin gebelik seyri üzerinde olumsuz etkileri olmadığını, gebeliğin BH aktivite ve seyrini etkilemediğini gösteren incelemeler de yayınlanmıştır.[7-9]

Bu çalışmada, tek bir merkezde takip edilen, BH olan kadınlarda fertilite, gebelik ve doğum ile ilgili verilerin retrospektif olarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem

Çalışma için Akdeniz Üniversitesi Tıp Fakültesi Etik Kurulu'ndan onay alındı (04.03.2020 tarih/KAEK: 207 sayılı karar). Akdeniz Üniversitesi Tıp Fakültesi Hastanesi Başhekimliği'nden yazılı izin alındıktan sonra hastaların verilerine ulaşıldı ve dosyaları incelendi.

Hastalar

Akdeniz Üniversitesi Tıp Fakültesi Hastanesi'nde 1 Ocak 2014- 31 Aralık 2021 tarihleri arasında değerlendirilen ve BH tanısı alan 18 yaş üzeri hastaların verileri retrospektif olarak tarandı. Tarama için yazılım sistemine kayıtlı International Classification of Disease (ICD) kodlamaları kullanıldı. BH için ICD kodu M35.2 idi. Toplam 400 kadın hastaya M35.2 kodu girilmişti.

BH tanı kodu alan toplam 400 kadın hastadan verileri eksik olan 126 hasta çalışmadan çıkarıldı. Uluslararası Çalışma Grubu (ISG) kriterlerine[10] göre BH tanı kriterlerini karşılayan 274 kadın hastanın evlilik, gebelik ve doğum öyküleri değerlendirildi.

Hastalığın ilk semptom başlangıç tarihi, tanı tarihi, klinik bulguları, kullanılan ilaçlar, gebelik sayısı ve gebelik tarihleri, gebelikte hastalık süreci, komplikasyonları ve aile öyküsü sorgulandı. Vizite gelen hastalarla yüz yüze görüşme, diğer hastalarla telefon görüşmesi yoluyla bilgiler elde edildi. Hastaların gebelikleri BH tanısından önce ve sonra olmak üzere iki grup şeklinde değerlendirildi.

Yirmi haftadan önce olan gebelik kayıpları düşük, 20 haftadan sonraki gebelik kayıpları ise ölü doğum olarak kabul edildi. Doğum kilosu 2.500 gram ve altında olan bebekler düşük doğum ağırlıklı, 4.500 gram ve üzeri bebekler ise kilolu bebek olarak kabul edildi. Otuz yedinci haftadan önce gerçekleşen doğumlar ise erken doğum olarak değerlendirildi.

İstatistiksel Analiz

İstatistiksel analizler için IBM SPSS 23 (Statistical Package of Social Science) programı kullanıldı. Çalışma popülasyonunun genel özelliklerini sunmak için tanımlayıcı istatistikler kullanıldı. Veriler toplam sayı ve yüzdelik dilimler ile tanımlandı. Parametrik veriler ortalama ± standart sapma olarak hesaplandı, sayısal değişkenler ortanca (median) değer [çeyrekler arası genişlik], kategorik değişkenler sayı (%) ile ifade edilmiştir. Gruplar arasındaki kategorik verilerin karşılaştırılmasında ki-kare testi veya Fisher's Exact test, sayısal (sürekli) değişkenlerin karşılaştırılmasında Student's t-testi kullanıldı. Normal dağılıma uymayan sürekli değişkenlerin karşılaştırılması Mann-Whitney U testi ile yapıldı. P değeri <0,05 ise istatistiksel olarak anlamlı kabul edildi.

Bulgular

Kohorttaki hastaların 58'i (%21,2) hiç evlenmemişti. Evlilik gerçekleştiren 216 kadında BH'nin fertilite, maternal, fetal ve neonatal komplikasyonlar üzerindeki etkisi, gebelik sürecinde hastalığın seyri analiz edildi. Çalışmaya dahil edilen hastaların ortalama yaşı 39,8 yıldı. Hastalığın ilk semptomlarının görüldüğü yaş 26,3 yıl; tanı alma yaşı ise 29,8 yıl idi. Ortalama tanı gecikme süresi 3 yıldı. Elli yedi (%20,8) hastada BH aile öyküsü vardı. Hastaların demografik özellikleri Tablo 1'de gösterilmiştir.

Toplam 202 hastada 563 gebelik gerçekleşmiştir. Gebelik oluşmayan 72 hastanın 58'i (%21,2) hiç evlilik yaşamamış, 20 (%7,3) hasta eşinden ayrılmış, 196 (%71,5) hasta halen

evliydi. Dokuz (%4,16) hastanın gebelik istemi olmamış, 5 (%2,3) hastada infertilite teşhisi konulmuştu. Üç (%1,4) hasta yardımcı üreme teknikleri ile gebe kalmıştır.

Çalışmaya dahil edilen 274 hastanın tamamında mukokutanöz bulgular vardı. Yüz yirmi beş (%46,0) hastada üveit öyküsü vardı; 77 (%35,6) hastada tek, 46 (%21,2) hastada ise çift taraflı tutulum saptanmıştı. Yirmi dört (%8,8) kadın hastada vasküler tutulum vardı. Nörolojik tutulum 18 (%6,6) hastada, gastrointestinal tutulum ise 12 (%4,4) hastada görülmüştür. Yüz elli dört (%56,2) hastada eklem tutulumu vardı.

BH tanısından önce 169 hastada 450 gebelik, hastalık tanısından sonra 69 hastada 113 gebelik gerçekleşmiştir. Yüz otuz dört hasta ise sadece tanıdan önce, 35 hasta hem tanı öncesi hem tanı sonrası, 34 hasta ise sadece tanıdan sonra gebelik yaşamıştır. Fertilite ile ilgili veriler Tablo 2'de gösterilmiştir. BH tanısından önce 39 (%23,1) hastada 1 gebelik, 55 (%32,1) hastada 2 gebelik, 33 (%12) hastada 3 gebelik, 42 (%19,5) hastada 4 veya daha fazla gebelik tespit edilmiştir. BH tanısından sonra 35 (%50,7) hastada 1, 25 (%36,2) hastada 2 gebelik, 8 (%11,6) hastada 3 gebelik, 1 (%1,5) hastada 4 veya daha fazla gebelik oluşmuştur. Tanı sonrası gebelik sayısı, tanıdan önceki gebelik sayısına göre daha düşüktü. BH tanısından sonra hastaların çoğu bir veya iki gebelik yaşamıştır. ≥3 gebelik gerçekleşen hasta sayısı istatistiksel olarak anlamlı derecede düşüktü (p<0,001).

BH tanısından önce 42 hastada (%24,8), BH tanısından sonra 12 (%17,4) hastada düşük saptanmıştır. Düşük oranı açısından gebelik öncesi ve sonrası gebelikler arasında anlamlı fark bulunmamıştır. Tanıdan önce gebelik gerçekleşen 11 hastada (%6,5), tanıdan sonra gebelik gerçekleşen 7 (%10,1) hastada intrauterin ölüm görülmüştür. İntrauterin ölüm oranları açısından anlamlı fark saptanmıştır (p=0,027). Tanı öncesi gebe grubunda 3 (%1,8) hastada ölü doğum gerçekleşmiş iken tanıdan sonraki grupta ölü doğum saptanmamıştır (Tablo 2).

Çalışmamızda tanıdan önce 450, tanıdan sonra 113 gebelik olmak üzere toplam 563 gebelik sonuçları incelenmiştir. Bu gebeliklerin 351'i (%62,3) normal doğumla, 140'ı

Tablo 1. Çalışmaya dahil edilen Behçet hastası kadınların (n=274) demografik özellikleri

Yaş, yıl (Ort. ± SD)	39,8±13,4	
İlk semptom yaşı, yıl (Ort. ± SD)	26,3±9,9	
Hastalık tanı yaşı, yıl (Ort. ± SD)	29,8±10,4	
	(n)	(%)
Ailede Behçet hastalığı	57	20,8
Evlilik		
Evli	196	71,5
Boşanmış	20	7,3
Evlenmemiş	58	21,2
İnfertilite*	5	2,3
IVF*	3	1,4
Gebelik Sayısı		
0	72	26,3
1	33	12,0
2	67	24,5
3	48	17,5
4	31	11,3
5	12	4,4
6	9	3,3
8	2	0,7
Klinik Bulgular		
Mukokutanöz	274	100
Oral aft	274	100
Genital ülser	241	88
Akne	84	30,7
Paterji pozitifliği	81	29,6
Eritema nodozum	123	44,9
Göz tutulumu	125	46,0
Vasküler tutulum	24	8,8
Derin venöz trombüs	16	5,8
Pulmoner tromboembolizm	5	1,8
Diğer damar	8	2,9
Nörolojik tutulum	18	6,6
Gastrointestinal tutulum	12	4,4
Eklem tutulumu	154	56,2

*IVF: İn vitro fertilizasyon, *Evlilik gerçekleştiren hastalar (n=216) dikkate alınmıştır*

Tablo 2. Fertilite ile ilgili veriler

	BH tanısından önce		**BH tanısından sonra**		**p**
Gebelik gerçekleşen hasta sayısı (n)	169		69		
Gebelik sayısı	n	%	n	%	
1	39	%23,1	35	%50,7	
2	55	%32,5	25	%36,2	**<0,001**
3	33	%19,5	8	%11,6	
≥4	42	%24,8	1	%1,5	
Düşük	42	%24,8	12	%17,4	0,624
İntrauterin ölüm	11	%6,5	7	%10,1	0,456
Ölü doğum	3	%1,8	0	-	-

(%24,9) ise sezaryen doğumla gerçekleşmiştir. Tanıdan önceki gebeliklerde normal doğum oranı %68,4 (n=308) iken, tanıdan sonraki gebeliklerde bu oran %38,1'e (n=43) düşmüştür. Toplam 140 (%24,9) gebelik sezaryen doğumla sonuçlanmıştır. Tanıdan önceki gebeliklerde sezaryen ile doğum oranı %20,2 iken tanıdan sonraki gebeliklerde %43,4'e yükselmiştir. Sezaryen oranı tanıdan sonraki gebeliklerde istatistiksel olarak anlamlı derecede yüksek bulunmuştur (p<0,001) (Tablo 3).

Tüm gebeliklerde düşük doğum ağırlıklı bebek ile sonuçlanan doğum sayısı 27 (%4,8) bulundu. Tanıdan önceki gebeliklerde düşük doğum ağırlıklı bebek oranı %3,8 (n=17) iken tanıdan sonraki gebeliklerde bu oran %8,8 (n=10) bulundu. Düşük doğum ağırlıklı bebek oranı açısından istatistiksel olarak anlamlı fark saptandı (p=0,024). Kilolu bebek (n=4) ve konjenital anomalili bebek (n=4) olgularının tümü tanıdan önceki gebeliklerde idi (Tablo 3).

Toplam 444 (%78,9) miadında doğumun 362'si (%80,4) tanıdan önceki, 82'si (%72,6) tanıdan sonraki doğumlarda kaydedildi. Miadında doğum oranı tanıdan önceki gebeliklerde daha yüksekti (p=0,043). Preterm doğum eylemi 20 (%3,6) gebelikte görüldü; bunların 13'ü (%2,9) tanı öncesi gebeliklerde, 7'si (%6,2) tanıdan sonraki gebeliklerdeydi (Tablo 3).

BH tanısından önceki gebeliklerde 51 (%11,3), BH tanısından sonraki gebeliklerde ise 20 (%17,8) olmak üzere toplamda 71 (%12,6) maternal komplikasyon gelişmişti. Gebelikte hipertansiyon oranı BH tanısından sonraki gebeliklerde daha yüksekti. (%4,4'e karşın %0,7, p=0,010) Hiperemezis gravidarum, eklampsi, proteinüri ve gestasyonel diyabet açısından ise fark yoktu (Tablo 3).

Hastalara "Gebelikte hastalığınız nasıl seyretti?" sorusu yöneltildi. On dokuz hasta (%27,9) hastalık semptomlarında artış olduğunu, 25 (%36,8) hasta gebelik sürecinde hastalık bulgularında ciddi bir değişiklik olmadığını, 23 (%33,8) hasta ise semptomların azaldığını ifade etmiştir (Tablo 4).

Gebelik sürecinde kullanılan ilaçlar olarak BH tedavisi sürecinde kullanılan ilaçlar dikkate alınmış; ek vitamin takviyeleri değerlendirmeye alınmamıştır. Gebelik öncesi kolşisin kullanan hasta sayısı 97 (%85,8) iken steroid kullanan hasta sayısı 60 (%53,1), metotreksat kullanan hasta sayısı 2 (%1,8), azatiopürin kullanan hasta sayısı 33 (%29,2), biyolojik ajan (infliksimab) kullanan hasta sayısı 1'di (%0,9). Gebelik sürecinde ise 33 (%29,2) gebelikte kolşisin, 3 (%2,7) gebelikte steroid, 2 (%1,8) gebelikte azatiopürin kullanımı görülmüştür. Gebelik sürecinde metotreksat ve biyolojik ajan kullanımı olan gebelik kayıt edilmemiştir (Tablo 5).

Fetal komplikasyon gözlenen (n=19) hastaların ortalama tanı yaşı, gebelik yaşı ve tanı ile gebelik arasında geçen süreleri diğer hastalardan istatistiksel olarak farklı değildi. Benzer şekilde, tanıdan önceki gebelik sayısı, tanıdan sonraki median gebelik sayısı, ciddi organ tutulumu, vasküler tutulumlar, gebelikte kullanılan ilaçlar ve gebelik komplikasyonlarının

Tablo 3. Gebelik dönemi ile ilgili veriler

	Genel (n=563)		**BH tanısından önce (n=450)**		**BH tanısından sonra (n=113)**		**p**
	n	**%**	**n**	**%**	**n**	**%**	
Doğum şekli							
Normal	351	62,3	308	68,4	43	38,1	<0,001
Sezaryen	140	24,9	91	20,2	49	43,4	
Doğum zamanı							
Miad	444	78,9	362	80,4	82	72,6	**0,043**
Erken doğum	20	3,6	13	2,9	7	6,2	0,089
Fetal komplikasyon (Toplam)	75	13,3	55	12,2	19	16,8	0,195
Düşük	55	9,6	42	9,8	12	10,6	0,678
İntrauterin ölüm	17	3,0	10	2,2	7	6,2	**0,027**
Ölü doğum	3	0,5	3	0,7	0	-	1,000
Neonatal anormallikler (Toplam)	35	6,2	25	5,6	10	8,8	0,195
Düşük doğum ağırlıklı bebek	27	4,8	17	3,8	10	8,8	**0,024**
Kilolu bebek	4	0,7	4	0,9	0	-	0,588
Anomalili bebek	4	0,7	4	0,9	0	-	0,588
Gebelik komplikasyonları							
Hiperemezis gravidarum	71	12,6	51	11,3	20	17,8	0,068
Eklampsi	53	9,4	43	9,6	10	8,8	0,818
Hipertansiyon	6	1,1	3	0,7	3	2,7	0,099
Gestasyonel diyabet	8	1,4	3	0,7	5	4,4	**0,010**
Proteinüri	4	0,7	2	0,4	2	1,8	0,181
	0	-	-	-	-	-	

Tablo 4. Gebeliğin hastalık aktivitesi üzerine etkisi hakkında hastaların düşüncesi

	Behçet hastalığı tanısından sonra gebe kalan kadın sayısı (n=69)	
Hastalık bulguları arttı	19	%27,9
Hastalık bulguları değişmedi	25	%36,8
Hastalık bulguları azaldı	23	%33,8
Bilinmiyor	2	%2,9

Tablo 5. Behçet hastalığı tanısı aldıktan sonra gerçekleşen gebeliklerde ilaç kullanımı (n=113)

	Gebelik öncesi		Gebelikte	
	(n)	(%)	(n)	(%)
Kolşisin	97	85,8	**33**	**29,2**
Kortikosteroid	60	53,1	3	2,7
Metotreksat	2	1,8	-	-
Azatiopürin	33	29,2	2	1,8
Biyolojik ajan	1	0,9	-	-

varlığı açısından yapılan karşılaştırmalarda da istatistiksel fark olmadığı görüldü (Tablo 6). Bebelik öncesi kolşisin ve immünosüpresif ilaç kullanımları açısından fark gözlenmezken, gebelik öncesi steroid kullanımı fetal komplikasyonlar gözlenen gebeliklerde istatistiksel olarak daha yüksekti (17/19'a karşı 44/89, p=0,013).

Düşük ile sonuçlanan 12 gebelik vardı. Bu kadınların hastalık ve ilaç kullanımları açısından diğer BH kadınlardan farkı yoktu. İntrauterin ölüm saptanan 7 gebeliğin tümünde gebelik öncesi kortikosteroid kullanımı varken, diğer gebelerde bu oran %51,5 olup, fark istatistiksel olarak anlamlıydı (p=0,015). Düşük doğum ağırlıklı bebek ile sonuçlanan gebeliklerin özellikleri ile diğer gebeliklerin özellikleri karşılaştırıldığında gruplar arasında fark saptanmamıştır (Tablo 6).

Tartışma

Bu çalışma, tek merkezli retrospektif bir çalışma olup, BH olan kadınlarda infertilite oranları ile gebeliğin obstetrik ve neonatal sonuçları değerlendirilmiştir. BH tanısından önce 169 hastada, tanıdan sonra ise 69 hastada gebelik gerçekleştiği görülmüştür. Tanıdan önce 3 gebelik gerçekleşen hasta sayısı 33 (%19,5), ≥4 gebelik gerçekleşen hasta sayısı 42 (%24,8) saptanmıştır. Hastalık tanısından sonra ise 3 gebelik yaşayan hasta sayısı 8 (%11,6), ≥4 gebelik gerçekleşen hasta sayısı 1 (%1,5) saptanmıştır. Bu iki grup arasında istatistiksel olarak anlamlı farklılık saptanmıştır (p <0,001). Hastalık tanısından sonra 3 ve daha fazla gebeliği olan kadınların sayısının daha az olduğu görülmüştür. BH'nin fertilite üzerine etkisi olmadığı ancak gebelik sayısına etkisi olduğu sonucuna varılabilir. Çalışmaya dahil edilen hastaların ortalama tanı alma yaşı 29,8 yıl olarak

Tablo 6. Fetal ve neonatal komplikasyonlar üzerine bazı değişkenlerin karşılaştırılması

	Fetal komplikasyonlar			Düşük			İntrauterin ölüm			Düşük doğum ağırlıklı bebek		
	(+) (n=19)	(-) (n=89)	p	(+) (n=12)	(-) (n=96)	p	(+) (n=7)	(-) (n=101)	p	(+) (n=10)	(-) (n=102)	p
Tanı yaşı, (yıl), (Ort. ± SD)	24,6±7,3	24,1±6,0	0,736	24,4±8,8	24,1±5,9	0,909	24,1±6,3	25,0±5,7	0,712	23,5±5,6	24,0±6,3	0,818
Gebelik yaşı, (yıl) (Ort. ± SD)	30,4±7,2	28,2±4,9	0,135	30,3±7,8	28,5±5,1	0,271	28,6±5,4	30,7±6,6	0,365	29,6±4,5	28,4±5,6	0,514
Tanı-Gebelik arası süre, (yıl) (Ort. ± SD)	5,9±4,5	4,0±3,8	0,063	5,8±4,8	4,1±3,8	0,184	4,2±4,0	6,2±4,4	0,240	6,1±5,9	4,2±3,8	0,166
Tanıdan önceki gebelik sayısı (Median: Min-Maks)	1 (0-1)	0 (0-6)	0,243	1 (0-2)	0 (0-6)	0,400	1 (0-2)	0 (0-6)	0,558	0 (0-2)	1 (0-6)	0,589
Tanıdan sonraki gebelik sayısı (Median: Min-Maks)	2 (1-3	2 (1-4)	0,179	2 (1-3)	2 (1-4)	0,556	2 (1-3)	2 (1-4)	0,456	2 (1-2)	2 (1-4)	0,225
Ciddi organ tutulumları (n)	5	24	0,954	3	26	1,000	2	27	1,000	2	28	1,000
Vasküler tutulum (n)	3	12	0,792	2	13	0,672	1	14	1,000	1	15	1,000
Gebelikten öncesi kullanılan ilaçlar (n)												
Kolşisin	17	76	0,641	10	83	0,768	7	86	0,272	7	90	0,132
Kortikosteroid	15	44	**0,013**	8	51	0,374	7	52	**0,015**	4	56	0,385
İmmünosüpresif	7	25	0,448				2	30	1,000	4	30	0,485
Gebelikte kullanılan ilaçlar (n)												
Kolşisin	8	22	0,125	4	26	0,734	4	26	0,092	2	31	0,721
Kortikosteroid	-	3	1,000	0	3	1,000	-	3	1,000	1	2	0,245
İmmünosüpresif	-	2	1,000	0	2	1,000	-	2	1,000	1	1	0,170
Gebelik Komplikasyonu (n)	5	15	0,335	4	16	0,161	1	19	1,000	1	19	0,688

saptanmıştır. Bu nedenle yaş faktörünün hastalık tanısından sonra görülen gebelik oranlarında düşüşte önemli rol oynadığı düşünülebilir. Aynı zamanda hastalık tanısı aldıktan sonra kadınların gebelikten korunma oranlarının artmasının da burada etkisi olabilir.

Daha önce yapılan çalışmalar BH'nin erkek hastalarda cinsel disfonksiyona sebep olduğunu göstermiştir.[11] Behçet hastalarında cinsel işlev bozukluğunun erkeklerde nörolojik ve vasküler (kavernoz ven trombozu ve endotel disfonksiyonun) tutuluma bağlı olduğu yapılan çalışmalarla kanıtlanmıştır.[12,13] Aynı zamanda azalmış vazodilatör nörotransmitter (NO) düzeylerinin Behçet hastalarında cinsel disfonksiyona sebep olabileceği gösterilmiştir.[14] Kadın hastalarda genital ülserasyona bağlı ağrının, aynı zamanda genital ülserasyonun neden olduğu depresyon ve duygu durumu değişikliğinin kadınlarda cinsel işlevi önemli ölçüde etkilediği bilinmektedir.[15] Majör organ tutulumu olsun veya olmasın, Behçet hastalarında depresyon, anksiyete ve genel psikiyatrik rahatsızlık oranının artmış olduğu ve bu durumun kadınlarda cinsel arzu ve uyarılmayı negatif etkilediği kanıtlanmıştır.[15,16]

Uzunaslan ve ark.[17] tarafından yapılan 190 Behçet hastasının dahil edildiği sağlıklı kontrol grubu ile karşılaştırma yaptığı çalışmasında Behçet hastalarının genel infertilite insidansında kayda değer bir artış olmadığı görülmüştür. Behçet hastalarında over rezervini değerlendiren çalışmada, 35 BH tanılı kadın hastanın FSH, LH, AMH, E2 ve prolaktin düzeyleri sağlıklı kontrol grupları ile karşılaştırıldığında anlamlı fark bulunmamıştır.[18] Bu çalışmanın aksine Mont'Alverne ve ark.[19] tarafından daha az sayıda hasta ile yapılan çalışmada, Behçet hastalarının kanında AMH düzeyi kontrol grubuna göre daha düşük görülmüştür. Bizim çalışmamıza dahil edilen 274 hastanın 72'si (%26,3) hiç gebelik yaşamamıştır. Elli sekiz (%21,2) hasta hiç evlilik yaşamamış olup, 9 (%4,16) hastada ise doğum kontrol yöntemi kullanımı yoluyla gebelik gerçekleşmemiştir. Çalışmamızda 5 (%2,3) hastada infertilite saptanmıştır. Üç (%1,4) hasta yardımcı üreme tetkikleri ile gebe kalmıştır. İnfertilite saptanan 3 hastada talasemi majör, erken yaşta geçirilmiş histerektomi ve polikistik over sendromu nedeniyle gebelik oluşmamıştır. Behçet hastalarında infertilite oranlarını tartışan kısıtlı sayıda çalışma mevcuttur. Uzunaslan ve ark.'nın.[17] çalışmasına benzer şekilde bizim çalışmamızda da infertilite oranının artmadığı görülmüştür.

Kolşisin Behçet hastalarında yaygın olarak kullanılmaktadır. Kolşisin kullanan 131 Behçet hastası üzerinde yapılan çalışmada 11 hastada oligospermi, 11 hastada ise amenore ve dismenore görülmüştür.[20] Daha önce kolşisin kullanan gut hastaları ve hayvan modelleri üzerinde yapılan çalışmalarda sitogenetik anomali saptanmış ve bu çalışmalara dayanarak kolşisin kullanımı gerekli olan gebelere amniyosentez önerilmiştir.[21] Ancak sonradan yapılan çalışmalarda bu doğrulanmamış ve amniyosentez koşulu ortadan kaldırılarak gebelerde kolşisin düzenli kullanımına izin verilmiştir.[22,23] Retrospektif yapılan diğer bir çalışmada kolşisin tedavisi altında olan 62 Behçet hastası incelendiğinde 23 hastada oligospermi, 2 hastada ise azospermi görülmüştür.[24] Bu çalışmalardan farklı olarak Both ve ark.[25] tarafından yapılan çalışmada düzenli kolşisin kullanımının fertilite üzerine negatif etkisi olmadığı gösterilmiştir. Kolşisin ve doğurganlık arasında ilişki olmadığı sonradan yapılan diğer çalışmalarda da kanıtlanmıştır.[17] Kolşisin kullanımı olan 238 gebelikte teratojenite sonuçlarını tartışan bir çalışmada, kolşisinin teratojen olmadığı, ancak preterm doğum eylemi ve düşük doğum ağırlıklı bebek oranının arttığı gösterilmiştir.[26] Diğer bir çalışmada gebelik sürecinde kolşisin kullanan kadınlarda hastalık bulgularının azaldığı ve gebelik komplikasyon riskinin artmadığı görülmüştür.[27] Çalışmamızda BH tanısı aldıktan sonra gerçekleşen 113 gebelikten 97'sinde (%85,8) gebelikte kolşisin kullanımı olduğu, 33 (%29,2) gebelikte de hamilelik sürecinde kolşisin kullanımına devam edildiği görülmüştür. Gebelik sürecinde bazı hastalar kendi isteği ile, bazıları ise doktorunun önerisi ile kolşisin kullanmayı bırakmışlardır. Önceki yapılan çalışmalara benzer şekilde kolşisin kullanımının fertilite üzerine etkisi olmadığı sonucuna vardık. Çalışmamızda gebelik sürecinde kolşisin kullanılan 33 gebelikte düşük doğum ağırlıklı ve konjenital anomalili bebek saptanmamıştır. Aynı zamanda çalışmamızda gebelik ve gebelik öncesi kolşisin kullanımı ile toplam fetal komplikasyonlar; düşük, intrauterin ölü doğum, gestasyon haftasına göre küçük bebek oranının da artmadığı görülmüştür. Bulgularımız, kolşisin tedavisinin kadın Behçet hastalarında gebelik öncesi ve gebelik süresince güvenle kullanılabileceği yönündeki gözlemleri desteklemektedir.

Romatolojik hastalıkları olan kişiler arasında çok yaygın kullanılan non-steroidal antienflamatuvar ilaçların (NSAİİ) kadınlarda reversibl infertiliteye neden olduğu gösterilmiştir.[28,29] Metotreksatın erkeklerde sperm anormalliklerine sebep olduğu olgu raporlarında gösterilse de kadınlarda fertiliteyi etkilemediği bilinmektedir.[30] Bizim çalışmamızda NSAİİ ile ilgili değerlendirme yapılmamıştır. Gebelikten önce 2 (%1,8) hastada metotreksat kullanımı görülmüş, gebelik sürecinde ise metotreksata devam edilmemiştir. Metotreksat kullanan hastaların birinde 3, diğerinde 2 gebelik yaşanmıştır. Metotreksat kullanan hasta sayısının az olması nedeniyle fertilite etkisi üzerine yorum

yapılamamıştır. BH tedavisinde kullanılan ek ajanlardan olan siklofosfamidin kadınlarda irrevesibl infertiliteye sebep olabileceği yayınlarda gösterilmiştir.[31]

Çalışmamızda siklofosfamid kullanımı olan gebelik saptanmamıştır. Azatiopürin ve TNF-alfa inhibitörleri kadın fertilitesini etkilememektedir. Araştırmamızda, 33 (%29,2) hastada gebeliklerden önce azatiopürin kullanımı, 2 (%1,8) hastada ise gebelikte azatiopürin kullanıldığı saptanmıştır. Gebelik sürecinde azatiopürin kullanımı olan gebeliklerden biri düşük, diğeri ise medikal terminasyon ile sonuçlanmıştır. Çalışmamızda azatiopürin kullanımının fertilite üzerine etkisi olmadığı sonucuna varılmıştır. Azatiopürin kullanımının fetal ve neonatal komplikasyon üzerine etkisi istatistiksel olarak anlamlı olmasa da komplikasyon riskini artırdığını saptadık. Erenel ve ark.[7] tarafından yapılan çalışmada 33 gebelik olgusu incelenmiş, steroid ve azatiopürin kullanan gebeliklerde herhangi bir komplikasyon görülmemiştir. Çalışmamızda toplam fetal komplikasyon ve intrauterin ölü doğum risk faktörleri analizinde komplikasyon görülmeyen grupta gebelik öncesi steroid kullanımı oranı yüksek saptanmıştır. Gebelikte steroid ve immünosüpresif ajan kullanımının ise fetal komplikasyon ve düşük doğum ağırlıklı bebek riskini artırmadığı görülmüştür.

BH'de gebelik komplikasyonlarını değerlendiren çalışmaların birinde hastalık tanısından sonra gebe kalan kadınlarda düşük oranı değişmemiş; hipertansiyon, gestasyonel diabetes mellitus, prematürite, enfeksiyonlar, erken membran rüptürü ve tromboembolik olay insidansı yüksek bulunmuştur.[3] Gungor ve ark.[4] tarafından yapılan 94 Behçet hastası ve 298 gebelik sonuçlarının incelendiği retrospektif bir çalışmada, sağlıklı kontrol grubu ile karşılaştırdığında Behçet hastalarında düşük, preterm doğum ve düşük doğum ağırlıklı bebek oranının yüksek olduğu görülmüştür. 2018 yılında yayınlanan 12 milyon doğum arasında BH insidansı, hastalığın gebelikte seyri ile ilgili bir araştırmada erken doğum, buna bağlı olarak preterm bebek, sezaryen doğum ve postpartum venöz tromboembolik olayların insidansı yüksek bulunmuş, diğer majör obstetrik ve neonatal sonuçlar arasında anlamlı fark bulunmamıştır.[32] Hastalığın gebelik üzerinde negatif etki yaratması konusunda destekleyici çalışmaların birinde, BH tanılı iki gebe hastaya ait plasentanın patolojik incelemesinde plasentada nekrotizan villus ve yoğun enflamasyondan oluşan çok sayıda nekroz alanları izlenmiştir. Aynı zamanda desudial dokuda da BH'nin organ tutulumununda görüldüğü gibi nötrofil ağırlıklı vaskülit bulguları görülmüştür. Plasenta ve desudial dokuda görülen bu patolojik bulgular gebeliğin erken döneminde hastalık alevlenmesinin devam ettiğini, fetal ve neonatal komplikasyonlara sebep olabileceği fikrini destekliyordu.[33] BH ve gebelik ilişkisi ile ilgili yapılan bir diğer çalışmada 23 Behçet hastasında 61 gebelik, BH tanısı olmayan rekürren oral ülseri olan 30 hastada 83 gebelik ve 20 sağlıklı kontrol grubunda 61 gebelik değerlendirmeye alınmış; çalışma sonucunda gruplar arasında gebelik komplikasyonları açısından anlamlı fark bulunmamış, konjenital malformasyon ve perinatal ölüm saptanmamıştır.[5] Noel ve ark.'nın[27] BH tanısı olan hastaların 76 gebelik durumunun incelendiği çalışmada 12 komplikasyon, 5 düşük, 1 HELLP sendromu ve 1 trombositopenisi olan olgu kaydedilmiştir. Diğer gebelik komplikasyonlarından intrauterin gelişme geriliği olgu serileri şeklinde literatürde bildirilmiştir.[34] Retrospektif randomize kontrollü diğer bir çalışmada ise ölü doğum, preeklampsi, erken doğum ve intrauterin gelişme geriliği ve düşük doğum ağırlığı oranlarının iki grup arasında benzer olduğu görülmüştür.[35] Çalışmamızda BH tanısından önceki ve sonraki gebeliklerde düşük, intrauterin ölü doğum ve ölü doğum gibi komplikasyon yaşayan hasta sayısı arasında istatistiksel farklılık saptanmamıştır.

BH'de gebelik sürecinde hastalık gidişatını değerlendirme üzerine yapılan çalışmalarda, semptomlarda %27,3 oranında alevlenme olduğu tespit edilmiştir.[9] Literatürde doğum sonrası prednizolon kullanımı gerektiren ciddi ve rekürren genital ve oral ülser olgu raporları da bildirilmiştir.[36,37] Yetmiş altı gebelik durumunun incelendiği bir diğer çalışmada en sık oral aft ve genital ülser olmak üzere hastaların %35,5'inde semptomlarda artış olduğu saptanmıştır.[27] Jadaon ve ark.'nın[3] yaptığı araştırmada ise gebelik sürecinde remisyon görülme sıklığı (%70,2) semptomlarda alevlenme görülmesine göre (%15,5) anlamlı oranda yüksek izlenmiştir. BH tanısı olan iki gebede postpartum dönemde Budd-Chiari sendromu görülürken, başka bir gebede ise serebral venöz tromboz geliştiği bildirilmiştir.[38,39] Bizim çalışmamızda ise 19 (%27,9) hastada hastalık semptomlarında artış görülmüş, 25 (%36,8) hastada stabil seyrettiği, 23 (%33,8) hastada ise semptomların azaldığı görülmüştür. Bir hastada gebelik sürecinde sinüs ven trombozu gelişmiş ve gebelik terminasyon ile sonuçlanmıştır.

Çalışmanın Kısıtlılıkları

Bu çalışmanın sonuçları değerlendirilirken bazı kısıtlılıklar göz önünde bulundurulmalıdır. Birincisi, sağlıklı ve başka bir hastalık kontrol gurubu yoktur. İkincisi, veriler retrospektif olarak toplanmış ve çoğunda hasta beyanı esas alınmıştır. Ayrıca, fetal komplikasyonlar üzerine paternal riskler değerlendirilmemiştir.

Sonuç

Sonuç olarak, tek merkez, retrospektif veri analizine dayalı bu incelememizin sonuçları, BH tanısı konulan kadınlarda doğurganlığın değişmediğini, intrauterin ölüm ve düşük doğum ağırlıklı bebek gibi fetal komplikasyonların arttığını göstermektedir. BH tanısı olan gebelerde sezaryen doğumun daha fazla tercih edildiği dikkati çekmektedir.

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Evaluation of the relationship between lymphoma predictors, disease activity, and netrin-1 in primary Sjögren's syndrome

Primer Sjögren sendromunda hastalık aktivitesi, lenfoma prediktörleri ve netrin-1 arasındaki ilişkinin değerlendirilmesi

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Abstract

Objective: One-third of patients with primary Sjögren's syndrome (PSS) do not have anti-SSA or -SSB antibodies. The risk of developing B-cell non-Hodgkin lymphoma (NHL) in PSS is significantly increased, and its prevalence is approximately 5%. There is a continuing need for new markers that can have diagnostic value in PSS and predict lymphoma development. In this study, we aimed to investigate the usability of netrin-1 as a diagnostic marker in PSS and its relationship with disease activity and predictors of lymphoma.

Methods: Fifty-two PSS patients and 62 healthy volunteers were included in the study. The European Alliance of Associations for Rheumatology Sjögren's syndrome disease activity index (ESSDAI) was used to evaluate systemic disease activity in PSS patients. Netrin-1 values were calculated by the quantitative sandwich enzyme immunoassay method using an ELISA kit (catalog number: E-EL-H2328; Elabscience, lot number: GZWTKZ5SWK, Texas, USA).

Results: Serum netrin-1 levels were similar in PSS [90.3 (43.87-166.41)] and healthy controls [111.6 (63.39-171.36)] (p=0.190). Netrin-1 serum levels were associated only with lymphopenia (p=0.014), one of the predictive markers of lymphoma in PSS, but not with other markers (p>0.05) and ESSDAI score (r=0.637, p=0.067).

Conclusion: Serum netrin-1 levels are not high in PSS and there is no significant correlation between netrin-1 and lymphoma predictive values, except lymphopenia, and the ESSDAI score, which is an indicator of disease activity.

Keywords: Primary Sjögren's syndrome, netrin-1, lymphoma

Öz

Amaç: Primer Sjögren sendromlu (PSS) hastaların üçte birinde anti-SSA veya -SSB antikorları negatiftir. PSS'de B-hücreli non-Hodgkin lenfoma (NHL) gelişme riski önemli ölçüde artar ve prevalansı yaklaşık %5'tir. PSS'de tanısal değere sahip olabilecek ve lenfoma gelişimini öngörebilecek yeni belirteçlere yönelik ihtiyaç devam etmektedir. Bu çalışmada, netrin-1'in PSS'de tanısal bir belirteç olarak kullanılabilirliğini ve onun hastalık aktivitesi ve lenfoma prediktörleri ile ilişkisini araştırmayı amaçladık.

Yöntem: Çalışmaya 52 PSS hastası ve 62 sağlıklı gönüllü dahil edildi. PSS hastalarında sistemik hastalık aktivitesini değerlendirmek için Avrupa Romatoloji Dernekleri Birliği Sjögren sendromu hastalık aktivite indeksi (ESSDAI) kullanıldı. Netrin-1 değerleri ELISA kiti (Elabscience, Texas, ABD; katalog numarası: E-EL-H2328; lot numarası: GZWTKZ5SWK) kullanılarak kantitatif sandviç enzim immunoassay yöntemi ile hesaplandı.

Bulgular: PSS [90,3 (43,87-166,41)] ve sağlıklı kontrollerde [111,6 (63,39-171,36)] serum netrin-1 düzeyleri benzerdi (p=0,190). Netrin-1 serum düzeyleri PSS'de lenfomanın prediktif belirteçlerinden sadece lenfopeni (p=0,014) ile ilişkili iken, diğer belirteçlerle (p>0,05) ve ESSDAI skoru (r=0,637, p=0,067) ile ilişkili değildi.

Sonuç: Serum netrin-1 seviyeleri PSS'de yüksek değildir ve netrin-1 ile lenfoma prediktif değerlerden lenfopeni hariç diğerlerinin ve hastalık aktivite göstergelesi olan ESSDAI skorunun anlamlı korelasyon ilişkisi yoktur.

Anahtar Kelimeler: Primer Sjögren sendromu, netrin-1, lenfoma

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Introduction

Primary Sjögren's syndrome (PSS) is a chronic autoimmune disease not related to other autoimmune diseases, characterized by lymphocytic infiltration of exocrine glands, mainly with glandular dysfunction of salivary and lacrimal glands. Keratoconjunctiva sicca (dry eyes) and xerostomia (dry mouth) are the main symptoms.[1] Since two-thirds of PSS patients are positive for anti-SSA/Ro or -SSB/La autoantibodies, these antibodies are considered one of the main criteria in the 2016 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) PSS classification.[2] Since anti-SSA or SSB antibodies are negative in one-third of PSS patients, many studies have been conducted to detect new autoantibodies that can be used in diagnosing PSS. However, the need for diagnostic biomarkers continues. These novel autoantibodies include autoantibodies against serum salivary gland protein-1, parotid secretion protein, muscarinic-3 receptor, and carbonic anhydrase-6.[3-5]

B-cell non-Hodgkin lymphoma occurs in approximately 5% of patients with PSS and is considered to be the main source of mortality.[6] Studies have been ongoing for a long time to determine the markers (laboratory, pathological and clinical) that may have predictive value in developing lymphoma in PSS. Among the best markers with prognostic value in the development of lymphoma are mixed cryoglobulinemia, cryoglobulinemic vasculitis, and persistent salivary gland swelling.[7-17] Other lymphoma predictive values include skin purpura which may be associated with cryoglobulinemia, low C4 level and organ involvement associated with cryoglobulinemic vasculitis (glomerulonephritis, peripheral neuropathy);[18,19] high MALT involvement in salivary gland histopathology; the presence of monoclonal gammopathy; RF positivity;[20-22] lymphopenia; neutropenia; increased serum beta-2 microglobulin; elevated free immunoglobulin light chains; splenomegaly; lymphadenopathy; cytokines; chemokines; growth factors; monoclonal B lymphocyte expansion in metachronous tissue histopathology; genetic abnormalities and EULAR Sjögren's syndrome disease activity index (ESSDAI).[23]

The need for new markers associated with diagnosis, disease activity indicators, and lymphoma development in PSS continues. The relationship of netrin-1 with PSS has yet to be evaluated. In this study, we investigated the value of netrin-1 molecule as a diagnostic marker and disease activity indicator in PSS and the relationship between serum levels and predictors of lymphoma. Netrin-1 is a laminin-like matrix protein from the axonal guide protein family. Netrin-1 acts as a chemorepulsan and inhibits the migration of neutrophils, monocytes, and lymphocytes through Unc5b and adenosine A2B receptors.[24-26] Netrin-1 plays a pathogenic role in obesity, the development of atherosclerosis,[27,28] the initiation of sepsis and inflammation,[24] osteoporosis by stimulating osteoclast differentiation,[29] and the development of inflammatory arthritis.[30] In our previous study, we showed that netrin-1 was found to be higher in the serum of patients with systemic sclerosis (SSc) compared to healthy controls ($p<0.0001$) and that it may be associated with the pathogenesis of systemic sclerosis.[31]. Deleted in Colorectal Carcinoma (DCC) is a transmembrane netrin-1 receptor that actively induces cell death when dissociated from the netrin-1 ligand. When netrin-1 binds to the DCC receptor, it causes inhibition of DCC-induced apoptosis. It contributes to the increase in the population of diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) tumor cells.[32] In addition, netrin-1 causes progression in plasma cell malignancies.[33] These associations of netrin-1 with lymphoid malignancies prompted us to investigate the relationship of netrin-1 with markers that can predict lymphoma in PSS.

Materials and Methods

Study Design

This study was designed as an analytical case-control study. Fifty-two patients (47 women, five men) followed in the rheumatology department of Ankara City Hospital and classified according to the 2016 ACR/EULAR criteria[34] for PSS were included in the PSS group. In the control group, 62 healthy volunteers (55 females, seven males) of similar age and gender to the PSS group were selected. Active infection, pregnancy, malignant disease, and the presence of rheumatological disease other than PSS were the exclusion criteria. Superficial and abdominal ultrasonography (USG) for lymphadenopathy and splenomegaly; pulmonary function test, carbon monoxide diffusion test or high-resolution tomography for interstitial lung disease; neurological examination and electromyography for peripheral neurologic involvement; urine microscopy and renal biopsy histopathology for glomerulonephritis; parotid gland USG for parotid gland swelling; joint examination and joint USG for arthritis; skin examination for purpura was used to detect lymphoma predictors in the PSS group. The ESSDAI score was used to evaluate systemic disease activity in PSS.[35] To calculate this index score, a total of 12 areas, 11 areas related to organ involvement and one biological place reflecting B-cell activity, were examined, and scores were given to the patients. According to the ESSDAI score, patients were divided into groups defining systemic disease

activity as low (5>), moderate (>5 and <14), or severe (>14). Individuals with hypertension, diabetes mellitus, chronic heart disease, or chronic lung disease were included in the study groups in minimum numbers, and individuals with any of these diseases were considered positive for the presence of comorbid disease. Informed consent was obtained from all individuals included in the study before the study. Dates are given in DD/MM/YYYY format.

Obtaining Serum Samples and Determination of Serum Netrin-1 Level

Venous blood samples in 10 mL vacuum tubes were centrifuged at 1300 x g for an average of 10 minutes. Serum samples were stored in eppendorf tubes at -80 °C until analysis. Serum netrin-1 levels were measured using a quantitative immunoassay method with the catalog number E-EL-H2328 from elabscience, lot number GZWTKZ5SWK, in Texas, USA. Before adding the specific detection antibody rich in biotin for netrin-1, serum samples and standards were incubated with their specific antibodies at 37 °C for approximately 1.5 hours after addition to the micro-ELISA plate wells. Biotin-rich human netrin-1-specific detection antibodies and Avidin-Horseradish Peroxidase (HRP) were then added, and the samples were then incubated at 37 °C for 30 minutes. After the free components were separated by washing, the substrate solution was added to all wells. After this process was completed, a blue color was observed only in the Avidin-HRP conjugate, human netrin-1 wells and biotin-rich detection antibodies. The enzyme-substrate reaction ended after the addition of the stopping solution, resulting in a yellow color in the reaction. A spectrophotometric microplate reader with a wavelength of 450 nm was used to detect optical density levels, which is considered an indirect indicator of Human netrin-1 concentrations. Serum levels of human netrin-1 were calculated using optical density standard curves. The sensitivity used for netrin-1 at levels in the range of 31.25 to 2.000 pg/mL was determined. Inter- and intra-assay precision of <10% was obtained for all levels of netrin-1 concentrations.

Statistical Analysis

The Statistical Packages for the Social Sciences (SPSS) version 22.0 package program was used for the evaluation of statistical analyzes, and the $p<0.05$ level was considered statistically significant. Normality distribution fit in continuous variables was determined using analytical methods such as Kolmogorov-Smirnov/Shapiro-Wilk tests and histogram/probability graphs. Descriptive statistical results were shown as mean and standard deviation for normally distributed variables, and median [interquartile range, (25%-75%)] for non-normally distributed variables. The Independent Samples t-test and Mann-Whitney U test were used to evaluate the statistical significance difference in pairwise comparisons. Spearman correlation test was used to evaluate the correlation analysis between continuous variables. One-Way ANOVA Post-hoc Tukey test was used to evaluate variables with normal distribution, and Independent Samples Kruskal-Wallis test was used to evaluate variables that did not show normal distribution. Bonferroni correction was performed before the One-Way ANOVA Post-hoc Tukey test and the Independent Samples Kruskal-Wallis test. The Fisher's exact tests and chi-square test were used to compare categorical data.

Results

This study was designed as an analytical case control study. The PSS group consisting of 52 patients with a mean age of 49.08±7.23 and a healthy control group consisting of 62 patients with a mean age of 51.06±9.41 were included in the study. Age, gender, body mass index, smoking and presence of comorbid disease in the control group were similar to the PSS group ($p<0.05$). No significant difference was found between PSS and control groups in comparison of median values for netrin-1 [90.3 (43.87-166.41), 111.6 (63.39-171.36), p=0.190, respectively]. Demographic characteristics and laboratory parameters of PSS and control groups are shown in Table 1.

There was no significant difference in median values of netrin-1 between patients with (n=4) and those without (n=48) interstitial lung disease (n=48) in the PPS group [respectively, 115.17 (35.3-395.2), 90.3 (47.2-162.5), p=0.882]. In PSS patients, the median values of netrin-1 were found to be similar between those with negative antibody (anti-SSA/RO52 and -SSB) (n=11) and those with any antibody positivity (anti-SSA/RO52 or -SSB) (n=41) [respectively, 90.54 (38.04-184.4), 90.06 (47.3-159.3), p=0.920].

In the multiple comparisons made in terms of netrin-1 levels between groups receiving different types of treatment in PSS, netrin-1 levels were found to be similar between groups receiving other types of treatment (p=0.342). There was no significant difference in netrin-1 levels between those who received any treatment for PSS and those who did not receive the same treatment ($p>0.05$). The comparison of netrin-1 levels according to medical treatment subtypes in the PSS group is shown in Table 2.

While netrin-1 serum levels are associated only with presence of lymphopenia [yes=159.34 (91.2-213.8),

Table 1. Comparison of demographic characteristics and laboratory results between groups

Parameters	PSS group	Control group	p-value
Gender female/male, n	47/5, 52	55/7, 62	0.509
Age, mean ± SD (years)	49.08±7.23	51.06±9.41	0.164
Body mass index, mean ± SD	23.1±5.14	24.9±6.4	0.18
Smoking, n (%)	3 (5.7)	1 (1.6)	0.33
Presence of comorbid disease			
Hypertension, n	3	5	0.726
Chronic obstructive pulmonary disease, n	3	1	0.330
Coronary artery disease, n	1	2	0.665
Diabetes mellitus, n	1	5	0.217
Disease duration, median (IQR) [years]	12 (7-16)		
Hemoglobin, mean ± SD [x10^9/L]	14.2±1.7	13.4±1.07	0.094
Platelets, mean ± SD [x10^9/L]	260.60±55.06	271.71±13.16	0.253
WBC, mean ± SD [x10^9/L]	5.97±1.95	6.16±2.12	0.062
Neutrophil, mean ± SD [x10^9/L]	4.61±1.51	4.98±1.74	0.072
Lymphocyte, mean ± SD [x10^9/L]	1.35±0.43	1.39±0.71	0.056
Creatinine, mean ± SD [mg/dL]	0.74±0.21	0.63±0.19	0.414
ALT, mean ± SD [U/L]	17.07±6.8	18.26±7.32	0.881
LDH, mean ± SD [U/L]	236.71±36.3	194.52±25.4	0.102
CRP, median (IQR) [mg/L]	2.9 (0.9-6.8)	3.5 (1.1-7.9)	0.095
ESR, median (IQR) [mm/h]	18 (9-24)	13 (8-17)	0.061
Spot urine protein/creatinine ratio	160±31.3	143±22.5	0.231
Netrin-1 levels, median (IQR) [pg/mL]	90.3 (43.87-166.41)	111.6 (63.39-171.36)	0.190
ESSDAI, median (IQR)	6.5 (3.25-14)		
RF, median (IQR) [IU/mL]	10 (9-33)		
C3, median (IQR) [g/L]	1.1 (1-1.28)		
C4, median (IQR) [g/L]	0.2 (0.18-0.3)		
IgG, median (IQR) [g/L]	13.2 (10.6-18.1)		
Presence of interstitial lung disease, n (%)	4 (9.6)		
Antibody negativity (anti-SSA/RO52 and -SSB), n (%)	11 (21.1)		

ALT: Alanine aminotransferase, C3: Complement-3, C4: Complement-4, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ESSDAI: EULAR Sjogren's syndrome disease activity index, IgG: Immunoglobulin G, LDH: Lactate dehydrogenase, RF: Rheumatoid factor, SD: Standard deviation, WBC: White blood cells

Table 2. Netrin-1 levels according to the types of medical treatment used in the PSS group

Medical therapy		n	Netrin-1 levels median (IQR) [pg/mL]	p-value
Hydroxychloroquine	yes	48	85.6 (42.08-161.5)	0.097
	no	4	95.62 (52.1-183.7)	
Corticosteroids	yes	11	90.54 (35.2-169.21)	0.439
	no	41	90.06 (49.24-159.85)	
Methotrexate	yes	7	85.7 (32.4-149.3)	0.167
	no	45	91.3 (47.3-174.5)	
Mycophenolate mofetil	yes	2	88.5 (40.3-156.9)	0.234
	no	50	92.12 (45.1-167.3)	
Rituximab	yes	2	91.4 (55.5-169.5)	0.42
	no	50	94.14 (60.1-172.3)	
Pilocarpine	yes	8	84.8 (39.6-149.3)	0.132
	no	44	91.3 (47.3-155.9)	

IQR: Interquartile range, PSS: Primary Sjogren's syndrome

no=81.29 (42.3-147.5) p=0.014], which is a predictive marker of lymphoma in PSS, it is not correlated with other features (p>0.05). The relationship between the factors predicting lymphoma and netrin-1 levels in PSS is shown in Table 3.

While there was a significant correlation between netrin-1 and spot urine protein amount (r=0.278, p=0.046) and lymphocyte level (r=-0.343, p=0.013), no significant correlation was found between other study parameters (p>0.05) (Table 4).

Discussion

The absence of anti-SSA or anti-SSB antibodies in one-third of PSS patients and the lack of markers that can be used in disease activation and lymphoma prediction have revealed the necessity of investigating new autoantibodies associated with PSS. It has been previously reported that netrin-1 may be related to different mechanisms in the pathogenesis of some lymphomas,[32] multiple myeloma,[33] solid tumors,[36] and SSc,[31] a connective tissue disease. In this study, we investigated the utility of netrin-1 as an indicator

Table 3. The relationship between lymphoma predictive markers and netrin-1 levels in the PSS group

Lymphoma predictive markers		n	Netrin-1 levels median (IQR) [pg/mL]	p-value
Hypocomplementemia (C3 or C4)	yes	18	76.68 (40.6-156.1)	0.459
	no	34	91.52 (47.4-173.4)	
Hypocomplementemia (C4)	yes	8	75.5 (39.2-212.6)	0.794
	no	44	90.3 (48.4-163.2)	
Hypocomplementemia (C3)	yes	14	68.45 (39.4-135.9)	0.227
	no	38	93.72 (47.4-173.4)	
Hypergammaglobulinemia (IgG)	yes	9	165.6 (79.4-238.8)	0.082
	no	43	77.89 (41.8-149.5)	
RF positivity	yes	15	81.29 (42.8-149.5)	0.724
	no	37	94.94 (44.23-175.5)	
Anti-SSA/RO52 positivity	yes	37	90.06 (38.5-169.2)	0.824
	no	15	90.54 (38.5-169.2)	
Anti-SSB positivity	yes	23	77.89 (35.6-149.5)	0.173
	no	29	94.94 (57.1-176.8)	
Purpura	yes	1	92.5	0.962
	no	51	90.06 (42.8 -166.6)	
Lymphadenopathy	yes	5	153.03 (59.3-175.8)	0.449
	no	47	90.06 (41.8-166.6)	
Splenomegaly	yes	3	165.6 (145.4-249.3)	0.094
	no	49	81.29 (42.3-159.8)	
ESSDAI	low	22	79.59 (47.4-146.4)	0.289
	moderate	19	90.06 (35.6-166.6)	
	high	11	153.03 (50.9-228.3)	
Parotid gland enlargement	yes	1	309.02	0.154
	no	51	90.06 (42.8-165.6)	
Monoclonal gammopathy	yes	3	126.01 (72.1-186)	0.429
	no	49	90.06 (42.3-166.1)	
Glomerulonephritis	yes	3	187.55 (116.1-249.3)	0.086
	no	49	81.29 (42.3-159.3)	
Leukopenia	yes	9	165.6 (70.4-235.9)	0.058
	no	43	81.29 (42.3-147.5)	
Neutropenia	yes	6	145.8 (77.8-229.3)	0.198
	no	46	79.59 (42.5-156.4)	
Lymphopenia	yes	16	159.34 (91.2-213.8)	0.014
	no	38	70.63 (41.01-116.3)	
Gender	Female	47	97.14 (56.5-169.7)	0.546
	Male	5	109.43 (51.5-152.7)	

C3: Complement-3, C4: Complement-4, ESSDAI: EULAR Sjogren's syndrome disease activity index, IgG: Immunoglobulin G, LDH: Lactate dehydrogenase, RF: Rheumatoid factor

Table 4. Correlation analysis results between netrin-1 and some parameters

Parameter r (p)	Age	Lymphocyte	CRP	C3	C4	IgG	AntiSSA\ RO52	AntiSSB	RF	ESSDAI	UPCR
Netrin-1	0.002 (0.981)	-0.343 (0.013)	0.056 (0.694)	-0.049 (0.729)	0.071 (0.618)	0.371 (0.074)	-0.039 (0.784)	-0.220 (116)	-0.031 (0.833)	0.067 (0.637)	0.278 (0.046)

C3: Complement-3, C4: Complement-4, CRP: C-reactive protein, ESSDAI: EULAR Sjogren's syndrome disease activity index, R: Spearman correlation coefficient, rF: Rheumatoid factor, UPCR: Spot urine protein/creatinine ratio

of disease activity in PSS and its relationship with known predictors of lymphoma. Our results showed that netrin-1 levels were not high in the serum of PSS patients, and there was no significant correlation between disease activity and ESSDAI score. In addition, this study showed a substantial relationship between netrin-1 levels and lymphopenia, one of the known predictors of lymphoma in PSS. Still, no critical relationship exists between other predictors.

There are a limited number of studies investigating the relationship of netrin-1 with rheumatological diseases. In two of these studies, the relationship between netrin-1 and antibodies in rheumatoid arthritis (RA) synovial tissues,[30,37] while in other studies, netrin-1 levels were investigated in the serum of patients with familial Mediterranean fever (FMF) [38] and SSc[31] patients. It was determined that there was a significant decrease in inflammation and joint erosion in the group treated with anti-netrin-1/anti-Unc5b monoclonal antibody injection (n=6) compared to the untreated group (n=10) from 8-week-old arthritis mice (p<0.001).[30] Unlike this study, Schubert et al.[37] reported that the expression of UNC5B (4-fold) and UNC5C (769-fold) from netrin-1 receptors was higher in RA (n=5) and osteoarthritis (OA) (n=6) synovial tissues compared to healthy subjects (n=3) synovial tissues. They also reported that treatment of RA and OA synovial tissues with netrin-1 results in the inhibition of the migration of synovial fibroblasts, and thus netrin-1 could reduce cartilage degeneration. In a study where we evaluated serum netrin-1 levels between FMF patients (n=42) and healthy controls (n=44), we found netrin-1 levels to be similar between the two groups (p=0.19).[38] In another study, we evaluated netrin-1 levels in the sera of SSc patients (n=56) compared to healthy controls (n=58). In this study, we found that netrin-1 levels were significantly higher in the sera of SSc patients (p<0.0001).[31] Studies supporting the possible contribution of netrin-1 to the pathogenesis of SSc showed that profibrotic cytokine and extracellular matrix protein synthesis in SSc were induced by M2 macrophages[39,40] and netrin-1 increased the expression of M2 macrophage markers.[41-43] It has also been reported that netrin-1 promotes the development of fibrosis in human SSc lung cell culture and bleomycin-induced mouse lung.[44,45] In this study, we compared serum netrin-1 levels between PSS patients (n=52) and healthy controls (n=62), we found netrin-1 levels to be similar between the groups, and we did not find a significant correlation between netrin-1 and the disease activation indicator ESSDAI score (p>0.05). Although the data on the relationship of netrin-1 with rheumatological diseases come mostly from small-scale or cross-sectional studies, further randomized controlled studies are needed to better understand its role in rheumatological diseases.

A study by Broutier et al.[32] using a transgenic mouse model showed that netrin-1 contributes to the development of DLBCL and MCL by inhibiting apoptosis on DCC receptors. In addition, this study determined that there was a decrease in tumor cell density and an increase in DNA fragmentation in tumor cell lines with antibodies blocking netrin-1. Nagoshi et al.[33] showed that transcriptional dysregulation of the netrin-1 receptor DCC in multiple myeloma cell lines plays a role in the progression of plasma cell malignancy. Netrin-1 has been found to cause the inhibition of p53-related apoptosis by stabilizing inactive p53 expression through its receptors.[46,47] It has been reported to be associated with hepatocellular, breast, lung, colorectal, and pancreatic cancers.[34] These associations of netrin-1 with lymphoid and solid malignant diseases prompted us to investigate its relationship with lymphoma predictors in PSS. In our study, a significant relationship was found between netrin-1 and only lymphopenia, but no significant relationship was found between other lymphoma predictive factors.

Study Limitations

The limitations of this study are that it is a cross-sectional study, there is an insufficient number of subjects in some groups that predict lymphoma, and ectopic germinal-like structures and focus scores were not evaluated in salivary gland biopsy. In our study, although the median values of netrin-1 were higher in some lymphoma predictor subgroups (hypergammaglobulinemia, lymphadenopathy, splenomegaly, ESSDAI, parotid gland enlargement, monoclonal gammopathy, glomerulonephritis, leukopenia, neutropenia), no statistically significant results could be obtained. This may be because the statistical results are affected due to the small number of subjects in the subgroups. Although we did not find a significant relationship between netrin-1 and most of the variables that predict lymphoma in PSS in this study, the close relationship of netrin-1

with lymphoproliferative and solid malignancies makes it necessary to investigate its role in the development of lymphoma in PSS with further prospective studies.

Conclusion

Serum netrin-1 levels are not high in PSS and there is no significant correlation between netrin-1 and lymphoma predictive values, except lymphopenia, and the ESSDAI score, which is an indicator of disease activity.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of the University where the study was conducted (Ankara City Hospital Ethics Committee - approval number: 460; date: 30.09.2020).

Informed Consent: Informed consent was obtained from all individuals included in the study before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K., H.E.K., E.F.O., Y.M., E.A., K.O., Ö.E., Ş.E., Design: A.K., H.E.K., E.F.O., Y.M., E.A., K.O., Ö.E., Ş.E., Data Collection or Processing: A.K., H.E.K., E.F.O., Y.M., E.A., K.O., Ö.E., Ş.E., Analysis or Interpretation: A.K., H.E.K., E.F.O., Y.M., E.A., K.O., Ö.E., Ş.E., Literature Search: A.K., H.E.K., E.F.O., Y.M., E.A., K.O., Ö.E., Ş.E., Writing: A.K., H.E.K., E.F.O., Y.M., E.A., K.O., Ö.E., Ş.E.

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Yeni kurulan bir romatoloji kliniğinde Behçet sendromu ve vasküler tutulum

Behçet's syndrome and vascular involvement in a new rhematology clinic

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Öz

Amaç: Behçet sendromu (BS), ağırlıklı olarak mukokutanöz tutulumla başlayan ancak hem ven hem de arterleri de etkileyebilen sistemik bir hastalıktır. Bu çalışmada; yeni kurulan kliniğimizde, BS tanısı ile takip edilmiş olan hastaların demografik ve klinik özelliklerini, tedavilerini gözden geçirmeyi ve esas olarak vasküler BS olgularının üzerinde durmayı amaçladık.

Yöntem: Temmuz 2020 - Aralık 2022 tarihleri arasında kliniğimize başvurmuş, BS tanısıyla takibe alınmış 127 hastaya ait veriler geriye dönük olarak gözden geçirildi. Hastaların 78'i (%61) erkek, 49'u (%39) kadındı. Hastaların 49'unda (%39) vasküler tutulum mevcuttu.

Bulgular: İzole dural sinüs trombozu olan 3 hasta dışlandı. Geri kalan 46 hastanın 37'sinde (%80,4) alt ekstremite derin ven trombozu, 12'sinde (%26) pulmoner arter tutulumu mevcuttu. Üç hastada koroner arter tutulumu ve 4 hastada da intrakardiyak trombüs mevcuttu. Vasküler tutulum nedeniyle tedavisi sürmekte olan hastalardan venöz trombozu olanlarda, glukokortikoidlerin yanı sıra ilk sırada tercih edilen immünosüpresif ajan azatiyoprin olmuştu. Pulmoner arter tutulumunda 2022 yılına kadar tedavi tercihimiz siklofosfamid ardından azatiyoprin ya da infliksimab idamesi şeklindeydi. 2022 yılı içinde 4 pulmoner arter tutulumlu olguda tedaviye doğrudan infliksimab ve azatiyoprin kombinasyonuyla başlanmıştı. Koroner arter tutulumu olan hastalarda tedaviye siklofosfamid ile başlanmıştı. Hastalardan ikisi ölmüştü ve ikisi de erkekti. Birinde santral sinir sistemi (SSS) tutulumu diğerinde ise koroner ve pulmoner arter tutulumları mevcuttu.

Sonuç: Vasküler tutulum BS'de önemli morbidite ve mortalite nedeni olma özelliğini sürdürmektedir. Bu hastaların erken tanınması ve tedavi edilmesi önemlidir.

Anahtar Kelimeler: Behçet sendromu, vaskülit, immünosüpresif ilaçlar

Abstract

Objective: Behçet's syndrome (BS) is a systemic vasculitis that can affect both veins and arteries. In this study, we aimed to review the demographic and clinical characteristics, treatments of patients who were followed up with the diagnosis of BS in our newly established clinic, and mainly focus on vascular BS cases.

Methods: The data of 127 patients who applied between July 2020 and December 2022 and were followed up with the diagnosis of BS were retrospectively reviewed. Of the patients, 78 (61%) were male, 49 (39%) were female. There was vascular involvement in 49 (39%) patients.

Results: Three of them had isolated dural sinus thrombosis and these patients were excluded. Of 46 patients, 37 (80.4%) had lower extremity vein thrombosis, 12 (26%) had pulmonary artery involvement. Three patients had coronary artery involvement and four had intracardiac thrombus. In addition to glucocorticoids, azathioprine was the first preferred immunosuppressive agent in patients with venous thrombosis. Until 2022, our treatment choice in pulmonary artery involvement was cyclophosphamide followed by azathioprine or infliximab maintenance. In 2022, treatment was started directly with the infliximab and azathioprine in 4 patients with pulmonary artery involvement. In patients with coronary artery involvement, treatment was started with cyclophosphamide. Two of the patients had died and both were male (central nervous system in one, coronary artery and pulmonary artery involvement in the other).

Conclusion: Vascular involvement continues to be an important cause of morbidity and mortality in BS. Early recognition and treatment of these patients is important.

Keywords: Behçet's syndrome, vasculitis, immunosuppressive drugs

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Giriş

Behçet sendromu (BS), hem ven hem de arterleri etkileyebilen sistemik bir vaskülit; mukoza, deri, göz, eklem, bağırsak ve santral sinir sistemini (SSS) tutabilen ve tekrarlayıcı karakterde olan sistemik enflamatuvar bir hastalıktır. Genel olarak, erkekler kadınlara göre daha şiddetli bir hastalık seyrine sahiptir ve hastalık şiddeti genellikle zamanla azalır. Genetik faktörlerin katkısını birçok çalışma göstermiştir. Hastaların yaklaşık %50'si HLA-B*51 allelini taşır.[1] BS insidans ve prevalansının özgün bir coğrafik dağılımı vardır. Orta Doğu ve Uzak-Doğu Asya'da artan sıklığı nedeniyle bazen İpek Yolu hastalığı olarak anılır.[1] En sık Türkiye'de (100.000'de 80-370 olgu) görülürken, prevalans Japonya, Kore, Çin, İran, Irak ve Suudi Arabistan'da 100.000'de 13,5-35 arasında değişmektedir.[2]

Vasküler tutulum, kesin bir erkek üstünlüğü ile %40'a varan oranlarda ve genellikle hastalığın erken evrelerinde gelişmektedir. Venöz tutulum arteriyel tutulumdan önemli ölçüde daha sıktır ve en sık da alt ekstremite derin ven trombozu (DVT) şeklinde görülür.[3]

Bu çalışmada; yeni kurulan kliniğimizde, BS tanısı ile takip edilmiş olan hastaların demografik ve klinik özelliklerini, tedavilerini gözden geçirmeyi ve esas olarak vasküler BS olguları üzerinde durmayı hedefledik.

Tablo 1. Demografik ve klinik özellikler

	Kadın	Erkek
Cinsiyet	49	78
Ortalama yaş	40,4	34,6
Oral aft %	100	98,7
Genital ülser %	87,7	76,9
Papülopüstül %	26,5	44,8
Eritema nodozum %	42,8	29,4
Eklem %	24,4	17,9
Göz %	28,5	26,9
Vasküler %	18,3	51,2
Parankimal SSS %	2	8,9
Paterji pozitifliği %	43,4 (23 hastada)	72,9 (37 hastada)
HLA-B*51 pozitifliği %	85,7 (7 hastada)	100 (9 hastada)

SSS: Santral sinir sistemi

Gereç ve Yöntem

Temmuz 2020 - Aralık 2022 tarihleri arasında kliniğimize başvurmuş ve BS tanısı ile takibe alınmış olan 127 hastaya ait veriler geriye dönük olarak gözden geçirildi.

İstatistiksel Analiz

Verilerin analizinde SPSS programı kullanılmıştır. Elde edilen parametrik veriler ortalama ± standart sapma değerleri ile ifade edilmiştir.

Bulgular

Hastaların 78'i (%61) erkek ve 49'u (%39) kadındı. Ortalama yaş 37±10 yıl (18-63), ortanca takip süresi 508 gündü (16-929). Tanı tarihleri 1996-2022 arasında değişmekte idi ve ortalama tanı yaşı 31±9 yıldı (7-52). Demografik ve klinik özellikler Tablo 1 ve Tablo 2'de özetlenmiştir.

Hastaların 49'unda (%39) vasküler tutulum mevcuttu. Üçü izole dural sinüs trombozu olup, bu hastalar dışlanmıştır. Geri kalan 46 hastanın 39'u (%84,7) erkek ve ortanca tanı yaşı 30'du (18-51). Hastaların 7'sinde (%15) ilk vasküler olay BS tanısından önce gelişmişti (bu hastaların 6'sında eş zamanlı ve/veya öncesinde tekrarlayan oral aft ve 2'sinde genital ülser öyküsü mevcuttu) ve bunların tamamı alt ekstremite DVT şeklindeydi. Kırk altı hastanın 37'sinde (%80,4) alt ekstremite DVT ve/veya yüzeyel tromboflebiti [25'inde izole DVT ve/veya yüzeyel tromboflebit (bunların da 3'ünde sadece yüzeyel tromboflebit)] mevcuttu. Üç hastada alt ekstremite DVT'ye ek olarak vena kava inferior, juguler ven ve/veya portal ven trombozları, 9 hastada da alt ekstremite DVT'ye ilave, koroner arter tutulumu, subklavian ve renal arter oklüzyonu, femoral-popliteal arter anevrizması, iliak arterlerde tromboz ile pulmoner arter anevrizma ve trombozları ve intrakardiyak trombüs mevcuttu (Tablo 3).

Tablo 2. Klinik manifestasyonlar

	Mukoza-deri izole	Eklem	Göz	Vasküler	Parankimal SSS	GİS
Prevalans	%24	%20	%28	%39	%6	-
Cinsiyet	K>E (%34>%16)	K>E (%24>%18)	K>E (%29>%27)	E>K (%51>%18)	E>K (%8>%2)	

E: Erkek, GİS: Gastrointestinal sistem, K: Kadın, SSS: Santral sinir sistemi

Tablo 3. Vasküler tutulum alanları

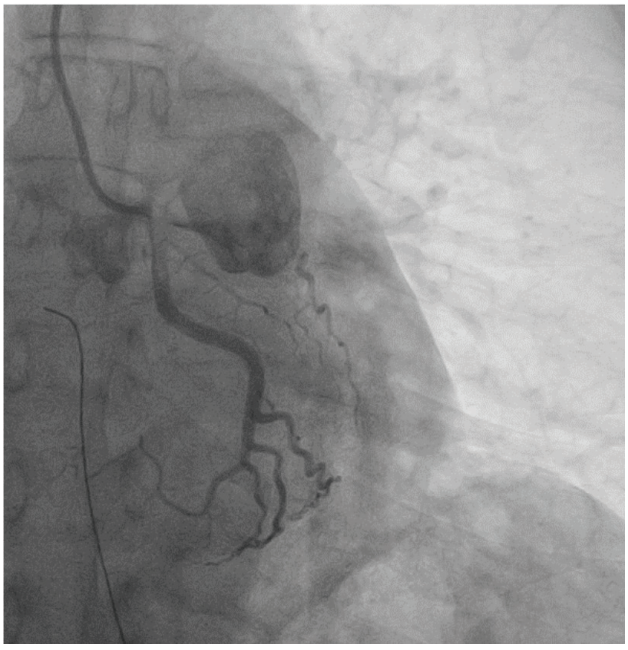
DVT/YVT (izole)	DVT/YVT Vena kava, juguler ven, portal ven	DVT/YVT Arter	PAA (izole)	PAT (izole)	PAA ve PAT	PAA/PAT Ven ve/veya arter
25	3	9	2	1	2	7

PAA: Pulmoner arter anevrizması, PAT: Pulmoner arter trombozu, YVT: Yüzeyel ven tromboflebiti

Hastaların 12'sinde (%26) pulmoner arter tutulumu (5'i izole olup, geri kalanlarda ilave ven ve/veya arteriyel tutulum ve 4'ünde intrakardiyak trombüs) mevcuttu (Tablo 3).

Üç hastada koroner arter tutulumu mevcuttu. Bunların 2'sinde tutulum akut miyokard enfarktüsü ile saptanmış ve birinde de göğüs ağrısı ile tetkik edildiği sırada akut hipotansiyon gelişmesi üzerine yapılan acil koroner anjiyografide dev anevrizma saptanmıştı (Şekil 1). Dört hastada intrakardiyak trombüs mevcuttu (Tablo 4).

Mukoza-deri ve eklem tutulumları nedeniyle tedavileri sürmekte olan 58 hasta vardı. Bunlardan 38'i (%65,5) kolşisin almaktaydı. Hastalardan 16'sına (%27,5) dirençli mukokutanöz bulgular ve/veya eklem tutulumları nedeni ile azatiyoprin başlanmıştı (bunlardan 2'sinde hepatotoksisite nedeniyle tedaviye adalimumab ile devam edilmişti). Baskın klinik bulgusu eklem tutulumu olan hastalarda; sulfasalazin, leflunomid, etanersept ve adalimumab tercih edilen diğer tedaviler olmuştu. Hastaların sadece birinde kolşisin dahil tedavi kesilmiş ve 7 yıldır ilaçsız takip edilmekteydi (58 yaş kadın).



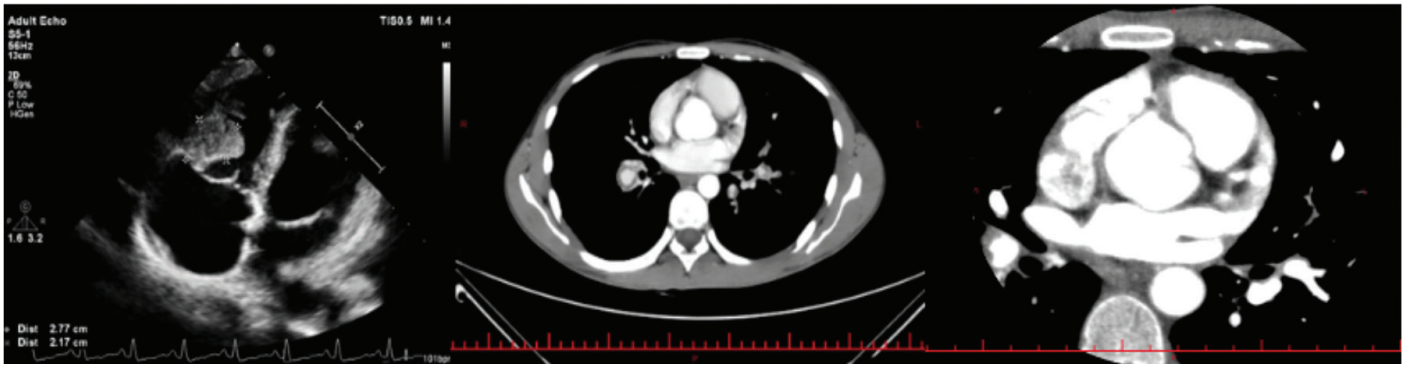
Şekil 1. Sol ön inen koroner arterde dev anevrizma

Göz tutulumu nedeniyle tedavisi sürmekte olan 27 hasta vardı. Bu hastalarda tercih edilen tedaviler sırasıyla; azatiyoprin, adalimumab, azatiyoprin ve adalimumab kombinasyonu, infliksimab, azatiyoprin ve siklosporin kombinasyonu şeklindeydi. Nörolojik tutulum nedeniyle tedavisi sürmekte olan hastalardan ise; 6'sı azatiyoprin, 2'si mikofenolat mofetil (birinde dural sinüs trombozu) almaktaydı. Pakimenenjit ile takip edilmekte olup mikofenolat mofetil altında progrese olan hastanın tedavisine infliksimab eklenmişti. Hastalardan biri pandemi döneminde COVID-19 pnömonisi nedeniyle yoğun bakım takibindeyken kraniyal kanama ile kaybedilmişti.

Vasküler tutulum nedeniyle tedavisi sürmekte olan hastalardan venöz trombozu olanlarda, glukokortikoidlerin yanı sıra ilk sırada tercih edilen tedavi azatiyoprin olmuştu. Kalıtsal trombofilisi de olan ve warfarin kullanmak zorunda olan bir hastada tedaviye azatiyoprin ile başlanmış ancak uluslararası normalleştirilmiş oranın efektif aralıkta tutulmasında zorlanılınca infliksimab ile devam edilmişti. Alt ekstremite DVT ve vena kava inferiorda trombozu olan hastada da tedaviye azatiyoprin ile başlandıktan sonra takipte sebat eden akut faz reaktan yüksekliği nedeniyle adalimumab eklenmişti. Alt ekstremite DVT, vena kava inferior ve portal ven trombozu olan bir başka hastada (2022) tedaviye azatiyoprin ve infliksimab kombinasyonu ile başlandı. Alt ekstremite DVT'ye ek olarak subklavian/renal arter oklüzyonları olan bir hastada (2021) ve periferik arter anevrizması olan bir başka hastada (2021) 6 siklus siklofosfamid tedavisinin ardından infliksimab ile devam edilmişti. Pulmoner arter tutulumunda 2022 yılına kadar tedavi tercihimiz siklofosfamid, ardından azatiyoprin ya da infliksimab idamesi şeklindeydi. 2022 yılı içinde 4 pulmoner arter tutulumlu olguda tedaviye doğrudan infliksimab ve azatiyoprin kombinasyonu ile başlandı [bunlardan pulmoner arter tutulumu ve intrakardiyak trombüsü olan bir hastanın tedavi uyumsuzluğu nedeniyle, infliksimab yükleme dozunu bile tamamlayamayacak şekilde takiplerini aksattığı için, tedaviye siklofosfamid ile devam edildi (Şekil 2)]. Koroner arter tutulumu olan hastalarda tedaviye siklofosfamid ile başlanmıştı. Bu hastalardan birinin takibine infliksimab idamesi ile devam

Tablo 4. Kardiyak tutulum

	Koroner arter (oklüzyon)	Koroner arter (anevrizma)	Koroner arter (oklüzyon/anevrizma)	İntrakardiyak trombüs
Kadın/Erkek	-/1	-/1	-/1	1/3
PAA/PAT	-	-	1	4
DVT	1	1	-	2
Hepatik ven, vena kava inferior, iliak ven	1	-	1	-



Şekil 2. Bilateral pulmoner arterlerde anevrizma ve tromboz ile sağ ventrikülde 54x37x24 mm trombüs

edilmekteyken, koroner arter ve pulmoner arter tutulumu olan diğer hasta takibinin üçüncü ayında masif hemoptizi ile kaybedildi. Koroner arter tutulumuna ilave Budd-Chiari Sendromu da olan, düşük ejeksiyon fraksiyonlu kalp yetmezliği olan ve warfarin kullanan diğer hastada ise siklofosfamid ardından mikofenolat mofetil ile devam edilmişti.

Tartışma

Hastaların 78'i (%61) erkek ve 49'u (%39) kadındı. Ortalama yaş 37±10 yıl (18-63), ortanca takip süresi 508 gündü (16-929). Tanı tarihleri 1996 ile 2022 arasında değişmekte idi ve ortalama tanı yaşı 31±9 yıldı (7-52). Demografik ve klinik özellikler Tablo 1 ve Tablo 2'de özetlenmiştir.

Türkiye BS'nin dünyada en sık görüldüğü ülkedir (100.000'de 80-370 olgu).[2] Damar tutulumu en önemli morbidite ve mortalite nedenlerinden biridir. Özellikle pulmoner arter anevrizması yaklaşık %25 gibi yüksek bir mortalite riski taşır.[4]

BS'de vasküler tutulumun erkeklerde daha sık görüldüğü bilinmektedir. Türkiye'de 2.319 hastanın dahil edildiği çalışmada vasküler hastalık prevalansı %14,3 (%53,3 yüzeyel tromboflebit, %29,8 DVT, %3,6 arteriyel tutulum) olarak bildirilmiş ve en yaygın olarak erkeklerde görüldüğü vurgulanmıştır.[5] Çin'de yapılan 796 hastanın dahil edildiği bir çalışmada ise; %12,8 oranında vasküler tutulum bildirilmiş ve erkek: kadın oranı yaklaşık 4:1 olarak bulunmuştur.[6] Kliniğimizin 2 yıllık verilerine göre ise; hastalarımızda %39 oranında vasküler tutulum mevcuttu ve erkek:kadın oranı yaklaşık 3:1'di. En sık görülen vasküler olay ise %80 ile alt ekstremite DVT şeklindeydi.

2018 EULAR BS tedavi önerilerinde akut DVT için; glukokortikoidler ile azatiyoprin, siklofosfamid veya siklosporin-A tercih edilebileceği belirtilmişti. Pulmoner arter anevrizması için yüksek doz glukokortikoid ve siklofosfamid önerisi mevcuttu. Hem aortik hem de periferik arter anevrizması için de gerekli ise onarım için müdahale öncesi de yine glukokortikoid ve siklofosfamid ile medikal tedavi önerisinde bulunulmuştu. Ek olarak refrakter venöz trombozlarda ve pulmoner arter tutulumunda monoklonal anti-tümör nekroz faktör (TNF) tercih edilebileceği bildirilmişti.[7] Bizim de hastalarımızda venöz trombozda ilk sırada tercih ettiğimiz immünosüpresif ilaç azatiyoprin olurken arteriyel tutulumda ise siklofosfamid olmuştu.

Anti-TNF'ler, özellikle infliksimab ve adalimumab, hastalık aktivitesi konvansiyonel immünosüpresiflerle kontrol edilemeyen BS hastalarında giderek daha fazla kullanılmaktadır. Retrospektif çalışmalar veya olgu serileri, anti-TNF ajanların, özellikle refrakter mukokutanöz, eklem, göz, gastrointestinal sistem (GİS) ve SSS tutulumu olan BS hastalarında etkinliğini göstermiştir.[8] On üç refrakter (tamamı öncesinde pulse metilprednizolon ve siklofosfamid almış olan) pulmoner arter tutulumlu hastanın dahil edildiği çalışmada; 12 hastaya infliksimab, 1 hastaya adalimumab verilmiş ve sonuçta takipten çıkan ve enfeksiyon nedeni ile tedaviye devam edilemeyen hastalar dışlandığında 6 hastada anti-TNF tedaviye devam etmekte iken remisyon bildirilmiş ve remisyon sonrası anti-TNF tedavinin durdurulduğu 4 hastadan ise 2'sinde ilk 3 yılda relaps gözlendiği belirtilmişti. Bu çalışmada altı çizilen bir diğer durum ise 2 hastada, ki bunlardan biri vena kava inferior trombozu diğeri SSS tululumu nedeniyle infliksimab almakta olan hastalar, anti-TNF tedavi devam etmekte iken pulmoner arter tutulumunun gelişmesi olmuştu.[9] Yirmi yedi refrakter vasküler BS hastasının dahil edildiği çok merkezli bir çalışmada ise; 24 hastaya infliksimab ve 3'üne de adalimumab verilmiş, 22 (%80) hastada 3. ayda tam remisyon bildirilmişti. Bu çalışmada ayrıca istatistiksel olarak anlamlı farklılık saptanmasa da infliksimab ve azatiyoprin kombinasyonunda (%93) infliksimab monoterapisine (%67) göre daha yüksek oranda remisyon görüldüğü belirtilmişti.[10] Pulmoner arter tutulumlu 3 hastamızın tedavisine infliksimab azatiyoprin kombinasyonu ile devam edilmektedir. Bir sonuç bildirmek için hasta sayısı ve takip süresi yetersiz

olmakla birlikte, en uzun takip süresine sahip hastamızda 7. ayda metilprednizolon 4 mg'lık doza düşülmüş halde ve bir diğerinde 4. ayda metilprednizolon 8 mg'lık dozda remisyon sürmektedir. Sol pulmoner arteri total oklüde ve başvuru semptomu hemoptizi olan üçüncü hastamızda ise hemoptizi tamamen durmamış olup azalmakta iken takibinin 2. ayında submasif hemoptizi ile başvurusunda glukokortikoid dozunun artırılması ile klinik kontrol altına alınmış ve bu hastada siklofosfamid tedavisine geçilmesi düşünülse de hastanın kabul etmemesi üzerine tedaviye infliksimab ve azatiyoprin ile devam edilmiştir.

BS'de semptomatik kalp hastalığı nadirdir. Perikardit, miyokardit, miyokard enfarktüsü olan veya olmayan koroner arterit, koroner arter anevrizmaları, atriyal septal anevrizmalar, ileti sistemi bozuklukları, endokardit, endomiyokardiyal fibroz, mitral kapak prolapsusu, intrakardiyak tromboz ve kapak yetmezlikleri görülebileceği bildirilmiştir.[11-18] Yapılan çalışmalarda aterosklerozun ise diğer otoimmün romatolojik hastalıkların aksine BS'de artmış bir oranda ortaya çıkmadığı görülmektedir.[19,20] Bizim hastalarımızdan üçünde koroner arter tutulumu (üçü de erkek) ve dördünde de intrakardiyak trombüs (üçü erkek) mevcuttu. İntrakardiyak trombüslü hastalarımızın tamamında eşlik eden pulmoner arter tutulumu mevcuttu.

BS ile takipli 127 hastamızdan ikisi ölmüştü ve ikisi de erkekti. Biri SSS tulumu ile takipli 59 yaşında, COVID-19 pnömonisi nedeniyle yoğun bakım ünitesinde iken kraniyal kanama nedeniyle ve bir diğeri 25 yaşında miyokard enfarktüsü ile prezente olan koroner arter (oklüzyon ve anevrizma) ve pulmoner arter tutulumları mevcut olup masif hemoptizi ile kaybedilmişlerdi.

Sonuç

Bu çalışmada; yakın zaman içerisinde kurulmuş yeni bir romatoloji kliniği olarak, bu kısa süre içerisindeki BS tanısı ile takipli hastalarla ilgili deneyimimizi paylaşmayı istedik. Özellikle vasküler tutulum bu hastalarda önemli morbidite ve mortalite nedeni olma özelliğini sürdürmektedir. Bu nedenle hastaların erken tanınması ve tedavi edilmesi önemlidir. Tedavide de anti-TNF ajanların giderek daha fazla kullanılması gibi yenilikler sürmekte olup bu tedavilerin hem etkinlik ve güvenilirliğini hem de optimal tedavi süresini belirlemek için prospektif randomize kontrollü çalışmalara ihtiyaç olduğu da aşikardır.

Etik

Etik Kurul Onayı: Bu çalışma etik kurul onayı gerektirmemektedir.

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Do we underestimate musculoskeletal ultrasonography in the diagnosis of polymyalgia rheumatica with or without giant cell arteritis?

Polimiyaljia romatika ve dev hücreli arterit tanısında muskuloskeletal ultrasonografi kullanımını azımsıyor muyuz?

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Abstract

Objective: We aimed to determine how often musculoskeletal ultrasonography (MSUS) is used in real-life practice for the evaluation of 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria in polymyalgia rheumatica (PMR) patients with or without giant cell arteritis (GCA).

Methods: All patients have been prospectively registered in the Hacettepe University Vasculitis Research Center database since October 2014. The clinical information, laboratory and MSUS findings of patients registered in database until January 2023 were also retrospectively analyzed from the hospital electronic files and patients' charts. MSUS findings were analyzed following the criteria. Patients were divided into two groups: those with or without GCA. The utility of the 2012 ACR/EULAR provisional PMR classification criteria was compared in two groups.

Results: As of January 2023, 106 patients were included in the analysis. Eighteen patients were excluded from the study due to missing data and the diagnosis changed to inflammatory arthritis during the follow-up period. The mean age at diagnosis of the patients was 66.8 (7.53). Sixty (68.2%) of these patients had solely PMR, while twenty-eight (31.8%) had GCA accompanying PMR. Only 45 (75%) of 60 PMR patients and 12 (42.9%) patients with concomitant GCA diagnoses met the criteria. The criteria were higher solely in PMR patients (p=0.007). MSUS was applied to only 22.7% of patients. We found that only three patients did not meet the criteria if MSUS was not performed, and the rate of meeting the criteria in all patients changed from 64% to 61.3%.

Conclusion: While the 2012 PMR provisional criteria are useful for solely PMR patients, they should be developed for patients with GCA accompanying PMR. In both groups, shoulder and hip ultrasonography

Öz

Amaç: Dev hücreli arteritin (DHA) eşlik ettiği ve izole polimiyalji romatika (PMR) hastalarında 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) sınıflandırma kriterlerinin değerlendirilmesinde kas-iskelet ultrasonografisinin (MSUS) gerçek yaşam pratiğinde ne sıklıkta kullanıldığını belirlemeyi amaçladık.

Yöntem: Tüm hastalar Ekim 2014 tarihinden itibaren tüm hastalar prospektif olarak Hacettepe Üniversitesi Vaskülit Araştırma Merkezi veri tabanına kaydedildi. Ocak 2023 tarihine kadar veri tabanımızda kayıtlı olan hastaların klinik bilgileri, laboratuvar ve MSUS bulguları da hastane elektronik sisteminden ve hasta dosyalarından incelendi. Hastaların ultrasonografi bulguları kriterlere göre analiz edildi. PMR hastaları DHA eşlik eden ve etmeyenler olarak iki gruba ayrıldı. 2012 ACR/EULAR geçici PMR sınıflandırma kriterlerinin karşılama oranı iki grupta karşılaştırıldı.

Bulgular: Ocak 2023 itibariyle 106 hasta analize dahil edildi. PMR kriterlerine ilişkin eksik veriler ve takip süresince tanının enflamatuvar artrit olarak değişmesi nedeniyle 18 hasta çalışma dışı bırakıldı. Bu hastaların 60'ında (%68,2) sadece PMR, 28'inde (%32,8) PMR'ye eşlik eden DHA vardı. Hastaların ortalama tanı yaşı 66,8 (7,53) idi. 60 PMR hastasının sadece 45'i (%75) ve eşlik eden DHA tanısı olan 12 (%42,9) hasta kriterleri karşıladı. Kriterler yalnızca PMR hastalarında daha yüksekti (p=0,007). MSUS hastaların sadece %22,7'sine uygulandı. Hastalara MSUS yapılmasaydı yalnızca üç hasta kriterleri doldurmayacaktı ve tüm hastalarda kriterleri karşılama oranı %64'ten %61,3'e değişecekti.

Sonuç: 2012 PMR geçici kriterleri sadece PMR hastaları için faydalı iken, PMR'ye eşlik eden DHA'lı hastalar için geliştirilmelidir. Anatomik güçlükler ve yetersiz eğitim nedeniyle her iki grupta da omuz ve kalça

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was performed less frequently due to anatomical difficulties and insufficient training. Therefore, clinicians should pay attention to using MSUS and recommended criteria when diagnosing PMR in daily rheumatology practice.

Keywords: Polymyalgia rheumatica, giant cell arteritis, the new 2012 EULAR/ACR PMR provisional classification criteria, musculoskeletal ultrasonography

ultrasonografisi daha az uygulandı. Bu nedenle klinisyenler günlük romatoloji pratiğinde PMR tanısı koyarken MSUS kullanımına ve önerilen kriterlere dikkat etmelidir.

Anahtar Kelimeler: Polimiyaljia romatika, dev hücreli arterit, 2012 ACR/EULAR PMR provizyonel sınıflama kriterleri, muskuloskeletal ultrasonografi

Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disease that generally affects people over 50, characterized by pain and stiffness in the neck-shoulder-hip region, with elevated acute phase reactants and negative autoantibodies. Different sets of criteria have been previously defined for diagnosing or classifying PMR. However, the specificity of these criteria in differentiating PMR from other rheumatic diseases is lower than expected. Therefore, 2012 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) provisional PMR classification criteria were developed using musculoskeletal ultrasonography (MSUS) in 2012.[1,2] As a result, the PMR classification criteria showed optimal sensitivity (92.6%) and specificity (81.5%) in discriminating PMR from inflammatory arthritis and other diseases which can mimic PMR in symptoms.

Furthermore, the specificity of the criteria increased to 91.3% with the addition of the MSUS examination.[3] While MSUS has been added to these criteria, how often they are used in daily practice still needs to be discovered. On the other hand, giant cell arteritis (GCA) is another common inflammatory disease in the elderly population and overlaps with PMR. PMR is related to GCA in 16-21% of cases, and up to 50-90% of GCA cases may have PMR at presentation.[1] Although PMR criteria have been previously studied solely in PMR patients, their sensitivity has not been demonstrated in patients with GCA. In a recent prospective study, the prevalence of GCA in newly diagnosed PMR patients was investigated, and 89% of PMR patients with GCA diagnoses fulfilled those criteria.[4]

We aimed to to determine how often ultrasound is used in real-life practice for evaluation of classification criteria in PMR patients with or without GCA.

Materials and Methods

All patients diagnosed with PMR have been prospectively registered at the Hacettepe University Vasculitis Research Center (HUVAC database) between October 2014 and January 2023. Patients diagnosed with PMR based on an experienced clinician were included. Eighteen patients with insufficient clinical and laboratory information at the time of diagnosis were excluded from the study. Demographic data, clinical characteristics, laboratory findings, and MSUS findings of the patients were recorded. The clinical information and laboratory findings of the patients registered in our database until January 2023 were also retrospectively analyzed from the hospital electronic files and patients' charts.

Laboratory data including erythrocyte sedimentation rate (ESR) (mm/h), C-reactive protein (CRP) (mg/dL), complete blood count, rheumatoid factor (RF; positive if >20 IU/mL), and anticitrullinated peptide antibody (ACPA; positive if >5 IU/mL) levels were recorded. The criteria were studied for patients who met the criteria required for the 2012 ACR/EULAR criteria to be applied (Table 1). Morning stiffness and duration, hip pain or range of motion, absence of RF/ACPA, absence of other joint involvement at baseline were documented. If the patient did not use USG, getting 4 points from these criteria would fulfill the criteria.

US Examination

MSUS was performed by experienced rheumatologists trained in ultrasound. Parameters of the MSUS were included according to criteria: Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis (1 point), at least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis (1 point).[2] If MSUS was done, 5 points were required to fulfill the criteria (Table 1).

PMR patients with GCA met the 1990 ACR criteria for GCA. In addition, they had a positive temporal artery biopsy/temporal artery ultrasonography or evidence of large vessel vasculitis at fluorodeoxyglucose-positron emission tomography/computerized tomography scan.[5] We divided the patients into two groups: Those solely with PMR and those with a concomitant GCA diagnosis. We analyzed the sensitivity of those criteria in diagnosing patients with solely PMR and patients with PMR and GCA concomitantly. Hacettepe University Ethics Commission has approved this study (GO 21/198).

Table 1. 2012 American College of Rheumatology/European League Against Rheumatism provisional criteria for the classification of polymyalgia rheumatica[2]

	Point without US (0-6)*	Point with US (0-8)*
Morning stiffness duration >45 min	2	2
Hip pain or limited range of motion	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	-	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	-	1

*A score of 4 or more is categorised as PMR in the algorithm without US and a score of 5 or more is categorised as PMR in the algorithm with US

ACPA: Anticitrullinated protein antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PMR: Polymyalgia rheumatica, RF: Rheumatoid factor, US: Ultrasound

Statistical Analysis

Statistical analysis was performed using SPSS version 25. Continuous data were described as median [interquartile range (IQR)] or mean [standard deviation (SD)], and categorical variables as percentages. The differences between two groups were investigated using the Mann-Whitney U and Student's t-test. The categorical variable was interpreted using the chi-square tests. The level of significance was chosen to be $p<0.05$.

Results

Patients Clinical Characteristics

We detected 106 patients with PMR, fourteen patients were excluded due to missing data and four patients due to an inflammatory arthritis diagnosis (3 of them elderly onset rheumatoid arthritis, one spondylarthritis) during the follow-up. The final analysis included 88 [n=60 (68.2%) female] patients. There were 60 patients in the PMR only group (68.2%). The prevalence of patients with both PMR and GCA diagnoses was 31.8%. PMR with GCA patients had a longer disease duration than the PMR only group (p=0.007).

All patients were older than 50 years and had elevated acute-phase reactants. The mean (± SD) age at diagnosis of PMR was 66.8 (±7.53) years. Characteristic features of the patients are shown in Table 2. The laboratory parameters at the time of diagnosis were as follows: Mean (± SD) ESR was 58.1 (±28.7) mm/h, median (IQR) CRP was 3.72 (1.1-23.2) mg/dL, mean (± SD) hemoglobin was 12.4 (±1.5) g/dL, and mean (SD) platelet count was 303,000 (±148,000)/mL. MSUS was performed in only 20 (22.7%) patients; 17 were PMR solely patients, and 3 were PMR with GCA patients. In MSUS examination, eight (40%) patients had bilateral shoulder MSUS findings in the examined regions; Biceps tenosynovitis subdeltoid bursitis or glenohumeral synovitis. In addition, 7 (35%) patients had unilateral inflamed shoulder findings with hip synovitis and/or trochanteric bursitis. MSUS examination of five patients (25%) was normal.

Applicability of Classification Criteria for Both Groups

A total of 57 (64.7%) patients met the 2012 ACR/EULAR provisional PMR classification criteria. While of the 60 patients with solely PMR, 45 (75%) met the criteria, only 12 (42.9%) of the 28 PMR with GCA patients met the criteria. Disease duration was longer in PMR with GCA patients (p=0.007). The rate of fulfilling the criteria in solely PMR patients was significantly higher than in PMR with GCA patients (Table 3). While almost all patients within the isolated PMR patients had morning stiffness, half of

Table 2. Characteristic features of all PMR patients

Age at the diagnosis, years*	66.8 (±7.53)
Disease duration, years**	3.54 (0.18-14.7)
PMR with GCA patients, n (%)	28 (31.8)
Constitutional symptoms (n=82)	67 (81.7)
Morning stiffness ≥45 min (n=73)	67 (91.7)
Hip pain or limited range of motion (n=74)	66 (89.1)
Absence of RF and/or ACPA (n=76)	65 (85.5)
Absence of other joint involvement (=51)	46 (90.1)
ESR (mm/h)*	58.1 (±28.7)
CRP (mg/dL)**	3.72 (1.1-23.2)
Leucocyte (x10^3/mm^3)	10.3 (±2.8)
Hemoglobin (gr/dL)*	12.4 (±1.5)
Platelets (x10^3/mm^3)*	303 (±148)
RF positivity (>20 IU/mL), n (%)	6 (7.1)
ACPA pozitivity, n (%), n=84	4 (4.7)
RF or ACPA positivity, n (%)	7 (8.35)

*ACPA: anti-cyclic citrullinated peptide antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GCA: Giant cell arthritis, MSUS: Musculoskeletal ultrasonography, PMR: Polymyalgia rheumatica, RF: rheumatoid factor, *mean (±standard deviation), **Median (IQR)*

Table 3. Comparison patients with solely PMR and PMR with GCA patients

	Patients swith solely PMR (n=60)	PMR with GCA patients (n=28)	p
Age at diagnosis, years, mean (± SD)	65.9 (8)	68.7 (6.0)	0.13
Sex (female), n (%)	40 (66.7)	20 (71.4)	0.42
Disease duration, years, median (min-max)	**3.4 (0.18-10.5)**	**5.5 (0.2-14.7)**	**0.007**
Morning stiffness ≥45 min, n (%)	**54 (96.4)**	**13 (76.5)**	**0.02**
Hip pain or limited range of motion (n=63), n (%)	52 (91.2)	14 (82.4)	0.2
Absence of RF/ACPA, n (%)	47 (88.7)	18 (78.3)	0.25
Absence of other joint involvement, n (%)	35 (89.7)	11 (91.7)	0.6
The patients for fulfilled of score 4 and more n, (%)	**45 (75)**	**12 (42.9)**	**0.004**
MSUS, n (%) • Normal • Both shoulders inflamed* • At least one shoulder and at least one hip inflamed**	15 (25) 4 (6.6) 6 (10) 5 (8.3)	5 (17.8) 1 (3.5) 2 (7.1) 2 (7.1)	0.3

**Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis, **At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis and at least one hip with synovitis and/or trochanteric bursitis, ACPA: Anticitrullinated protein antibodies, GCA: Giant cell arteritis, MSUS: Musculoskeletal ultrasonography, RF: Rheumatoid factor, PMR: Polymyalgia rheumatica, SD: Standard deviation*

PMR with GCA patients had morning stiffness. There was no difference between the groups regarding other criteria. In PMR patients with GCA, a lower rate of MSUS was performed. MSUS was performed on only 20 patients. Even if MSUS was not performed in 17 of these patients, it was observed that they filled the criteria. We found that only three patients did not meet the criteria if MSUS was not performed, and the rate of meeting the criteria in all patients changed from 64% to 61.3%.

Discussion

In this present study, we performed the 2012 EULAR/ACR provisional classification criteria in our PMR and GCA cohort. Our data showed that these criteria are not used adequately in PMR with GCA patients. Even though criteria have been developed to diagnose PMR, the clinician's experience is still important for the diagnosis of those patients. Our results showed that MSUS did not significantly alter the sensitivity of the criteria. Although MSUS is part of the criteria, it was used less frequently in the diagnosis of the disease for some valid reason.

Until 2012, Bird[5] and Hailey's[6] criteria were used to diagnose PMR. Macchioni et al.[7] showed that Bird[5] and Healey's[6] criteria were insufficient to distinguish between inflammatory rheumatic diseases such as RA and PMR from each other. Because of these reasons, 2012 ACR/EULAR provisional PMR classification criteria set was developed in 2012.[2] After the 2012 provisional PMR criteria were developed, their performance was evaluated in previous studies, but there has yet to be a new update on the provisional PMR criteria.[7,8] However, the efficiency of these criteria has yet to be evaluated in PMR with GCA patients. It has yet to be compared regarding efficiency in PMR patients solely and PMR with GCA patients.

In our present study, the ACR/EULAR criteria frequency was 64.7% in all PMR patients; this ratio was lower compared to other studies. Especially in PMR with GCA patients, we noticed that patients previously diagnosed with GCA and had pain in the shoulder and hip girdle was followed up with the diagnosis of PMR, even if they did not meet the 2012 criteria. The sensitivity of the criteria was 42% in patients with GCA. In a Korean cohort study involving 98 patients with PMR, they found that 80 (81.6%) patients achieved ≥4 points, and particularly 26 patients (26.5%) achieved 6 points. Besides, the most common finding in their study was hip pain or restricted range of motion (84.7%), while the least seen symptom was morning stiffness for more than 45 minutes (54.1%). Our data showed that the percentage of all criteria was similar (morning stiffness: 96.1%, hip pain or restricted range of motion: 91.2%).[8,9]

In a Japanese PMR cohort, the rate of patients fulfilling the criteria was less than in our cohort (42% vs. 75%). While almost all patients in our PMR cohort had morning stiffness, one in five patients in the Japanese PMR cohort had morning stiffness. For this reason, our rate of meeting the criteria may have been higher than theirs.[10] Macchioni et al.[7] reported that morning stiffness was 91%, similar to our cohort. However, our PMR with GCA patients' morning stiffness duration was 76.5%. The difference in filling those criteria between these studies may have been due to racial differences and hospital registry systems.

Morning stiffness and absence of RF/ACPA positivity had a higher score than others in the criteria set. In particular, RF positivity is a score that increases with age, and it can be found positive in 10 percent of individuals.[11] In our cohort, 7 (8.3%) patients had RF or ACPA positivity. However, only two of them met the criteria. Considering that PMR and GCA can be seen in the elderly, it is possible to detect age-

related RF positivity in those patients. Therefore, it may be helpful to reconsider the score given to RF positivity.

When we look at the criteria items in detail, morning stiffness was higher in patients with solely PMR than the PMR with GCA patients ($p<0.02$). Other criteria domains were similar. As a result, patients with solely PMR diagnosis met the criteria at a higher rate than the PMR with GCA patients in our cohort. When we look at the literature, there was another study in which morning stiffness was less common in patients with GCA, although it was not statistically significant. Again in this study, the usefulness of the criteria between groups was similar.[4]

Our study evaluated 20 patients (22.7%) with MSUS. After implementing MSUS into the classification criteria guideline, the total score ≥5 had increased to a sensitivity of 66% and specificity of 81%, differentiating it from other inflammatory rheumatic diseases.[2,12] However, there are conflicting results in the literature regarding the sensitivity and specificity of these criteria. Macchioni et al.[7] emphasized that adding the US to the criteria increased the specificity. In contrast, in another study, the sensitivity increased when the US was added to the criteria, and the specificity decreased.[3] Although MSUS was performed in a few patients in our study, the sensitivity did not change significantly when we excluded the US findings from the criteria. In a retrospective study conducted on 98 PMR patients, the sensitivity of the criteria was 81.6% without using the US. In our PMR cohort, the sensitivity of the criteria was 61.3% without using the US.[9] The findings in our study show that US does not contribute to the sensitivity of the criteria. In the study of Burg et al.[4], the sensitivity of the criteria was 89% in PMR-GCA patients.[4] On the other hand, in our study, it was found to be 42.9%. The other study was prospective, with no missing data, and US was performed on all patients. This may be the reason why our results are different.

Although recommended, there may be some valid reasons for the insufficiency of MSUS in the diagnosis:

1. Application of shoulder and hip sonograhpy is more difficult due to the anatomy of those joint regions and inexperience of many clinicians in handling it.

2. Some of these patients may have undergone MSUS, but there was no any recorded report of their sonographies.

3. There could be less emphasis on shoulder and hip ultrasonography education during the rheumatology fellowship education.

Study Limitations

Our present study has several limitations. Firstly, our study was performed at a single tertiary referral center. For this reason, more patients with a pre-diagnosis of GCA may be referred to us, and therefore the frequency of GCA may be higher, which may be a potential bias/limitation. Secondly, although this is a prospectively recorded database, only some criteria could be evaluated because information on every patient in the database could not be reached. On the other hand, only some patients underwent MSUS, so it is difficult to determine how much the US contributes to the criteria.

Conclusion

Our study demonstrated the usefulness of PMR classification criteria in rheumatology. These results suggest that MSUS should be included explicitly in the diagnostic process. It seems important for clinicians to make MSUS a part of rheumatology education. Clinician experience is still one step ahead in diagnosing PMR. The differential diagnosis of inflammatory arthritis should be made quite well. Therefore, when diagnosing PMR patients, clinicians should consider all criteria and the use of MSUS in their daily clinical practice.

Ethics

Ethics Committee Approval: Hacettepe University Ethics Commission has approved this study (GO 21/198).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Design: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Data Collection or Processing: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Analysis or Interpretation: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Literature Search: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Writing: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K.

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Behçet hastalığı ile takipli hastalarda obstetrik süreçlerin retrospektif değerlendirmesi

Retrospective evaluation of obstetric processes in patients with Behçet's disease

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Öz

Amaç: Behçet hastalığı (BH), her iki cinsiyeti de etkileyen ve genellikle üreme çağında tanı konulan multisistemik bir vaskülittir. Bu çalışmada, BH ile gebelik arasındaki ilişkiyi hem maternal hem de fetal açıdan araştırmayı amaçladık.

Yöntem: Bu retrospektif, tek merkezli, tanımlayıcı çalışmada 18 Behçet hastasının toplam 61 gebeliği incelendi. Klinik ve demografik veriler, hasta yaşı, hastalık öyküsü, obstetrik öykü, gebelik sonucu ve hem maternal hem de fetal komplikasyonlara ilişkin kayıtlardan elde edildi. Hatırlama yanlılığını önlemek için, her hastanın yalnızca son gebeliği, hastalık aktivitesi ve gebelik sırasında ilaç kullanımı veya revizyonu açısından değerlendirildi.

Bulgular: Hastaların tanı anındaki ortanca yaşı 25 ve ilk gebelik yaşı 24,5 idi. Gebelikte ortanca BH süresi 3,5 yıldı. Sadece bir hastanın gebelik için in vitro fertilizasyon desteği gerekti. Tüm hastalar son gebelikten önce remisyondaydı. On dört (%77,8) hastada gebelikte herhangi bir semptom görülmezken, geri kalan 3 hastada mukokutanöz ve 1 hastada vasküler aktivite mevcuttu. Canlı doğum oranı %74,1, abortus %20,7, preterm doğum %11,6, preeklampsi %5,6 olup, doğumsal fetal anomali izlenmedi.

Sonuç: Gebelikte vasküler komplikasyonlar dışında majör organ tutulumu tanımlanmadı. Sağlıklı gebeliklere kıyasla daha yüksek abortus oranları gözlemlendi. Obstetrik morbidite ve fetal sonuçlarda BH ilişkili olumsuzluk görülmedi. BH gebelik başlangıcı için bir kontrendikasyon olmayıp, gebelik öncesi hastalık aktivitesinin kontrolü, potansiyel teratojenik ajanların revizyonu ve olası komplikasyonlar açısından hastaların sık takibi riskleri en aza indirmek için önemlidir.

Anahtar Kelimeler: Behçet hastalığı, gebelik, fetal morbidite, gebelik morbiditesi

Abstract

Objective: Behçet's disease (BD) is a multisystemic vasculitis affecting both gender and usually diagnosed in reproductive age. In this study, we aimed to investigate the relation between BD and pregnancy on the both maternal and fetal aspects.

Methods: In this retrospective, single-center, descriptive study we analysed total 61 pregnancies of 18 BD patients. Clinical and demographic data were obtained from patients records regarding maternal age, disease histroy, obstetric history, pregnancy outcome and both maternal and fetal complicaitons. To prevent recall bias, only the recent pregnancy of each patient were evaluated for disease activity and use or revision of medicaitons during pregnancy.

Results: The median age of the patients at diagnosis was 25 and first pregnancy age was 24.5 years. The median duration of BD during pregnancy was 3.5 years. Only one patient needed to in vitro fertilization to become pregnant. All patients were in remission before recent pregnancy. Fourteen (77.8%) patients had no symptoms during recent pregnancy, while remaining 3 patients had mucocutaneous and 1 patient had vascular activity. The rate of live birth was 74.1%, abortus was 20.7%, preterm labor was 11.6%, pre-eclampsia was 5.6%, and no congenital fetal abnormality was observed.

Conclusion: Except for vascular complications, no major organ involvement was described during pregnancy. Higher miscarriage rates were observed compared the healthy pregnancyies. Obstetric complications were not increased and fetal outcomes were not negatively affected by BD. BD is not a contraindication for the onset of pregnancy but control of disease activity before pregnancy, revision of potentially teratogenic agents, and frequent follow-up of patients in view of potential complicaitons are important to minimize risks.

Keywords: Behçet's disease, pregnancy, maternal morbidity, obstetric complications

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Giriş

Behçet hastalığı (BH), kronik, multisistemik bir vaskülittir. Tipik triad tekrarlayan oral aft (TOA), genital ülser (GÜ) ve üveit olsa da; eklem, her çap ve tipte vasküler, pulmoner, gastrointestinal ve santral sinir sistemi tutulumu da görülebilir. Organ tutulumları morbidite ve mortalitede temel belirleyicilerdir.[1] Erkek hastalarda özellikle genç yaş grubunda vasküler, pulmoner, nörolojik tutulum daha sıkken, eritema nodozum gibi mukokutanöz bulgular kadınlarda daha sık bildirilmiştir.[2] Morbidite ve mortalite belirleyicisi klinik bulgular erkek bireylerde daha sık olduğundan BH'nin erkek predominan bir hastalık olduğu düşünülse de prevalans olarak kadın ve erkek sıklığı eşittir.[2]

Literatürde, BH olanlarda BH ilişkili klinik bulguların ve gebelik seyrinin olumsuz olmadığına dair veriler olsa da,[3-5] gebelik sürecinin BH olanlarda daha olumsuz seyrettiği ve çeşitli obstetrik patoloji ve komplikasyonlarda artış olabileceğine dair veriler de mevcuttur.[6,7]

Bu çalışmada, üçüncü basamak bir romatoloji kliniğinde 2,5 yıllık süre içerinde BH tanısı ile takip edilirken en az bir gebelik saptanan hastalarda gebelik süreci ve sonuçları retrospektif olarak incelenmiştir.

Gereç ve Yöntem

Kliniğimizde 01.06.2020 ve 28.02.2023 tarihleri arasında Uluslararası Çalışma Grubu Kriterlerine[8] göre BH tanısı alarak takip edilirken en az bir gebelik süreci saptanan, gebelik süreci tamamlanmış ya da halen gebeliği devam eden hastaların dosyası retrospektif olarak incelendi. Demografik, klinik ve obstetrik verileri standart veri formu kullanılarak kaydedildi. Hastaların tanı ve gebelik yaşları, gebelik öncesi hastalık süreleri, klinik bulguları, aldıkları tedaviler, obstetrik geçmişleri, gebelik sürecinde görülen klinik bulgular, gebelik öncesi ve sırasındaki tedavi değişiklikleri, obstetrik ve fetal komplikasyonlar ve gebelik sonuçları incelendi. Tekrar veri olmaması ve hatırlama hatalarından kaçınmak için gebelik sürecinde görülen klinik bulgular, tedavide kullanılan ajanlar ve tedavi revizyonları sadece son gebelik verisi üzerinden analiz edildi. Yetersiz verisi olan hastalar çalışma dışında bırakıldı.

Sadece hasta grubu verisi tanımlandığından, nicel veriler için medyan ve aralık değerler ve nitel değişkenler için de sıklık verildi. Çalışma protokolü Marmara Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır (no: 404, tarih: 03.03.2023).

Bulgular

Takibimiz sırasında en az 1 gebelik tespit edilen ve medyan yaşı 30 yıl (26-43) olan 18 hastanın toplam 61 gebeliğine ait verisi analiz edildi. Hastaların medyan semptom başlangıç yaşı 23 (9-36), medyan tanı yaşı 25 (9-43) ve medyan ilk gebelik yaşı 24,5 (23-27) yıl olarak saptandı. Son gebelikte medyan hastalık süresi 3,5 (0-22) yıldı. Beş hastanın ailesinde en az 1 Behçet hastası olduğu öğrenildi. Hastaların komorbiditeleri; 1 hastada sistemik lupus eritamatozus, gestasyonel hipertansiyon ve epilepsi; 1 hastada geçirilmiş akut romatizmal ateş; 1 hastada hipotiroidi; 1 hastada gluten enteropatisi, tip 1 diabetes mellitus, hipotiroidiydi. Hiçbir hastada gestasyonel diabetes mellitus saptanmamıştı. Mükerrer abortusu olan hastalarda yapılan karyotip analizlerinde patoloji saptanan hastamız yoktur. Ek trombofili gibi abortus riskini artıran predispozan faktörü olan hastamız yoktur. Yalnız bir hastada yardımcı üreme teknikleri (in vitro fertilizasyon) sonrası gebelik sağlanabilmişken, 17 hastada spontan gebelik öyküsü vardı.

Hastaların tümü gebelik öncesinde klinik ve laboratuvar olarak remisyon halindeydi. Tüm hastalık süresince ve son gebelik esnasında saptanan klinik bulgular Tablo 1'de verilmiş olup, 1 hastada görülen alt ekstremite derin ven trombozu dışında gebelik süresinde majör organ tutulumu gelişen hasta saptanmadı.

Tablo 1. Hastaların tüm takipleri ve gebelikleri sırasında saptanan klinik bulguları

Klinik bulgular (n=18)	Tüm takipte n, (%)	Son gebelik sırasında n, (%)
Oral aft	18 (100)	1 (5,6)
Genital ülser	11 (61,1)	2 (11,1)
Artralji	8 (44,4)	1 (5,6)
Artrit	4 (22,2)	0
Akneiform lezyon/folikülit	5 (27,8)	0
Eritema nodozum	10/18 (55,6)	2 (11,1)
Oküler tutulum	4 (22,2)	0
Derin ven trombozu	1 (5,6)	1 (5,6)
Pulmoner tutulum	0	0
Parankimal nörobehçet	0	0
Dural sinüs trombozu	1 (5,6)	0

Hiçbir hasta teratojen bir ilaç altında plansız gebelik ile başvurmazken, hastaların tüm takipleri ve gebelik öncesi son vizit sırasında aldıkları tedaviler Tablo 2'de verilmiştir. Gebelik öncesi son vizitte kortikosteroid (KS) alan 6 hastanın 3'ü metilprednizolon, 3'ü prednizolon oral tablet almaktaydı. Gebelik planı veya son gebelik sırasında ilaç değişimi 6 hastada gözlendi. Dört hasta kolşisin ve 1 hasta metilprednizolon tedavisini kendisi keserken, 1 hasta kolşisin dozunu günde 3 tabletten 1 tablete indirmişti. Sekiz hasta (%44,4) gebelik öncesi son vizitte ve gebelik süresince kolşisin veya immünosupresif (IS) ilaç olmadan izlenmiştir. Kadın hastalıkları ve doğum tarafından yalnızca azatiopürin (AZA) ve KS alan 1 hastada tedavi kesilmesi için konsültasyon istenmiş ancak majör organ tutulumu (üveit ve dural sinüs trombozu) olduğundan tedavi devam ettirilmiştir.

Toplam 61 gebeliğin 3'ü devam ederken, tamamlanmış 58 gebeliğin 43'ü canlı doğumla (%74,1) sonuçlanmıştır. Preterm doğum (37. gestasyonel hafta ve öncesindeki doğumlar), 4 hastada toplam 5 gebelikte olmak üzere; canlı sonlanan gebelerde %11,6, tüm tamamlanan gebeliklerde %8,6 sıklıkta saptanmıştır. Bu hastaların biri gebelik boyunca tedavisiz izlenmişken, üçü kolşisin altında izlenmiştir. Bir hastada gebelik sırasında eritema nodozum ile alevlenme izlenirken, diğer üç hastanın gebelik sırasında klinik bulgusu olmamıştır. Tedavi altında olan ya da olmayan gebeliklerin sonucunda perinatal mortalite veya konjenital anomali izlenmemiştir. Diğer maternal ve fetal komplikasyonlar ve detaylı obstetrik öykü Tablo 3'de verilmiştir.

BH'ye ilaveten sistemik lupus eritematozis tanısı olan bir hastamızın eşlik eden antifosfolipid sendromu için uygun aralıkta üç kez anti-kardiyolipin ve anti-beta 2 glikoprotein immünoglobulin (Ig)M ve IgG ve lupus antikoagülanı içeren antikor paneli taranmış ve negatif saptanmıştır. Bu hastanın toplam 8 gebeliğinin, 5'i abortus, 2'si C/S ile canlı doğum ve 1'i çalışma yapıldığı sırada yürüyen gebelik şeklindedir. Abortusu olan hastaların karyotip analizi yapılanlarda veya trombofili paneli bakılanlarında abortusa yönelik ek risk faktörü saptanmamıştır.

En az 1 abortus öyküsü olan hasta sayısı 8 iken 10 hastamızın abortus öyküsü alınmamıştır. Abortusu olan ve olmayan hastaların yaşları, ilk gebelik yaşları, hastalık süreleri, ailede BH olan birey varlığı benzer saptanmıştır. Gebelik sırasında aktivite için değerlendirildiğinde abortusu olan hastaların birinde EN ile, birinde TOA, GÜ ve artralji ile mukokutan ve birinde derin ven trombozu ile vasküler aktivite saptanmışken; abortusu olmayan hastaların birinde mukokutan aktivite olmuştur. Abortusu olan hastaların 5/8'i (%67,5) gebelik öncesi kolşisin alırken, abortusu olmayan hastaların hiçbiri gebelik öncesi kolşisin almamıştır (p<0,001). Gebelik öncesi son vizitte AZA ve kortikosteroid kullanımı ise benzer bulunmuştur.

Tartışma

BH'nin özellikle puberte ve sonrası döneminde oral aft başta olmak üzere mukokutanöz bulgularla başladığı ve genellikle beşinci dekattan sonra remisyona girme eğilimi gösterdiği düşünülürse, etkilenen kadın hasta gurubunun fertil çağ kadınlardan oluştuğu görülmektedir. Bu hastaların tedavisinde başta kolşisin, KS ve AZA olmak üzere pek çok IS ve immünmodulatuvar ajan kullanılmaktadır. Bunların birçoğu için gebelik ve laktasyon dönemine ait güvenlik ve kullanım datası olsa da her olgu bazında tekrar Romatoloji ve Jinekoloji branşları arasında konsültasyonlarla sonuçlanan bir süreç ve hasta takibinde kaygılar görülmektedir.[9] Bunun yanı sıra, majör organ tutulumu olan hastalarda siklofosfamid (CYC) gibi gebelik sürecinden kullanımı uygun olmayan birçok ilaç da bu süreçte kullanıldığından fertilizasyonun korunması ve plansız gebeliklerin önlenmesi, gebelik saptanırsa yakın takibi önemli hususlardır.

Hastalık aktivitesine etki edebilecek hastalık süresi, tanı ve ilk gebelik yaşı önceki çalışmalarda sırasıyla 3-7 yıl, 21-26 yıl ve 25-26 yıl olarak bildirilmiş olup bulgularımıza benzerdir.[4,10,11] Çalışmamızda BH olanlarda klinik alevlenme, maternal morbidite veya fetal komplikasyonlar için artmış bir risk gözlenmemiştir.[11] Alevlenme sıklığı önceki çalışmalarda ise %2'den %70'e kadar değişken

Tablo 2. Hastaların tüm takipleri ve gebelik öncesi son vizitleri sırasında aldıkları tedaviler

Tedavi (n=18)	Tüm takipte n, (%)	Son gebelik öncesi son vizit n, (%)
Kolşisin veya immünosupresif almayan	0	8 (44,4)
Kolşisin	17 (94,5)	5 (27,8)
Azatiopürin	6 (33,3)	5 (27,8)
Kortikosteroid	8 (44,4)	6 (33,3)
İnfliximab	1 (5,6)	1 (5,6)
Adalimumab	1 (5,6)	0
Asetilsalisilik asit	4 (22,2)	3 (16,7)
DMAH	2 (11,1)	2 (11,1)
Warfarin	1 (5,6)	0

DMAH: Düşük molekül ağırlıklı heparin

sıklıkta bildirilmiş olup, bazı çalışmalarda aktif hastaların remisyona girdiği ve hastalık seyrinin iyileştiği de bildirilmiş olup, gebelik sırasındaki seyir verisi tartışmalıdır.[5,7,10-14] Büyük meta-analizlerde de, gebelikte görülen bulguların sıklıkla TOA, GÜ, EN şeklinde mukokutanöz alevlenmeler olduğu ve kolaylıkla kontrol edilebildiği gösterilmiştir.[3,5,11,15] Vasküler komplikasyonlar ve vasküler alevlenme BH grubunda en önemli organ tutulumlardan biri olup gebelik döneminde birçok bulguda stabil gidiş veya iyileşme olurken vasküler komplikasyonlar en önemli morbidite nedeni olarak bildirilmiştir.[6,10,16] Çalışmamızda da tek majör organ alevlenmesi derin ven trombozu gelişen bir hastamızda saptanmıştır.

Obstetrik öykü çalışmamızda önceki kohort analizleri ile benzer olup canlı doğum hemen her çalışmada %70-75 civarında bildirilmiştir.[4,6,11] Gebelik seyrinde en önemli obstetrik komplikasyonlar ve fetal olumsuz sonuçlar; artmış abortus, büyüme gelişme geriliği ve sezaryen oranı olarak gösterilmiştir.[6]

Çalışmamıza benzer şekilde, abortus ve sezaryen sıklığında artış daha önceki çalışmalarda da BH grubunda sağlıklı gebelere göre yüksek bulunmuştur.[6,16] Barros ve ark.[11] sağlıklı gebeler ve BH olan gebeleri karşılaştırdıkları çalışmalarında, BH grubunda %24,5 oranında ve sağlıklı gebelere göre daha yüksek abortus sıklığı gözlemiştir. Sezaryen sıklığı çalışmamızda %51,2 olarak saptanırken, literatürde de %40-45 civarında ve sağlıklı gebelere göre yüksek bulunmuştur.[11,16]

Preterm doğum konusunda veriler çelişkili olup, çalışmamızda canlı sonlanan gebelerde %11,6, tüm tamamlanan gebeliklerde %8,6 sıklıkta saptanmıştır. Önceki çalışmalarda BH grubunda Orgul ve ark.[4] %24 ve Lee ve ark.[16] %12,5 sıklıkta ve sağlıklı grupta %7-8 sıklıktaki preterm doğumda artış bildirirken, Barros ve ark.[11] sağlıklı toplumla benzer sıklıkta %9.2'lik bir preterm doğum sıklığı bildirmiştir. Orgul ve ark.[4] preterm doğum olan 12 hastanın 5'inde (%46,7) kolşisin altında gebelik tamamlandığını bildirmiştir.

Preeklampsi sıklığı çalışmamızda literatürle benzer sıklıkta saptanmış olup, literatürde de sağlıklı bireylere göre BH grubunda artış göstermediği bildirilmiştir.[11,16] BH'nin perinatal mortalite ve konjenital fetal anomaliler için bir risk teşkil ettiğine dair bulgu gösterilmemiştir.[10,16]

Tablo 3. Hastaların obstetrik geçmişi, maternal ve fetal komplikasyonlar

Toplam gebelik, (n, %)*	**61**
Devam eden gebelik	3
Toplam canlı doğum	43/58 (74,1)
Normal vajinal doğum	21 (48,8)
Sezaryen	22 (51,2)
Abortus	12/58 (20,7)
Küretaj	1/58 (1,7)
Ektopik gebelik	2/58 (3,5)
In vitro fertilizasyon	1/18 (5,6)
Çoklu gebelik	16/18 (88,9)
Doğum haftası, medyan (aralık)	39 (33-41)
Maternal komplikasyonlar, n (%)**	
Düşük tehditi	3/18 (16.7)
20. gestasyonel hafta öncesi kanama	2/18 (11,1)
Plasenta abruptia	0
Plasenta previa	1/18 (5,6)
Preeklampsi	1/18 (5,6)
Over torsiyonu	1/18 (5,6)
Fetal komplikasyonlar, n (%) ***	
Preterm doğum	5/43 (11,6)
Oligohidramniyoz	2/43 (4,7)
Polihidramniyoz	1/43 (2,3)
Fetal şilotoraks	1/43 (2,3)
Fetal distress	1/43 (2,3)
Konjenital anomali	0
Perinatal mortalite	0

**Sonlanan gebelikler üzerinden hesaplama yapılmıştır.*

***Tekrarlayan gebeliklerde preeklampsi ve düşük tehditi tekrarladığından hasta sayısı üzerinden hesaplanmıştır.*

***Canlı doğumlar üzerinden komplikasyonlar hesaplanmıştır*

BH ilişkili kontrolsüz enflamasyon, özellikle gebeliğin de etkisi ile artacak trombotik vasküler komplikasyonlar gebelik süresince morbidite ve mortalite için esas riski teşkil etmekte olduğundan etkin tedavi önemlidir.[7,17] Kolşisin, AZA, siklosporin ve infliksimab gibi ilaçlar gebelik döneminde güvenle kullanılabileceği gösterilen ajanlarken, metotreksat, mikofenolat mofetil, talidomid, CYC kaçınılması ve gebelik planı olduğunda uygun süre önceden kesilmesi gereken ajanlardır.[3,9] Gebelik sırası ve postpartum dönemde de tromboembolik olayların önlenmesi ile tedavisinde düşük molekül ağırlıklı heparin en sık, en güvenle seçilen ajan olup çalışmamızda da bu endikasyon varlığında seçilen ajan olarak saptanmış, warfarin teratojenik olduğundan gebelik planı olan hiçbir hastada kullanılmamıştır. Gebelik sırasında %44,4 hastamız tedavisiz izlenmişken, bu oran önceki bir çalışmalarda da %30-89 olarak bildirilmiştir.[4,10,11]

Çalışmanın Kısıtlılıkları

Çalışmanın kısıtlılıkları, retrospektif dizaynı, sağlıklı veya hasta kontrol grubunun bulunmaması, hasta sayısının azlığı ve tek merkez verisiyle sınırlı olmasıdır. Gebeliklerin planlı olması ve hasta beyanlarının hatırlama usulü olması birer yanlılık nedeni olmuş olabilir. Kohortumuzda vasküler trombozu ve gebelik öyküsü tek hastamızın olması bu datanın yorumlanabilirliğini sınırlandırmaktadır.

Sonuç

Sonuç olarak çalışmamızda BH'nin gebeliğe bir engel teşkil etmediği ve gebelik sırasında klinik bulgularda gebeliğin de ayrıca yatkınlık oluşturduğu derin ven trombozu gibi vasküler hadiseler dışında ciddi bir alevlenme beklenmediği gözlenmiştir. Ancak hastaların gebelik öncesi teratojenik ilaçlar açısından tedavi revizyonu için değerlendirilmesi, mümkünse remisyon döneminde gebelik planı yapılması, gebe hastaların sık ve yakın izlemi; hem maternal hem fetal riskleri azaltmak açısından önemli görünmektedir.

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Hypogammaglobulinemia and severe infection risk in patients with autoimmune diseases during rituximab treatment

Otoimmün hastalığı olan hastalarda rituksimab tedavisi sırasında hipogamaglobulinemi ve enfeksiyon riski

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Abstract

Objective: To assess the frequency and related factors of hypogammaglobulinemia (HGG) and severe infections in patients who received rituximab (RTX) for rheumatic diseases during routine follow-up.

Methods: Patients who were followed in Marmara University Rheumatology Clinic and received RTX are evaluated retrospectively. The immunoglobulin (Ig) G, IgM, IgA levels and clinical manifestations were obtained from patient files. The HGG frequency and related factors were assessed. Severe infections were also analysed.

Results: A total of 144 patients were included (F/M: 105/39, mean age 52.8±13.8). In the majority of the patients (67%) the diagnosis was rheumatoid arthritis (RA). At least one subgroup of HGG was observed in 30% (43/144) of the patients. During follow-up 17 (11.8%) patients had low IgG, 37 (26%) low IgM, and 7 (4%) had low IgA levels. HGG rate was similar between RA, connective tissue diseases and anti-neutrophil cytoplasmic antibody associated vasculitis patients (25%, 30%, 47%, respectively, p=0.13). HGG was more frequent in men (p=0.028), in patients with higher accumulated RTX dose (p=0.006) and with hypertension (p=0.033). Concomitant use of disease-modifying anti-rheumatic drugs, glucocorticoid use and prior cyclophosphamide was not associated with higher HGG. Methotrexate use with RTX was a protective factor for HGG (HGG rate methotrexate + vs -: 12% vs 33%, p=0.032). Two patients with HGG (5%) received intravenous immunoglobulin replacement. Twenty-seven patients (18%) had severe infections. Lower IgG levels [IgG levels odds rato (OR)

Öz

Amaç: Bu çalışmanın amacı rutin takip sırasında romatizmal hastalığı için rituksimab (RTX) alan hastalarda hipogamaglobulinemi (HGG) ve ciddi enfeksiyon sıklığı ve ilişkili faktörleri değerlendirmektir.

Yöntem: Marmara Üniversitesi Romatoloji Kliniği'nde takip edilen ve RTX tedavisi alan hastalar retrospektif olarak değerlendirildi. İmmünoglobulin (Ig) G, IgM, IgA seviyeleri ve klinik bulgular hasta dosyalarından elde edildi. HGG sıklığı ve ilişkili faktörler değerlendirildi. Ciddi enfeksiyonlar da ayrıca analiz edildi.

Bulgular: Çalışmaya toplam 144 hasta dahil edildi (K/E: 105/39, ortalama yaş 52,8±13,8). Hastaların çoğunluğunda (%67) tanı romatoid artrit (RA) idi. Herhangi bir subgrup HGG %30 (43/144) hastada gözlendi. İzlem sırasında 17 (%11,8) hasta düşük IgG, 37 (%26) hasta düşük IgM, 7 (%4) hasta ise düşük IgA seviyelerine sahipti. RA, bağ doku hastalıkları ve anti-nötrofil sitoplazmik antikor ilişkili vaskülitlerde HGG oranı benzerdi (sırasıyla %25, %30, %47, p=0,13). HGG erkeklerde (p=0,028), kümülatif RTX dozu yüksek olan hastalarda (p=0,006) ve hipertansiyonu olan hastalarda (p=0,033) daha sık idi. Eşlik eden hastalık modifiye edici anti-romatizmal ilaç kullanımı, glukokortikoid ve siklofosfamid kullanım öyküsü HGG ile ilişkili değildi. RTX ile metotreksat kullanımı HGG gelişimi için koruyucu bir faktördü (HGG oranı metotreksat +vs -: %12 vs %33, p=0,032). HGG gelişen 2 (%5) hastaya intravenöz immünoglobulin verildi. Yirmi yedi (%18) hastada ciddi enfeksiyon geliştiği görüldü. Çok değişkenli analizde düşük IgG seviyeleri [IgG düzeyi risk oranı (RO) (%95 güven aralığı [GA]) 0,82 (0,70-0,96), p=0,018] ve kronik akciğer hastalığı (KAH)

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(95% confidence interval [CI]) 0.82 (0.70-0.96), p=0.018] and chronic lung disease (CLD) [CLD present OR (95% CI) 3.7 (1.2-10.8), p=0.017] were associated with severe infections in multivariate analysis. A total of 38 patients died during follow-up. Mortality was more frequent in patients with HGG [mortality rate HGG+ vs HGG -: 40% (17/43) vs 21% (20/101), p=0.02].

Conclusion: While male gender, increased number of RTX courses and hypertension were found to be risk factors for HGG, CLD and lower IgG levels were associated with severe infections. Therefore, measuring Ig levels and assessing risk factors for HGG and severe infections during RTX treatment may provide information to prevent both conditions.

Keywords: Rituximab, hypogammaglobulinemia, severe infection, rheumatic diseases

[KAHv arlığı RO (%95 GA) 3,7 (1,2-10,8), p=0,017] ciddi enfeksiyonda artış ile ilişkili idi. İzlem sırasında 38 hastada ölüm görüldü. Mortalite HGG gelişen hastalarda daha sık idi [mortalite oranı HGG+ vs HGG -: %40 (17/43) vs %21 (20/101), p=0,02].

Sonuç: Erkek cinsiyet, RTX doz artışı ve hipertansiyon HGG için risk faktörü iken, kronik akciğer hastalığı ve düşük IgG düzeyi ciddi enfeksiyon ile ilişkiliydi. Bu nedenle RTX tedavisi sırasında Ig düzeylerinin ölçümü ve HGG ve ciddi enfeksiyon için risk faktörlerinin değerlendirilmesi her iki durumun önlenmesinde yarar sağlayabilir.

Anahtar Kelimeler: Rituksimab, hipogamaglobulinemi, ciddi enfeksiyon, romatolojik hastalıklar

Introduction

Rituximab (RTX) which targets CD20 expressing B-cells, is indicated in a wide spectrum of diseases such as rheumatoid arthritis (RA) and anti-neutrophil cytoplasmic antibody associated vasculitis (AAV). In addition, RTX is used in the treatment of other rheumatic diseases including systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) which are resistant to multiple other treatment options.[1-5]

The development of hypogammaglobulinemia (HGG) has been reported after repeated doses of RTX and being explored increasingly.[6] However, this effect is expected to be temporary since stem cells are not targeted.[7] Although B cell depletion is expected to last for 6-9 months after RTX infusion, it has been reported that this period may be longer in some of the patients.[8] HGG duration was prolonged to 18-24 months in patients receiving additional chemotherapy due to malignancy.[9] In a review evaluating HGG and infection risk in patients receiving RTX, malignancy, pre-treatment low immunoglobulin (Ig) levels, cumulative RTX dose, baseline Ig levels and concomitant use of immunosuppressives such as mycophenolate mofetil (MMF) or purine analogues were found to increase the risk of HGG.[10]

There are conflicting data in the literature regarding the development of serious infections due to RTX treatment and RTX related HGG.[3,8,11,12] Although RTX seems safe in initial studies, subsequent studies have shown that RTX may increase the risk of severe infections.[8] Especially low IgG levels were reported to be associated with increased serious infections.[4,13] Older age, the number of RTX courses, prolonged low IgG levels, granulocyte colony-stimulating factor use, chronic lung disease (CLD), cardiac insufficiency and extra-articular involvement in RA patients were other risk factors for infections in patients under treatment with RTX.[10]

In this study we aimed to assess HGG, severe infection rates and related factors in patients receiving RTX treatment.

Materials and Methods

Consecutive patients who were followed in Marmara University Rheumatology Clinic and received RTX therapy between October 2016 and January 2019 were involved in this retrospective cohort study. The study was approved by the local Ethics Committee (no: 09.2023.1332). All patients received at least one course of RTX. Patients who did not complete at least 1 course of RTX treatment were excluded from the study. In routine practice, RTX was administered as 1.000 mg on 1st and 14th days every 6 months, unless lower doses deemed appropriate.

IgG, IgA, and IgM levels which were tested during routine follow-up. Ig levels were measured 6 months after the previous RTX dose and before the next infusion. Normal ranges were 6.5-16 g/L for IgG, 0.4-3.5 g/L for IgA and 0.5-3 g/L for IgM g/L based on our local laboratory cut-off values. In addition, IgG levels between 5-6.5 g/L was defined as mild, 3-5 g/L as moderate, <3 g/L as severe HGG.[14] Severe infection was defined as infection requiring parenteral antibiotic therapy or hospitalization.[3]

Additional data including age, gender, disease duration, comorbidities, previous cyclophosphamide (CyC) and concomitant immunosuppressive use, concomitant glucocorticoid (GC) use and cumulative RTX dose were recorded from patient files.

Statistical Analysis

SPSS statistics 22 was used for the statistical analysis. Dichotomous variables were expressed as number and frequencies. The continuous variables were expressed as mean ± standard deviation (SD) in case of normal distribution. In non-normal distribution median (25-75

percentile) was presented. Chi-square, Mann-Whitney U and Kruskal-Wallis tests were used to compare the data. A p-value <0.05 was considered statistically significant. Binary logistic regression was performed to assess the predictive factors for HGG and severe infections. HGG and severe infection were dependent variables for separate logistic regression analysis. Age, gender, disease duration, cumulative RTX dose, comorbidities, concomitant DMARDs, GC were used as covariates. Low IgG, IgM, IgA levels were additional covariates for the logistic regression analysis of severe infections. Variables with a p-value of <0.2 in univariable analysis were involved in multivariable analysis.

Results

One hundred and forty-four (105 female, 39 male) patients were included in the study. Mean (± SD) follow-up duration under RTX treatment was 3.4 (2.3) years. The diagnosis was RA in 96 (67%), AAV in 21 (15%), SLE in 15 (10%), scleroderma (SSc) in 6 (4%), primary SS in 3 (2%) and polyarteritis nodosa in 2 (1%) patients. Two patients with RA had secondary SS and 2 SLE patients had secondary antiphospholipid syndrome. Table 1 shows demographic and clinical characteristics of the patients.

A total of 198 visits (number of the patients with one visit 144, two visits 43, three visits 11) were evaluated. During the follow-up, 43 (30%) patients had any subgroup of HGG. Thirteen (9%) patients had at least two subgroups of low Ig and 4 (2.8%) patients had HGG in all three subgroups. Low IgG levels were observed in 17 (11.8%), low IgM in 37 (26%), low IgA in 7 (4%) patients at any time of the follow-up. In most of the patients with low IgG the HGG was mild (13/17, 77%) (Table 2). Between RA, connective tissue diseases (CTD) (SLE, SSc and PSS were included in this group) and AAV groups, there were no difference in terms of HGG frequency (25%, 30%, 47%, respectively, p=0.13) and severe infections (16%, 18%, 29% respectively, p=0.42).

Among the 43 patients who had recurrent Ig measurements, low levels of IgG persisted in 67% (4/6) patients. The remaining 2 patients had IgG levels <7 g/L but in the normal range. In 70% (12/17) of the patients with low IgM and 33% (1/3) patients with low IgA, the HGG persisted during follow-up. The follow-up IgM levels were median 0.53 (0.42-0.56) g/L and the IgA levels were 0.62 and 1.11 g/L in the patients who had HGG in one visit and did not persist in the follow-up visits.

HGG was more frequent in male patients (M vs F: 44% vs 25%, p=0.028). Similar HGG rates were found between patients with and without concomitant azathioprine (p=0.08), leflunomide (p=0.74), MMF (p=0.25), hydroxychloroquine

Table 1. Demographic and clinical characteristics of the patients who received rituximab treatment

Diagnosis, n (%)	
Rheumatoid arthritis	96 (67)
ANCA associated vasculitis	21 (15)
Systemic lupus erythematosus	15 (10)
Scleroderma	6 (4)
Primary Sjögren syndrome	3 (2)
Poliarteritis nodosa	2 (1)
Age, years, mean ± SD	52.8±13.8
Gender, female, n (%)	105 (71)
Comorbidities, n (%)	
Diabetes	24 (17)
Hypertension	45 (32)
Chronic kidney disease	13 (9)
Chronic obstructive lung disease	12 (9)
Coronary artery disease	20 (15)
Asthma	9 (7)
Lung involvement of the rheumatological disease	3 (2)
Disease duration, years, mean ± SD	
Rheumatoid arthritis	15.9±8.7
ANCA associated vasculitis	3.9±4.4
Systemic lupus erythematosus	5.3±3.4
Scleroderma	8.1±5.6
Primary Sjögren syndrome	7.5±0.7
Poliarteritis nodosa	*
Prior cyclophosphamide, n (%)	10 (7)
Concomitant hydroxychloroquine use, n (%)	17 (12)
Concomitant csDMARD use, n (%)	
Azathioprine	14 (10)
Leflunamide	54 (38)
Methotrexate	25 (17)
Mycophenolate mofetil	3 (2)
Concomitant GC use, present, n (%)	71 (50)
Cumulative rituximab dose, g, mean ± SD	11.5±7.6
Ig levels, mean ± SD, g/L	
IgG	10.53±3.99
IgM	0.79±0.62
IgA	2.06±1.24
Severe infection, present, n (%)	27 (18%)

**Disease duration for the patients diagnosed with PAN was 4 and 6 years, ANCA: Anti-neutrophil cytoplasmic antibody, csDMARD: Conventional synthetic disease-modifying antirheumatic drug, GC: Glucocorticoid, Ig: Immunoglobulin, PAN: Polyarteritis nodosa, SD: Standard deviation*

Table 2. The frequency of hypogammaglobulinemia during follow-up

Any subgroup of hypogammaglobulinemia, n (%)	43 (30)
Low IgG, n (%)	17 (12)
Mild	13 (77)
Moderate	3 (18)
Severe	1 (6)
Low IgM, n (%)	37 (26)
Low IgA, n (%)	7 (4)

Ig: Immunoglobulin

(p=0.52) and GC (p=0.37) use and prior CyC (p=0.46) treatment. HGG was less frequent in patients who were using concomitant methotrexate (MTX) (HGG rate MTX +vs -: 12% vs 33%, p=0.032). Age (p=0.20) and disease duration (0.37) were similar between patients with and without HGG. Higher RTX dose (RTX dose HGG + vs - : 13.6±8.3 vs 9.6±6.8 g, p=0.006) and presence of hypertension (HT) (HT present in HGG+ vs-: 44% vs 26%, p=0.033) were associated with HGG (Table 3). In multivariate logistic reression analysis, male gender [odds ratio (OR) (95% confidence interval [CI]) 2.39 (1.01-5.68), p=0.047], HT [OR (95% CI) 2.68 (1.15-6.22), p=0.021], higher cumulative RTX dose [OR (95% CI): 1.08 (1.02-1.14), p=0.005] and not using MTX [MTX use OR (95% CI) 0.18 (0.04-0.73), p=0.016] were related to more frequent HGG (Table 4). RTX treatment was discontinued in 2 of the patients with HGG and intravenous Ig (IVIG) replacement was used. In one patient with SLE, IVIG was given for autoimmune hemolytic anemia in addition to RTX treatment. A total of 38 patients died during follow-up. Mortality was more frequent in patients with HGG [mortality rate HGG+ vs HGG -: 40% (17/43) vs 21% (20/101), p=0.02].

Twenty-seven (18%) patients had severe infections during follow-up. In most of the severe infections (19/27 patients, 70%) the source of the infection was respiratory tract. Three (11%) of the patients had urinary tract infections, 3 (11%) patients had an infection related to joint prothesis, 1 (4%) patient had cholecystitis and 1 (4%) patient had dental abscess. The increased cumulative RTX doses (p=0.04), presence of CLD (p=0.03) and lower IgG levels (p=0.03) were related to severe infections in univariate analysis. Age (p=0.73), disease duration (p=0.41), IgM (p=0.46) and IgA

Table 3. The features of patients who had and did not have hypogammaglobulinemia

	HGG present n=43	HGG absent n=101	p
Age, years, mean ± SD	55.2±12.7	51.2±14.4	0.20
Male gender, n (%)	17 (44)	22 (25)	**0.028**
Disease duration, years, mean ± SD	11.2±8.5	12.7±9.1	0.37
RTX cumulative dose, g, mean ± SD	13.6±8.3	9.6±6.8	**0.006**
Comorbidities, n (%)			
Diabetes	6 (14)	18 (18)	0.54
Hypertension	19 (44)	26 (26)	**0.033**
Coronary artery disease	4 (9)	15 (15)	0.34
Chronic lung disease	10 (23)	13 (13)	0.12
Renal disease	3 (7)	12 (12)	0.36
Prior CyC, n (%)	4 (9)	6 (6)	0.46
Concomitant DMARDs, n (%)			
Azathioprine	7 (16)	7 (7)	0.08
Leflunomide	17 (39)	37 (37)	0.74
Methotrexate	3 (7)	22 (22)	**0.032**
Mycophenolate mofetil	0 (0)	3 (3)	0.25
Hydroxychloroquine	4 (9)	13 (13)	0.52
Concomitant GC use, present, n (%)	16 (37)	46 (46)	0.37

CyC: Cyclophosphamide, DMARD: Disease modifying anti-rheumatic drugs, GC: Glucocorticoid, HGG: Hypogammaglobulinemia, RTX: Rituximab, SD: Standard deviation

Table 4. The multivariate analysis for the risk factors of hypogammaglobulinemia and severe infection

Variable	OR (95% CI)	p
Hypogammaglobulinemia		
RTX dose, g	1.08 (1.02-1.14)	**0.005**
Hypertension	2.68 (1.15-6.22)	**0.021**
Male gender	2.39 (1.01-5.68)	**0.047**
MTX use	0.18 (0.04-073)	**0.016**
Severe infections		
RTX dose, g	1.03 (0.98-1.09)	0.20
IgG levels, g/L	0.82 (0.70-0.96)	**0.018**
Lung disease	3.70 (1.27-10.82)	**0.017**

CI: Confidence interval, Ig: Immunoglobulin, MTX: Methotrexate, OR: Odds ratio, RTX: Rituximab

(p=0.52) levels were not associated with severe infections (Table 5). Multivariate logistic regression analysis showed that lower IgG levels [IgG levels OR (95% CI) 0.82 (0.70-0.96), p=0.018] and CLD [CLD present OR (95% CI) 3.7 (1.2-10.8), p=0.017] were associated with increased severe infections. The cumulative RTX dose did not differ significantly between the patients with and without severe infections in multivariate analysis [OR (95% CI) 1.03 (0.98-1.09), p=0.20] (Table 4).

Discussion

In the current study any subgroup of HGG occurred in 30% of the patients with systemic autoimmune diseases receiving RTX in routine follow-up. Low IgG, IgM and IgA levels were found in 12%, 26% and 4% patients respectively. Higher RTX cumulative doses, male gender, HT and absence of concomitant MTX treatment were predictive factors for more frequent HGG. Severe infections were observed in 18% of the patients which was associated with low IgG levels and CLD.

HGG was reported in 10-56% of the patients with autoimmune diseases.[1,14-18] Factors such as the cumulative RTX dose, RTX dose regimens, the timing of the Ig measurement after RTX and cut-off values for HGG may have affected the variability of the HGG frequency in the literature. In AAV, patients who received 500 mg as maintenance dose developed HGG less frequently compared to patients who received 1000 mg.[19] In different studies the cut-off for HGG was considered as 565 mg/dL,[12] 600 mg/dL[3] or 700 mg/dL[14] for IgG. The values <55 mg/dL, <50 mg/dL, <40 mg/dL for IgM and <80 mg/dL, <70 mg/dL for IgA were evaluated as HGG in different studies.[3,12,14] In our cohort, almost one third of the patients had HGG in any subgroup of Ig during follow-up in line with the literature.

Data about the predictive factors of HGG is contradictory. Age was identified as a risk factor for RTX-related HGG and serious infections in several studies.[15,20] HGG was more frequent in female patients in a study which reported RTX associated HGG in autoimmune diseases.[21] In contrast, Besada et al.[19] found that male gender was a risk factor for severe HGG and withdrawal of RTX due to HGG.

Table 5. The comparison of the characteristics of the patients with and without severe infections

	Severe infections (+) n=27	Severe infections (-) n=117	p
Age, years, mean ± SD	57.3±10.3	50.9±14.6	0.73
Gender, female, n (%)	20 (74)	84 (72)	0.86
Disease duration, years, mean ± SD	14.8±12.6	11.5±8.1	0.41
Cumulative rituximab dose, g, mean ± SD	14.5±7.2	10.3±8.1	**0.04**
Prior CyC use, n (%)	2 (7)	8 (7)	0.92
Concomitant csDMARD use, n (%)			
Azathioprine	1 (4)	13 (11)	0.23
Leflunomide	8 (30)	46 (39)	0.33
Methotrexate	7 (26)	18 (15)	0.20
Mycophenolate mofetil	0 (0)	3 (3)	0.39
Hydroxychloroquine use, n (%)	3 (11)	14 (12)	0.90
Concomitant GC use, n (%)	10 (37)	52 (44)	0.87
Comorbidities, n (%)			
Diabetes	5 (19)	19 (16)	0.76
Hypertension	10 (37)	35 (30)	0.46
Coronary artery disease	2 (11)	17 (14)	0.32
Chronic lung disease	8 (30)	15 (13)	**0.03**
Renal disease	5 (19)	10 (8)	0.12
Hypogammaglobulinemia, n (%)			
Low IgG	6 (22)	11 (9)	0.06
Low IgM	10 (37)	27 (23)	0.11
Low IgA	2 (7)	5 (4)	0.47
Ig levels, g/L, mean ± SD			
IgG	9.9±9.6	11.5±4.6	**0.03**
IgM	1.0±0.9	0.8±0.6	0.46
IgA	1.9±0.6	2.2±1.3	0.52

csDMARD: Conventional synthetic disease-modifying antirheumatic drug, CyC: Cyclophosphamide, GC: Glucocorticoid, Ig: Immunoglobulin, SD: Standard deviation

Association of male gender with HGG in our study is consistent with the second study. Age was similar in patients with and without HGG. Stabler et al.[22] reported that diabetes and malignancy were risk factors for HGG in terms of comorbidities. Diabetes was not a predictive factor for HGG in our study, whereas HT was related. It has been shown that there is an immune activation, including B-cells, in the pathogenesis of HT.[23] However, HT has not been linked to RTX-related HGG in the studies. HT may be a result of higher cumulative GC doses which may be related to HGG development in our study. In addition, HT, which occurred because of renal involvement, may have affected the frequency of HGG.

Concomitant medications such as CyC, MMF and GC use were found to be predictors of HGG in previous studies.[15,17,24,25] Also, prior CyC was shown to increase the HGG rate.[21] In contrast, HGG was not associated with conventional disease-modifying anti-rheumatic drugs (cDMARD) or CS use in a retrospective study including 83 RA patients.[14] In our study the use of additional cDMARDs and GC did not seem to affect the HGG rate other than MTX. Interestingly, concomitant MTX therapy was associated with a reduced risk of HGG in patients who were mostly diagnosed with RA (23/25). In the literature the data about the effect of MTX on Ig levels are scarce. In a study, juvenile RA patients, who were treated with MTX, had lower Ig levels compared to patients without treatment.[26] In another study MTX was not associated with HGG in inflammatory bowel disease patients.[27] Boleto et al.[11] studied predictive factors for HGG in RA patients and reported MTX had a protective role for HGG.[28] Not using concomitant MTX was a risk factor[14] for HGG in another trial similar to our results. This may be related to the characteristics of patients receiving concomitant MTX treatment. However, this result was not well explained and this protective effect of MTX on HGG remains to be confirmed in other studies.

The diagnosis of the patient is one of the factors that may influence the development of HGG in the literature. In a study which compared HGG between AAV and SLE patients after 3-6 months after RTX administration, HGG was found more frequently in AAV patients.[15] Similarly, Thiel et al.[29] reported more frequent and long-lasting HGG in AAV patients compared to RA and CTD. Although HGG was numerically higher in the AAV group compared to RA and CTD patients, the difference was not statistically significant in our study.

HGG is not an absolute contraindication for continuing RTX therapy and may be transient in some of the patients. In a longitudinal observational study HGG was temporary in 73% of the AAV cases.[15] In contrast to this study Evangelatos et al.[14] found that HGG was persistent in all of the 37 patients with RA who developed HGG at any time of the follow-up. Consistent with the results of the latter, HGG was 65% persistent in our patients during follow-up.

In several studies higher cumulative RTX dose was shown not to increase the HGG and severe infection frequencies in RA patients.[28,30] According to our results higher cumulative RTX dose was associated with increased HGG rate but did not have a significant effect on severe infections.

The effect of HGG on severe infection rate is controversial in the literature. Although there are reports about an increase of severe infections in patients with HGG,[3,11,12] in some of the previous studies severe infection rate was similar between patients with and without HGG.[14,31-33] The risk of infection is also reported to be associated with the deficient Ig subgroup. IgG deficiency is considered to be more important in terms of infection risk compared to IgA and IgM.[34] Md Yusof et al.[3] reported that serious infection risk was increased in patients with IgG <6 g/L. In our study lower IgG levels were associated with severe infections.

Severe infection rate was reported 20-40% of the patients on RTX treatment.[22,35-37] Focus of the infection was mostly sino-pulmonary infections.[15,16]. CLD, diabetes and heart failure were predictors for severe infections in musculoskeletal diseases during RTX treatment.[3] CLD (including lung involvement of the primary rheumatic disease) was also a risk factor for severe infections in our results. In a study including RTX-treated patients with rheumatic diseases, MTX was found a protective factor for severe infections.[38] We observed that MTX was not related with a decrease in serious infections, unlike HGG.

IVIG replacement was found to decrease the annual infection rate but not severe infections in a study in which 20% of the patients with HGG received IVIG.[21] In our cohort, fewer patients with HGG received IVIG (5%) replacement. According to recommendations which were created specifically for RTX-related HGG, it has been suggested that the decision for IVIG replacement should be made according to the severity of HGG, presence of severe, recurrent, or unusual infections, or lack of response to vaccines. In addition, it is recommended that the Ig levels should be checked every 6-12 months in patients with autoimmune rheumatic disease receiving RTX.[34] However, there is not a global consensus on the frequency of Ig measurement and the indications for IVIG replacement.

Mortality is another outcome that has been associated with HGG. Bartmettler et al.[8] showed increased risk of mortality in RTX-related HGG. Similarly, in our results mortality rate was higher in patients with HGG.

Study Limitations

Our study has some limitations. The main limitation was the retrospective design of the study. The baseline Ig levels was shown to be related with an increase in HGG risk in the literature.[17,19,39,40] As a second limitation, since a small number of our patients had baseline Ig measurement, baseline IgG levels were not included in the analysis. However, presence of follow-up Ig measurements allowed the assessment of whether HGG was persistent or transient.

Conclusion

In the current study we observed HGG almost in one-third of the patients which was associated with higher cumulative RTX doses, male gender and HT. Although low IgG levels were associated with severe infection, the risk of serious infections was similar in patients with and without low IgG type HGG. CLD was a risk factor for severe infections. Since RTX can improve CLD in rheumatic diseases, the risk of infection may be affected, especially in fibrotic type CLD. There are no globally accepted algorithms for IVIG treatment and monitoring Ig levels during RTX treatment. Therefore, determining risk factors for HGG and serious infections, which is a major concern for HGG, is important in the follow-up of the patients and making clinical decisions.

Ethics

Ethics Committee Approval: The study was approved by the local Ethics Committee (no: 09.2023.1332).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.K.T., F.A.Ö., E.A., Z.S.T., H.D., Design: S.K.T., F.A.Ö., H.D., Data Collection or Processing: S.K.T., F.A.Ö., T.K., Y.Y., N.İ., M.P.A., D.B.A., E.A., Z.S.T., H.D., Analysis or Interpretation: S.K.T., F.A.Ö., N.İ., M.P.A., D.B.A., E.A., Z.S.T., H.D., Literature Search: S.K.T., F.A.Ö., T.K., Y.Y., H.D., Writing: S.K.T., F.A.Ö., T.K., Y.Y., N.İ., M.P.A., D.B.A., E.A., Z.S.T., H.D.

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Case Report / Olgu Sunumu

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Metformin-induced systemic vasculitis: A rare case report and literature review

Metformine ilişkili sistemik vaskülit: Nadir bir olgu sunumu ve literatür taraması

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Abstract

Leukocytoclastic vasculitis is a cutaneous small-vessel vasculitis characterized by inflammation and necrosis of the vessel wall. It is usually limited to the skin but may rarely affect organs such as the kidney. A 58-year-old female patient presented with palpable petechiae-purpura on the skin after initiating metformin for type 2 diabetes mellitus. Renal biopsy was performed due to hematuria and proteinuria. The renal biopsy showed proliferative glomerulonephritis. After other causes of vasculitis were excluded, a diagnosis of metformin-induced vasculitis was considered. The patient was started on methylprednisolone and azathioprine treatment. Skin findings disappeared completely after two months, and glomerulonephritis resolved at 9 months.

Keywords: Glomerulonephritis, diabetes, metformin, systemic, skin, vasculitis

Öz

Lökositoklastik vaskülit, damar duvarında enflamasyon ve nekroz ile karakterize kutanöz küçük damar vaskülitidir. Genellikle deri ile sınırlıdır, ancak nadiren böbrek gibi organları etkileyebilir. Elli sekiz yaşında kadın hasta, tip 2 diabetes mellitus için metformin kullandıktan sonra ele gelen peteşi-purpura ile başvurdu. Hematüri ve proteinüri nedeniyle böbrek biyopsisi yapıldı. Renal biyopsi sonucu proliferatif glomerülonefrit ile uyumlu bulundu. Hastada diğer vaskülit nedenleri dışlandı. Metformin ilişkili vaskülit düşünüldü. Hastaya metilprednizolon ve azatiopürin tedavisi başlandı. İkinci ayda deri bulguları tamamen kayboldu. Dokuzuncu ayda böbrek bulguları tam remisyona girdi.

Anahtar Kelimeler: Glomerülonefrit, diyabet, metformin, sistemik, deri, vaskülit

Introduction

Leukocytoclastic vasculitis (LCV) denotes a histopathological finding of hypersensitivity vasculitis (HSV). It is a cutaneous small-vessel vasculitis characterized histologically by inflammation and necrosis of the blood vessel walls and accompanied by various skin lesions such as palpable purpura, necrosis, ulcer, nodule, urticaria, livedo reticularis.[1] Although often confined to the skin, LCV can also affect organs such as the kidney. Various infections, drugs, serum sickness disease, connective tissue diseases (CTD), and malignancies are the most common causes for LCV. However, the etiology is unclear in many cases. The most prominent clinical finding is palpable purpura which is frequently observed in the lower extremities, in feet, ankles, around hydrostatic pressure-dependent areas, or at vascular bifurcations.[2] Less commonly, it can occur in the abdomen, arms, or hips. Many drugs have been reported to cause LCV, such as propylthiouracil, phenytoin, guanidine, sulphonamides, penicillins, granulocyte-macrophage colony-stimulating factors, non-steroidal anti-inflammatory drugs, antiaggregants and anticoagulants, certain antiepileptics, and allopurinol.[3]

Metformin is an oral drug belonging to the biguanide class of antidiabetics which is widely used to treat diabetes mellitus (DM) and generally well tolerated.[4] Cutaneous side-effects such as rash, urticaria, photosensitivity, and

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lichenoid and psoriasiform drug eruption due to metformin use have been rarely reported.[5] Here, we present a case of metformin-induced LCV with renal involvement.

Case Report

A 58-year-old female patient presented with red dots on her anterior lower extremities that had appeared 2 months prior, subsequently spreading to the hip, abdomen, and arms. The patient tried 1% topical methylprednisolone (MP) and oral desloratadine 5 mg therapy. Then she was referred to our rheumatology clinic due to increased acute-phase reactants, petechiae, palpable purpura, and proteinuria. Her medical history revealed that she had been on metformin 1 gr/day for type 2 DM. Her BMI was 36 kg/m^2. There was no history of asthma, CTD, and systemic infection. On skin examination, red and brown colored, old and new petechiae, and palpable purpura were identified on all four limbs and abdominal region (Figure 1A, 1B). Fundoscopic examination revealed no signs of diabetic retinopathy or uveitis. The Schirmer's test (15/14 mm) result was normal. The rest of the physical exam was unremarkable.

The patient's laboratory test results are shown in Table 1. Screening tests for vasculitis and CTD were negative. There was no serological evidence of infection. Coagulation tests, protein electrophoresis and levels of serum complement, immunoglobulin (IgA, IgE, IgM, IgG), and creatinine were normal. The eosinophil count was normal in the blood. The urinalysis showed 2+ proteinuria, 30 erythrocytes/hpf and 14/hpf leukocytes with negative urine culture.

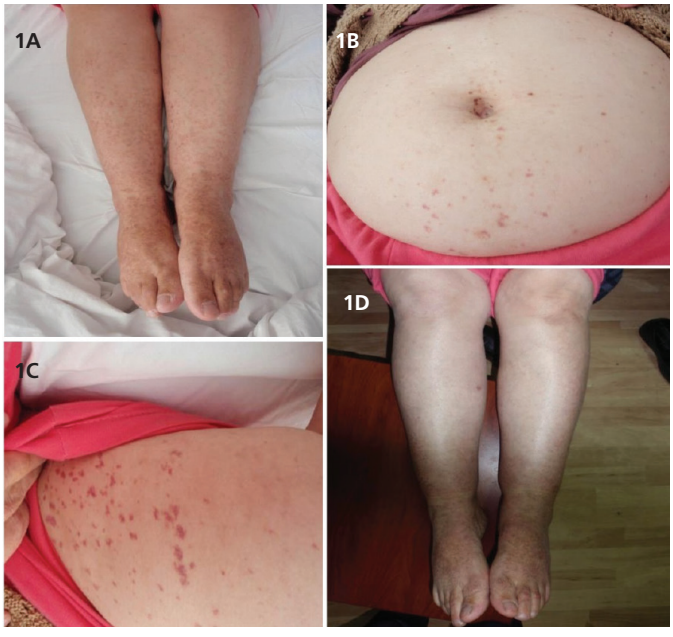

Figure 1A. Petechiae and purpura, **1B.** Petechiae and purpura in the abdomen, **1C.** New petechiae and purpura in the thigh, **1D.** Post-treatment control

The patient was screened for malignancy. The following test and clinical examination results were normal/negative: fecal occult blood test, gynecological examination and smear test, otorhinolaryngological examination and endoscopy, chest and neck X-ray, abdominopelvic ultrasound (USG); bilateral mammography and breast USG. Venous and color Doppler USG of the lower extremity arteries were normal. Fasting and postprandial blood glucose screening also revealed normal glucose levels. Both the HbA1c value of 5.9% (4.8 to 6) and urine microalbumin levels were within the normal limits. We discontinued metformin due to suspicion of drug-induced vasculitis. A skin biopsy was performed, which showed mild to moderate keratosis in the epidermis, and congestion in the dermis, as well as sparse mild perivascular lymphocytic infiltrates (Figure 2A). Immunofluorescence (IF) test results were negative, which did not imply active vasculitis. These findings suggested that the biopsy could have been taken from inactive lesions

Table 1. Laboratory tests

Parameters	Results	Normal
Leukocyte (u/L)	7.05	4.3-10.3
Haemoglobin (gr/dL)	**12.8**	13.6-17.2
Platelet (u/L)	245	156-373
CRP (mg/L)	**14**	0-6
ESR (mm/Hour)	33	0-20
ASO (IU/mL)	25	0-200
RF (IU/mL)	10	<25
ANA (IF)	Negative	Negative
Anti dsDNA (IF)	Negative	Negative
ANCA (IF)	Negative	Negative
Hepatitis B and C test	Negative	Negative
Salmonella test	Negative	Negative
Brucella test	Negative	Negative
HIV test	Negative	Negative
Cryofibrinogen	Negative	Negative
Cryoglobulin	Negative	Negative
ACA-IgM (U/mL)	2	0-12
ACA-IgG (U/mL)	6	0-12
C3 (mg/dL)	176	89-187
C4 (mg/dL)	27	16.5-38
Creatinin (mg/dL)	0.5	0.8-1.2
BUN (mg/dL)	7	5-20
AST (IU/L)	22	<31
ALT (IU/L)	17	<31
aPTT (sec)	11.13	10.5-13.2
INR	0.95	0.85-1.2

ANA: Antinuclear antibodies, anti-dsDNA: Anti-double stranded DNA antibodies, ANCA: Antineutrophil cytoplasmic antibodies, ACA: Anticardiolipin antibodies, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, aPTT: Activated partial thromboplastin time, ASO: Antistreptolysin-O, BUN: Blood urea nitrogen, C3-C4: Complement, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, INR: International Normalization Rate, RF: Rheumatoid factor, HIV: Human immunodeficiency virus

or that a vasculitis could have been masked by the topical steroid and antihistamine therapy.

Over the course of the outpatient follow up, lower extremity skin lesions improved, but new lesions had appeared on the thighs (Figure 1C). The patient refused a biopsy from the new lesions. Her 24-hour urine sample had 2.5 g/day proteinuria as well as eosinophilia (10%). A renal biopsy was performed due to non-nephrotic range proteinuria and abnormal urinary sediment findings. Among the 12-13 glomeruli specimens, we saw complete sclerosis in 1 glomerulus; segmental mesangial cell proliferation, polymorphonuclear leukocyte infiltration, nuclear dust, and adhesions between the glomerular tuft and Bowman's capsule in 3 glomeruli, and enlargement and congestion in the rest. Focal fibrosis (5%), tubular atrophy, and mononuclear cell infiltration were detected in the interstitium, scattered hyalinization and thickening in some vessel walls, and hyaline and erythrocyte casts in the tubular lumen. Crystal violet stain showed no amyloid deposition. IF staining were negative. Histopathological and immunohistochemical findings were consistent with focal proliferative glomerulonephritis (FPGN) (Figure 2B). In addition to glomerulonephritis findings, mild interstitial nephritis findings were also found on renal biopsy.

We excluded primary or other secondary vasculitis, CTD, infection, and malignant diseases and considered the patient as having metformin-induced systemic vasculitis based on clinical and laboratory findings, drug use, and eosinophiluria. We did not restart metformin because metformin-induced vasculitis cases have been reported in the literature and the HbA1c and glucose levels of the patient were normal. We also did not initiate supportive therapy including ACE inhibitors and statins.

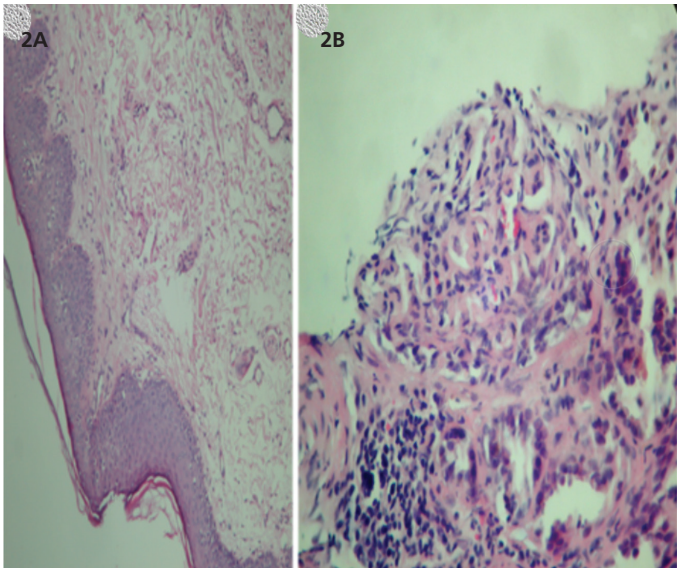

Figure 2A. Skin biopsy (HE 100x). Rare perivascular lymphocytes, **2B.** Kidney biopsy (HE 200x). Segmental mesangial cell proliferation and Polymorphonuclear leukocytes infiltration in the glomeruli

Oral MP 1 mg/kg/day and azathioprine (AZA) 100 mg/day were started due to relapsed/refractory skin findings and renal involvement. Skin findings disappeared completely in follow-up (Figure 1D). Then we reduced the dose of oral MP and continued AZA therapy. At 3-month follow-up visit, C-reactive protein and erythrocyte sedimentation rate had returned to normal levels. Proteinuria levels decreased to 2500 mg/day, 1218 mg/day, 1000 mg/day, and 120 mg/day at 0, 3, 6, and 9 months, respectively. Currently, the patient continues using MP 4 mg/day and AZA 100 mg/day.

Discussion

LCV is a histological term commonly used to refer to manifestations such as neutrophil-rich exudate involving postcapillary venules, endothelial dysfunction, fibrin deposition, and leukocytoclasia. LCV can be primary (idiopathic) without an identifiable cause or secondary to identifiable causes. In the latter, typical causes include skin involvement of systemic vasculitis, CTD, infectious diseases, and lymphoplasmacytic malignancies. More than 30% of malignant cases are reported to be hematologic (IgA monoclonal gammopathy). However, the cause remains obscure in many cases.[6] Cutaneous vasculitis affects all ages but is less common in children than adults and slightly more in females than in males.[3] Characteristic lesions are nonpruritic petechiae and palpable purpura, and are more prevalent in the lower extremities.

The pathogenic mechanism of drug-induced vasculitis is not fully defined and varies depending on the underlying causes. Immune complexes are considered responsible for the pathogenesis of LCV. An immune-mediated adverse reaction occurs against a triggering antigen. Some studies have attempted to establish the correlation of deposition of immune complexes and complement activation inside the vascular walls with LCV.[7] In a study on 61 patients by Khetan et al.[8], HSV (37.7%), Henoch-Schönlein purpura (HSP) (26.2%), drugs (19.7%), infections (11.4%), and CTD (6.5%) were implicated in the etiology of cutaneous vasculitis. Currently, there is no laboratory method or pathological finding to distinguish drug-induced vasculitis from the other types. In drug-induced LCV, symptoms mostly resolve after the discontinuation of the causative agent. Lesions recur in only 10% of cases. LCV is often limited to the skin but may also show systemic involvement. Drug-induced vasculitis accounts for approximately 10-20% of all cases.[9]

Metformin is a biguanide-derivative oral antidiabetic drug widely used in managing type 2 DM and particularly preferred in overweight patients. Cutaneous side-effects such as rash, urticaria, photosensitivity, and lichenoid and psoriasiform drug eruption have been rarely reported due to metformin use.[5] These findings usually disappear days to weeks after the discontinuation of the drug. However, in most cases, the findings recur after metformin is restarted. The diagnosis of drug-induced LCV requires the exclusion of other potential causes. In our case, IF staining was not observed in the renal biopsy. There was no finding suggesting lupus nephritis, diabetic nephropathy, pauci-immune GN, or HSP. The findings were consistent with FPGN. We suspected renal involvement due to metformin-induced LCV. We started AZA because of non-nephrotic proteinuria and non-severe clinical findings. FPGN and skin symptoms responded well to combination therapy with MP and AZA.

The diagnosis of drug-induced LCV is quite difficult as it is based on the history of drug exposure, the exclusion of other types of vasculitis, and disappearance/reappearance of lesions after discontinuation/restarting of the drug.[6] In our case, skin biopsy was not typical for LCV, but histopathological findings might have regressed as the patient's rashes had appeared 2 months earlier. When she had initially presented to our clinic, she was using topical steroid cream and antihistamine. This may explain the sparse distribution of lymphocytes detected in the biopsy performed later. Besides, her skin lesions initially recurred on the thighs but totally resolved after the combination therapy.

In literature (PubMed, Scopus, and Google Scholar), only 3 cases with metformin-induced LCV have been reported so far. The first was a 59-year-old female patient. She had developed skin rash and pneumonitis during DM treatment with metformin. Metformin was discontinued. Her skin biopsy was compatible with LCV. Oral prednisone was started for the treatment of pulmonary symptoms. The findings subsequently regressed. In her follow-up, metformin had been restarted 2 weeks after prednisolone was discontinued and the skin findings reappeared. They disappeared after the discontinuation of metformin once more.[10] The second case was a 33-year-old female patient using metformin 850 mg/day to lose weight. She had developed skin lesions. When metformin was discontinued, they disappeared. However, in her follow-up visit, the findings had recurred after resuming the metformin.[11] The third case was a 60-year-old female patient. She had developed bullous skin lesions in the lower extremities after using metformin 850 mg/day for DM. Her skin biopsy was compatible with LCV, and IF test results were negative. No etiology of vasculitis other than metformin was found. Topical and systemic steroids were started after the discontinuation of metformin. In her follow-up visit two months later, the skin lesions had completely disappeared.[12] The comparison of the characteristics of our case and 3 metformin-induced vasculitis cases reported so far are given in Table 2.

The common feature of these three cases is that skin findings had occurred after metformin use. In the first two cases, skin findings recurred after reinitiating the metformin. Metformin-induced rashes usually occur within the first week of drug use, but this period may go up to months or even years. The durations of vasculitis development due to metformin use in all cases are given in Table 2.

Conclusion

Our case is the first published metformin-induced proliferative GN. Currently, it is the fourth reported case of metformin-induced LCV. Drug-induced LCV often resolves with the discontinuation of the drug and rarely requires systemic treatment. Metformin rarely causes LCV and systemic findings may occur as in our case. Further studies are needed to establish the relationship between metformin and LCV.

Table 2. Cases of metformin-induced vasculitis

Patients	Age/Sex	Purpose	Skin rash	Semptoms	Period**	Biopsy	Treatment
Case-1	59-F	T2DM	Purpuric papules	Pneumonitis	4 month	LCV	Oral prednizolon
Case-2	39-F	Weight loss	Palpable purpura	No	5 day	LCV	Topical chlorhexidine and aqueous eosine
Case-3	60-F	T2DM	Hemorrhagic papules, Vesicles, and Bullae	No	1 month	Bullous LCV	Topical corticosteroids and antibacterials Oral prednisone
Present Case	58-F	T2DM	Petechiae Palpable purpura	Leukocyturia Hematuria Proteinuria	2 month	Perivascular lymphocytic infiltrates in skin biopsy. Focal proliferative GN	Oral MP Azathioprine

DM: Diabetes mellitus, GN: Glomerulonephritis, LCV: Leukocytoclastic vasculitis, MP: Methylprednisolone.

***The time between initiation of metformin and development of vasculitis*

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.Y., B.K., E.E., Design: F.Y., B.K., E.E., Data Collection or Processing: F.Y., B.K., E.E., Analysis or Interpretation: F.Y., B.K., E.E., Literature Search: F.Y., B.K., E.E., Writing: F.Y., B.K., E.E.

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Case Report / Olgu Sunumu

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FMF presented by aseptic abscesses

Aseptik apselerle tanı alan bir FMF olgusu

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Abstract

A 23-year-old otherwise healthy female with family history of familial Mediterranean fever (FMF) in 2 siblings who are on colchicine presented with fever, pleuritis, pericarditis, peritonitis and multiple abscesses in the liver. Sampling from the liver abscess showed neutrophil predominance with no findings of granuloma, vasculitis, lymphoma or malignancy. Similarly, samples from peritoneum and pleural fluids are exudative and showed foamy histiocytes, polymorphonuclear leukocytes. No pathogens, including bacterial, viral and fungal agents, were grown in cultures. The inflamatuary markers were very high, and despite multiple antibiotherapy, the clinical status and biochemistry picture did not improve. After excluding malignancy and infection, the picture was evaluated as an autoinflammatory disease and steroid treatment was started as anti-inflammatory therapy. Anti-interleukin 1 was added to the treatment of the patient who showed a dramatic radiological and clinical response to the steroid, and the steroid dose was reduced. Genomic DNA sample isolated from peripheral blood test showed homozygous MEFV m694v gene mutation diagnosing the patient with FMF.

Keywords: Aseptic abscesses, FMF, autoinflammation, steroid therapy, IL-1 antagonists

Öz

Yirmi üç yaşında kadın hasta bilinen bir hastalık öyküsü olmayıp 2 kardeşi ailevi Akdeniz ateşi (FMF) tanısı ile kolşisin kullanmaktadır. Hasta postpartum 5. ayda ateş, plevra, perikard, peritonda sıvı ve karaciğerde multipl apseler ile görüldü. Karaciğer biyopsisinde karaciğerdeki apselerde nötrofil ağırlıklı hücreler görüldü ve granülom, vaskülit, lenfoma ve epitelyal malignite açısından bulguya rastlanmadı ve apse iltihabı olarak rapor edildi. Benzer şekilde periton ve plevral sıvı örneklerinde eksuda ve köpüksü histiyositler, polimorfonükleer lökositler izlendi. Hastanın kültürlerinde bakteriyel, viral ve fungal ajanlar dahil olmak üzere hiçbir patojen üremedi. Hastanın enflamatuvar belirteçleri çok yüksekti ve çoklu antibiyoterapiye rağmen klinik durumu ve biyokimya tablosu düzelmedi. Hastanın yapılan tüm tetkiklerinde malignite ve enfeksiyon ekarte edildikten sonra mevcut tablo otoenflamatuvar hastalık olarak değerlendirildi ve anti-enflamatuvar tedavi olarak steroid tedavisi başlandı. Steroide radyolojik ve klinik olarak dramatik yanıt veren hastanın tedavisine anti-interlökin-1 ajanı eklendi ve steroid dozu azaltıldı. Periferik kandan izole edilen genomik DNA örneği MEFV m694v homozigot mutasyonu olarak sonuçlandı.

Anahtar Kelimeler: Aseptik apseler, FMF, otoenflamasyon, steroid tedavisi, IL-1 antagonistleri

Introduction

Aseptic abscesses are deep-seated, round, and sterile lesions that are rich in neutrophils. They do not respond to antibiotic therapy but do respond to steroid therapy. These lesions are not well-known.[1] On closer examination, we can say that sterile inflammation is at the center of the disease pathogenesis. Although the majority of patients respond dramatically to steroids, approximately half of these patients relapse during the period when the steroid dose is reduced. In such cases, there are case-based studies in the literature that state tumor necrosis factor (TNF) alpha inhibitors and interleukin-1 (IL-1) antagonists successfully keep the patient on remission, and protect them from the side effects of steroids.[2,3]

Case Report

A 23-year-old otherwise healthy post-partum female with family history of familial Mediterranean fever (FMF) in 2 siblings who are on colchicine presented with fever, pleuritis, pericarditis, peritonitis and multiple abscesses in the liver (Figure 1). Prior to this, the patient had no FMF findings such as fever, abdominal pain, joint pain, chest pain, or rash.

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Sampling from the liver abscess showed neutrophil predominance with no findings of granuloma, vasculitis, lymphoma or malignancy. Similarly, exudate and foamy histiocytes, as well as polymorphonuclear leukocytes, were observed in samples from the peritoneum and pleural fluids. No pathogens, including tuberculosis, *salmonella*, *brucella*, viruses, and fungi, were grown in cultures. Parameters sent from the patient to exclude differential diagnoses, such as vasculitis, other connective tissue disorders, antiphospholipid syndrome, sarcoidosis, tuberculosis, neutrophil phagocytosis disorder, and macrophage activation syndrome, were negative (Table 1). Despite multiple antibiotic therapies, the patient's blood levels of procalcitonin, C-reactive protein, and sedimentary were very high, and the clinical status and biochemistry picture did not improve. Once malignancy and infection were excluded, with the preliminary autoinflammation diagnosis, steroid treatment was continued at a dose of 60 mg/day after 3 days of 1 g steroid infusion. Most of the abscesses in the liver regressed, and the pleural and pericardial effusion resolved (Figure 2). With the steroid taper to 30 mg/day, anakinra 100 mg/day was added to the treatment. Gradually, the steroid dose was reduced to 5 mg/day. At the first month of this treatment, the patient's C-reactive protein and procalcitonin levels decreased (Table 2). Clinically, fever, pain, and fluid collection were not documented (Figure 3).

Based on all of this data, the patient was evaluated as having aseptic abscess syndrome (AAS) in the background

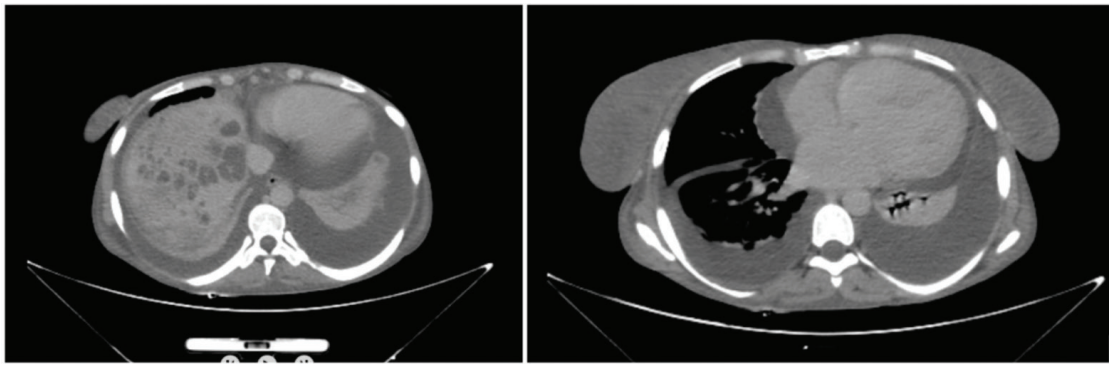

Figure 1. Before treatment CT images (bileteral pleural and pericardial effusions. Multiple hypodense abscess lesions in the liver)
CT: Computed tomography

Table 1. Some laboratory values of the patient at the time of diagnosis

Anti CCP: Negative	**Anticardiolipin Ig M/G: Negative**
Rheumatoid factor: Negative	Anti B2 Gliycoprotein Ig M/G: Negative
ssA/ssB: Negative	Ig G1/G2/G3/G4 levels: High
ANA: Negative	Serum ACE level: Normal
Anti dsDNA: Negative	Pleural ADA level: Normal
SmRNP/anti sentromer/anti Scl 70: Negative	Serum Ig E level: Normal
p-ANCA, c-ANCA: Negative	Plasma NBT activity: Normal
MEFV gene (Met694Val): Homozygous mutation	

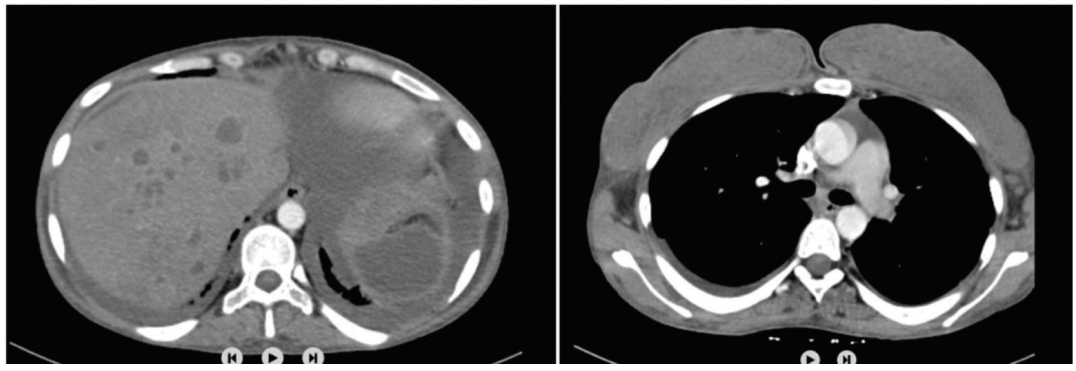

Figure 2. CT Images 2 weeks after starting steroid therapy (marked improvement in abscesses and effusions)
CT: Computed tomography

Table 2. Blood levels before and after treatment

Blood levels before treatment	Blood levels after 1st month treatment
WBC/neutrophil: 22.400/19.100 µL	WBC/neutrophil: 6800/4500 µL
CRP: 248 mg/L	CRP: 12.16 mg/L
Ferritin: >2000 ng/mL	Ferritin: 359 ng/mL
Sedimentation rate: 89	Sedimentation rate: 14
Procalsitonin: 33.02 ng/mL	Procalsitonin: 0.398 ng/mL
Plasma lipid level: Normal	Plasma lipid level: Normal

CRP: C-reactive protein, WBC: White blood cell

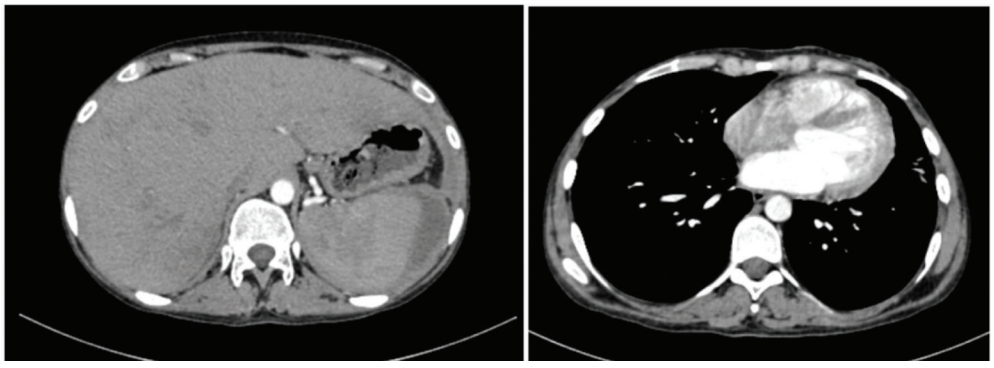

Figure 3. CT images at the end of first month (loss of abscess and effusions)
CT: Computed tomography

of an autoinflammatory disease which led to the diagnosis of FMF given the homozygous M694V mutation.

Discussion

AAS is a part of the large group of diseases that form the topic of neutrophilic diseases. It is a condition in which tissues are infiltrated by neutrophils and granuloma/vasculitis symptoms are not observed. No microorganisms can be produced in tissue and blood cultures, and antibiotic response is not obtained.[4] AAS is characterized by typical features that include regional, systemic, clinical, and biological abnormalities. The clinical presentation usually includes fever (90%), weight loss (50%), and visceral pain (67%). Abscesses are usually found in the spleen (97%), followed by the liver (40%), abdominal lymph nodes (48%), and pancreas (7%). When looking at extra-abdominal locations, lung (17%), brain (7%), superficial lymph nodes, and skin were observed.[2,5] Considering the blood analysis of the cases, it was seen that 70% had neutrophilic hyperleucocytosis, 95% had high C-reactive protein levels, and 47% had increased liver enzyme levels. Lesions are sterile in terms of bacteria, fungi, parasitosis, and viral agents. In addition, antinuclear antibody, rheumatoid factor, antineutrophilic cytoplasmic antibody, and anti-phospholipid antibody levels are also negative.[4]

AAS is often associated with other diseases that need to be investigated and treated. For example, chronic inflammatory bowel disease, relapsing polychondritis, spondyloarthropathy, neutrophilic dermatitis, monoclonal gammopathies, myelodysplasia, and sarcoidosis.[6-10] The feature that makes this case interesting is that FMF has been detected as a result of this situation.

The specific criteria used in the diagnosis of AAS were radiologically demonstrated deep abscesses, neutrophilic cell dominance in the tissue samples taken from these abscesses, negative culture and serological results, no response to antibiotherapy and dramatic response to immunosuppressive therapy.[11] AAS can occur in patients with FMF and is often misdiagnosed as infection. Failure to recognise this entity can lead to unnecessary morbidity and healthcare costs. AAS must be considered when patients develop deep abscesses that do not respond to conventional antibiotic therapy. The initial treatment of choice for AAS is high-dose intravenous glucocorticoids. Maintenance therapy should include a disease-modifying antirheumatic drug or biologically targeted agent or a combination of the two. The ideal regimen for maintenance therapy is still evolving. In patients placed on steroid maintenance therapy alone relapse occurred in some, but not all patients.[12] Disease-modifying antirheumatic drugs (DMARDs) and biological targeted agents have been used as maintenance therapy. DMARDs that have been used to treat AAS include azathioprine, colchicine, cyclophosphamide, ciclosporin, methotrexate and mycophenolate mofetil. Biological targeted therapies that have been used include infliximab,

adalimumab, etanercept, anakinra, canakinumab and tocilizumab.

In the literature, it is observed that many treatment recommendations for AAS are based on clinical observations and experiences instead of randomized controlled clinical research results. Steroids are the cornerstone of treatment.[12,13] For 2-4 weeks, 0.5 mg/kg/day can be started orally or intravenously, and the dose can be gradually reduced according to the clinical response. The prognosis for AAS is variable, and to date, death from AAS has not been reported. However, 60% of patients presented with relapses and required chronic immunosuppressive therapy.[2,4] In addition to steroids, relapse cases can be treated with azathioprine (2-3 mg/kg), pulse cyclophosphamide, or methotrexate. In these cases, the use of anti-TNF-alpha or recombinant IL-1 receptor antagonists and anti-IL-1B monoclonal antibodies may be considered when relapsed.[14,15]

IL-1B is an essential cytokine of the innate immune system. It is produced from myeloid cells as pro-IL1B and converted into its active form, IL-1B, with caspase 1 activity. The activation of caspase 1 depends on the inflammasome pathway. Uncontrolled activation in the Caspase 1 and IL-1B pathways leads to systemic and multi-organ sterile inflammation. In autoinflammatory diseases, fever, arthritis, serositis, rash, and sterile abscesses are observed, while neutrophils and high acute phase reactants are used to monitor treatment response. In summary, the uncontrolled activation of the innate immune response can manifest itself with a clinical picture such as aseptic abscess, fever, and serositis, as in our case (inflammasome formation → caspase 1 activation → IL-1B release). Successful treatment modalities aimed at suppressing this pathway have been observed, where IL-1B plays a crucial role in the pathophysiology of aseptic abscess.

Conclusion

In conclusion, IL-1B blockade is a good treatment option in cases of AAS that require a high steroid dose and are not well controlled, as in our case.[3]

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.B., S.U., Design: S.B., S.U., Analysis or Interpretation: S.B., S.U., Literature Search: S.B., Writing: S.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report / Olgu Sunumu

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A case that developed acute generalized exanthematous pustulosis after hydroxychloroquine use and did not follow the ordinary healing process despite drug discontinuation

Hidroksiklorokin kullanımından sonra akut generalize ekzantematöz püstüloz gelişen ve ilaç kesilmesine rağmen olağan iyileşme sürecini takip etmeyen bir olgu

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Abstract

Acute generalized exanthematous pustulosis is a disease that usually presents with sudden onset and widespread rash over the body. It is a condition characterized by non-follicular, sterile pustules that develop acutely with a base of edematous erythema. Acute generalized exanthematous pustulosis is usually drug-related, and hydroxychloroquine, an antimalarial drug frequently used in rheumatology practice, is one of the rare causes of acute generalized exanthematous pustulosis. Generally, spontaneous regression is expected after drug discontinuation. A sixty-year-old female patient developed acute generalized exanthematous pustulosis while receiving hydroxychloroquine. Despite drug discontinuation and steroid treatment, the lesions were persistent. The patient was treated with methotrexate and the lesions had resolved. It is aimed to raise awareness of the rare hydroxychloroquine-acute generalized exanthematous pustulosis relationship and its treatment with methotrexate by presenting this case.

Keywords: Acute generalized exanthematous pustulosis, case report, hydroxychloroquine, methotrexate

Öz

Akut generalize ekzantematöz püstüloz, genellikle ani başlangıçlı ve tüm vücutta yaygın döküntülerle seyreden bir hastalıktır. Ödemli eritem zemininde akut gelişen, steril püstüllerle karakterize bir durumdur. Genellikle ilaca bağlıdır ve romatoloji pratiğinde sıklıkla kullanılan hidroksiklorokin, akut generalize ekzantematöz püstülozun nadir nedenlerinden biridir. Genellikle ilaç kesildikten sonra spontan gerileme beklenir. Altmış yaşında bir kadın hastada hidroksiklorokin tedavisi sırasında akut generalize ekzantematöz püstüloz gelişti. İlaç kesilmesine ve steroid tedavisine rağmen lezyonlar dirençliydi. Bunun üzerine methotrexate başlanan hastanın tedaviyle lezyonları tamamen geriledi. Bu olgu sunumu ile nadir görülen hidroksiklorokin-akut jeneralize ekzantematöz püstüloz ilişkisi ve metotreksat ile tedavisi konusunda farkındalık yaratmak amaçlanmıştır.

Anahtar Kelimeler: Akut generalize ekzantematöz püstüloz, olgu sunumu, hidroksiklorokin, methotrexate

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a disease that usually presents with sudden onset and widespread rash over the body. Mucosal or internal organs are not expected to be affected but can be involved in severe case.[1] Intertriginous areas are the most involved. Most common two reasons are medication (beta-lactam antibiotics) and viral infections.[2] The incidence of AGEP is estimated to be one to five cases per million people per year. Only 18% of these are non-antibiotic drugs.[3] Hydroxychloroquine (HCQ) is an antimalarial drug used in many rheumatological diseases due to its anti-inflammatory and immunomodulatory effects. Although well-known

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side effects include retinopathy, hypoglycemia, and skin pigmentation, it is generally well tolerated by patients and is one of the rare drugs that cause AGEP.[4] AGEP is more common in women.[5] The duration of the latent period may vary depending on the type of drug used. Fever may accompany the rash in AGEP.

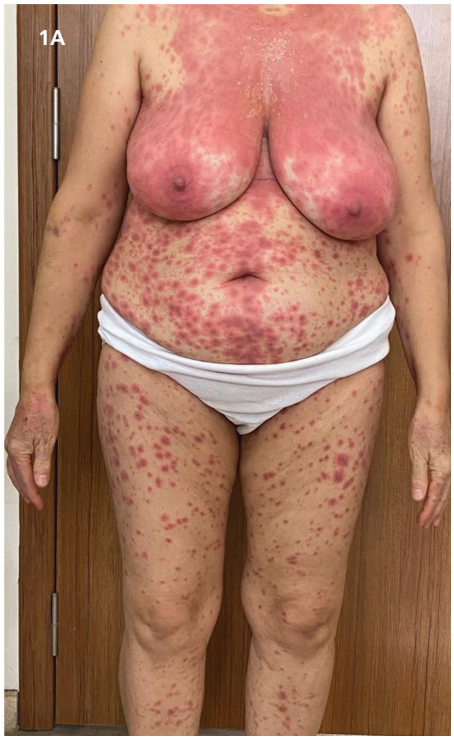
Histopathological examination typically reveals spongiform sub-corneal and/or intraepidermal pustules, and edema in the papillary dermis.[6] In the laboratory, especially leukocytosis with neutrophil dominance is observed. Spontaneous regression is seen with discontinuation of the agent and supportive treatment, which is the mainstay of treatment.

During the healing period, desquamation occurs in the affected areas. HCQ has an exceptionally long half-life; therefore, AGEP caused by HCQ may not follow the typical rapid recovery time.[7]

Here, we present a case of AGEP who developed AGEP after HCQ use and did not follow the usual recovery process after discontinuing the drug.

Case Report

A sixty-year-old female patient with joint complaints for six months was followed by our rheumatology outpatient clinic. Her rheumatological examination showed dry mouth and joint tenderness, especially in the small joints. The ophthalmologist also confirmed dry eye with the Schirmer test. Anti-nuclear antibody of 1/160 titer, and anti-SSA (++) were found. Connective tissue disease/Sjögren's syndrome was considered as a preliminary diagnosis hence HCQ and prednisolone were started. Three weeks later, the patient presented with a widespread rash, mainly on the trunk. Pustular lesions and erythematous plaques were accompanied by desquamation (Figure 1A, 1B). Her fever was subfebrile, the rest of the physical exam was normal. She did not have psoriasis in her past medical and family history. Remarkable labs included a hemoglobin level of 10.4 g/dL, leukocyte of 20,000/mm^3 (81% neutrophil), Erythrocyte sedimentation rate of 5 mm/s, C-reactive protein (CRP) of 62.4 mg/L, and normal rheumatoid factor, anti-cyclic citrulline peptide levels. Cultures of peripheral blood, urine and pustules remained negative. A biopsy was performed from the lesions and reported as "subcorneal pustular dermatosis, findings consistent with AGEP" (Figures 2A, 2B). AGEP was considered clinically and histopathologically in the patient who consulted dermatology. HCQ was discontinued, and 64 milligrams (mg) of methylprednisolone, antihistamine, and topical moisturizer were started. Methylprednisolone dose was reduced to 48 mg after ten days. Due to the recovery of the lesions, the dose of methylprednisolone was reduced by 8 mg per week. Although it responded well to high-dose methylprednisolone, the lesions were resistant to 16 mg of methylprednisolone treatment. Upon this, the patient was given methotrexate (MTX) 15 mg/week. Improvement of



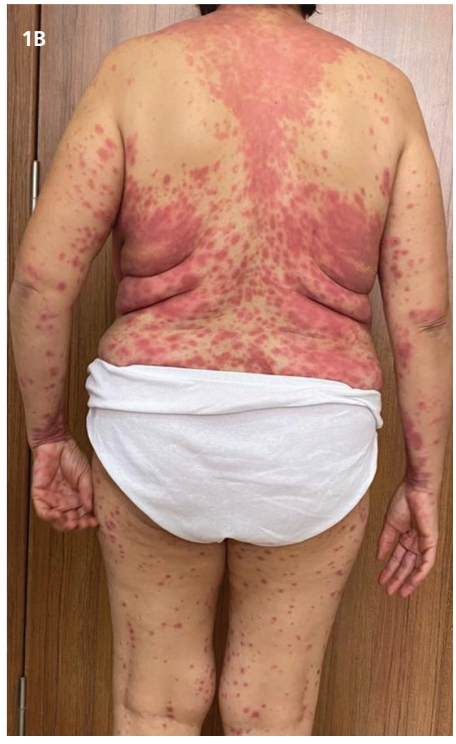
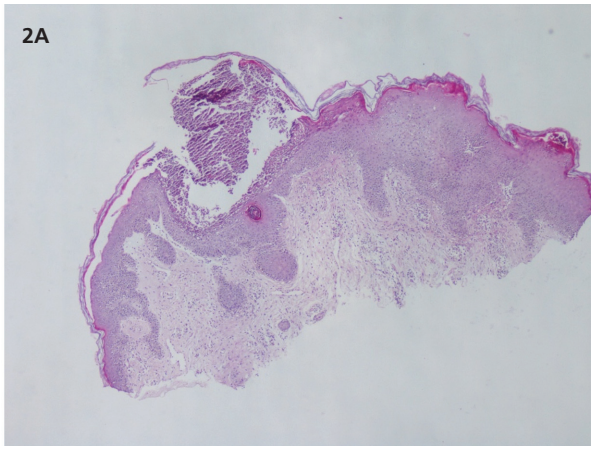


Figure 1A, 1B. Widespread pustular lesions and erythematous plaques on the trunk

cutaneous findings, symptoms, and laboratory parameters including neutrophilia were evident within four weeks of starting MTX (Figure 3). Steroid treatment was gradually tapered and stopped at six weeks. After ten weeks of MTX administration, the lesions resolved. Three months after initiation of MTX at 15 mg/week, tapering by 7.5 mg/week was attempted and the treatment was terminated at four months.

Discussion

Although AGEP was previously described as a form of pustular psoriasis, it was first described in 1980 by Beylot et al.[8] and defined as a clinical picture different from psoriasis. In subsequent studies, the characteristic features of the disease were determined as intraepidermal or subcorneal pustules, dermal edema, perivascular eosinophil/neutrophil predominance, and fever. Although the cause is unknown, acute phase reactant elevation is sometimes observed. In our case, there were neutrophil-dominated white blood cell elevation, CRP elevation, fever, recent suspected drug use, and sudden onset pustular rashes. The pathology result confirmed the diagnosis.



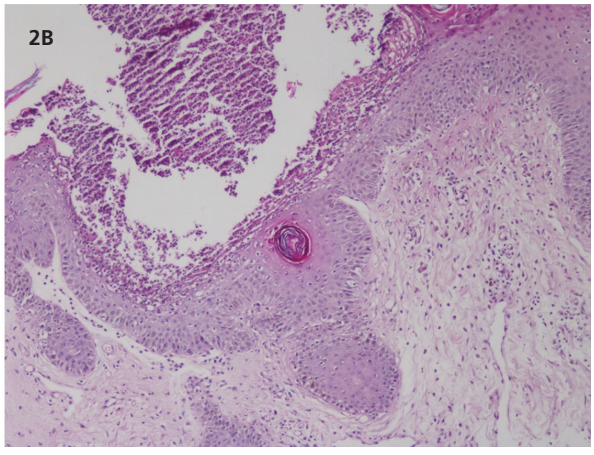


Figure 2A, 2B. Subcorneal pustular dermatosis and perivascular inflammatory reaction

AGEP is a rare disease, but in a 2007 study, the development rate of AGEP due to HCQ was found to be 7%.[9] In the literature, a case series from 2022 of 297 patients, reported a rate of 12.8% for AGEP due to HCQ.[5] The increase in this rate in current studies, especially in 2022, may be due to the everyday use of HCQ in treating COVID-19.

The duration of clinical development in AGEP may differ according to the drug and may last for hours, days, or weeks. In case of antibiotic related AGEP, the most common cause, this period is 48 hours, but it may take 2-4 weeks in HCQ. In addition, AGEP usually regresses within two weeks after discontinuation of the drug, although after HCQ, resistance to systemic therapy and delayed response have been observed. These may be due to the metabolic characteristics of HCQ, such as the half-life of 40-50 days and immune dysregulation of the concomitant disease.[9] Non-follicular eruptions on an erythematous surface spreading on a large scale are clinical features. Fever accompanies most of the patients (64.3%). Oral mucosal involvement is rare and generally seen in severe cases.[1] In our case, there was only skin involvement and fever without involvement of the oral mucosa. It also had the characteristics of HCQ in terms of duration.

There is no specific method for the treatment of AGEP. The most critical step is the elimination of the agent, the illness should respond in a few days. AGEP is generally self-limited and has a favorable prognosis. However, sometimes it can be severe enough to require hospitalization. Death was reported in a case of AGEP due to HCQ use. Except for drug discontinuation, topical corticosteroids benefit patients with itching and inflammation.[1] In severe or

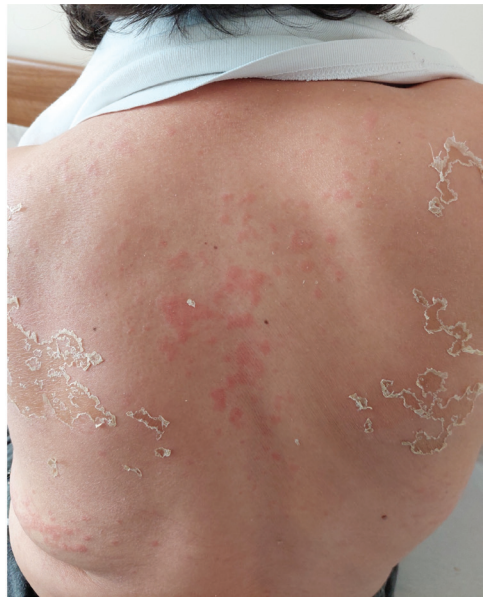


Figure 3. The erythematous eruption and pustules were resolved, followed by desquamation

resistant cases, systemic corticosteroids, and cyclosporine may help accelerate disease clearance.[1,4] Also, treatment with systemic steroids was associated with decreased hospital stays in patients with AGEP.[10] Despite systemic steroid treatment, our case did not follow the ordinary healing process and MTX (15 mg/week) helped with resolution within four weeks. The mechanism of action of MTX correlates with the pathophysiology of AGEP which is a neutrophilic inflammatory response associated with T cells. MTX is generally known as an antimetabolite that inhibits dihydrofolate reductase. It is an anti-inflammatory and immunosuppressive agent that inhibits lymphocytes. The reduction of neutrophil release is another effect.[11]

Although it has been used frequently in rheumatology practice, AGEP due to HCQ is rare in the literature. Due to the causative drug or the underlying disease, the latent period may take longer and may be resistant to steroid therapy.

To our knowledge, only one case of AGEP treated with MTX has been previously reported. There is very limited data about this subject.[11] Thus, our report shows that MTX can also be considered as a treatment option in steroid resistant AGEP.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.K., Design: M.K., Data Collection or Processing: A.S.Ş., Analysis or Interpretation: M.K., Literature Search: M.K., E.O.K., Y.Ö.E., S.Ş., Critical Review: M.K., E.O.K., Y.Ö.E., S.Ş., A.S.Ş., Writing: M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Letter to the Editor / Editöre Mektup

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Ulus Romatol Derg 2023;15(3):175-177

The lymph node involvement in a patient with rheumatoid arthritis

Romatoid artritli bir hastada lenf nodu tutulumu

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Keywords: Rheumatoid arthritis, lymph node, lymphoma
Anahtar Kelimeler: Romatoid artrit, lenf nodülü, lenfoma

Dear Editor,

A 63-year-old male patient with chronic renal failure and hypertension was referred to the hematology department after hypergammaglobulinemia was detected as part of the work up. Rheumatoid arthritis (RA) was part of the patient's past medical history. Past surgical history included aortic aneurysm. Physical examination revealed small lymphadenopathies in the left inguinal region, the largest of which was 1 cm in size. Hepatosplenomegaly was not observed. Livedo reticularis was present in both legs which can occur with RA. It is caused by spasms or lack of blood flow in the blood vessels supplying skin. The rest of the physical exam was normal. In complete blood count, C-reactive protein (CRP) was 24.98 mg/L (reference range 0-5 mg/L), erythrocyte sedimentation rate as 110 mm/hr (reference range 0-15 mm/hr), hgb was 6.8 g/dL. Sedimentation and CRP are non-specific tests that indicate inflammation associated with disease severity in patients with RA but are used in diagnosis of the disease and monitoring its activity. The rest of the blood tests were normal. Computed tomography showed more lymphadenopathy less than 1 cm in size in the neck, paratracheal area, aortopulmonary area, subcarinal area and bilateral hilar levels 1, 2 and 5. Superficial ultrasonography showed lymph nodes in the left inguinal region, the largest of which was 42x15 mm in size, with a visible fatty hilus and increased cortical thickness. Bone marrow biopsy that was done six months prior to presentation revealed increased myeloid lineage cells, and plasma cells stained polyclonally with lambda and kappa.

Excisional biopsy of lymphadenopathy in the inguinal region was performed. On microscopic examination, the lymph node structure was preserved. There was no effacement in the lymph node structure as seen in lymphoma. No Reed-sternberg like large cells were seen. There were areas of reactive follicular hyperplasia (Figure 1). Increased plasma cells were observed in the medulla and interfollicular area. The lambda and kappa immunohistochemical studies showed polyclonal staining of plasma cells (Figure 2). The findings observed in the patient who was followed up due to RA were primarily compatible with rheumatoid lymphadenopathy. Since the findings were compatible with rheumatoid lymphadenopathy and CRP remained elevated, it was decided to start the patient on a drug with interleukin inhibitor effect.

RA is an autoimmune disease that may affect all systems, especially the joints.[1] Enlarged lymph nodes are not uncommon in RA. In a study involving one hundred patients, lymphadenopathy was observed in 82% of patients

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and was most seen in the axillary region.[2] However, lymphadenopathy can be seen anywhere in the body.[3-5] Lymphadenopathy may be localized or systemic. Clinically, it may lead to suspicion of lymphoma.[3] Lymph nodes are mobile and not tender. Systemic findings including fever, anemia and weight loss may be associated with rheumatoid lymphadenopathy. Splenomegaly, polyclonal hypergammaglobulinemia and cryoglobulinemia may be observed.[6]

The risk of lymphoma is twice as high in patients with RA compared to the normal population.[7,8] Hodgkin lymphoma is more common than non-Hodgkin lymphoma.[9] Hodgkin lymphoma cases are of classical type. Most of the non-Hodgkin lymphomas occurring in RA patients are of the diffuse large B-cell lymphoma type.[10,11] The use of methotrexate (MTX) in RA treatment may also lead to severe bone marrow suppression and development of lymphoproliferative diseases.[12-14]

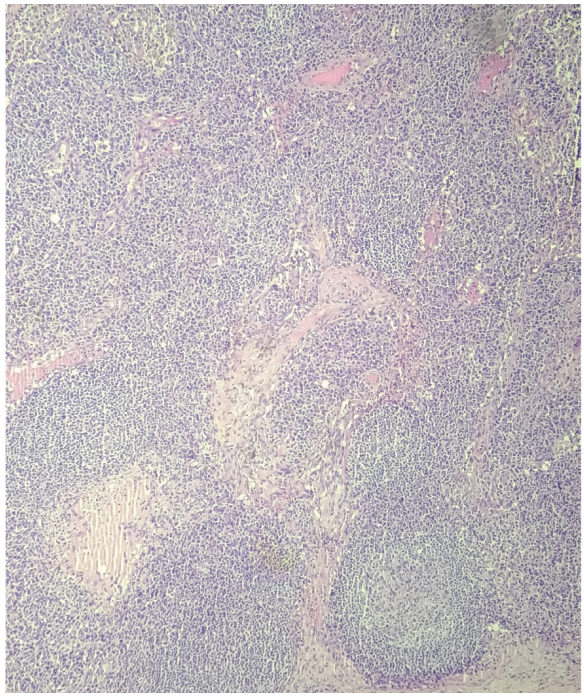

Figure 1. The areas of reactive follicular hyperplasia (H&E x100)

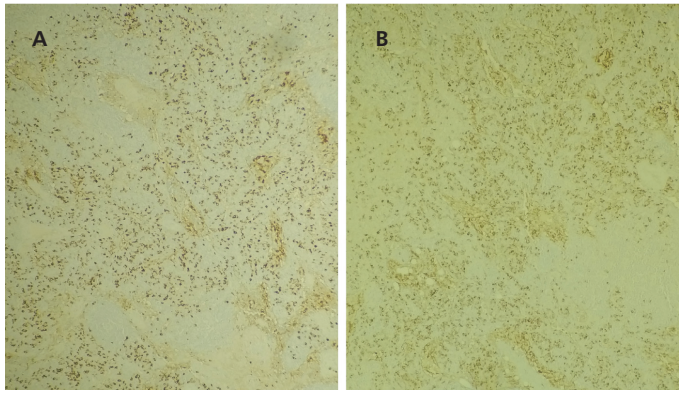

Figure 2. The plasma cells showing polyclonal staining. A) Kappa (IHC x200). B) Lambda (IHC x200)
IHC: Immunohistochemistry

When lymphadenopathy develops in a patient with RA, lymphomas and lymphadenopathy secondary to the disease may be considered in the differential diagnosis. Multicentric Castleman disease should also be included in the differential diagnosis due to increased plasma cells. Immunohistochemical positivity with human herpes virus 8 allows an easy differentiation from rheumatoid lymphadenopathy.

Conclusion

In conclusion, although the risk of lymphoma increases in RA patients with or without treatment, it should not be forgotten that RA also causes lymphadenopathy.

Ethics

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declare that they have no relevant financial disclosures.

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Hazırlayan: Gülay Koca

2023 YILINDAN HABERLER

2023 yılının ilk etkinliği;

"XVII. Romatoloji Uzmanlık Öğrencileri ve Uzmanları İçin Eğitim Kursu & IX. Romatolojide Yaklaşımlar ve Profesörler ile Yuvarlak Masa Toplantıları"

Düzenleme kurulunda Dr. Umut Kalyoncu, Dr. Timuçin Kaşifoğlu, Dr. Cemal Bes, Dr. Gülen Hatemi ve Dr. Fatma Alibaz'ın bulunduğu kursa 48 konuşmacı ve 185 katılımcı katkıda bulunmuştur.

18-21 Mayıs 2023 tarihlerinde bu yıl ikincisi düzenlenen Black Sea Rheumatology Kongresi, 54 konuşmacı-oturum başkanı ve 126 katılımcı ile Türkiye Romatoloji Derneği ile Romanya Romatoloji Derneği tarafından Prof. Vedat Hamuryudan ve Prof. Simona Rednic'in ortak başkanlığında Romanya'nın Cluj kentinde düzenlenmiştir.

Bildiri Sayısı: 39
Katılımcı Sayısı: 126
Bilimsel Görevli: 54

Bu yıl ikincisi düzenlenen TRD Yaz Okulu, 33 konuşmacı-oturum başkanı ve 97 katılımcı ile 15-18 Haziran 2023 tarihleri arasında Trabzon'da düzenlenmiştir.

Düzenleme Kurulu:

Dr. Fatoş Önen, Dr. Servet Akar, Dr. Timuçin Kaşifoğlu, Dr. Gökhan Keser, Dr. İsmail Sarı

XXIII. ULUSAL ROMATOLOJİ KONGRESİ

TÜRKİYE CUMHURİYETİ 100 Yaşında

30 yıl TÜRKİYE ROMATOLOJİ DERNEĞİ

11 - 15 Ekim 2023

Susesi Deluxe Otel & Kongre Merkezi, Belek, Antalya

Cumhuriyetimizin 100. Derneğimizin 30. yılında 23.'sü düzenlenen Ulusal Romatoloji Kongresi 763 katılımcıyla başarı ile tamamlandı. Kongrede sunulan toplam 326 bildiri Ulusal Romatoloji Dergisi özel sayısı olarak Kasım ayında yayınlanacaktır. Katılan tüm Öğretim üyesi Hocalarımıza, romatolog ve Romatoloji eğitimi alan üyelerimize, Romatoloji hemşirelerine, öğrencilerimize ve ilaç endüstrisi temsilcilerine çok teşekkür ederiz.

Kongremize gönderilen 326 bildiri arasından aşağıda isimleri sıralanan çalışmalar TRD Bildiri Ödülünü almaya hak kazandı. Ödül almaya hak kazanan üyelerimizi tebrik ederiz.

BİRİNCİLİK ÖDÜLÜ

LUPUS NEFRİTİ HASTALARINDA MİKROTROMBÜS OLUŞUMU MORTALİTE İLE İLİŞKİLİ OLABİLİR

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[4]İzmir Katip Çelebi Üniversitesi, İç Hastalıkları Ana Bilim Dalı, Romatoloji Bilim Dalı, İzmir

İKİNCİLİK ÖDÜLÜ

NON-SPESİFİK AKSİYAL SEMPTOMU OLAN PSÖRİASİS VE PSÖRİATİK ARTRİT HASTALARININ DÜŞÜK DOZ BT İLE DEĞERLENDİRİLMESİ

Şerife Asya Germe[1], Gizem Ayan[1], Sibel Doğan Günaydın[2], Başak Yalıcı Armağan[2], Levent Kılıç[1], Umut Kalyoncu[1]
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ÜÇÜNCÜLÜK ÖDÜLÜ

BEHÇET HASTALIĞINDA ORAL VE SİSTEMİK HASTALIK AKTİVİTESİ İLE NETOSİS BULGULARI ARASINDAKİ İLİŞKİ

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2023 yılında Profesörlük, Doçentlik unvanı alan ve doktor öğretim üyesi kadrosuna atanan üyelerimizi tebrik eder, akademik yaşamlarında başarılar dileriz.

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Ankara Üniversitesi Tıp Fakültesi İbn-i Sina Hastanesi İç Hastalıkları Ana Bilim Dalı Romatoloji Bilim Dalı öğretim üyesi ve derneğimizin üyesi değerli hocamız **Prof. Dr. Gülay Kınıklı** emekli oldu. 3 Ekim 2023 tarihinde Ankara Üniversitesi Hasan Ali Yücel Konferans Salonunda düzenlenen törende hocamızı tebrik ederek derneğimiz adına plaket takdiminde bulunduk. Hocamıza ülkemizde Romatoloji Bilim Dalının gelişmesine ve derneğimize yapmış olduğu değerli katkılar nedeniyle teşekkür eder, sağlık ve mutluluklar dileriz.

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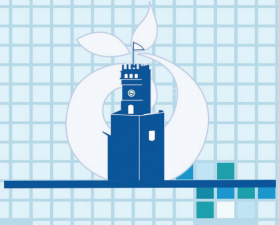

X. ROMATOLOJİDE YAKLAŞIMLAR VE PROFESÖRLER İLE YUVARLAK MASA TOPLANTILARI

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