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Case Report / Olgu Sunumu

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A case of Schnitzler syndrome with recurrent fever and urticarial rash

Tekrarlayan ateş ve ürtikeryal döküntü ile seyreden Schnitzler sendromu olgusu

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Abstract

Objective: Schnitzler syndrome is a rare, late-onset, autoinflammatory disorder characterized by chronic urticarial rash and monoclonal gammopathy, typically of the immunoglobulin M (IgM) type, accompanied by systemic inflammation and recurrent fever.

Case Presentation: We report a 57-year-old woman who was admitted with recurrent episodes of fever and a widespread skin rash. Laboratory evaluation revealed markedly elevated inflammatory markers, including C-reactive protein at 155 mg/L (normal <5 mg/L) and ferritin at 446 ng/mL (normal 30-300 ng/ml), in the absence of an identifiable infectious or autoimmune cause. A skin biopsy was performed, revealing a neutrophilic dermal inflammatory reaction. Serum immunofixation electrophoresis demonstrated an IgM monoclonal gammopathy. Bone marrow aspiration and biopsy were performed, and no evidence of Waldenström macroglobulinemia or other overt lymphoproliferative disorder was detected at the time of diagnosis. The patient fulfilled the Strasbourg criteria for Schnitzler syndrome. Treatment with the interleukin-1 (IL-1) receptor antagonist anakinra was initiated, leading to a rapid resolution of fever and skin lesions, and a decrease in inflammatory markers. She remains afebrile with normal acute-phase reactants during outpatient follow-up.

Conclusion: This case highlights the importance of considering Schnitzler syndrome in adults presenting with recurrent fever, chronic urticarial rash, elevated inflammatory markers, and IgM monoclonal gammopathy; it also illustrates the dramatic clinical response to IL-1 blockade with anakinra.

Keywords: Schnitzler syndrome, autoinflammatory disease, IgM monoclonal gammopathy, anakinra, interleukin-1 blockade

Özet

Amaç: Schnitzler sendromu, kronik ürtikeryal döküntü ve tipik olarak immünoglobulin M (IgM) tipinde monoklonal gammopati ile karakterize, sistemik enflamasyon ve tekrarlayan ateş ataklarının eşlik ettiği, nadir görülen, geç başlangıçlı bir otoenflamatuvar hastalıktır.

Olgu Sunumu: Tekrarlayan yüksek ateş atakları ve eş zamanlı yaygın deri döküntüsü yakınmaları nedeniyle kliniğimize kabul edilen 57 yaşındaki kadın hasta sunulmaktadır. Enfeksiyöz veya otoimmün neden saptanmamış olup yapılan laboratuvar incelemelerinde akut faz reaktanlarından C-reaktif protein düzeyi 155 mg/L (normal <5 mg/L) ve ferritin düzeyi 446 ng/mL (normal 30-300 ng/mL) olarak belirgin yüksek saptandı. Deri biyopsisinde nötrofilik dermal enflamatuvar reaksiyon izlendi. Serum immünofiksasyon elektroforezinde IgM tipinde monoklonal gammopati saptandı. Bunun üzerine gerçekleştirilen kemik iliği aspirasyonu ve biyopsisi incelemesinde, tanı anında Waldenström makroglobulinemisi veya diğer belirgin lenfoproliferatif bozukluklara ait herhangi bir bulguya rastlanmadı. Strasbourg kriterlerini karşılayan hastaya Schnitzler sendromu tanısıyla interlökin-1 (IL-1) reseptör antagonisti olan anakinra tedavisi başlandı. Tedavi sonrasında ateş ve deri lezyonlarında hızlı gerileme ile birlikte akut faz reaktanlarında belirgin düşüş izlendi. Hasta, polikliniğimizde hala ateşsiz durumda ve akut faz reaktanları normal sınırlarda olacak şekilde izlenmektedir.

Sonuç: Bu olgu, tekrarlayan ateş, kronik ürtikeryal döküntü, yüksek akut faz reaktanları ve IgM tipinde monoklonal gammopati ile başvuran erişkin hastalarda Schnitzler sendromunun ayırıcı tanıda akılda tutulması gerektiğini vurgulamakta; ayrıca anakinra ile sağlanan IL-1 blokajına verilen dramatik klinik yanıtı ortaya koymaktadır.

Anahtar Kelimeler: Schnitzler sendromu, otoenflamatuvar hastalık, IgM monoklonal gammopati, anakinra, interlökin-1 blokajı

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Introduction

Schnitzler syndrome is a rare, acquired autoinflammatory disorder first described in 1972.[1] It is characterized by the association of a chronic urticarial rash and a monoclonal gammopathy, most frequently of the immunoglobulin M (IgM) type, accompanied by systemic inflammatory manifestations such as recurrent fever, arthralgia, bone pain, and elevated acute phase reactants.[2] The pathogenesis is thought to involve dysregulated interleukin-1 (IL-1) signaling.[3] Due to its nonspecific symptoms and overlap with infectious, autoimmune, and hematologic diseases, the diagnosis is often delayed.[4] It usually responds dramatically to IL-1 blockade.[5] In view of the elevated risk of lymphoproliferative disorders, most notably Waldenström's macroglobulinemia, it is important to closely monitor patients.[6]

We describe a 57-year-old woman who presented with recurrent fever and rash, was diagnosed with Schnitzler syndrome based on clinical and laboratory features, and responded well to treatment with anakinra.

Case Presentation

A 57-year-old woman was admitted to our clinic with recurrent episodes of fever up to 40.3 °C accompanied by a pruritic skin rash over the 6 months preceding presentation. These episodes occurred every 2-3 weeks, lasted for 2-3 days, and were characterized by one to two daily fever spikes, predominantly in the evening, and were associated with malaise, diffuse myalgias, and occasional chills but no rigors. She denied weight loss, night sweats, or recent travel. She had no significant comorbidities. There was no known family history of autoinflammatory or autoimmune diseases.

On admission, her body temperature was 39.6 °C. Physical examination revealed a diffuse, pruritic, urticarial-like erythematous rash predominantly involving the trunk and proximal extremities. There was no palpable lymphadenopathy or hepatosplenomegaly. Joint examination showed no synovitis.

Initial laboratory investigations showed marked systemic inflammation with an elevated C-reactive protein (CRP) level of 155 mg/L (normal <5 mg/L) and a ferritin level of 446 ng/mL (normal 30-300 ng/mL). The erythrocyte sedimentation rate was 79 mm/h.

Complete blood count revealed normochromic, normocytic anemia, with a haemomoglobin level of 11.9 g/dL (normal 12.0-16.0 g/dL), a mean corpuscular volume of 91.6 fL (normal 80-96 fL), and a mean corpuscular haemoglobin of 30.3 pg (normal 28-33 pg).

An extensive infectious workup, including blood and urine cultures, serological testing for viral and bacterial pathogens, and imaging for occult infection, was negative. Although the rheumatoid factor was slightly elevated, other autoimmune screening parameters, including antinuclear antibodies, anti-CCP antibodies, anti-neutrophil cytoplasmic antibodies, complement levels, and other relevant autoantibodies, did not reveal an underlying connective tissue disease.

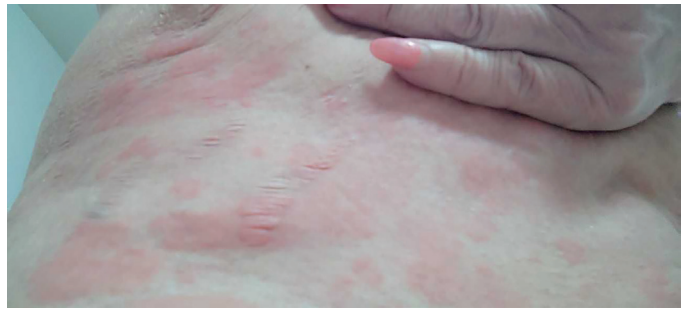

Figure 1. Multiple, extensive erythematous, partially confluent urticarial plaques on the trunk

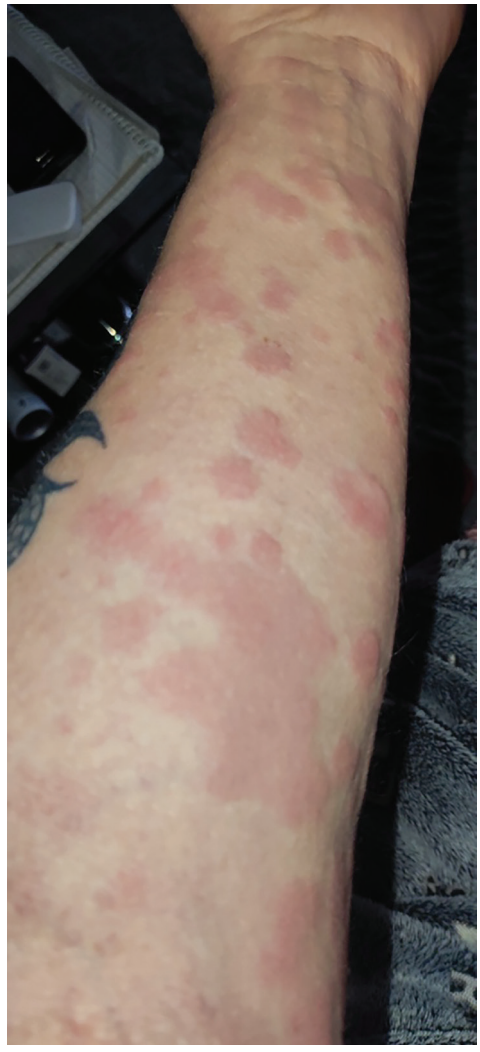

Figure 2. Multiple, disseminated erythematous, partially annular urticarial plaques on the forearm

A skin biopsy was performed to determine the cause of skin lesions. Histopathological examination revealed a neutrophilic dermal inflammatory reaction with an eosinophilic component.

Serum protein electrophoresis showed a monoclonal spike, and immunofixation electrophoresis identified an IgM monoclonal gammopathy of the light-chain type.

Quantitative immunoglobulin levels revealed an elevated IgM level at 297 mg/dL (normal 40-230 mg/dL), a normal IgG level at 1100 mg/dL (normal 700-1600 mg/dL), and a normal IgA level at 253 mg/dL (normal 70-400 mg/dL). The serum free light chain assay showed normal concentrations and a normal ratio, indicating no evidence of monoclonal free light chain excess. Urine protein electrophoresis showed no pathological findings.

Bone marrow aspiration and biopsy were performed to evaluate for an underlying lymphoproliferative disorder. Histopathological examination revealed "normocellular bone marrow with 0.2% lymphoplasmacytic cells, without diagnostic features of Waldenström macroglobulinemia or multiple myeloma". Consequently, Waldenström macroglobulinemia was ruled out.

The patient fulfilled the Strasbourg criteria for Schnitzler syndrome based on the presence of a chronic urticarial rash, recurrent fever, elevated inflammatory markers, and an IgM monoclonal gammopathy, together with exclusion of infectious and autoimmune causes.

Initial symptomatic treatment with non-steroidal anti-inflammatory drugs and short courses of systemic corticosteroids provided only partial and transient relief. Given the presumed IL-1 driven autoinflammatory mechanism, therapy with the IL-1 receptor antagonist anakinra was initiated at a dose of 100 mg subcutaneously once daily. The patient experienced rapid and dramatic clinical improvement including resolution of fever within 24-48 hours and complete disappearance of the rash within a few days. CRP and ferritin levels normalized within 10 days. At the most recent follow-up visit in our outpatient clinic, after 12 months of continuous anakinra therapy, the patient remained afebrile, had no recurrence of rash, and had persistently normal inflammatory markers. No serious adverse effects related to anakinra were observed.

Discussion

Schnitzler syndrome is a rare but likely underdiagnosed autoinflammatory condition, typically presenting in middle-aged to elderly patients, with a slight male predominance.[7] The hallmark features are chronic urticarial rash and monoclonal gammopathy, most often IgM, in combination with systemic inflammatory manifestations such as recurrent fever, arthralgia, bone pain, lymphadenopathy, and elevated acute phase reactants.[2]

The Strasbourg criteria are widely used for diagnosis and require the presence of chronic urticarial rash and monoclonal IgM or IgG gammopathy as obligate criteria, plus at least two minor criteria (fever, objective bone remodeling, neutrophilic dermal infiltrate on skin biopsy, leukocytosis and/or elevated CRP) after exclusion of other causes.[2] Our patient fulfilled these criteria, presenting with chronic urticarial rash, recurrent fever, markedly elevated CRP and ferritin, and IgM monoclonal gammopathy; extensive evaluations ruled out infectious and autoimmune etiologies.

In Schnitzler syndrome, the differential diagnosis is broad because the combination of chronic urticarial rash, recurrent fever, myalgia/arthralgia, and elevated inflammatory markers overlaps with several autoinflammatory, autoimmune, and hematologic disorders. Adult-onset Still disease is an important consideration; however, it more typically presents with quotidian fever, a salmon-colored rash, marked hyperferritinemia, and the absence of a monoclonal gammopathy.[8] Cryopyrin-associated periodic syndromes, particularly Muckle-Wells syndrome, may also resemble Schnitzler syndrome because of urticaria-like lesions and systemic inflammation, but they usually begin earlier in life, may show a positive family history, and are more often associated with sensorineural hearing loss and pathogenic variants in *NLRP3*.[9,10] Urticarial vasculitis and chronic spontaneous urticaria should likewise be considered: vasculitic lesions generally persist for more than 24 hours, may resolve with residual pigmentation, and demonstrate leukocytoclastic vasculitis on skin biopsy, whereas chronic spontaneous urticaria is typically not accompanied by persistent systemic inflammation or monoclonal paraproteinemia.[11,12] Therefore, the diagnosis of Schnitzler syndrome relies on recognition of its characteristic constellation of chronic urticarial rash, intermittent fever, inflammatory syndrome, and monoclonal gammopathy, and the systematic exclusion of alternative diagnoses.

An important aspect of Schnitzler syndrome is the association with lymphoproliferative disorders, particularly Waldenström macroglobulinemia and, less frequently, other B-cell malignancies and the risk of transformation increase with disease duration.[6] In our case, bone marrow evaluation at the time of diagnosis did not demonstrate Waldenström macroglobulinemia; however, long-term hematological follow-up is warranted due to the ongoing presence of IgM monoclonal gammopathy.

The pathogenesis of Schnitzler syndrome is not fully understood but involves dysregulated innate immunity with overproduction of IL-1.[3] This is supported by the remarkable clinical responses to IL-1 blockade observed in most patients.[13] Conventional therapies such as antihistamines, non-steroidal anti-inflammatory drugs, and corticosteroids generally provide incomplete and short-lived benefit, whereas IL-1 inhibitors

(anakinra, canakinumab, rilonacept) usually induce rapid and sustained remission of fever, rash, and systemic inflammation.[14]

In our patient, initiation of anakinra led to rapid symptom resolution and normalization of inflammatory markers, consistent with previous reports. Moreover, continuous treatment is typically required, as discontinuation often leads to relapse.[15]

This case emphasizes the need for heightened awareness of Schnitzler syndrome among clinicians evaluating adults with recurrent fever, chronic urticarial rash, and elevated inflammatory markers, particularly when an IgM monoclonal gammopathy is present. Early recognition allows timely initiation of IL-1 blockade, which can dramatically improve quality of life and may mitigate long-term complications related to chronic systemic inflammation and lymphoproliferative evolution.

Conclusion

Schnitzler syndrome should be considered in middle-aged or older adults presenting with recurrent fever, chronic urticarial rash, markedly elevated inflammatory markers, and monoclonal IgM gammopathy, after exclusion of other causes. Our case illustrates the utility of the Strasbourg criteria and highlights the effectiveness of IL-1 inhibition with anakinra, which led to rapid and sustained clinical and laboratory remission. Long-term follow-up is essential to monitor for relapse and potential progression to lymphoproliferative disease.

Ethics

Ethics Committee Approval: Ethics approval was not required.

Informed Consent: Written informed consent was obtained.

Footnotes

Authorship Contributions

Design: T.K., Literature Search: X.K., Writing: T.K., X.K.

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

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