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A challenging diagnosis in a male presented with ascites: Pseudo-pseudo Meigs syndrome and systemic lupus erythematosus

Asit ile başvuran erkek hastada tanısal zorluk: Psödo-psödo Meigs sendromu ve sistemik lupus eritematoz

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Abstract

Gastrointestinal involvement as an initial presentation of systemic lupus erythematosus (SLE) is seen uncommonly. Among such presentations, ascites is an extremely rare clinical condition that requires extensive diagnostic investigation for nephrotic syndrome, tuberculosis, congestive heart failure, constructive pericarditis, and malignancy besides of SLE-related conditions such as lupus peritonitis, protein losing enteropathy, and pseudo-pseudo Meigs syndrome (PPMS). PPMS is still a debatable clinical description, characterized by ascites, elevated CA-125 levels, and absence of malignancy in an SLE patient. Notably, the clinician should keep in mind that all these possibilities could be the anchor manifestation of SLE as well. Therefore, definitive diagnosis might be challenging in case of ascites in an SLE patient. Herein, we aimed to share the difficulties from the first presentation to the definitive diagnosis in a patient with PPMS in the light of similar cases in the literature.

Keywords: Systemic lupus erythematosus, male, ascites, pseudo-pseudo Meigs syndrome

Öz

Gastrointestinal sistem tutulumu, sistemik lupus eritematozus (SLE) hastalarında nadir olarak başlangıç bulgusu olabilir. Asitle başvuran bir SLE hastasında; SLE ile ilişkili olan lupus peritoniti, protein kaybettiren enteropati ve pseudo-pseudo Meigs sendromu (PPMS) gibi tanıların yanısıra, nefrotik sendrom, tüberküloz, kalp yetmezliği, konstriktif perikardit ve malignite gibi SLE dışı klinik durumlar da ayırıcı tanıya girmesi nedeniyle detaylı bir inceleme gereklidir. PPMS, SLE hastasında asit, yüksek CA-125 seviyeleri ve malignite dışlandıktan sonra tanı konan tartışmalı bir klinik durumdur. SLE'nin bu klinik tablolardan biriyle ortaya çıkabileceği unutulmamalıdır. Bu nedenle, SLE hastasında asit durumunda kesin tanı koymak zor olabilir. Bu yazıda, literatür verileri ışığında PPMS tanısının ilk belirtiden kesin tanıya kadar olan süreçte yaşanan zorlukları paylaşmayı amaçladık.

Anahtar Kelimeler: Sistemik lupus eritematoz, asit, erkek, psödo-psödo Meigs sendromu

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disorder characterized by exaggerated T and B-cell response and loss of immune tolerance to self-antigens leading to various types of clinical manifestations that range from mild pain and skin involvement to severe, life-threatening organ damage.[1] Serosal involvement, particularly in the form of pleuritis and pericarditis, is a well-described manifestation of SLE, whereas ascites is infrequent, consisting of wide range of differential diagnoses, in which an extensive evaluation is crucial whether it is directly attributed to SLE and/or occurs secondary to a concomitant disease.[2,3] Pseudo-pseudo Meigs syndrome (PPMS) is generally proposed as a clinical diagnosis of exclusion in a patient with SLE manifested by ascites, elevated CA-125 with no evidence of malignancy, but it can be the initial presentation as well. Here, our aim with this case is to draw attention to

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the diagnostic difficulties of ascites in an SLE patient, and particularly discuss PPMS in the light of literature.

Case Presentation

A 50-year-old male was admitted by pleural and pericardial effusion, ascites, and positive serologic findings [antinuclear antibody (ANA) and double stranded (ds)-DNA]. 5 months prior, the patient was presented with acute abdominal pain. Computed tomography (CT) of abdomen was remarkable for increased thickness in the ascending colon (Figure 1) and colonoscopy demonstrated widespread mucosal inflammation in the ascending colon, with histopathologic features of non-specific colitis. These symptoms subsided with 2 week-course of antibiotic treatment. Two months later, the patient was hospitalized due to acute pulmonary thromboembolism. Laboratory findings were remarkable for high-titer lupus anticoagulant and positive anti-cardiolipin antibodies. The analysis of ascites and pleural fluid was consistent with exudative form, but no evidence of acid-fast bacilli and malignant cells was found. He was discharged with the administration of low molecular weight heparin with referral to our center for further investigation. Until admission to our center, the patient also reported remarkable weight loss and episodic non-bloody diarrhea. Physical examination showed decreased breath sounds bilaterally on lower lung fields, abdominal distention with shifting dullness, and severe pitting edema over both legs, with no evidence of muscle weakness and organomegaly. Laboratory investigations revealed hemoglobin 10 (13.5-16.9 g/dL), white blood cell count 2850 (3910-10900), absolute lymphocyte 390 (1.100-3.300), platelets 117000 (166000-308000), C-reactive protein (CRP) 98 (0-5 mg/dL), serum albumin level 2.8 (3.5-5.2 g/dL), lactate dehydrogenase 246 (135-225 U/L), serum C3 level 0.577 (0.9-1.8), C4 level 0.117 (0.1-0.4), serum ferritin level 1803 (13-150 ng/mL), CA-125 450 (0-30 ng/mL). Serum-ascites albumin gradient (SAAG) was 0.4. Urine examination was remarkable for hematuria (erythrocyte: 116/hpf), pyuria (leukocyte: 30/hpf), and proteinuria (1.8 gram/24-hour) without evidence of dysmorphic erythrocytes. Serologic tests showed positive ANA (1/1000-1/3200, homogenous pattern) and high dsDNA titer >200 (>20). Lupus anticoagulant titer was 2.01 (0.8-1.2), and anti-cardiolipin antibody was found 41.6 (9.9-10). The stool microscopic examination was normal. Radiologic examination revealed bilateral pleural and mild pericardial effusion, as well as ascites with normal liver parenchyma (Figures 2,3). Renal biopsy could not be performed due to massive ascites causing immobility and positioning issues. Lympho-scintigraphy of bowels was performed to rule out protein losing enteropathy (PLE), showing no evidence of extra-lymphatic leakage. Of note, we were not able to study fecal collection and plasma alpha-1 antitrypsin level in our institution. Positron emission tomography (PET)/CT showed increased fluorodeoxyglucose uptake in the peritoneum, suggesting malignant mesothelioma, but the peritoneal biopsy revealed areas of marked and extensive chronic inflammation with reactive mesothelial hyperplasia and no evidence of malignant cells. The bone marrow examination was non-contributory. Based on polyserositis, cytopenia and strongly suggestive lupus serology after exclusion of other possibilities, diagnosis of SLE-related PPMS was considered. SLE disease activity index (SLEDAI) score was calculated 21 (proteinuria=4, pyuria=4, hematuria=4, pleurisy=2, pericarditis=2, low complement=2, increased DNA binding=2, leukopenia=1). The patient was placed on high dose steroid (1 mg/kg/day prednisolone) treatment and furosemide dependening on daily weight record. The

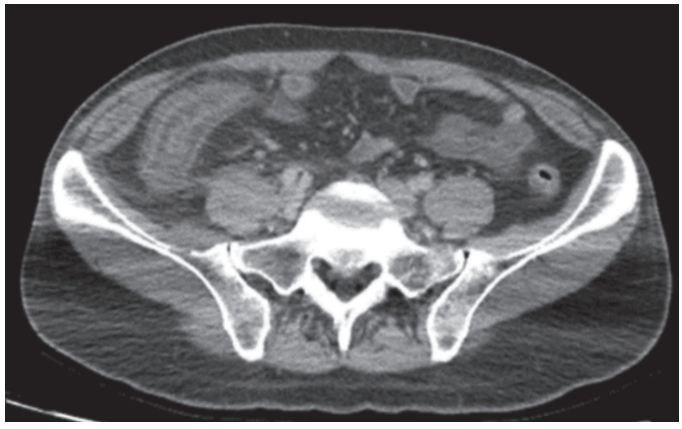

Figure 1. Computed tomography of abdomen was remarkable for increased thickness in the ascending colon

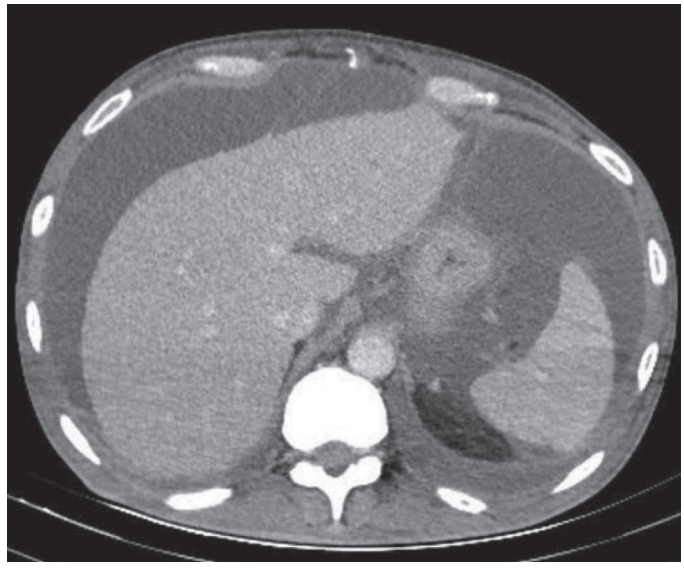

Figure 2. Radiologic examination revealed massive abdominal ascites with normal liver and spleen parencyhma

patient was discharged following marked laboratory and partial clinical improvement. At the first-month outpatient visit, due to persistent pedal edema and insufficient decline in abdominal ascites, azathioprine (AZA) was added to steroid monotherapy. At the following visit, a mild to moderate decrease in ascites was achieved but AZA was suspended because of marked elevation in liver transaminases and development of neutropenia. After normalization of laboratory parameters, oral cyclophosphamide (CYC) (50 mg twice a day) was initiated instead of AZA. At the last visit, physical examination revealed no evidence of pedal edema, normal abdominal circumference, but still absent breath sound in the right lung base. Laboratory parameters were within normal range and no detectable ascites was found on control abdominal ultrasound imaging, but right sided pleural effusion persisted (Figure 4). Despite achievement in clinical remission with CYC, the treatment was replaced with mycophenolate mofetil (MMF) after reaching cumulative doses for CYC (10 gram). The patient is currently receiving hydroxychloroquine and MMF in complete remission with SLEDAI score of 2 (pleurisy=2).

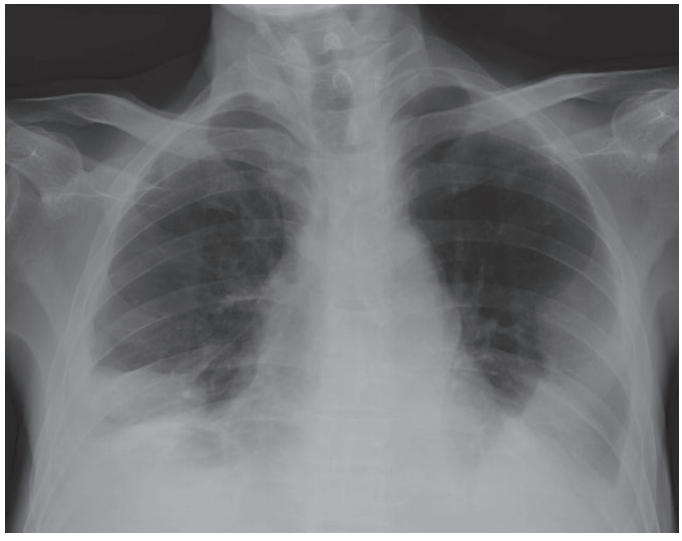

Figure 3. Bilateral pleural effusion on chext X-ray at admission

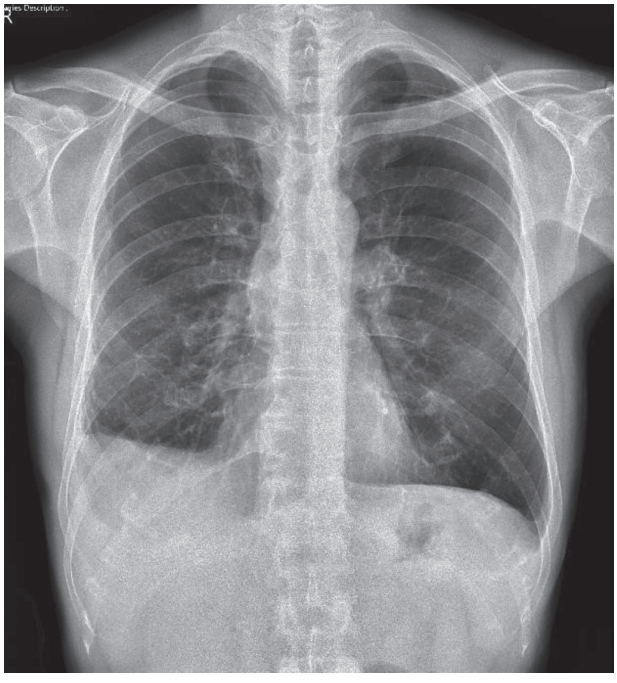

Figure 4. Persistent right sided pleural effusion on chext X-ray at month

Discussion

Despite the high rate of peritoneal inflammation reported by autopsy series, ascites in SLE is a challenging clinical condition including variable differential diagnoses; malignancy, nephrotic syndrome, heart failure, tuberculosis, PLE, lupus peritonitis (LPE), and PPMS.[4] Of note, we may not eliminate the possibility of lupus nephritis because renal biopsy could not be performed due to massive ascites related improper positioning. However, we considered that the degree of proteinuria was less likely to play a role in the development of massive ascites.

LPE is a rare clinical condition characterized by acute abdominal pain mimicking surgical abdomen and occasionally accompanying mild to moderate ascites. However, painless ascites may sometimes gradually develop during SLE, described as chronic LPE. The ascites due to LPE is generally exudative (SAAG <1.1).[5] Although acute abdominal pain and accompanying bowel wall thickening at first admission may be suggestive features of acute LPE, the insidious development of massive ascites in our case was atypical.

PLE is another plausible diagnosis that should be kept in mind, especially when a patient manifests with ascites, diarrhea, edema, and hypoalbuminemia in the absence of marked proteinuria. It may arise very rarely as a presenting manifestation of SLE. Loss of serum proteins into gastrointestinal tracts due to mucosal inflammation and lymphatic obstruction are proposed as some of not well-defined pathogenic mechanisms. Tc-99m HAS (99m-labeled human serum albumin) scan and clearance of alpha-1 antitrypsin level might be helpful, but a definitive diagnosis is still based on exclusion of all other possible causes.[6] Moreover, other valuable tests including fecal collection and plasma alpha-1 antitrypsin level were not available in our centre. The history of diarrhea, evidence of mucosal inflammation on colonoscopy, hypoalbuminemia, pedal edema, and ascites in our case suggested PLE. However, SAAG in PLE-related ascites is greater than 1.1, whereas it was lower than 1.1 in our case. Furthermore, marked elevation of CRP is unlikely to be encountered in PLE regardless of the presence of SLE.[6] Indeed, it can be

sometimes challenging to confirm a definitive diagnosis. Gao et al.[7] published a similar case with the overlapping clinical picture of PLE and PPMS such seen in our case that it might sometimes be so challenging to conclude an accurate diagnosis.

CA-125 is a glycoprotein mainly expressed in epithelial cells and used as a marker either in the diagnosis and following of ovarian malignancy. Of note, elevations in the presence of ascites due to nephrotic syndrome, tuberculosis and other malignancies infiltrating the peritoneum may be seen, possibly due to mesothelial cells activation. Studies have demonstrated that serum CA-125 levels are correlated with the extensiveness of serosal involvement in SLE.[8-12]

Pseudo-Meigs's syndrome is a condition described in a patient with constellation of abdominal tumour, pleural effusion and ascites. PPMS is a clinical condition mimicking pseudo-Meigs syndrome identified in SLE as a diagnosis of exclusion with no evidence of malignancy.[9] In the literature, over twenty cases of PPMS have been reported so far. Analysis of these cases revealed that PPMS might either emerge as an initial manifestation or after SLE diagnosis, in nearly half of cases. All reported cases were female and middle-aged adults. The characteristic feature of PPMS-related ascites is exudative and moderate to massive in nature (SAAG <1.1). It is widely known that SLE mainly affects premenopausal female population (9:1). PPMS is originated from the terminology of Meigs and pseudo-Meigs syndrome, typically seen in female population. However, SLE can be seen in male individuals, albeit rare, and these patients may be also exposed to PPMS. To the best of our knowledge, no PPMS in a male has been published until today. What makes our case unique is to announce the first PPMS in a male case in the literature.

No consensus on treatment has been available due to the rarity of this entity. Unlike SLE-related peritonitis and pleuritis, ascites during PPMS might be less responsive to steroid monotherapy. Therefore, addition of an immunosuppressive agent is generally required for a better long-term outcome. Based on present data, the most preferred immunosuppressive agents are AZA and MMF followed by CYC and rituximab.[10-22] Of note, clinicians should tailor the initial drug choice based on the patient's disease activity as well as the type of organ involvement. Our case was unresponsive to steroid monotherapy and were unable to mainstay on AZA due to adverse events. We preferred initiating with CYC because he had also evidence suggestive for renal involvement despite the absence of kidney biopsy. CYC was effective in controlling the disease both clinically and serologically, but it was replaced by MMF because of reaching cumulative doses. MMF provided complete and sustainable remission in this case.

Conclusion

Albeit uncommonly seen, PPMS should be among differentials when a patient manifest by abdominal ascites and positive lupus serology even if it presents in a male. Diagnosis remains challenging and is based on exclusion of other disorders with similar manifestations.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Authorship Contributions

Concept: R.Y., H.O., C.K., Design: R.Y., H.O., C.K., Data Collection or Processing: R.Y., M.D., D.Ü.C., Analysis or Interpretation: R.Y., H.O., M.D., D.Ü.C., C.K., Literature Search: R.Y., M.D., D.Ü.C., Writing: R.Y., H.O., C.K.

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

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