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OLGU SUNUMU / CASE REPORT

Sjögren's syndrome and catastrophic antiphospholipid syndrome with severe skin involvement

Sjögren sendromu ve şiddetli cilt tutulumu mevcut olan katastrofik antifosfolipid sendromu

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Abstract

Catastrophic antiphospholipid syndrome is a rare but rapidly progressing form of antiphospholipid antibody syndrome with high mortality. The syndrome causes multiorgan failure associated with diffuse micro-thromboses. Necrotic-appearing ecchymotic lesions emerging from the distal aspect of both lower extremities and progressing to the upper leg region, and to the upper extremities developed in a 58-year-old woman. Histopathological examination of the biopsy specimen revealed intravascular microthrombi in the dermis. Laboratory findings for anti-cardiolipin antibodies IgM and lupus anticoagulant resulted positive. Lung and kidney involvement was observed. The clinical course progressed very quickly, and catastrophic antiphospholipid syndrome was diagnosed with these findings. Two-thirds of catastrophic antiphospholipid syndrome cases develop due to secondary causes, the most common being infections. Catastrophic antiphospholipid syndrome may also accompany autoimmune diseases, particularly systemic lupus erythematosus. This report is presented to emphasize that Sjögren's syndrome should be considered in the etiology of catastrophic antiphospholipid syndrome.

Keywords: Antiphospholipid syndrome, catastrophic, sjögren syndrome, skin involvement

Öz

Katastrofik antifosfolipid sendromu; nadir görülen hızlı seyirli mortalitesi yüksek antifosfolipid antikor sendromunun ciddi bir formudur. Sendrom, yaygın mikro trombozlara bağlı olarak multiorgan yetmezliğine neden olur. Bu olguda; 58 yaşında kadın hasta da alt extremite distal bölgeden başlayan ekimozlar üst bacak bölgesine ve üst extremiteye yayılan lezyonlar hızlı seyir göstererek nekrotik alanlara dönüştü. Histopatolojik incelemede dermiste intravasküler trombüsler tespit edilen hastanın laboratuvar bulgularında IgM anti-kardiyolipin antikor ve Lupus antikoagülan'ı pozitifti. Klinik seyir çok hızlı ilerleyen hastada akciğer ve böbrek tutulumu da eşlik etti. Mevcut bulgularla hastaya katastrofik antifosfolipid sendromu tanısı konuldu. Katastrofik antifosfolipid sendromu vakalarının üçte ikisin de, en sık enfeksiyonların tetiklemesine sekonder olarak gelişmektedir. Katastrofik antifosfolipid sendromu'na otoimmün hastalıklar özellikle sistemik lupus eritematozus eşlik etmektedir. Olgumuz; Sjögren sendromunun katastrofik APS etyolojisinde düşünülmesini gerektiğini vurgulamak amacıyla sunulmaktadır.

Anahtar kelimeler: Antifosfolipid sendromu, cilt tutulumu, katastrofik, sjögren sendromu

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune entity distinguished by arterial and venous thrombosis resulting from antiphospholipid antibodies. Catastrophic APS is a rare, life-threatening form of APS in which diffuse intravascular thrombosis results in multiorgan ischemia and failure[1,2]. Catastrophic APS was first described by Asherson in 1992[3]. Four criteria need to be met for definite diagnosis: 1. Objective evidence that at least three organs, systems and/or tissues are involved, 2. Manifestations developing either

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concurrently or within one week, 3. Histopathological evidence of small-vessel occlusion, and 4. Presence of antiphospholipid antibodies confirmed by laboratory tests[4]. Catastrophic APS develops due to secondary causes in two-thirds of patients, the most common being infections. Other causes include malignancies, surgery, pregnancy, and discontinuation of anticoagulation[5,6]. It may also accompany autoimmune diseases. Cervera et al. reported accompanying systemic lupus erythematosus (SLE) (40%), lupus-like syndrome (5%) and other autoimmune diseases (9%) among 280 CAPS patients[5].

Catastrophic APS is an uncommon but potentially life-threatening condition. We report a case of catastrophic APS accompanied by Sjögren's syndrome in whıch no trigger factors were detected. This case is presented to emphasize that Sjögren's syndrome may rarely accompany catastrophic APS.

CASE

A 58-year-old woman presented to the internal diseases clinic due to fever and diffuse body pain and was hospitalized for follow-up. Two days after admission, ecchymosis starting from the distal aspect of both lower extremities progressed rapidly to the upper leg region, and lesions were observed on the upper extremities. Tests revealed WBC:1.180/uL, Hgb:10 g/dl, Plt: 39,000/uL, and D-Dimer:1483, and the patient was transferred to the hematology clinic with a preliminary diagnosis of disseminated intravascular coagulation (DIC). The patient had a history of hypertension (15 years) and a diagnosis of Sjögren's syndrome for 10 years, but had not undergone follow-ups for the previous two years. The diagnosis of Sjögren's syndrome was obtained from the hospital files and drug reports from hospitals to which she had previously presented. The patient had five healthy children, no recurrent pregnancy loss, and no previous thrombotic history.

Dermatological examination revealed ecchymotic areas with clearly defined borders in the inguinal region, starting from both lower extremities and extending to the pubis and sacrum and persisting over the joints, non-tense bullae behind the bilateral tibias, diffuse ecchymotic patch lesions on both upper extremities, and necrosis in the uvula (Figure 1). The patient was re-evaluated after five days, at which dermatological examination revealed that the ecchymotic areas had spread to the feet and patellae, together with expansion in the bullae in the ecchymotic areas, and areas of erosion associated with opened bullae (Figure 2). Two biopsy specimens were collected using a 5-mm punch device. At follow-up, cyanosis was observed to have started from the tips of the bilateral toes to the ankle. This was cold at palpation, and no pulses (tibialis posterior- dorsalis pedis) could be detected. Necrotic areas with defined demarcation lines developed in both lateral femoral regions, the right breast, and the bilateral upper arms (Figures 3-5). No apoptotic and necrotic keratinocytes or marked inflammatory reaction were observed at histopathological examination of the biopsy specimen, although dermoepidermal separation and intravascular microthrombi in the dermis were present (Figure 6), while direct immunofluorescence imaging (X400) revealed IgM (+++) and fibrinogen (+++) accumulation in the vascular walls in the upper dermis (Figure 7). At laboratory evaluation during follow-up, despite the administration of six units of erythrocyte suspension, Hgb was 6.6 g/dl, WBC<4000, and platelet count 31,000/uL. Activated partial thromboplastin time (APTT) and normal prothrombin time (PT), International normalized ratio (INR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), kidney and liver function, glycemia, albumin, ferritin, creatine kinase (CK), C3 and C4 complement factors and thyroid stimulating hormone (TSH) values are shown in Table 1. Positive anti-nuclear antibodies (ANA), (1:640, speckled pattern), Factor XIII (normal), and anti-Cardiolipin (aCL) antibodies IgM (>120 PL-U/mL, range <12) and IgG (2.75 PL-U/mL range <12) were identified at immunological examination. The lupus anticoagulant (LAC) test also resulted positive. Sjögren's antibodies (Anti-SS-A/Anti-SS-B) and c-ANCA (anti- neutrophil cytoplasmic antibody) were also positive, while rheumatoid factor (RF), anti-double stranded DNA (anti- dsDNA), extractable nuclear antigens (ENA), anti-cyclic citrullinated peptide antibodies (anti-CCP), antibodies to ribonucleoproteins (RNP), anti-Smith (Sm) antibody, anti–Jo-1 (antihistidyl transfer RNA synthetase) antibodies, anti-topoisomerase I (anti-Scl-70) antibodies and p-ANCA were negative.

The patient's general condition worsened, and she was transferred to intensive care. Blood gas analysis performed at room temperature on admission revealed lactate 1.3 mmol/dL and a PaO_2/FiO_2 ratio of 310 mm Hg. Tachypnea and oxygen requirements subsequently developed. The patient's FiO_2 requirement increased to 45%, her PaO_2/FiO_2 value

decreased to 210, and her lactate values ranged between 2.7 and 3.4. Her Glasgow Coma Score (GCS) of 15 decreased to 11 after transfer to intensive care. Her creatinine value of 0.21 mg/dl on admission rose to 1.42 mg/dl on day 3, and vasopressor therapy was initiated due to low blood pressure refractory to fluid therapy.

Anti-coagulant therapy, pulse steroid, and 1 g/kg intravenous immunoglobulin for three days were applied for CAPS in our institution, and plasmapheresis was performed six times in another hospital to which the patient was referred. Despite these treatments, mortality occurred on day 35.

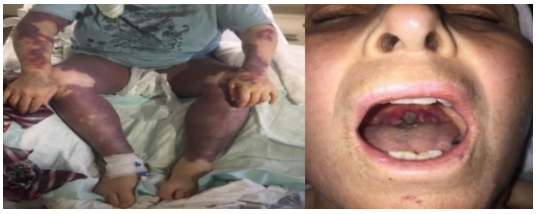

Figure 1. Diffuse ecchymotic patch lesions, and necrosis in the uvula (at first)

Figure 2. Ecchymotic areas, and areas of erosion associated with opened bullae (5 days after)

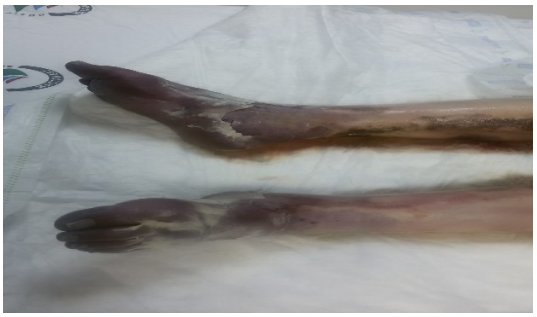

Figure 3. Cyanosis, tips of the bilateral toes to the ankle region (10 days after)

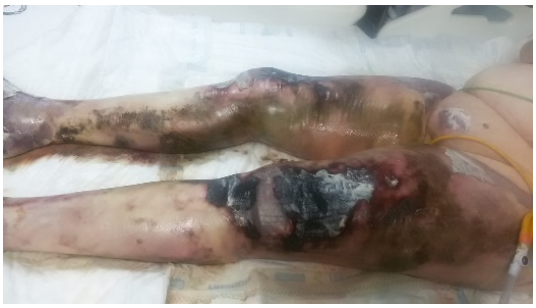

Figure 4. Necrotic areas, lateral femoral regions (after 2 weeks)

Figure 5. Necrotic areas, the right breast, and the bilateral upper arms (after 2 weeks)

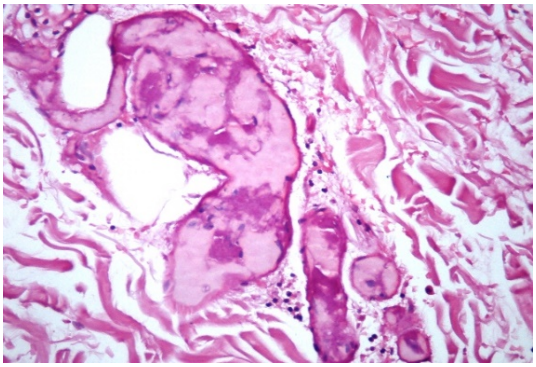

Figure 6. PAS x400→ Intravascular PAS positive thrombus formation, HE x100: Dermoepidermal separation, intravascular thrombus with fibrin in the dermis

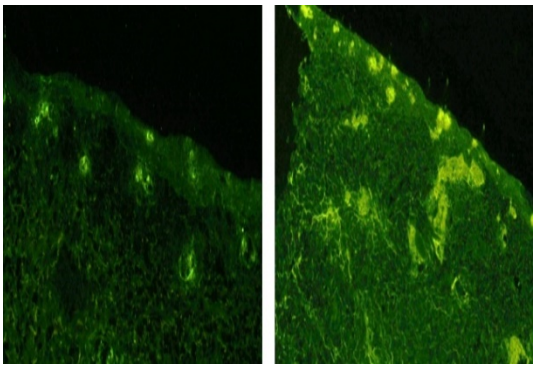

Figure 7. IgM (+++) accumulation in vascular walls in the upper dermis at direct immunofluorescence x400

Table 1. Laboratory data of the patient

Laboratory data	Patient's results	Normal range
WBC*	1.180	3-15 10^3 /uL
Hgb†	6.6gr/dl	8-17
PLT‡	31 10^3/uL	50-500
AST§	30 U/L	0-35
ALT‖	18 U/L	0-35
Urea	61.8 mg/dl	17-43
Creatine	1.42 mg/dl	0,5-0,9
Glucose	111mg/dl	74-106
Ferritin	333ng/ml	10-120
ESR¶	78mm/saat	0-20
CRP**	44 mg/dl	0-0.8
Complement 3	29.9mg/dl	79-152
Complement 4	1.98mg/dl	16-38
Creatine kinase	914U/L	0-145
Albumin	1.39gr/dl	3.5-5.2
Thyroid stimulating hormone	0.061 uIU/ml	0.34-5.6
PT††	11.7	10-14
APTT ††	24.8 sn	22.1-28.1
INR‡‡	1.08	0.85-1.15

*WBC: White blood cell †Hgb: Hemoglobin ‡PLT: Platelet §AST: Aspartate aminotransferase ‖ALT: Alanine aminotransferase ¶ESR: Erythrocyte sedimentation rate **CRP: C-reactive protein; ††PT: Prothrombin time, APTT: Partial thromboplastin time ‡‡INR: International normalized ratio

Table 2. Classification criteria for CAPS

Definite CAPS All four criteria present
1. Evidence of involvement of three or more organs, systems and/or tissues 2. Development of manifestations simultaneously or in less than a week 3. Confirmation by histopathology of small-vessel occlusion 4. Laboratory confirmation of the presence of antiphospholipid antibodies
Probable CAPS
• All four criteria, except only two organs, systems, and/or tissues involved • All four criteria, except for the absence of laboratory confirmation of antiphospholipid antibodies • Criteria 1, 2, and 4 • Criteria 1, 3, and 4, with the development of a third event more than 1 week but within 1 month of presentation, despite anticoagulation

DISCUSSION

Catastrophic APS was first described by Asherson in 1992 in reference to patients developing widespread thrombotic events in association with antiphospholipid (APL) antibodies[3]. Catastrophic APS occurs as a complication in fewer than 1% of patients with APS. Catastrophic APS is a rare but potentially fatal entity requiring high clinical awareness on the part of health professionals. An aPL-triggered sudden disturbance of the coagulation or fibrinolytic systems is an expected finding. In the light of the rarity of the condition, the European Forum on Antiphospholipid Antibodies established an international list of patients with catastrophic APS (the CAPS Registry) in 2000[7,8]. Catastrophic APS is assessed based on diagnostic criteria, and diagnosis may be definite or probable (Table 2). Catastrophic APS criteria are 90.3% sensitive and 99.4% specific[4,9,10].

Previous studies have reported that women constitute 69-72% of patients, with a mean patient age of 38[2,5,11]. Nearly two-thirds of catastrophic APS result from a secondary cause, although the etiology is still not fully understood. However, various triggering factors have been identified. The most common triggering factor is infection (46.7%), and the condition can also develop after malignancy (17.6%), surgery (16.8%), birth control pill use, pregnancy/puerperium, withdrawal of warfarin, systemic lupus erythematosus flare-up, and trauma[12-14]. The most common infections are those involving the respiratory tract (33%), the urinary tract (19%), and skin (13%). Infection was investigated in our case due to the fever and diffuse body pain observed at initial presentation, but no infectious focus was identified5. Catastrophic APS may be comorbid with autoimmune diseases, particularly SLE (40%), lupus-like syndrome (5%) and other autoimmune diseases (9%). A greater probability of higher mortality has been reported in catastrophic APS cases associated with SLE (48%)[5,11]. Antiphospholipid antibody positivity was determined in 73.3% (n:55) of the SLE group, and in 13.3% of both the mixed connective tissue disease (n:19) and systemic sclerosis (n:16) groups. However, it was not detected in patients diagnosed with primary Sjögren's syndrome (n:12)[15]. Nonetheless, antiphospholipid antibody positivity was detected in 36 of 402 patients diagnosed with primary Sjögren's syndrome in a previous study[16]. The frequency of thrombosis in patients with SLE in one meta-analysis was 24%[17]. Thromboembolic events have also been detected in 1.44% of patients with primary Sjögren's syndrome18. Thromboembolic events occur in Sjögren's syndrome, but catastrophic APS often developing in SLE overlap Sjögren's syndrome[19].A diagnosis of Sjögren's syndrome was present in our case, but the patient had not continued with treatment for the previous two years. Since no etiological cause could be identified, we think that Sjögren's syndrome may have triggered catastrophic APS.

In the clinical setting, catastrophic APS is characterized by the involvement of various different organs, particularly the kidneys (73%), lungs (60%), brain (56%), heart (50%), and skin (47%).11 Another study of 220 patients identified involvement in the kidneys (70%), lungs (66%), brain (60%), heart (52%), and skin (47%)[9]. Renal involvement has been defined by serum creatinine concentrations increasing by 50% or more, and proteinuria (>0.5 g/day)[2]. Cutaneous complications have been described as livedo reticularis in 42.3% of cases, skin necrosis in 23.5%, and digital ischemia in 10% in one previous study. Those authors also reported that the peripheral vascular system was involved in 36.2% of episodes, while venous involvement was observed in 69.2%, although arterial vessels were significantly less involved (47.8%)[20]. Severe thrombocytopenia and hemolytic anemia are common findings in patients with catastrophic APS. The thrombocytopenia results from widespread thrombosis and platelet consumption[4,14,20].

Cutaneous findings predominated in our case, first with marked thrombocytopenia-associated ecchymotic areas and later with thrombotic event-related necrosis. The patient's creatinine value on admission, 0.21 mg/dl, rose to 1.42 mg/dl on the third day, indicating renal involvement. The fall in PaO2/FiO2 indicated pulmonary involvement. The lesions resolved in less than one week, and cutaneous-renal-pulmonary involvement was present. Intravascular thrombi were detected at histopathological examination, and anti-Cardiolipin antibodies IgM and lupus anticoagulant positivity was detected at laboratory tests. The four diagnostic criteria were thus met, and definite catastrophic APS was diagnosed. The patient's history of Sjögren's syndrome and the fact that no etiological cause could be identified suggested the possibility that Sjögren's syndrome may have led to catastrophic APS development.

In conclusion, catastrophic APS is an uncommon but potentially life-threatening condition requiring high clinical awareness. The majority of patients with this condition manifest microangiopathy – i.e. occlusive vascular disease predominantly affecting the small vessels of different organs, particularly the kidney, lungs, brain, hear, liver and skin. Catastrophic APS may be comorbid with SLE (40%) and other autoimmune diseases (9%). In this case, catastrophic APS was detected in a patient with Sjögren's syndrome with severe skin necrosis. We wish to emphasize that catastrophic APS should be considered in the differential diagnosis in patients with skin necrosis.

Yazar Katkıları: Çalışma konsepti/Tasarımı: -; Veri toplama: -; Veri analizi ve yorumlama: EK, BÖ, TA, MG; Yazı taslağı: EK, TA; İçeriğin eleştirel incelenmesi: MG; Son onay ve sorumluluk: EK, BÖ, TA, MG; Teknik ve malzeme desteği: -; Süpervizyon: -; Fon sağlama (mevcut ise): yok.
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