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CASE REPORT / OLGU SUNUMU

Primary catastrophic antiphospholipid syndrome in an 8 year-old-girl

Primer katastrofik antifosfolipid sendrom: 8 yaşında kız çocuk

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ABSTRACT

Antiphospholipid syndrome (APS) is a disease characterized by recurrent arterial and venous thromboses. Rapidly progressive multiple thromboses leading to multiorgan failure occur in less than 1% of patients and named as catastrophic antiphospholipid syndrome (CAPS). We, hereby, describe an 8 year-old-girl with erythematous skin lesions progressing into purpura fulminans. The patient developed CAPS with the findings including proteinuria, microangiopathic hemolytic anemia, thrombocytopenia, arterial and venous thromboses demonstrated on skin biopsies. She was admitted to intensive care unit and received empirical antibiotics, anticoagulants, antiaggregants, steroids and intravenous immunoglobulins. The diagnosis of APS was confirmed by positive lupus anticoagulants, elevated anti beta-2 glycoprotein IgG and antiphospholipid IgG titers. Moreover, other than MTHFR-A1298C, MTHFR-C677T, factor V H1299R, beta fibrinogen-455 G>A heterozygosity indicating low risk for thrombophilia, no infectious, rheumatological or malignant etiologies were identified. Family history revealed Raynaud's phenomenon in a sister, similar skin lesions in the paternal aunt, interstitial lung disease, proteinuria and hematuria in paternal grandmother in addition to lupus anticoagulant positivity in the father and 2 elder sisters. Her treatment included debridement of necrotic skin tissue, grefting and local mesenchymal stem cell application to upper thigh and lower leg region following oral azathioprine administration.

Keywords: Catastrophic antiphospholipid syndrome, Child, Purpura fulminans

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ÖZ

Antifosfolipid antikor sendromu (AFAS) tekrarlayan venöz ve arteriyel trombozlarla seyreden bir hastalıktır. Hastaların %1'inden azında görülen hızlı seyirli, çoklu trombozlara bağlı multiorgan yetmezlik tablosu katastrofik antifosfolipid antikor sendromu (KAFAS) olarak adlandırılmaktadır. Burada eritematöz cilt lezyonlarıyla başvuran, takibinde alt ekstremitelerde yaygın purpura fulminans gelişen 8 yaşında kız çocuk sunulmaktadır. Hastada cilt tutulumuna ek olarak izlemde proteinüri, mikroanjiyopatik hemolitik anemiye eşlik eden trombositopeni gelişmesi ve cilt biyopsilerinde arteryel ve venöz trombozlar gösterilmesi nedeniyle KAFAS geliştiği düşünüldü. Hastaya yoğun bakım desteği ve geniş spektrumlu antimikrobiyal tedavilerin yanısıra antikoagulan, antiagregan, steroid, intravenöz immünoglobulin tedavileri uygulandı. Bu aşamada hastada lupus antikoagulan, anti beta-2 glikoprotein ve antifosfolipid IgG pozitifliği saptanması üzerine AFAS tanısı doğrulandı. Ancak etiyolojiye yönelik araştırmalarda trombotik riski düşük MTHFR-A1298C, MTHFR-C677T, faktör V H1299R, beta fibrinojen-455 G>A mutasyonlarının heterozigot pozitifliği dışında romatolojik, enfeksiyöz ve malign nedenler saptanmadı. Aile öyküsünde; ablada Raynaud fenomeni, halada benzer cilt lezyonları, babaannede intersitisyel akciğer hastalığı ve proteinüri olmasının yanında baba ve iki ablada lupus antikoagulan pozitifliği saptandı. Yaygın cilt nekrozuna yönelik debridman, greftleme ve lokal mezankimal kök hücre tedavisinin yanısıra azatioprin tedavileri de uygulanan hastada cilt bulgularında belirgin düzelme gözlendi.

Anahtar kelimeler: Katastrofik antifosfolipid antikor sendromu, Çocuk, Purpura fulminans

Introduction

Purpura fulminans (PF) is a rapidly progressive thrombotic disorder with hemorrhagic infarcts of skin and disseminated intravascular coagulation (DIC). In the etiology of childhood PF, infections, sepsis, autoimmune disease, protein C and S deficiency and antiphospholipid syndrome (APS) can be listed [1]. Among those, APS is characterized by

recurrent venous or arterial thrombosis and the presence of antiphospholipid antibodies including anticardiolipin, lupus anticoagulant, antibeta-2 glycoprotein [2]. Although concomitant autoimmune diseases may predispose to APS, it may also present without any underlying condition called primary APS [2]. Regardless of the etiology, less than 1% of patients with APS develop devastating form of the disease, called catastrophic APS (CAPS). This accelerated form of APS, with multiple thromboses leads to multiple organ failure and even death [3-5].

We, hereby, report a pediatric case of CAPS due to primary APS with mildly affected family members.

Case Report

An eight-year-old otherwise healthy girl presented with painful necrotic and bullous lesions on the lower extremities. Reddish-purple lesions on the medial side of both calves gradually extended to purpura fulminans within one week (Figure 1). Physical examination was noted for large necrotic ulcer on the left leg and thigh, ecchymosed-indurated lesions and a large bulla on her right leg (Figure 1). Laboratory findings revealed; WBC:6.3x10^3/uL, absolute neutrophil count:3,500/uL, absolute lymphocyte count:2,100/uL, ESR:8 mm/hour, CRP:3.1mg/lt (0-8mg/lt), PT:17s (11-13), APTT:33.4s (28-36), INR:1,39, fibrinogen: 129 mg/dl (200-400) and D-dimer: 0.31ug/ml (0-0.5). Blood smear was not compatible with blastic transformation. Blood and urine biochemistries were in normal range for the age. Following the initial work-up of thrombophilia, hereditary thrombophilic and rheumatologic diseases were not detected. Protein C, S and antithrombin III levels were all within the normal ranges (Protein C: 145% (70-130), Protein S: 73% (70-113), AT3: 102% (80-120); respectively). Autoimmune markers including ANA, anti-ds DNA, c-ANCA, p-ANCA, anti-histon, anti SS-A and SS-B antibodies were all negative. Complement screen for C3 and C4 levels were normal. Screening for thrombophilia revealed heterozygosity of MTHFR-A1298C, MTHFR-C677T, factor V H1299R, beta fibrinogen-455 G>A. Lower extremity Doppler ultrasonography revealed no arterial or venous thrombi in large vessels, whereas skin biopsies demonstrated plugging of numerous small vessels in the dermis and subcutaneous fatty tissue with thrombi.

In the follow-up, she developed hematuria and proteinuria (730mg/day). Skin lesions deteriorated and new lesions developed (Figure 1) despite the treatment with low molecular weight heparin (1 mg/kg/dose Q12hr) and empirical wide spectrum antimicrobials. On the 10th day of admission, she developed profound anemia (Hb: 5.5g/dL (12.0-17.0)). Laboratory investigations were compatible with disseminated intravascular coagulation (DIC): thrombocytopenia (platelets: 31x 10^3/ uL (150-440x 10^3/ uL)), prolonged prothrombin time of 17.8s (11-13s), activated partial thromboplastin time of 140s (28-36s) and decreased fibrinogen levels of 107.00 mg/dL (200-400 mg/dL). In the pediatric intensive care unit, she received heparin infusion (75U/kg loading dose followed by 20U/kg/hr infusion), corticosteroid therapy (2mg/kg/day) and fresh frozen plasma. Further studies showed the positivity of lupus anticoagulants, elevated anti-β_2 glycoprotein IgG and antiphospholipid IgG titers (Table I). Diagnosis of CAPS was settled by the positive sera, rapid clinical deterioration, characteristic skin lesions and thrombi at skin biopsy.

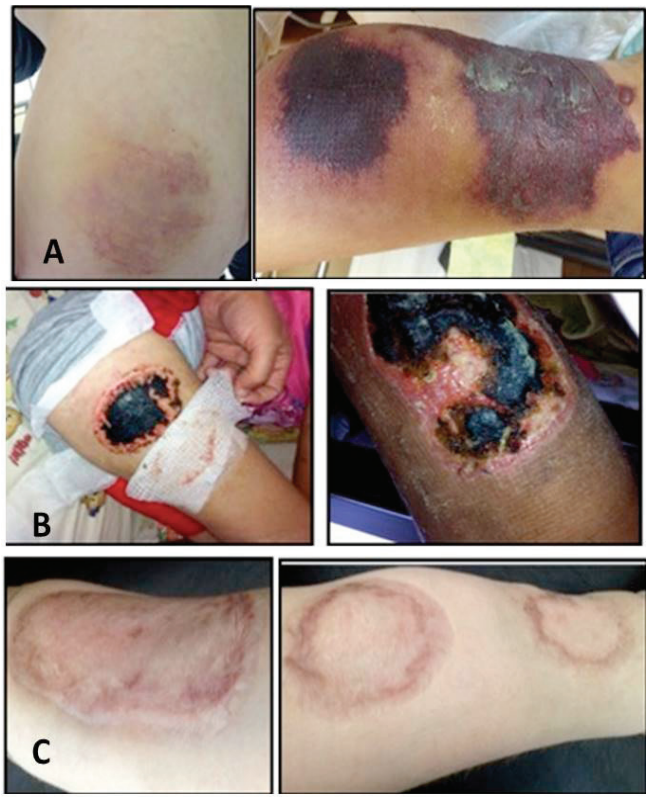

Figure 1: Clinical follow-up of purpura fulminans. A: Large necrotic ulcers and ecchymosed-indurated lesions at presentation. B: Necrotic tissue is debrided before skin grafting C: Healed lesions after skin grafting and local mesenchymal stem cell application by plastic surgery

Family history was remarkable for a sister describing Reynaud's phenomenon, the paternal aunt with similar skin lesions and paternal grandmother with interstitial lung disease, hematuria and proteinuria. The family members

were all screened twice for antiphospholipid antibodies. Results of the lupus anticoagulant tests were positive for two sisters and the father (Table I). Maintenance therapy included a combination of corticosteroids (2mg/kg/day), intravenous immunoglobulins (1gr/kg/day for 3 days), azathioprine (1mg/kg/day), low molecular weight heparin (1 mg/kg/dose Q12hr) and asetylsalicylic acid (80mg/day), nifedipine (0.5mg/kg/day), pentoxifylline 400 mg/dose (Q12hr). In 3 months' time, her necrotizing skin lesions healed following debridement, skin grafting and local mesenchymal stem cell application by plastic surgery (Figure 1). During one-year follow-up, no new lesions or thrombotic event developed, antiphospholipid antibodies remained negative. She is currently on warfarin (0.1mg/kg/day maintenance dose) and tapering regimen for azathioprine without any clinical and laboratory deterioration.

Table I: Antiphospholipid antibodies and clinical findings of family members

	Index	**Sister 1**	**Sister 2**	**Father**	**Paternal Grandmother**	**Paternal Aunt**
Lupus anticoagulant (31.4- 43.4 s)	**48,4/100.1/ 48.9**/30.9	**45.7**/39.4	**44.5**/39.1	**56.3**/39.3	39.7/41.7	NA
Anti-β_2 glycoprotein IgG (0-8 s)	**17.7**/2.6	3.1/	2.4/	6.2	3.1	NA
Anti-β_2 glycoprotein IgA (0-8 s)	1.5/1.2	1.4	0.6	6.1	**10.7**/1.6	NA
Anti-β_2 glycoprotein IgM (0-8 s)	1.6/1.7	1.5	1.7	3.3	1.9	NA
Anti- phospholipid IgG (0-9 s)	**10.4**/2.5	8.2	4.7	6.9	7.7	NA
Anti- phospholipid IgM (0-9 s)	1.5/2.5	1.6	1.4	3.5	4.7	NA
Anti- cardiolipin IgG (0-10 s)	5.1/3.7	2.6	2.8	2.7	1,8	NA
Anti- cardiolipin IgM (0-10 s)	1.3/3.1	1.0	0.7	2.0	0,9	NA
VDRL	negative	negative	negative	negative	negative	NA
Clinical features	CAPS PF		Raynaud's phenomenon		Interstitial lung disease, hematuria, proteinuria	PF

Abbreviations: **CAPS**: Catastrophic Antiphospholipid Syndrome **PF:** Purpura Fulminans **NA:** Not applicable **VDRL:** Venereal Disease Research Laboratory Test

Discussion

We hereby present a pediatric case of primary APS with purpura fulminans that rapidly progressed into CAPS. APS in pediatric population is a very rare entity and characterized by arterial and/or venous thrombosis and persistent presence of antiphospholipid antibodies [6]. Other characteristics of the disease are: clinical conditions such as livedo reticularis, chorea, thrombocytopenia, fetal loss and cardiac valve lesions with accompanying serological evidence of antiphospholipid antibodies that can cause thrombotic events of APS, especially in adults [7]. Newly suggested subset of APS is defined as microangiopathic antiphospholipid syndrome (MAPS) including thrombotic microangiopathic conditions such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome

and CAPS without large vessel occlusion [7]. Clinical heterogeneity at presentation and vast number of diseases in the etiology of APS keep the high index of suspicion as the best diagnostic tool.

Patients with CAPS may present with a wide range of symptoms depending on the involved system with multiple organ system involvement over a short period of time. Histopathological evidence of multiple small vessel thrombosis and presence of antiphospholipid antibodies confirm the diagnosis [4]. CAPS patients are classified either as definitive CAPS or according to the classifications proposed by Asherson et al. [8]. Our patient fulfills the criteria of definitive CAPS with skin, renal and hematological involvement along with antibody positivity [9].

Widespread cutaneous necrosis as an initial symptom is a rare presentation in childhood period [10]. Severe cutaneous necrosis was the first manifestation in our patient. In 2/3 of patients with primary CAPS there is a precipitating event, most frequently an infection [11]. In our case, the upper respiratory tract infection may be speculated as the precipitating factor by history. Besides, it may be assumed that the presence of heterozygosity of low thrombophilic genes may have contributed to the rapid clinical deterioration in our patient, whereas there is inconsistent data about the association of these mutations with clinical symptoms in antiphospholipid antibodies positive patients [12,13]. Pediatric APS registry also investigated single nucleotide polymorphisms of inflammatory mediators for the role of development of APS in pediatric patients which ended without any firm conclusion [14]. Different options of treatment including steroids, anticoagulation, antiaggregants, plasma exchange, intravenous immunoglobulins, cyclophosphamide, rituximab, prostacyclin, ancrod and defibrotide [11,15,16] reflect the vast variety of etiology and organ involvement. Our patient who had received most of these agents completed 1 year follow-up period without any new thrombotic event.

In conclusion, clinical heterogeneity and etiology of APS and CAPS make the high index of suspicion the best diagnostic tool. Keeping the mortality in mind, prompt treatment is essential to provide a better clinical outcome.

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