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Case Report

Catastrophic antiphospholipid syndrome accompanied by complement regulatory gene mutation

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ABSTRACT

Background. Antiphospholipid syndrome (APS), particularly the catastrophic antiphospholipid syndrome (CAPS), is one of the rare causes of thrombotic microangiopathy (TMA). CAPS is the most severe form of APS, especially when accompanied by complement dysregulation, causes progressive microvascular thrombosis and failure in multiple organs. In this report, a case of CAPS with TMA accompanied by a genetic defect in the complement system is presented.

Case. A 13-year-old girl was admitted to the hospital with oliguric acute kidney injury, nephrotic range proteinuria, Coombs positive hemolysis, refractory thrombocytopenia, a low serum complement C3 level and anti-nuclear antibody (ANA) positivity. The kidney biopsy was consistent with TMA. She was first diagnosed with primary APS with clinical and pathological findings and double antibody positivity. As initial treatments, plasmapheresis (PE) was performed and eculizumab was also administered following pulse-steroid and intravenous immunoglobulin treatments. Her renal functions recovered and she was followed up with mycophenolate mofetil, hydroxychloroquine, low dose prednisolone and low molecular weight heparin treatments. The patient presented with severe chest pain, vomiting and acute deterioration of renal functions a few months after the diagnosis of TMA. A CAPS attack was considered due to radiological findings consistent with multiple organ thrombosis and intravenous cyclophosphamide (CYC) was given subsequent to PE. After pulse CYC and PE treatments, her renal functions recovered, she is still being followed for stage-3 chronic kidney disease. Complement factor H-related protein I gene deletion was detected in the genetic study.

Conclusions. The clinical course of complement mediated CAPS tends to be worse. Complement system dysregulation should be investigated in all CAPS patients, and eculizumab treatment should be kept in mind if detected.

Key words: antiphospholipid antibody syndrome, thrombotic microangiopathy, complement activation, human complement factor H-related protein.

Antiphospholipid syndrome (APS) is an autoinflammatory disease characterized by arterial/venous thrombosis and/or recurrent pregnancy losses. The disease may be seen as primary or secondary to other autoinflammatory diseases such as systemic lupus erythematosus (SLE). The presence of anticardiolipin antibody (ACA), anti-beta 2 glycoprotein 1 antibody (anti-β2GP1) and lupus anticoagulant (LAC) is required for diagnosis.[1,2] Catastrophic antiphospholipid syndrome (CAPS), a life-threatening subgroup of APS, is characterized by multiple thrombosis and organ failure that

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develops within days.[1,2] Because of its high mortality rate (33-50%), early recognition is important.[1] CAPS is typically characterized by microthrombosis, whereas medium and large vessels are involved in APS. Systemic inflammatory response syndrome (SIRS) may also develop due to excessive cytokine release in CAPS.[1]

Thrombotic microangiopathy (TMA) is characterized by microthrombotic hemolytic anemia, thrombocytopenia and involvement of various organs. Antiphospholipid syndrome, especially the catastrophic form, is a rare cause of TMA due to characteristic microvascular involvement. Endothelial and/or complement activation play a crucial role in the pathogenesis of CAPS.[3] Additionally, it is important to recognize the crosstalk between the coagulation and complement systems. Complement activation due to various complement regulatory gene mutations seen in CAPS patients causes more serious complications.[3] The most common complement gene mutation in these patients is the complement factor H-related protein (CFHR) deletions.[3] Herein, a case of CAPS with TMA accompanied by a genetic defect in the complement system is presented.

Case Report

A 13-year-old female was admitted to the hospital with abdominal pain and swelling on both knees. Her medical history revealed that thrombocytopenia was detected during her hospitalization for severe menstrual bleeding two months ago. On admission, she had diffuse edema and decreased urine output; blood pressure was 163/100 mmHg. Bicytopenia was detected in the complete blood count, and the hemoglobin and platelet counts were 9.7 gr/dl and 35.000/mm^3, respectively. Her laboratory and clinical findings indicated oliguric acute kidney injury (AKI), serum urea and creatinine levels were 209 mg/dl and 3.97 mg/dl, respectively. Nephrotic range proteinuria (46 mg/m^2/h) was detected in 24-hour collected urine, but the serum albumin level (3.6 g/dl) was normal. Hemodialysis was initiated because of volume load and acute hypertensive encephalopathy unresponsive to antihypertensive drugs and diuretics. Schistocytes were detected in her peripheral smear. Anti-nuclear antibody (ANA) and direct Coombs were positive. Laboratory findings showed reticulocytosis (4%), low serum haptoglobulin (<8 mg/dl) and elevated LDH (1080 U/L) levels consistent with hemolysis. There was no evidence of malignancy in the bone marrow aspiration. The patient was considered to have TMA. Serum complement C3 level was low (72 mg/dl, normal range: 88-201 mg/dl), ADAMTS-13 enzyme level and activity (130.94 IU/ml and 94%, respectively) were normal. A renal biopsy was performed because of prolonged oliguric course and to detect the etiology of AKI. Pathological examination showed glomerular congestion, polymorphonuclear leukocyte infiltration, fibrin thrombi in capillary loops and cortical necrosis consistent with the clinical diagnosis of TMA (Fig. 1). No specific finding of lupus nephritis was detected in the kidney biopsy. Three doses of pulse-steroid (methylprednisolone, 30 mg/kg/dose) and intravenous immunoglobulin (1 gr/kg single dose) treatments were given and high dose oral prednisolone (60 mg/m^2/day) and mycophenolate mofetil (800 mg/m^2/day) were continued as there was still clinical suspicion of SLE. Plasmapheresis (nine sessions, 1.5 fold of estimated plasma volume, replaced with fresh frozen plasma) was performed to clear out possible sources of antibody and complement-related TMA, and the patient received three doses of eculizumab (600 mg/dose). After twenty days on hemodialysis, her urine output increased and her blood pressure stabilized at normal percentiles.

The differential diagnosis of cortical necrosis and thrombosis was evaluated. The anticardiolipin antibody was negative. Lupus anticoagulant (Screen levels 123.3

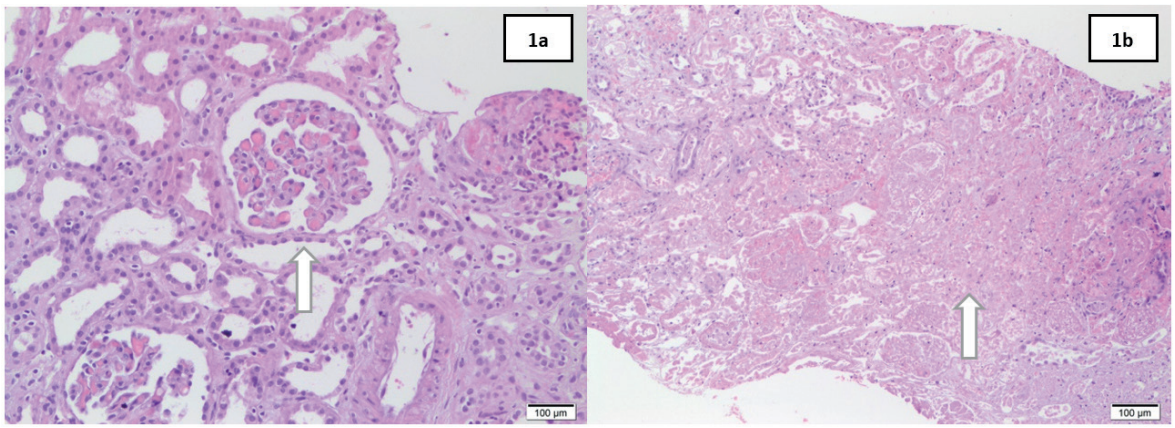

Fig. 1. Histopathological findings of kidney. (a) H&E staining shows fibrin thrombi in glomerular capillary loops (Hematoxylin-eosin stain, original magnification ×100) (b) H&E staining shows a wide cortical necrosis in the right side (Hematoxylin eosin stain, original magnification ×100)

and 93.5 seconds respectively, normal range: <44 seconds; confirmation levels 48.5 and 40.4 seconds respectively, normal range: <37 seconds; and screen/confirmation ratio: 2.54 and 2.31 respectively, normal range: <1.3) and anti- β2GP1 IgM (31.25 and 41.38 RU/ml respectively, normal range: 0-19 RU/ml) were found to be positive twice, 12 weeks apart. The patient was diagnosed with primary APS with histopathology and antibody positivity (Table I). She was followed up with mycophenolate mofetil (800 mg/m^2/day), hydroxychloroquine (5 mg/kg/day), low dose prednisolone (5 mg on alternate days) and low molecular weight heparin (2000 IU/day) treatments. Our patient's urine output increased first, then her eGFR increased to 41 ml/min/1.73m^2. Hemodialysis was discontinued after a significant recovery of kidney functions.

Table I. Antiphospholipid syndrome (APS) and catastrophic APS diagnostic criteria[1,7]

Antiphospholipid Syndrome Diagnostic Criteria*	
Clinical	Laboratory
1) Vascular thrombosis	1) Lupus anticoagulant
• One or more arterial, venous, or small vessel thrombosis in any tissue	- At least 2 times, 12 weeks apart
2) Prenatal mortality	2) Anticardiolipin antibody
• One or more unexplained fetal deaths >10 weeks	- IgG and/or IgM
• Preterm birth of one or more normal fetuses <34 weeks	- At least 2 times, 12 weeks apart
• Three or more <10 weeks unexplained miscarriage	Medium and high titer
	3) Anti beta-2 glycoprotein 1 antibody
	- IgG and/or IgM
	- At least 2 times, 12 weeks apart, high titer
Catastrophic APS Diagnostic Criteria**	
• Involvement of at least 3 organs, tissues or systems	
• Organ manifestations develop within a week	
• Antibody positivity (high titer)	
• Exclusion of other causes	

*2006 Sydney Criteria, 1 clinical and 1 laboratory criteria must be met.
**All criteria must be met.

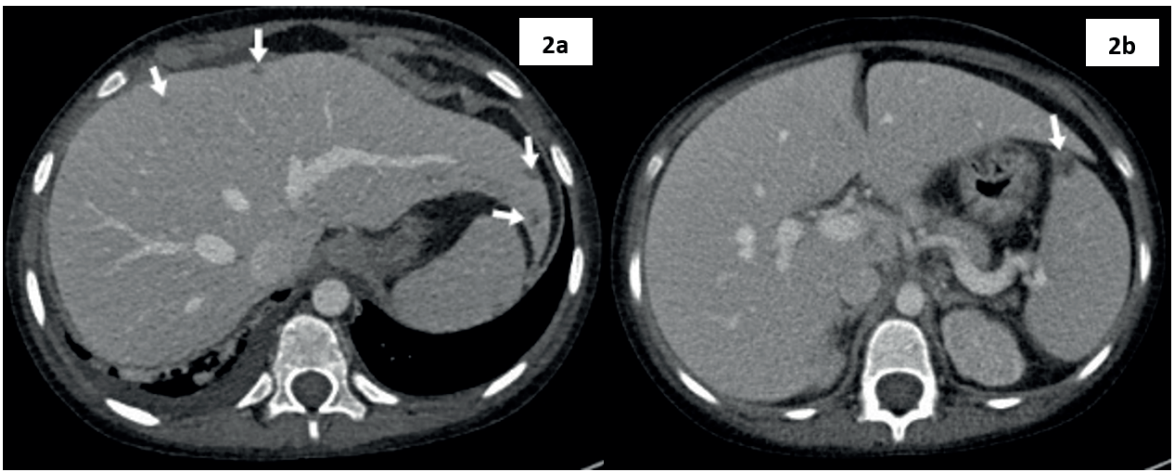

Fig. 2. Radiological findings. Ischemic areas are visible in intravenous contrast-enhanced abdominal computed tomography: (a) subcentimetric hypodense areas (arrow) in both lobes of the liver, and (b) a hypodense area (arrow) in the anterior midsection of the spleen.

She was readmitted to the hospital after two months due to severe chest pain and vomiting. Clinical and radiological investigations revealed acute deterioration of chronic renal damage, as well as hepatic and splenic ischemia (Fig. 2). CAPS was considered with clinical findings and multiple ischemic lesions (Table I). Intravenous cyclophosphamide (1000 mg/m^2/dose) was given subsequent to the three sessions of plasmapheresis (1.5 fold of estimated plasma volume, replaced with fresh frozen plasma). After three doses of pulse cyclophosphamide, she is still being followed for stage-3 chronic kidney disease (eGFR 45 ml/min/1.73m^2 with Schwartz formula), clinically stable with oral mycophenolate mofetil (800 mg/m^2/day), hydroxychloroquine (5 mg/kg/day), low-dose prednisolone (5 mg on alternate days) and low molecular weight heparin (2000 IU/day) treatments. Because of the widespread thrombosis with multiple organ involvement, genetic studies were done. Genetic analysis revealed a large deletion in the *CFHR1* gene (exon 2, 3, 4), however, the anti-factor-H antibody was negative.

Biochemical and mutational analysis

Anti-cardiolipin antibody and anti-β2GP1 were measured by enzyme-linked immunoassay (ELISA), according to the manufacturer's protocol. Values for ACA >12 IU/ml and anti-β2GP1 >19 RU/ml were identified as positive. The simplified Dilute Russell's Viper Venom Test (dRVVT) was performed for LAC1 screening reagent and LAC2 confirmatory reagent according to the manufacturer's protocol. Lupus anticoagulant was considered positive when the dRVVT ratio (LAC1 screen/LAC2 confirmation) was above 1,3.

For genetic studies, after detailed informed consent was obtained, the patient's total genomic DNA was extracted from peripheral blood using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). *ADAMTS13*, *C3*, *CD46*, *CFH*, *CFB*, *CFHR1 (NM_002113.2)*, *CFI*, *DGKE*, *MMACHC* and *THBD* genes were sequenced using the Sophia Clinical Exome Solution (CES) kit via Next-Generation Sequencing (NGS) (Illumina Nextseq 500). Bioinformatic analyzes and variant sequencing were performed using the Sophia-DDM-V3 bioinformatics analysis program. Based on the ClinVar database, only pathogenic and possibly pathogenic variants associated with the patient's clinic were reported. Retained variants were evaluated according to the American College of Medical Genetics and Genomics (ACMG) 2015 guideline. Data from the 1000 Genome Project, database of

Single Nucleotide Polymorphisms (dbSNP) and Exome Aggregation Consortium (ExAC) were used as the control population.

An informed consent was received from the patient's family about the publication of this report.

Discussion

CAPS is a rare disease characterized by progressive microvascular thrombosis and failure in multiple organs or systems and diagnosed by the presence of responsible antibodies and exclusion of other etiologies. It may be primary or secondary to autoinflammatory diseases such as SLE or APS. Anti beta-2 glycoprotein 1, LAC and ACA are detected at high titers in patients' sera twice at least 12 weeks apart.[1,2] There is usually a trigger to initiate the inflammation and thrombosis cascade, especially infections and malignancies.[1,3] This entity is distinguished from severe APS by the type of affected vessel and the evidence of a systemic inflammatory response. While thrombosis in medium and large vessels is commonly seen in APS, microvascular involvement is typical for CAPS. In addition, SIRS is also a distinctive clinical finding for CAPS compared to APS.[1] CAPS is a rare clinical entity that occurs in approximately 1% of patients with APS.[4] According to the international CAPS registry, CAPS was the first presentation form of APS in 86% of pediatric patients.[5] In the same study, 60 of 500 (12%) patients had symptoms before the age of 18; these were predominantly female (67%) and primary CAPS (59%). The association with autoinflammatory diseases is less in CAPS compared to APS. According to the Pediatric-APS registry, 49% of patients with APS had an underlying autoimmune disease, compared to 24% of patients with CAPS.[1] The diagnosis is delayed mostly due to the similarity of clinical and laboratory findings with other autoinflammatory diseases and unfortunately its mortality rate is about 33-50% if untreated.[5,6] Although TMA is a rare condition in APS, it can be seen especially in patients with CAPS which is characterized by microvascular thrombosis. Our patient was considered to have primary APS because there were no clinical, laboratory, or pathological findings of any concomitant autoinflammatory disease.[1,7]

There are many theories concerning the pathophysiology of CAPS, the best known are; excessive cytokine release, thrombosis, endothelial injury and complement activation.[1-3] Usually, a bacterial or viral product and lipopolysaccharides initiate inflammation and bind to Toll-like receptor 4, allowing the release of proinflammatory cytokines. This inflammatory environment itself provides a prothrombotic basis.[8,9] Besides, anti-β2GP1 antibodies directly induce endothelial cell activation and promote platelet aggregation and adhesion.[1,10] Thrombosis is a crucial finding in several complement-related diseases, such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS).[11,12] Although the mechanism of complement activation is unclear in CAPS, it is obvious that a crosstalk between evolutionarily related complement and coagulation pathways has a critical role in thrombosis formation, as a "third hit" in the pathogenesis that aggravates the basal procoagulant and inflammatory state, and in turn worsens the clinical course.[1,3,13-16] Activated C3a and C5a, alternative pathway members of the complement system, provides the release of pro-inflammatory and pro-coagulant cytokines from monocytes and endothelial cells. The terminal pathway product C5b-9 also induces the release of procoagulant vWF and P-selectin.[3] Several animal studies have shown that C3a-receptor knock-out mice are less susceptible to experimental thrombosis.[17] A prospective experimental study evaluating complement activation in APS/CAPS patients with modified Ham assays by complement-dependent cell death and cell surface depositon of C5b-9 by flow cytometry, resulted in significantly higher complement activation in CAPS (85.7%) against APS (35.6%) and SLE (6.8%) patients. Likewise, patients with CAPS are more likely to have

mutations in complement dysregulatory genes (60%) compared with patients with APS (21.8%) or SLE (28.6%) or normal controls (23.3%) and have a similar incidence to patients with aHUS (51.5%).[3] In conclusion, besides endothelial cell activation, anti-β2GP1 antibody activates complement system and contributes to the formation of thrombosis, also accompanied complement dysregulation causes more severe thrombotic tissue damage especially in CAPS patients, like in our patient. In addition, the detection of renal cortical necrosis associated with extensive thrombosis in the pathological examination of our patient was also assumed to be an effect of the *CFHR1* mutation. In our case, the low C3 level at admission was one of the indirect indicators of complement activation. Normal C4 levels also supported the diagnosis of primary CAPS by reducing the possibility of diseases such as SLE that activate the complement system via the classical pathway. The lack of SLE-specific findings in kidney biopsy also supports this hypothesis.

In recent years, limited studies have revealed that there are some complement gene variants associated with CAPS. Patients with CAPS were found predominantly to have homozygous *CFHR1-CFHR3* deletions.[3] This is a relatively common genetic variation that occurs in 2% of the general population.[18] However, their product CFHR proteins have a prominent role in complement regulation by competing for factor H or inhibiting C5 convertase activity directly.[19] Commonly, *CFHR1-CFHR3* deletions are seen together with the presence of an anti-factor H antibody that inhibits factor H functions.[20,21] Anti-factor H is one of the common complementopathies in aHUS etiopathogenesis but to the best of our knowledge, no anti-factor H antibody-associated CAPS cases has been reported. Similar to previous studies, our patient has a large *CFHR1* deletion and the anti-factor H antibody was negative.

Eculizumab, a long-acting C5 blocking antibody, has been used for many years especially for aHUS and some other complement-related diseases.[13,22-24] Eculizumab inhibits the formation of pro-inflammatory and pro-thrombotic C5a and C5b, thus preventing the formation of the membrane attack complex.[12] In recent years, there have been many case reports showing the success of eculizumab therapy in CAPS patients; who were resistant to anticoagulant, immunosuppression and plasma exchange therapies.[3,13,25-27] According to the pathogenesis of thrombosis in CAPS, blockage of the complement system can prevent wide-spread thrombosis and/or poor clinical outcome. We believe that the presented patient with acute renal damage who required dialysis responded effectively to eculizumab treatment in the first attack, and eculizumab can be administered again if CAPS attacks recur due to the genetic mutation we found in the patient. Eculizumab treatment should be kept in mind in CAPS patients, especially in genetic forms and as a prophylaxis after transplantation, according to the clinical course and response to classical treatments.

Antiphospholipid syndrome should be considered in patients presenting with TMA especially with an atypical medical history such as refractory thrombocytopenia. CAPS, a subgroup of APS, is a rare and mortal entity which is characterized by multiple organ failure within days. However, mortality decreases with early diagnosis and effective treatment especially in complement mediated CAPS. Complement system dysregulation should be studied in all patients. Mutations associated with complement system dysregulation tend to be seen with a severe clinical course in patients with CAPS. Complement system blockage with eculizumab is promising for treating patients with CAPS.

Ethical approval

An informed consent was received from the patient's family about this report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: IG; data collection: SP, IG; interpretation of results: EDB, SG, NÇ, MS, ÖNT, DF, CP, BS, HA; draft manuscript preparation: SP, IG; critically review of the manuscript: EDB, SG, NÇ, MS, ÖNT, DF, CP, BS, HA. All authors reviewed the manuscript and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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