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Catastrophic antiphospholipid syndrome with concurrent thrombotic and hemorrhagic manifestations

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Antiphospholipid syndrome (APS) is a distinct autoimmune prothrombotic disorder due to pathogenic autoantibodies directed against proteins that bind to phospholipids. APS is characterized by arterial and venous thrombosis and their clinical sequelae. Catastrophic antiphospholipid syndrome (CAPS) is a rare and often fatal form of APS characterized by disseminated intravascular thrombosis and ischemic injury resulting in multiorgan failure. Rarely, intravascular thrombosis in CAPS is accompanied by hemorrhagic manifestations such as diffuse alveolar hemorrhage. Here, we report a 43-year-old woman who presented with anemia, acute gastroenteritis, abnormal liver function tests, bilateral pulmonary infiltrates, and a systemic inflammatory response syndrome. The patient developed respiratory failure as a result of diffuse alveolar hemorrhage followed by acute renal failure. Laboratory tests disclosed hematuria, proteinuria, and reduced platelet count. Microbiologic tests were negative. A renal biopsy demonstrated acute thrombotic microangiopathy and extensive interstitial hemorrhage. Serologic tests disclosed antinuclear antibodies and reduced serum complement C4 concentration. Coagulation studies revealed the lupus anticoagulant and autoantibodies against cardiolipin, beta 2-glycoprotein I, and prothrombin. High-dose glucocorticoids and plasma exchange resulted in rapid resolution of pulmonary, renal, and hematological manifestations. This rare case emphasizes that CAPS can present with concurrent thrombotic and hemorrhagic manifestations. Rapid diagnosis and treatment may result in complete recovery. *Lupus* (2013) **22,** 855–864.

Key words: Catastrophic antiphospholipid syndrome; CAPS; hemorrhage; diffuse alveolar hemorrhage; interstitial hemorrhage; thrombotic microangiopathy; plasmapheresis; plasma exchange; glucocorticoids

Case presentation

A 43-year-old woman was admitted to the hospital because of abdominal pain, diarrhea, and shortness of breath.

The patient was in her usual state of health until one week prior to the admission to this hospital when she developed new-onset upper abdominal pain associated with nausea, vomiting, and diarrhea. The abdominal pain fluctuated in intensity, was at times moderately severe (7/10), radiated to the back, and was not associated with meals. She vomited clear liquid and passed semiliquid non-bloody stools three to four times a day. She also experienced headache accompanied by transient double vision. A few days later, she developed cough productive of scant white sputum, respirophasic chest pain, and dyspnea on exertion. A review of systems was otherwise negative.

The patient was a native of Cuba who immigrated to the United States approximately a year prior to the current presentation. Her past medical history was remarkable for obesity and hypertension. She was taking metoprolol 50 mg/day, atenolol 50 mg/day, and captopril 25 mg/day. Since childhood, she suffered from ''migraine'' headache, for which she took acetaminophen and ibuprofen as needed. Headaches were sometimes associated with double vision. Two years prior to admission, when she was still in Cuba, she developed

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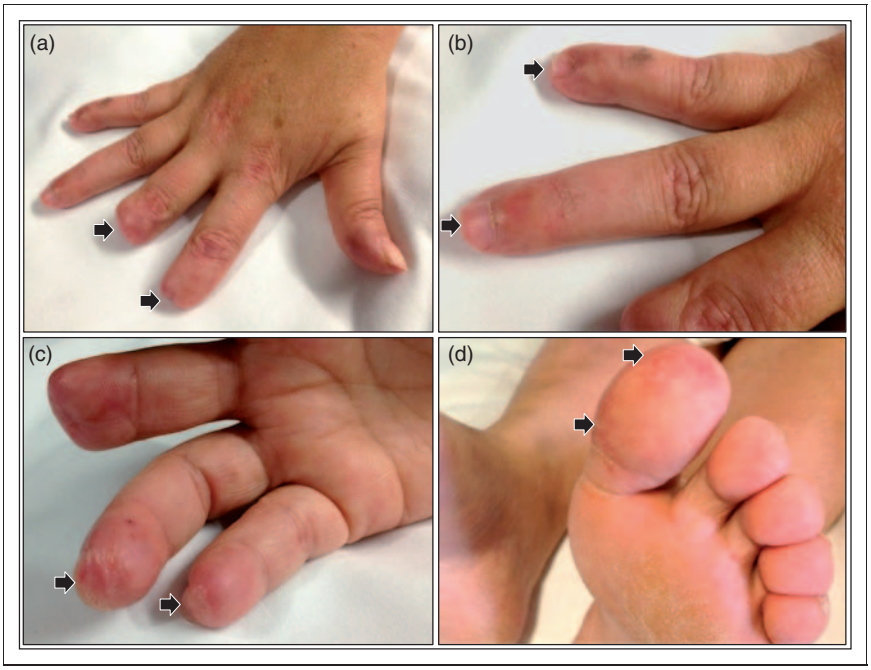

Figure 1 Physical examination findings. Photograph showing amputated distal phalanges of the right middle and index fingers (a). Atrophic distal phalanges of the right little and ring fingers are shown (b). Cutaneous scars at the tip of distal phalanges of the right little and ring fingers are demonstrated (c). Netlike red-purple discoloration of the left great toe resembling livido reticularis (d).

spontaneous ischemia of her right middle and index fingers resulting in gangrene of distal phalanges. She sought medical attention and was referred to a surgeon who performed the amputation of affected phalanges. She was not instructed to take any particular medication for the condition that might have caused gangrene of her fingers. Furthermore, she had no recollection of any special blood tests that might have been performed. She denied a history of spontaneous miscarriage, deep vein thrombosis, menometrorrhagia, or excessive bleeding after minor trauma. She had no known drug allergy. She had been working as a pharmacy technician until a year prior to the current illness. She denied use of alcohol, tobacco, and illicit drugs. The family history was notable for diabetes mellitus, hypertension, and coronary artery disease.

On physical examination, the patient was a well-developed middle-aged woman in respiratory distress. The temperature was 37.8°C, the blood pressure 178/107 mm Hg, the pulse 117 beats per minute, the respiratory rate 22 breaths per minute, the oxygen saturation 94% while breathing ambient air, and the body mass index 33 kg/m^2. The jugular venous distention was within normal limits. The cardiovascular examination was unremarkable. Auscultation of the lungs demonstrated scattered crackles. There was mild epigastric and right upper quadrant tenderness, but no guarding or rebound. A fecal occult blood test was negative. The extremities did not show cyanosis, clubbing or edema. The distal phalanges of the right middle and index fingers were amputated (Figure 1(a)). The distal phalanges of the right little and ring fingers were short and demonstrated atrophy of the pads and cutaneous scars at the tip (Figure 1(b), (c)). The great toes demonstrated net-like red-purple discoloration suggestive of livedo reticularis (Figure 1(d)).

Laboratory data are summarized in the Table 1. Abnormal liver function tests, a normocytic normochromic anemia, elevated lactate dehydrogenase, hypokalemia, and hypoalbuminemia were noted upon admission. The activated partial thromboplastin time and prothrombin time were mildly elevated. A urinalysis revealed 30 mg/dl proteinuria. A chest radiograph demonstrated bilateral patchy airspace opacities with mid and lower lung zone predominance (Figure 2(a)). Computed tomographic angiography showed no evidence of pulmonary embolism. However, bilateral, patchy, ground-glass opacities in the lungs, and mediastinal and hilar lymphadenopathy and mild hepatosplenomegaly were noted (Figure 2(b–d)). The hepatobiliary system was normal by abdominal ultrasound.

Table 1 Laboratory data

Analyte	*Reference range*	*Day 1*	*Day 5*	*Analyte*	*Reference range*	
Sodium (mmol/l)	135–145	139	136	Activated PTT (sec)	24.5–35.7	**38.6**
Potassium (mmol/l)	3.4–4.8	**2.8**	4.5	Prothrombin time (sec)	10.1–12.6	**12.8**
Chloride (mmol/l)	99–109	**97**	105	Lupus anticoagulant (LA) panel	Negative	**Positive**
Carbon dioxide (mmol/l)	21–30	**34**	**20**	Silica clotting test ratio	< 1.17	**1.69**
Urea nitrogen (mg/dl)	7–22	7	**22**	DRVV ratio	< 1.2	**1.65**
Creatinine (mg/dl)	0.5–1.4	1.1	**1.7**	Staclot LA clotting time (sec)	< 10	**17.8**
Glucose (mg/dl)	65–99	101	78	Anti-cardiolipin Ab	Negative	**Positive**
Hemoglobin A1C (%)	< 6.0	5.5		Immunoglobulin G (U/ml)	< 10	**974**
Calcium (mg/dl)	8.6–10.3	8.8	**7.6**	Immunoglobulin A (U/ml)	< 8	**21**
Protein (g/dl)	6.3–8.2	6.2	**5.8**	Immunoglobulin M (U/ml)	< 10	**16**
Albumin (g/dl)	3.5–5.5	**3.2**	**2.5**	Anti-beta 2 glycoprotein I Ab	Negative	**Positive**
Globulin (g/dl)	2.3–3.5	**3.0**	3.3	Immunoglobulin G (U/ml)	< 20	**153**
Aspartate transaminase (IU/liter)	15–46	**56**	33	Immunoglobulin M (U/ml)	< 20	**23**
Alanine transaminase (IU/liter)	9–52	**78**	33	Anti-prothrombin Ab	Negative	**Positive**
Alkaline phosphatase (IU/liter)	38–126	**277**	126	Immunoglobulin G (U/ml)	< 20	< 20
Lipase (IU/l)	22–51	18		Immunoglobulin M (U/ml)	< 20	**66**
Amylase (IU/l)	28–100	38		Protein C activity (%)	87–187	103
Creatine phosphokinase (IU/liter)	38–234	27		Protein S activity (%)	89–167	**82**
Bilirubin, total (mg/dl)	0.3–1.3	0.6	0.6	Anti-thrombin III activity (%)	79–110	**57**
Bilirubin, indirect (mg/dl)	0.2–0.9	0.4		Factor II activity (U/ml)	0.76–1.4	0.78
Lactate dehydrogenase (IU/liter)	313–618	**1201**	**1362**	Factor VIII activity (U/ml)	0.54–1.55	1.04
Haptoglobin (mg/dl)	30–200	**311**	**379**	Factor IX activity (U/ml)	0.59–1.47	1.13
Bilirubin, total (mg/dl)	0.3–1.3	0.6	0.6	Factor XI activity (U/ml)	0.54–1.10	0.77
Bilirubin, indirect (mg/dl)	0.2–0.9	0.4		Anti-PF4 (IgG/M/A) (OD value)	< 0.4	**0.53**
Hemoglobin (g/dl)	13.6–16.7	**8.2**	**6.4**	Fibrinogen (mg/dl)	190–380	**431**
Hematocrit (%)	40.0–49.0	**25.8**	**19.3**	Autoantibodies		
MCV (μm^3)	82–93	86.9	84.8	Anti-nuclear Ab titer	< 1:40	**1:160**
MCHC (g/dl)	30–35	31.8	33.3	Anti-nuclear Ab pattern		**Homogeneous**
White-cell count ($\times 10^3$ per mm^3)	4.8–10.8	9.7	10.0	Anti-dsDNA (IU/ml)	< 5.0	**6.0**
Neutrophils	1.5–7.0	**7.7**	**8.4**	Anti-centromere	Negative	Negative
Lymphocytes	1.0–3.7	1.1	1.2	Anti-chromatin	Negative	Negative
Monocytes	0.0–0.7	0.6	0.4	Anti-GBM	< 1.0	< 1.0
Eosinophils	0.0–0.4	0.1	0.0	Anti-Jo-1	Negative	Negative
Basophils	0.0–0.1	0.0	0.0	Anti-myeloperoxidase	Negative	Negative
Platelet count ($\times 10^3$ per mm^3)	130–350	299	259	Anti-proteinase 3	Negative	Negative
Erythrocyte sedimentation rate (mm/hr)	0–20		**136**	Anti-ribonucleoproteins	Negative	Negative
C-reactive protein (mg/dl)	< 1.0		**15.4**	Anti-ribosomal	Negative	Negative
Urinalysis				Anti-Smith	Negative	Negative
Color	Yellow	Yellow	Yellow	Anti-SSA/Ro	Negative	Negative
Turbidity	Clear	Clear	Clear	Anti-SSB/La	Negative	Negative
pH	4.6–7.8	7.5	6.5	Anti-scleroderma 70	Negative	Negative
Specific gravity	1.001–1.035	1.005	1.015	Anti-smooth muscle	Negative	Negative
Glucose	Negative	Negative	Negative	C3 (mg/dl)	90–180	117
Ketones (mg/dl)	Negative	Negative	10	C4 (mg/dl)	15–47	**7.8**
Bilirubin	Negative	Negative	Negative	Rheumatoid factor (IU/ml)	< 14	< 10
Blood (mg/dl)	Negative	**0.03**	**1.0**	Cryocrit	0	**1%**
Protein (mg/dl)	Negative	**30**	**70**	Serum protein electrophoresis	Normal pattern	Normal pattern
Nitrites	Negative	Negative	Negative	Serum globulins (g/dl)	2.0–4.0	2.95
Leukocyte esterase (leu/µl)	Negative	Negative	**75**	Alpha 1 (g/dl)	0.13–0.36	0.18
White blood cells (per hpf)	0–2	0	**3**	Alpha 2 (g/dl)	0.56–1.22	0.87
Red blood cells (per hpf)	0–4	3	**>100**	Beta (g/dl)	0.68–1.33	0.81
				Gamma (g/dl)	0.62–2.00	1.09

MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; hpf: high-power field; PTT: partial thromboplastin time; OD: optical density; anti-dsDNA: anti-double-stranded DNA; anti-GBM: anti-glomerular basement membrane.

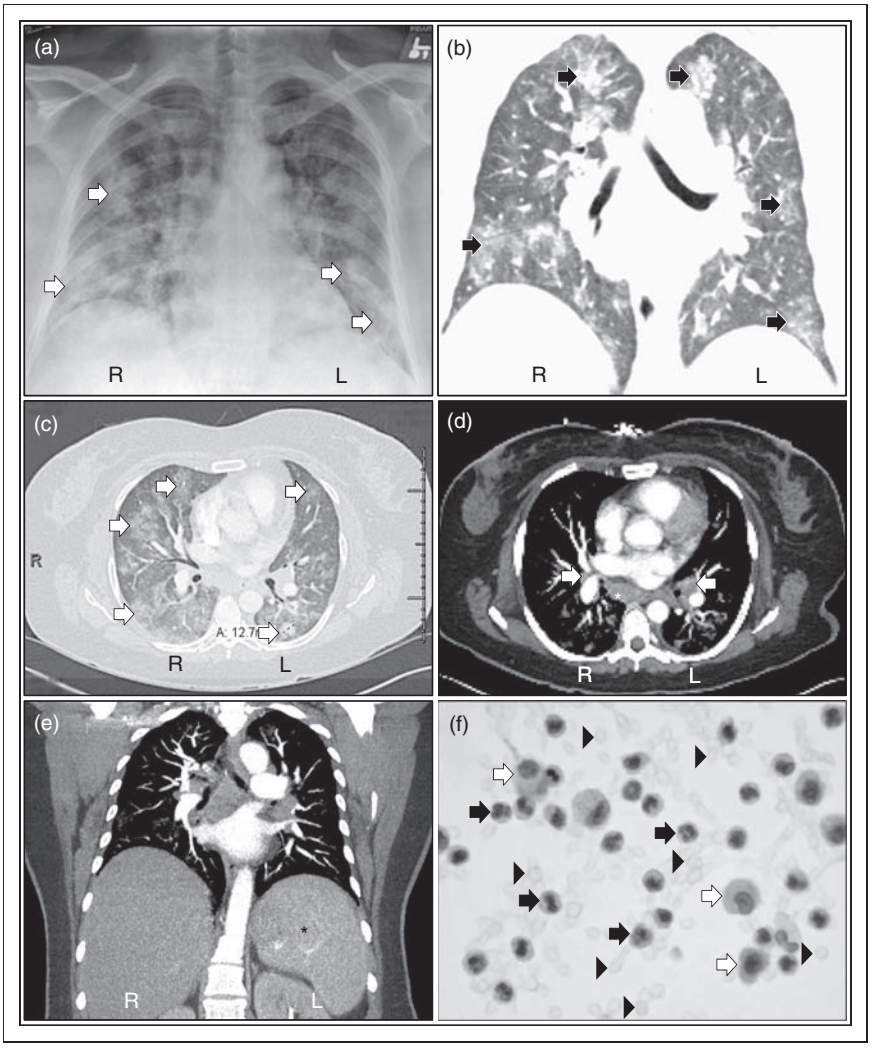

Figure 2 Diffuse alveolar hemorrhage. A chest radiograph demonstrating bilateral patchy airspace opacities (arrows) in the lungs (a). Computed tomographic angiography of the chest and upper abdomen showing bilateral patchy ground-glass opacities (arrows) in the lungs (b, c), enlarged mediastinal (asterisk) and hilar (arrows) lymph nodes (d) as well as enlarged spleen (asterisk) (e). Bronchoalveolar lavage fluid disclosing numerous erythrocytes (arrowheads), polymorphonuclear leukocytes (black arrows), and alveolar macrophages (white arrows) (f).

The patient was initially diagnosed with community-acquired pneumonia, gastroenteritis, and dehydration. Intravenous fluids and antibiotics were administered. Examination of stools for ova, parasites, and clostridium difficile toxins A and B were negative. Stool cultures revealed normal gut flora. Blood and urine cultures showed no growth. Nasopharyngeal cultures for common respiratory viruses were negative. Legionella antigen was not detected in the urine. All tests for hepatitis B and C viruses and human immunodeficiency virus (HIV) were negative. On the third hospital day, the patient developed respiratory failure requiring mechanical ventilatory support. The white blood cell rose to 16,500 per microliter with 90% neutrophils. On the fourth hospital day, a bronchoscopy demonstrated friable mucosa of upper airways and grossly bloody fluid from a bronchoalveolar lavage (BAL). Examination of a BAL specimen disclosed numerous erythrocytes, leukocytes (neutrophils 84%, lymphocytes 13%, mononuclear cells 2%, eosinophils 1%), and reactive bronchoalveolar cells (Figure 2(f)). No evidence of viral cytopathic effects, fungi, or malignant cells was found. Special stains of BAL fluid for bacteria, acid-fact bacilli, fungi, and pneumocystis carinii were negative. Cultures of BAL fluid for respiratory viruses, bacteria, acid-fact bacilli, mycoplasma, ureaplasma, and fungi were negative. The patient was diagnosed with diffuse alveolar hemorrhage.

On the fifth hospital day, the patient was extubated. The hemoglobin level was 6.4 g/dl and there was a positive direct antiglobulin (Coombs) test. Erythrocyte sedimentation rate and the levels of lactate dehydrogenase, haptoglobin, and C-reactive protein were elevated. All cultures remained negative. Despite 1.3 liters of urine flow on hospital day 5, the serum creatinine rose to 1.7 mg/dl. A urinalysis revealed >100 erythrocytes/high-power field (hpf) and 70 mg/dl protein, suggestive of approximately 1 g/day. Renal ultrasonography demonstrated the right and left kidney measuring 13.2 and 12.6 cm in length, respectively, with normal echogenicity. There was no hydronephrosis, stones, cysts, or masses.

Serological studies are summarized in the Table 1. Antinuclear antibodies by indirect immunofluorescence were detected at a titer of 1:160 with a homogeneous pattern. Antibodies directed against double-stranded DNA were borderline positive on two occasions (6.0 IU/ml and 5.0 IU/ml). While the level of complement C3 was within normal range, low levels of complement C4 were measured on two occasions (8.9 mg/dl and 7.8 mg/dl). Cryoglobulins (cryocrit 1%) were present on two occasions. Serum protein electrophoresis revealed a normal pattern. Anti-neutrophil cytoplasmic antibodies (ANCA) (indirect immunofluorescence) were not detected. Antibodies against glomerular basement membranes, myeloperoxidase, and proteinase-3 were not detected. On the seventh hospital day, the patient was started on methylprednisolone 1.0 g/day intravenously for a presumptive pulmonary-renal syndrome. On the eighth hospital day, patient's respiratory status remained tenuous, requiring 100% supplemental oxygen administered via a face mask. Serum creatinine was 2.4 mg/dl. The platelet count of 139,000 per microliter of blood represented a decline of greater than 50% over a five-day period. A review of blood smears disclosed occasional fragmented erythrocytes (schistocytes), scattered spherocytes, erythrocyte agglutination and mild thrombocytopenia. The patient received three units of fresh frozen plasma for a presumptive diagnosis of thrombotic microangiopathy.

On the eighth hospital day, a renal biopsy was performed. There were approximately 23 glomeruli per level, none of which was globally sclerosed. All glomeruli appeared congested and more than half contained capillary microthrombi (Figure 3(a)). Microvascular thrombosis also involved arterioles and interstitial capillaries (Figure 3(a–c)). There was marked multifocal interstitial hemorrhage (Figure 3(d)). Although occasional marginating neutrophils were present in glomeruli, there was no endo- or extracapillary proliferation or fibrinoid necrosis. There was extensive acute tubular injury manifested by flattening, vacuolization, and loss of brush border of the epithelium as well as dilation of tubular lumina. Occasional proximal tubular epithelial cells contained prominent protein reabsorption droplets. There was focal interstitial fibrosis and tubular atrophy. Immunofluorescence examination revealed prominent immunoreactivity with antiserum to fibrinogen in the glomerular capillaries, arterioles, and interstitium (Figure 3(e)). Occasional podocytes and tubular epithelial cells demonstrated immunoreactivity with antisera to albumin, IgG, IgA, C3, kappa and lambda light chains corresponding to protein reabsorption droplets. There was no immunoreactivity for C1q. On ultrastructural examination, glomerular capillaries frequently contained platelet aggregates and fibrin thrombi (Figure 3(f)). Podocyte demonstrated extensive foot process effacement and contained very large protein and lipid droplets. Glomerular endothelial cells showed loss of fenestration. No tubuloreticular inclusions, electron-dense or organized deposits were identified. A histological diagnosis of acute thrombotic microangiopathy and interstitial hemorrhage was rendered.

The results of coagulation studies performed on blood samples obtained before the treatment with plasma exchange and glucocorticoids are summarized in the Table 1. The lupus anticoagulant and antibodies directed against cardiolipin, beta 2-glycoprotein I, and prothrombin were detected. The levels of antithrombin III and protein S activity were mildly reduced. The level of anti-platelet factor 4 was mildly elevated. Based on the clinical manifestations, histological findings, and results of laboratory tests, the patient was diagnosed with catastrophic antiphospholipid syndrome (CAPS). On the ninth hospital day, intravenous methylprednisolone was continued and daily plasma exchange with fresh frozen plasma (one plasma volume per treatment) was started. Over the ensuing days, her pulmonary and renal function as well as thrombocytopenia gradually improved (Figure 4(a)). The patient received a total of six plasma exchanges. At the time of discharge on the 20th hospital day, she was ambulatory, serum creatinine was 1.0 mg/dl, and the platelet count was 231,000 per microliter. Chest radiographs showed clear lungs (Figure 4(b, c)). To suppress pathogenic autoantibody production, she was discharged home on prednisone 40 mg/day and mycophenolate mofetil 250 mg twice a day. Because of diffuse alveolar hemorrhage, she was not anticoagulated.

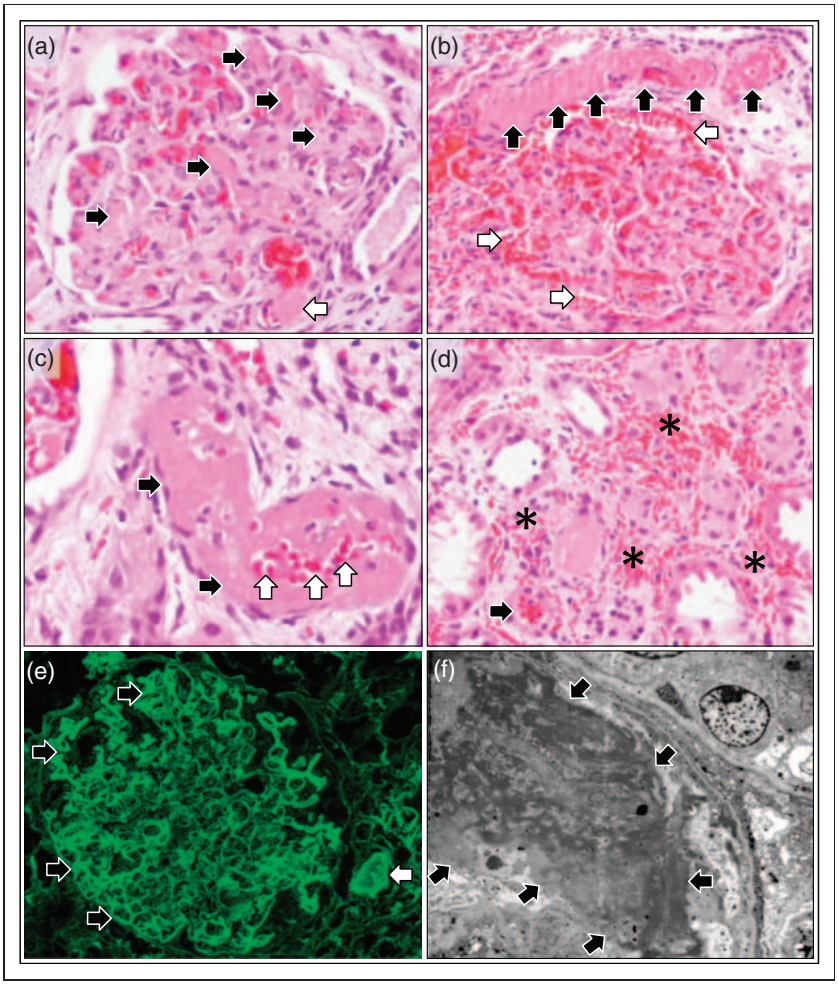

Figure 3 Thrombotic microangiopathy and interstitial hemorrhage in the kidney. A glomerulus showing microthrombi (black arrows) in the glomerular capillaries (a). An arteriole adjacent to the vascular pole of the glomerulus containing a partially occluding thrombus (white arrow) (a). A longitudinally cut arteriole (black arrows) containing a thrombus resulting in severe narrowing of the lumen (b). A congested glomerulus showing red blood cells (white arrows) in the Bowman's space (b). Higher magnification of a thrombosed arteriole (black arrows) revealing red blood cells (white arrows) in the residual lumen (c). Interstitial hemorrhage (asterisks) and red blood cells in the lumen (arrow) of a tubule (d). Immunostaining for fibrinogen highlighting capillary walls of a glomerulus (black arrows) and a thrombus (white arrow) in an adjacent arteriole (e). Ultrastructural examination disclosing a thrombus containing fibrin (arrows) in a glomerular capillary (f). Tissue sections in panels (a–d) were stained with hematoxylin and eosin.

Discussion

Antiphospholipid (Hughes) syndrome (APS) is an autoimmune disease characterized by arterial and venous thrombosis due to pathogenic autoantibodies directed against proteins that bind to phospholipids such as beta 2-glycoprotein I.[1] The disorder is referred to as primary APS when it occurs in the absence of another autoimmune disease. Secondary APS is accompanied by an underlying autoimmune disorder such as systemic lupus erythematosus. CAPS is a rare life-threatening form of APS in which disseminated vascular thrombosis results in multiorgan ischemia and failure.[2] The patient presented had involvement of the lungs, kidneys, gastrointestinal (GI) tract, liver, and likely central nervous system (CNS). She fulfilled all four criteria required for a definite diagnosis of CAPS: 1) involvement of three or more organs, systems and/or tissues; 2) development of manifestations simultaneously or in less than a week; 3) histopathological evidence of small vessel occlusion in at least one organ or tissue; 4) presence of antiphospholipid antibodies (a lupus anticoagulant and/or anticardiolipin antibodies).[3]

Approximately 72% of patients diagnosed with CAPS are women.[4] The age of patients diagnosed with CAPS ranges from 11 to 60 years with a mean

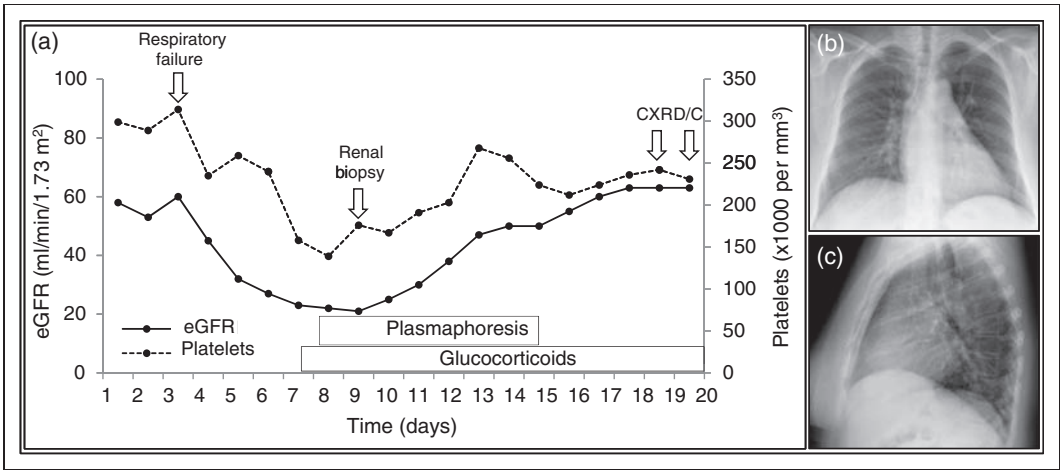

Figure 4 Hospital course. Estimated glomerular filtration rate (eGFR) and platelet count during hospitalization (a). Chest radiographs before discharge from the hospital (b, c). FFP: fresh frozen plasma; CXR: chest radiograph; D/C: discharge.

of 37 years.[4] A precipitating factor such as infection (22%), surgery (10%), discontinuation of anticoagulation (8%), medication (7%), obstetric complication (7%) or a neoplastic process (5%) is identified in about half of patients with CAPS.[4] Although examination of stools did not disclose a pathogen, we cannot exclude infectious gastroenteritis as the precipitating factor in our patient. However, it is noted that CAPS involves the GI tract and the liver in one-third of patients.[5]

Despite widespread thrombi in renal microvasculature and most likely in other vascular beds, microangiopathic hemolysis and severe thrombocytponeia were not prominent features in our patient. We found only occasional schistocytes on the blood smear, and the level of haptoglobin was not reduced. In line with these findings, hemolysis is reported in only 26% (13/50) of patients with CAPS, and a platelet count above 100,000 per microliter was present in 32% (16/50) of patients with CAPS.[2] Moreover, only a small number of schistocytes were found on the blood smear from patients with CAPS, less than in hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).[6] In fact, in an earlier description of laboratory features of CAPS, schistocytes were observed in only 14% (seven of 50) of cases.[2] The low prevalence of schistocytes in CAPS was confirmed in a later study involving 250 patients.[4] An explanation for a paucity of schistocytes in CAPS is not readily available. It can be postulated that the rapidity of onset and completeness of microvascular occlusion prevented enough blood flowing through thrombotic vessels to cause fragmentation of erythrocytes. With respect to normocytic normochromic anemia, we propose a multifactorial origin due to systemic microvascular thrombosis, systemic inflammatory response, and bleeding into tissues. Elevated serum haptoglobin levels measured on three separate occasions exclude the possibility of significant intravascular hemolysis as a cause of anemia.

Approximately one-half of patients who present with CAPS have a preexisting history of APS.[4] Although our patient had not been diagnosed with APS prior to her current presentation, a history of spontaneous ischemic necrosis of fingers provides some evidence in support of the existence of an underlying APS.[1] In addition, she had been suffering from frequent migraine headache, which could have been a manifestation of APS.[1] Close to one-half of patients with CAPS have a concomitant autoimmune disorder such as systemic lupus erythematosus (40%), lupus-like syndrome (5%) or another autoimmune disease (9%).[4] Although our patient did not have a history of clinical autoimmune disease, serologic studies revealed antibodies directed against nuclear antigens (1:160), including double-stranded DNA (borderline positive) and erythrocyte membrane antigens (a positive Coombs test). Of note, approximately 45% of patients with primary APS demonstrate antibodies directed against nuclear antigens including double-stranded DNA.[7] The titer of antinuclear antibodies in CAPS is usually below 1:320.[8] Nevertheless, despite the presence of several autoantibodies, the patient did not meet the American College of Rheumatology classification criteria for systemic lupus erythematosus.[9] We found low levels of circulating cryoglobulins on two separate occasions. The biological relevance of this finding is uncertain, as histological examination of the kidney did not

demonstrate evidence of cryoglobulin-associated renal disease.

Pulmonary disease is the presenting feature in 24% of patients with CAPS.[4] However, lungs are eventually involved in 64% of patients during the course of disease.[4] Although acute respiratory distress syndrome and pulmonary embolism are the most common pulmonary manifestations of CAPS, alveolar hemorrhage is occasionally encountered.[4] In a study by Asherson and colleagues, alveolar hemorrhage was present in 6% (three of 50) of patients diagnosed with CAPS.[2] The pathogenesis of alveolar hemorrhage in CAPS is poorly understood. However, pathological examination of lung biopsies from patients with APS and alveolar hemorrhage revealed microvascular thrombosis with or without capillaritis.[10] Pulmonary capillaritis is characterized by the presence of inflammatory cells, particularly neutrophils, in and around capillaries in the alveolar walls. Endothelial and immune cell activation is a critical step in the pathogenesis of microvascular injury induced by antiphospholipid antibodies.[11] Because of rapid improvement in pulmonary function with high-dose glucocorticoids and plasma exchange therapy, we did not pursue a lung biopsy in our patient.

Although renal disease is the presenting feature in only 18% of patients with CAPS, kidneys are eventually involved in 71% of patients during the course of the disease.[4] The most frequent renal manifestations are hypertension, proteinuria, hematuria, and acute renal failure.[2,4,12] Proteinuria ranged between 0.6 g/day and 6.1 g/day with the mean of 2.8 g/day.[12] Hypertension is often severe, and renal infarction rarely develops.[2] Histopathologically, the most common finding is acute thrombotic microangiopathy characterized by deposition of fibrin thrombi in glomeruli, arterioles, or both.[2,12] Immune complex deposition is rarely observed.[2] In some cases, the presence of interstitial fibrosis, tubular atrophy, and concentric laminations of fibrotic intima of arteries and arterioles (onion skin pattern) indicates chronic damage.[12] An inflammatory cell infiltrate involving approximately 10% of the interstitium was noted in 33% (two of six) of patients with CAPS.[12] In line with these observations, our patient presented with hypertension, proteinuria, and acute renal failure. A renal biopsy revealed acute thrombotic microangiopathy with fibrin thrombi in glomeruli and arterioles.

Another intriguing feature of renal disease in our case is the finding of extensive interstitial hemorrhage. Although alveolar hemorrhage has been reported in 6% of patients with CAPS, to date there has been only a single case report of renal thrombotic microangiopathy accompanied by coagulative necrosis with interstitial hemorrhage in CAPS.[13] Interstitial hemorrhage represents a nonspecific pattern of interstitial injury that usually occurs as a result of vascular injury such as thrombosis, viral infection, medullary angiitis, antibody-mediated rejection, and ischemia-reperfusion injury either as a primary event or reperfusion to injured tissue. Nonetheless, the question remains why renal interstitial hemorrhage has not been reported more frequently in patients with CAPS. Hemorrhagic complications in APS have been observed in the setting of severe qualitative or quantitative platelet disorders.[14] Although we did not perform specific platelet function tests, our patient was not severely thrombocytopenic (the lowest platelet count: 139,000 per microliter). Furthermore, she did not report any previous bleeding or bruising history. Rarely, a bleeding diathesis in patients with APS is due to the presence of anti-prothrombin antibodies that lead to a reduction of prothrombin level below 20% of normal values.[14] Our patient had detectable anti-prothrombin antibodies (IgM), but normal levels of coagulation factor II activity. While circulating prothrombin activity was not reduced, it is tempting to postulate that a tissue-level effect of the anti-prothrombin antibodies might have led to local loss of hemostatic control in the lungs and kidney. Paradoxically, anti-prothrombin antibodies are also markers of thrombotic risk, which is consistent with the histopathological findings in this case.[14,15] Antigen targets in APS are known to be heterogeneous, with autoimmune reactivity ultimately tipping the hemostatic balance toward a prothrombotic state. It is notable that this patient had four positive tests for antiphospholipid antibodies (anti-cardiolipin, anti-beta 2 glycoprotein I, anti-prothrombin as well as three of three positive tests in the lupus anticoagulant screening panel). On clinical grounds, we could not elicit a specific precipitating factor such as infection that triggered CAPS in this patient.

At times, the clinical manifestations of CAPS are mostly a consequence of microvascular disease in the form of a thrombotic microangiopathy. Therefore, the differential diagnosis includes HUS and TTP, which are characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic injury to organs.[16] While fever and neurologic manifestations frequently dominate the clinical picture in patients with TTP, most patients with HUS suffer from renal disease.[14] The differentiation

between HUS/TTP and CAPS is sometimes difficult.[6] As a general rule, thrombocytopenia and schistocytosis are marked in HUS/TTP and mild or absent in CAPS. Activated partial thromboplastin time is usually normal in HUS/TTS, but it may be elevated in CAPS in the presence of the lupus anticoagulant. Whereas the presence of antiphospholipid antibodies is a serologic hallmark of CAPS, plasma activity of ADAMTS-13 (a disintegrin and metalloprotease, with thrombospondin-1-like domains) is less than 5% of normal in most patients with TTP.[16] Based on these considerations, we excluded the diagnosis of TTP and HUS in our patient.

Disseminated intravascular coagulation (DIC) may mimic CAPS.[6] DIC is characterized by systemic activation of coagulation leading to microvascular thrombosis, consumptive coagulopathy, and hemorrhagic diathesis.[17] Although CAPS is typically due to vascular thrombosis, DIC usually manifests signs of thrombosis and bleeding at the same time. DIC is not a primary disorder; it can be a complication of a variety of disorders that lead to activation of coagulation. In fact, DIC may complicate CAPS in one-third of patients.[6] Laboratory features of DIC include absolute or relative thrombocytopenia, prolonged clotting times, reduced plasma concentration of fibrinogen, and elevated plasma concentrations of fibrin degradation products.[17] In the case presented, plasma fibrinogen concentration was not reduced, and prothrombin time was not significantly elevated. Prolonged activated partial thromboplastin time was likely due to the presence of the lupus anticoagulant.

Another intriguing feature of the case presented was the presence of low-level antibodies against platelet factor 4 (PF4). Antibodies against PF4-heparin complex can give rise to a prothrombotic disorder known as heparin-induced thrombocytopenia (HIT).[18] HIT is characterized by relative or absolute thrombocytopenia and vascular thrombosis following exposure to heparin.[18] However, circulating antibodies against PF4-heparin complex have also been reported in patients without preceding heparin therapy.[19] It is postulated that presence of antibodies against PF4-heparin complex could also be a reflection of immune activation such as those leading to the formation of antiphospholipid antibodies.[19] In the case presented, to the best of our knowledge, unfractionated or low-molecular-weight heparin was not administered.

CAPS is accompanied by a systemic inflammatory response syndrome (SIRS).[5] Our patient was diagnosed with SIRS based on established criteria.[20] We also found that the serum concentrations of several positive acute-phase proteins such as C-reactive protein, fibrinogen, and haptoglobin were elevated, while the serum concentration of albumin (a negative acute-phase protein) was reduced.[21] The erythrocyte sedimentation rate was also markedly elevated. SIRS in CAPS is believed to be a result of the extensive tissue damage.[5] However, antiphospholipid antibodies induce activation of the complement system, a principal effector system of antibody-mediated immunity.[11,22,23] Activation of the complement system by immune complexes results in generation of anaphylatoxins C3a, C4a, and C5a that are potent inflammatory mediators.[23] Although we did not measure the plasma concentrations of anaphylatoxins, reduced serum level of C4 in our patient suggested activation of the complement system by immune complexes.

A life-threatening systemic disease, CAPS requires an aggressive multidisciplinary collaborative treatment strategy.[2] The following treatments, often in combination, have been used for CAPS: anticoagulation (87%), glucocorticoids (86%), plasma exchange (39%), cyclophosphamide (36%), intravenous immunoglobulins (22%), and anti-platelet agents (10%).[4] A recent decline in the mortality rate in CAPS from 53% to 33% has been attributed to use of the aforementioned treatment strategies in combination (Bucciarelli).[24]

Final diagnosis: catastrophic antiphospholipid syndrome.

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Conflict of interest

The authors have no conflicts of interest to declare.

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