Catastrophic antiphospholipid syndrome: A case with unusual findings revealed in autopsy and a brief literature update
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Abstract
Catastrophic antiphospholipid syndrome (CAPS) is a rare and life-threatening disease. It is characterized by multiple arterial and/or venous thrombotic events, including the microcirculation, occurring in a short period, and can affect any system. Catastrophic antiphospholipid syndrome can occur in individuals with known APS under treatment, or it can be its first manifestation; in most cases, there is a triggering factor that can be identified. In this case report, we report a case of CAPS with multiple thromboses at unusual sites, including the lungs, coronary arteries, stomach, thyroid, gastrocnemius muscles, lymph nodes, and bladder, in a patient with previous diagnosis of systemic lupus erythematosus.

Keywords: Asherson’s syndrome, catastrophic antiphospholipid syndrome, antiphospholipid syndrome, antiphospholipid antibodies, multiple thromboses

Introduction
Catastrophic antiphospholipid syndrome (CAPS) is characterized by multiple arterial and/or venous thrombotic events occurring in any organ system over a short period. Catastrophic antiphospholipid syndrome may develop in individuals with previously diagnosed APS, or it may present as the first manifestation of APS. (1)

The prevalence of CAPS is currently estimated to be 1%, with a mortality rate of 37%. In most cases, a triggering event can be identified including infection, withdrawal of (or subtherapeutic levels of) anticoagulation, and coexistence of systemic lupus erythematosus (SLE) flare (1, 2). When CAPS is suspected, prompt initiation of treatment in the intensive care setting is crucial for an optimal outcome.

We report here a case of CAPS induced by infection where multiple thrombotic events occurred at unusual sites.

Case Presentation
A 32-year-old nulliparous woman with a history of two episodes of lower extremity deep vein thrombosis (DVT) was referred to our clinic with bilateral post-thrombotic syndrome. Each episode of thrombosis had been treated with warfarin only for several months by her previous physician. At the time of the thromboses, the patient was a current smoker and was using oral estrogen contraception. She reported previous episodes of arthritis, but the medical history was otherwise unremarkable. On examination, the patient had three skin ulcers on each lower extremity, the largest on the right leg was 8 cm in maximum diameter. Laboratory testing revealed a positive antinuclear antibody (ANA) in both a nuclear coarse speckled pattern (titer, 1:640) and homogeneous pattern (titer, 1:1280). Other positive autoantibodies included anti-dsDNA antibody, lupus anticoagulant (LA; confirmed on two occasions more than 12 weeks apart), IgG anti-cardiolipin antibodies (aCL) of 64 GPL and IgM anti-cardiolipin of 6 MPL (performed once; they were not previously performed and there was no time to perform a confirmatory test). Anti-ß2glycoprotein-I antibodies and anti-cardiolipin IgA tests were not performed because these assays were not available at our hospital.

Systemic lupus erythematosus was diagnosed on the basis of the patient’s history of polyarthritis, high-titer ANA, positive anti-dsDNA, low C3, positive direct Coombs without hemolysis, false-positive veneral disease research laboratory (VDRL), positive LA, and positive aCL IgG. Concomitant APS was diagnosed given the history of recurrent venous thromboses and detection of persistent LA. The patient was started on hydroxychloroquine, low-dose prednisone, and warfarin targeting an international normalized ratio (INR) goal range between 2.0 and 3.0.
Two months after her admission, she developed bilateral lower extremity edema, with dyspnea. Computed tomography (CT) pulmonary angiography was normal. A repeat TTE showed new bilateral lower extremity edema. Duplex scan ultrasound imaging showed bilateral thrombotic occlusions of both common femoral and superficial femoral veins. The INR value was 2.1 on admission. Biopsy of the major skin ulcer was compatible with pyoderma gangrenosum. The INR target range was increased to 3.0-4.0 due to the development of recurrent thromboses while on therapeutic levels of warfarin. Low-dose aspirin (LDA) was also added.

Two months after her first visit, the patient was admitted with worsening pain and edema of the bilateral lower extremities. Duplex scan ultrasound imaging showed new bilateral thrombotic occlusions of both common femoral and superficial femoral veins. The INR value was 2.1 on admission. Biopsy of the major skin ulcer was compatible with pyoderma gangrenosum. The INR target range was increased to 3.0-4.0 due to the development of recurrent thromboses while on therapeutic levels of warfarin. Low-dose aspirin (LDA) was also added.

Two months after her admission, she developed an episode of progressive dyspnea; pulmonary embolism was confirmed using scintigraphy. INR at admission was 2.7. Thoracic echocardiogram (TTE) showed a pulmonary artery systolic pressure (PASP) of 50 mmHg with right ventricular failure. Treatment was continued and warfarin dosing was again adjusted to achieve an INR target of 3.0-4.0.

Three months after the hospital admission, the patient reported a recurrent episode of worsening lower extremity edema with dyspnea at rest. Computed tomography (CT) pulmonary angiography was normal. A repeat TTE revealed a dramatic worsening in PASP to 101 mmHg. Serum creatinine was 1.0 mg/dL and urine protein-to-creatinine ratio was 386 mg/g at that time. INR was 1.62 and anticoagulation was again adjusted. She was discharged while still symptomatic, although with improvement of edema with diuretics.

Seven months after her initial admission, the patient was admitted again with systemic congestion and new oliguric acute kidney injury after taking over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs). Her medications at that time included prednisone, hydroxychloroquine, furosemide, nifedipine, LDA, and warfarin. The admission INR was supra-therapeutic at 6.18 and creatinine was 2.5 mg/dL. The SLE disease activity score (SLEDAI) score was 2 (low complement). Hemolysis was detected and platelet count was normal. Serial daily INRs during hospitalization were 6.0, 3.3, 2.4, 4.2, and 4.5. Eight days after admission, her leg ulcers were infected and piperacillin/tazobactam was prescribed. One day later she developed circulatory shock, requiring mechanical ventilation and vasoactive drugs, and the patient died the following day. A diagnosis of CAPS was suspected in this patient with SLE and APS due to the acute onset of respiratory, circulatory, and renal failure. Her family members provided written consent to perform necropsy and report the case in potential publications.

Histomorphological review of various tissue samples was performed under light microscopy (stained with hematoxylin-eosin) and revealed unsuspected arterial microthromboses at multiple sites, including thyroid, gastric, bladder, gastrocnemius muscle, and mediastinal lymph nodes. The patient also had pulmonary and coronary artery thromboses. Histological features are displayed in Figure 1, 2. There was no DVT of the lower extremities. Class IV lupus nephritis was identified with no evidence of thrombosis. The ultimate diagnosis was CAPS with concomitant lupus flare and sepsis; the final cause of death was related to pulmonary thrombosis.

**Discussion**

CAPS was first described by Asherson et al. (3) in 1992. The most recent update on the CAPS Registry includes 522 CAPS episodes in 500 patients; 75% of them had SLE and 69% patients were females. CAPS was triggered by infection in almost half of the episodes. The most frequently involved sites are the kidneys (73%), lungs (60%), brain (56%), and heart (50%) (4).

The diagnosis of the case reported here was established after performing the autopsy. We highlighted the occurrence of multiple thromboses at unusual sites, including the thyroid, stomach, bladder, gastrocnemius muscle, and lymph nodes, in addition to the more common sites of lungs and coronary arteries and catastrophic development over 2 days. In reviewing the CAPS literature, we found three reported cases of thromboses in the thyroid, two in the stomach, one in the bladder, and three in...
muscles in CAPS patients (3, 5-8). Chinnery et al. (8) reported a female SLE patient with multiple thrombosis, including gastric and bladder involvement as observed in our patient, with positive tests for LA and IgG aCL. Cisternas et al. (5) described a CAPS case that presented with thyroid and muscle thromboses, in addition to intestinal, adrenal, pancreatic, and renal thromboses, with LA and IgG aCL positivity. Mizuno et al. (6) also reported a female SLE patient with multiple unusual sites of thromboses, including the thyroid, brain, fingers, liver, spleen, pancreas, and kidneys with positive assays for LA and IgG aCL. Asherson et al. (3) reported an SLE patient with gastric thrombosis who also had renal and splenic thromboses with positive IgG aCL.

All the patients described above were females, and the most commonly positive antiphospholipid tests were LA and IgG aCL. It is important to note however that anti-ß2glycoprotein-I was added to the APS laboratory criteria only in 2006 and the testing was not widely available earlier; most of the cases cited above were reported prior to 2006 (9). The kidney is the leading site of thrombosis in CAPS, occurring in 73% of cases; however, unlike the other reports mentioned, there was no renal thrombosis in our patient (4). In addition, it is noteworthy that CAPS developed while our patient was on LDA and with all recorded INRs > 3.0, with the exception of one value of 2.4.

Since CAPS is a rare disease, case reports are important to provide a better understanding of its various clinical aspects to facilitate future diagnosis. This case illustrates that CAPS may present with unusual areas of thrombosis and that multiple unusual manifestations may occur simultaneously. CAPS is truly a rheumato logic emergency, requiring prompt recognition and diagnosis as well as aggressive treatment to avoid the fulminant irreversible complications related to its devastating prognosis.

Ethics Committee Approval: N/A.
Informed Consent: Written informed consent was obtained from patient’s parents who authorized the necropsy and the publication of this report.

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