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## A 51-Year-Old Woman With Blanched Skin, Coagulopathy, Abdominal Pain, and Cardiopulmonary Failure\*

Mariam A. Al-Ansari, MD

(CHEST 2007; 131:1603–1607)

A 51-year-old woman with a history of hypertension developed sudden confusion, drowsiness, and severe abdominal pain 4 days after undergoing clipping of an anterior communicating cerebral artery aneurysm. Her social history was significant for migraines and two abortions.

### Physical Examination

On physical examination, she was noted to be confused, agitated, and in pain. Her respiratory rate was 30 breaths/min, BP was 90/60 mm Hg, and heart rate was 125 beats/min. Her oxygen saturation was 96% while breathing room air. The findings of a cardiac examination were normal with no detectable murmur. Her extremities were slightly cold with a mottled appearance of the skin (Fig 1).

### Laboratory Investigations

The hemoglobin and hematocrit were normal, while the WBC count was 22,000 cells/ $\mu$ L, with 8% band cells and platelet count of  $94 \times 10^9$  cells/L. The concentration of serum  $\text{HCO}_3^-$  was 6 mmol/L, sodium was 115 mmol/L, potassium was 5.5 mmol/L, and chloride was 107 mmol/L. The concentration of creatinine was 97 mmol/L, urea was 5 mmol/L, and glucose was 10 mmol/L. Serum lactate dehydrogenase concentration was 900 U/L. Serum lactic acid concentration was 14 mmol/dL. Coagulation

studies revealed an international normalized ratio of 2 and an activated partial thromboplastin time of 45 s (normal range, 24 to 34 s). Few schistocytes were noted on the peripheral blood smear. Initial arterial blood gas analysis while the patient was breathing room air showed a  $\text{PaO}_2$  of 90 mm Hg, a  $\text{PaCO}_2$  of 19 mm Hg, and a pH of 7.1.

The patient was treated for sepsis of unknown origin with placement of a central venous catheter, rapid fluid infusions, and therapy with piperacillin/tazobactam (Tazocin; Wyeth Pharmaceuticals; Madison, NJ), 4.5 g IV q8h. The initial central venous pressure was 6 cm  $\text{H}_2\text{O}$ . Therapy with IV hydrocortisone for adrenal insufficiency of sepsis (50 mg IV q6h) was also added in view of the septic picture with hyponatremia and hyperkalemia.

The findings of her portable plain abdominal film were normal. A CT scan of the abdomen is shown in Figure 2. A CT scan of the brain showed loss of gray matter/white matter differentiation on the right hemisphere compared to the left side, indicating an infarcted middle cerebral artery territory. An MRI of the brain, which had been performed earlier, showed multiple parenchymal hyperdense lesions that were suggestive of vasculitis. No echocardiogram was performed.

When the patient returned from the radiology department, hypotension and respiratory failure with increasing dyspnea developed, which required intubation and mechanical ventilation. Vasopressor therapy was initiated. A chest radiograph showed bilateral diffuse infiltrates. Therapy with activated protein C could not be used in view of her recent subarachnoid hemorrhage. During the next 2 h, the patient's skin became progressively mottled. A repeat lactic acid measurement 2 h later revealed that the level were still high (12 mmol/dL).

What is the most likely diagnosis?

What clinical course may be expected?

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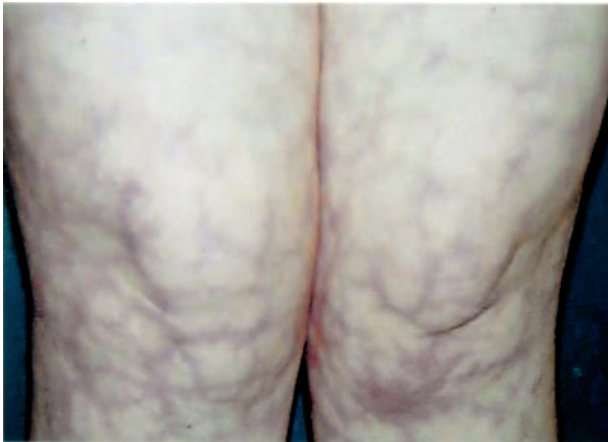


FIGURE 1. Fishnet-like, nonblanchable, bluish-red discoloration surrounding a pale center on the lower limbs.

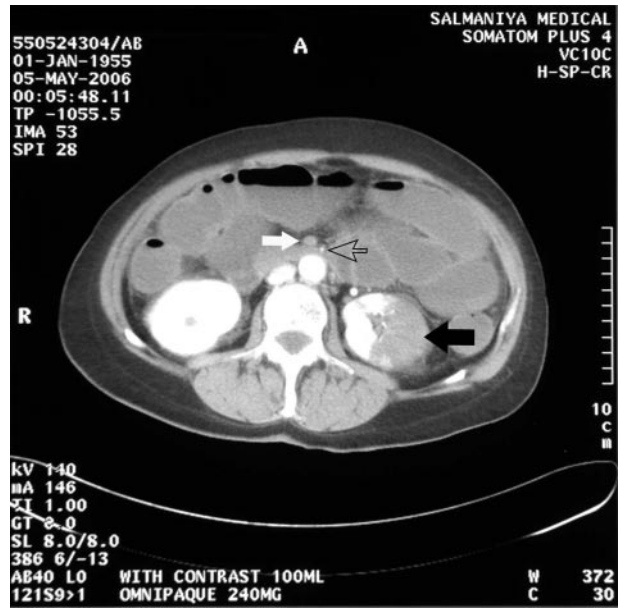


FIGURE 2. CT scan of the abdomen on ICU admission (arrows point to abnormalities).

## Diagnosis: Catastrophic antiphospholipid antibody syndrome

Antiphospholipid syndrome (APS) is a condition resulting from derangements of the coagulation system and causing systemic episodes of thrombosis. The term was introduced to define a group of patients who exhibited episodes of thrombosis, thrombocytopenia, or recurrent fetal loss with increased levels of antiphospholipid antibodies (aPLs) in the circulation. A subset of patients with APS exhibit a fulminant clinical course with widespread vascular occlusions, often resulting in rapid death (called *catastrophic APS* [CAPS]). CAPS is defined as a vasoocclusive process, involving at least three organs. The syndrome can occur in patients with primary APS or secondary APS (*ie*, with concomitant systemic lupus erythematosus), and less frequently in patients without a history of thrombosis. The mortality rate is 50%, and death is usually due to multiorgan failure.

The predominant pathology in CAPS is a noninflammatory, thrombotic microangiopathy of small vessels, resulting in multiorgan failure. It involves widespread thrombosis within the circulatory system. As a result, some patients present with sepsis inflammatory response syndrome. The term *thrombotic storm* has been used to describe this process of the hypercoagulable state. This causes tissue ischemia and necrosis. The situation is characterized by the activation of endothelial and neutrophils cells (induced by aPLs, alone, or as a component of antibody-antigen complexes) with the release of inflammatory mediators that affect hemostasis through the extrinsic pathway.

Up to 55% of the patients may have identifiable precipitating factors. Infections have been identified as dominant triggers in up to one third of patients. Trauma and surgical procedures, such as biopsy, endoscopic retrograde cholangiopancreatography, arterial manipulation, and pregnancy, have all been cited as precipitating factors for CAPS. Patients with

vascular surgery have the greatest risk. Unfortunately, serious thrombotic perioperative complications in these patients occur despite prophylaxis and adequate anticoagulation therapy. The induction of autoimmune disease processes secondary to stress and increased production of tissue factors are possible explanations for this association. The association of malignancies and HIV with CAPS has recently emerged as a precipitating factor.

The withdrawal of anticoagulation therapy or a decrease in the international normalized ratio may lead to the development of CAPS. Additional situations cited as precipitating factors include systemic lupus erythematosus flare-ups, the use of oral contraceptives, and the use of the drugs thiazide and captopril. In approximately 35% of patients, a causative factor was not identified. Table 1 shows the percentage of organ involvement in CAPS patients.

**Table 1—Organ Involvement in CAPS Patients**

| Organ                                  | %     |
|--|-------|
| Kidney                                 | 78    |
| Lungs                                  | 66    |
| Thrombocytopenia                       | 60–68 |
| CNS                                    | 56    |
| Heart                                  | 50    |
| Skin                                   | 50    |
| Disseminated intravascular coagulation | 25    |
| Adrenal gland                          | 10–26 |

The presentation of CAPS is one of rapidly progressing multiorgan failure. It is progressive cardiopulmonary failure, however, that usually brings patients to the ICU needing acute life-saving intervention. Widespread thrombotic microangiopathy seems to be the basic pathologic condition in whatever organ is examined. However, thrombosis of large cerebral and peripheral vessels can occur in 15 to 20% of patients.

In a series of patients with CAPS, ARDS devel-

**Table 2—Sapporo Criteria**

| Clinical Criteria*   | Laboratory Criteria†   |
|--|--|
| Vascular thrombosis ( <i>ie</i> , at least one episode of a blood clot occurring without any clear explanation)  | The presence of either anticardiolipin antibody or lupus anticoagulant on at least two occasions at least 6 weeks apart. |
| Pregnancy morbidity ( <i>ie</i> , a single unexplained pregnancy loss after 10 wk of gestation; three or more consecutive, unexplained losses at < 10 wk of gestation; or a premature birth at < 34 wk of gestation, when delivery is due to severe preeclampsia, eclampsia, or severe placental insufficiency). |  |

\*Note that thrombocytopenia and other clinical manifestations are not included in this definition.

†The anticardiolipin antibody must be IgG or IgM in a medium or a high titer, which has been detected using a standardized enzyme-linked immunosorbent assay.

oped in 34 to 41% of patients, who required intubation and mechanical ventilation. This resulted from microvascular emboli causing vascular endothelial damage with neutrophil influx and the release of cytokines. This pathogenesis was suspected but not confirmed.

When CAPS develops, a range of cardiac abnormalities may be seen in the form of progressive dyspnea and radiographic evidence consistent with decompensated congestive heart failure. Microvascular thrombi involving the myocardium have been reported as the prominent feature causing cardiac failure and circulatory collapse.

Systemic hypertension is also a prominent feature in APS patients, often in the form of malignant hypertension. If CAPS presentation is dominated by myocardial failure or by infection with sepsis, however, hemodynamic support with vasopressors and inotropic agents is required.

Renal abnormalities during CAPS are quite common. Renal failure may initially be nonoliguric but can rapidly progress to oliguria requiring urgent dialysis.

A range of CNS findings have been reported in CAPS patients. Altered mental status, causing stupor and coma, or seizures can compromise respiratory function. Large-vessel infarctions are seen less frequently (13%).

Abdominal pain is a common presenting symptom. Abdominal tenderness may be elicited. In a series of 80 CAPS patients, 10% of thrombotic episodes involved the adrenal glands. Abdominal and flank pain, hypotension poorly responsive to therapy with vasopressor agents, and laboratory findings of hyponatremia with or without hyperkalemia suggest adrenal hypofunction. Adrenal gland involvement seems to be frequently missed in the ICU. CT imaging of the abdomen provides a timely diagnosis.

Skin involvement (*eg*, livedo reticularis, digital ischemia, splinter hemorrhages, ulcerations, and superficial gangrene in the lower limbs, cheeks, and ears) is common in CAPS and has been reported in 50 to 52% of patients. The development of multiple new lesions of livedo reticularis reflects ongoing microvascular thrombosis reflecting the progress of CAPS.

The Sapporo criteria offer a standardized definition of the APS. At least one clinical and one laboratory criterion are required to make a definitive diagnosis (Table 2). The major disadvantages of anticardiolipin antibody testing are that many laboratory diagnostic kits lack the standard threshold for abnormal values. In addition, they are often transiently positive or can vary dramatically over time in patients with APS. The absence of aPLs in the acutely sick patient does not exclude a diagnosis of APS.

The treatment of CAPS requires supporting the

failing organ systems and suppressing the widespread microvascular thrombotic process. Treatment modalities include anticoagulation therapy (in the form of heparin, then switching to warfarin), fibrinolytic agents, high-dose steroids, plasmapheresis, and cyclophosphamide. Patients receiving a combination of anticoagulation therapy, steroids, plasmapheresis, or IV gamma-globulin have a survival rate of up to 70%.

Anticoagulation therapy alone reduces the mortality rate from 75 to 38%. Higher than usual doses of heparin are suggested. Given the extreme hypercoagulability of these patients along with heparin resistance, more than the usual doses of heparin must be administered (*eg*, 15,000 to 20,000 U daily). The addition of steroids to therapy is recommended to reduce the cytokine effects in CAPS patients, even in the absence of evidence of adrenal insufficiency.

The present patient did not undergo testing for anticardiolipin antibodies. She died despite resuscitative efforts soon after intubation. A review of her abdominal CT scan (Fig 2) demonstrated left renal infarction (black arrow), thrombotic superior mesenteric artery (open arrow) with dilated small bowel, and delayed venous phase of a contrast study (white arrow), as well as an infarcted left adrenal gland (not shown in the cut scan in Fig 2). These findings combined with the septic-appearing presentation in the postoperative setting supported the diagnosis of CAPS. This is consistent with many other reported cases of CAPS in the ICU. An autopsy was not performed, but all antemortem cultures were negative.

#### CLINICAL PEARLS

1. CAPS is a fulminant form of APS, and is characterized by derangements of coagulation and noninflammatory thrombotic microangiopathy with failure of three or more visceral organs.
2. Only 55% of patients with CAPS have cases with an identifiable cause, which includes infections, surgery, intraarterial interventions, retrograde cholangiopancreatography, pregnancy, cancer, and HIV infection, to name a few.
3. Ischemia of the adrenal gland occurs in 10% of patients and can result in acute adrenal insufficiency with hyponatremia and hyperkalemia.
4. Early recognition of CAPS is the key to patient survival. Prompt initiation of therapy with heparin anticoagulation, corticosteroids, IV Igs, and plasma exchange is associated with a 70% survival rate.

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