Atypical Subacute Recurrence of Catastrophic Antiphospholipid Syndrome in a Japanese Female Patient

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Abstract

Catastrophic antiphospholipid syndrome (CAPS) survivors rarely relapse. We herein report a case of a second CAPS episode with an unusual subacute course and no microangiopathic hemolytic anemia (MAHA), a common CAPS symptom. During the first episode, the 69-year-old woman responded well to high-dose glucocorticoids and plasma exchange. On relapse, these treatments plus rituximab were ineffective and she died of multi-organ failure and bacterial cholangitis. The absence of MAHA and a subacute course do not exclude a CAPS recurrence.

Key words: catastrophic antiphospholipid syndrome, microangiopathic hemolytic anemia, relapse, rituximab

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Introduction

Catastrophic antiphospholipid syndrome (CAPS), a rare subtype of antiphospholipid syndrome (APS), is characterized by multiple organ dysfunctions due to thrombosis of the small vessels occurring over a short period of time, typically less than 1 week. The mortality of CAPS is about 30% even when treated with high-dose glucocorticoids (GCs) and plasma exchange (PE) (1, 2), but patients who survive the initial event rarely have recurrent events (3). We herein report a case of CAPS relapse in a Japanese woman with an atypical slow clinical course and the absence of microangiopathic hemolytic anemia (MAHA).

Case Report

In July 2013, a 69-year-old Japanese woman with a 7-year history of recurrent cerebral infarction due to APS, presented with symptoms of fever at a local hospital. She was diagnosed with aspiration pneumonia and successfully treated with antibiotics. She also exhibited dysphasia due to a cerebral infarction, and was transferred to our hospital at the behest of her family for rehabilitation. Three years prior to this admission, she was referred to our hospital because of fever and a disturbance of consciousness, and was subsequently diagnosed with CAPS based on the presence of multiple organ impairment, including the brain, liver and kidney, and the presence of an antiphospholipid antibody, which had been detected previously. The patient had hemolytic anemia with peripheral schistocytes, thus suggesting MAHA. She was successfully treated by anticoagulation, high-dose GC, and PE, and has since been on 6-mg prednisolone (PSL) maintenance therapy.

At the current admission, the patient was afebrile and well oriented. She had been bed-bound for years and needed help with her daily activities. A physical examination revealed a systolic ejection murmur in the apex and mild to moderate muscle weakness of the extremities. She did not have any skin manifestations. The complete blood count, aspartate transaminase (AST), alanine transaminase (ALT), creatinine levels, and a urinalysis including urine sediment were normal, except for slight anemia. The activated partial thromboplastin time was prolonged (79.5 s; normal range <39.0 s) as was the prothrombin time due to anticoagulation with warfarin (international normalization ratio 1.69). The immunological tests were positive for β2 glycoprotein 1 dependent anticardiolipin antibody (>125 U/mL; normal range...
Figure 1. (a) Palpable purpura on the palm (arrow) on hospital day 35. (b) Skin biopsy (Hematoxylin and Eosin staining) of the purpura revealed fibrin thrombi in dermal small vessels.

Table. Laboratory Data on Admission and on Hospital Day 37.

| Variable      | Reference Range | On Admission | On hospital day 37 |
|---------------|-----------------|--------------|-------------------|
| WBC (per mm³) | 3,700-8,000     | 7,400        | 20,900            |
| Differential count (%) |                  |              |                   |
| Neutrophils   | 45-65           | 72.1         | 83.0              |
| Lymphocytes   | 27-43           | 24.8         | 7.0               |
| Monocytes     | 2-8             | 2.0          | 3.0               |
| Eosinophils   | 2-6             | 0.8          | 1.0               |
| Basophils     | 0.5-2           | 0.3          | 0                 |
| Hemoglobin (g/dL) | 11.5-15        | 10.7         | 8.3               |
| PLT (<10⁴ per mm³) | 13-40        | 14.7         | 3.8               |
| AST (IU/L)    | 10-40           | 15           | 92                |
| ALT (IU/L)    | 5-40            | 14           | 153               |
| LDH (IU/L)    | 118-240         | 210          | 545               |
| Creatinine (mg/dL) | 0.5-1.2   | 0.87         | 0.89              |
| CRP (mg/dL)   | 0-0.3           | 0.19         | 7.34              |
| CH50 (U/mL)   | 23-46           | 37           | 53                |
| APTT (sec)    | 0.9-1.1         | 1.69         | 0.98              |
| PT-INR        | 200-400         | 386          | 514               |
| D-dimer (ug/mL) | 0-1            | 0.7          | 48.0              |

WBC: white blood cell, PLT: platelet
AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase
CRP: C-reactive protein
CH50 (50% hemolytic unit of complement)
APTT: Activated partial thromboplastin time
PT-INR: prothrombin time-international normalization ratio

<3.4 U/mL), whereas the anti-nuclear antibody titer was low (1:40, homogenous/speckled pattern) and the anti-dsDNA was negative. Chest radiograph showed a slight infiltration in the right lower lung field, which was attributed to the preceding pneumonia.

A central venous catheter was inserted into the right femoral vein for parenteral nutrition. Three days after the catheter insertion, however, the patient developed fever, anemia, and thrombocytopenia. Computed tomography (CT) revealed diffuse lung infiltration and venous thrombosis at the insertion site. The catheter was removed and anticoagulation with unfractionated heparin and antibiotics was started. Over the next 4 weeks, the patient developed a diffuse gastric and bladder mucosal hemorrhage as revealed by gastroscopy and cystoscopy, the elevation of AST and ALT, proteinuria, hypertension, and the elevation of the creatinine level (0.87 mg/dL on admission, 1.18 mg/dL on hospital day 38). A fever was persistent and refractory to antibiotics, including meropenem, cefepime, and clindamycin. The procalcitonin levels were constantly positive (1.49 ng/mL on hospital day 23, 1.07 ng/mL on hospital day 50). Three weeks after hospitalization, the patient gradually developed palpable purpura in the bilateral palms (Fig. 1a). A skin biopsy revealed multiple fibrin thrombi in dermal small vessels (Fig. 1b). On the basis of multiple organ dysfunction and microthrombosis in small vessels, a relapse of CAPS was diagnosed on hospital day 38. The laboratory data on admission and on hospital day 37 are summarized in Table.

We started methylprednisolone (mPSL) at a pulse dose of 1,000 mg/day for 3 days followed by 40 mg daily, which resulted in a dramatic improvement of fever, lung infiltration, partial improvement of thrombocytopenia, and liver enzyme
One month later, however, the patient again exhibited fever, thrombocytopenia, and liver enzyme elevation. Intravenous immunoglobulin (IVIg) at 400 mg/kg/day for 4 days had no effect. Plasma exchange every other day was effective during treatment only, and symptoms and laboratory parameters worsened during the 2-day interval. Renal dysfunction and proteinuria were refractory to these treatments. As the patient had primary CAPS (CAPS without systemic lupus erythematosus), we decided to administer rituximab as further treatment rather than cyclophosphamide. However, 4 administrations of rituximab at 375 mg/m² had no effect. Despite increasing mPSL to 60 mg, she developed petechiae in the lower palpebral conjunctiva and on the toes around hospital day 110 (Fig. 2). The patient died on hospital day 120. The entire treatment course is summarized in Fig. 3.

An autopsy revealed the presence of multiple thrombi in small vessels in multiple organs. In the liver, organized thrombi were detected in the interlobular portal veins and arteries (Fig. 4a). Organized thrombi were also detected in the arterioles of the gastric mucosa and pancreas. A kidney specimen showed a thickened and swollen intima of the afferent arterioles and fibrin thrombi in the glomerular tufts, compatible with renal thrombotic microangiopathy (Fig. 4b, c). Fibrin thrombi were detected in the small arteries of the left ventricle and Libman-Sacks vegetation was seen on the tricuspid valve. In addition to these findings which are consistent with APS, the common bile duct was obstructed by stones. Neutrophil and histiocyte infiltration, as well as bacterial colonies, were seen at the site of the bile duct obstruction, which is consistent with bacterial cholangitis.

**Discussion**

The subacute clinical course and lack of MAHA in the present case were atypical for CAPS. The major differential diagnoses were infective endocarditis, thrombotic thrombocytopenic purpura (TTP), and heparin-induced thrombocytopenia (HIT). Blood cultures were taken at least once every
week and the findings were negative. Transthoracic echocardiography showed no vegetation. Fragmented red blood cells were not detected in blood smears, which is atypical for TTP. Changing the anticoagulant first to dalteparin and then to fondaparinux, which are less likely to cause HIT, did not improve the patient’s status or thrombocytopenia. She was refractory to intensive immunosuppressive therapy, including rituximab. Multiple organ failure gradually worsened her general status and she eventually died. The autopsy findings indicated that the cause of death was bacterial cholangitis and sepsis due to a common bile duct obstruction. The obstruction likely occurred a few days prior to death because it was not evident on the abdominal enhanced CT 1 month prior and the total bilirubin level had been <2 mg/dL. Moreover, a blood culture taken just 2 days before death was negative.

There are few reports on the prognosis of CAPS patients who survive the initial event. Erkan et al. reported that none of the 58 CAPS patients who survived the initial event developed further catastrophic events during an average follow-up of 67.2 months (3). Moreover, since the first CAPS relapse case was reported in 1999 (4), only 10 additional cases have been documented (5-9). An international registry of patients with CAPS was created in 2000 (2, 10-12). Espinosa et al. reviewed 9 cases from the CAPS registry (9). The exception of 1 case in which detailed data were not available, 13 of 18 catastrophic episodes in the 8 cases were complicated by MAHA and the presence of schistocytes in the peripheral blood smear. Furthermore, in 2 relapsed cases reported in 2012 and 2014, all 5 episodes (2 in one and 3 in the other) were complicated by MAHA (7, 8). Thus, MAHA has been detected in 18 of 23 episodes (78%) in the 10 reported relapsing CAPS patients. In our case, however, schistocytes were not detected in the peripheral smear and MAHA was not clinically diagnosed, although it was present during the first event 3 years prior. The absence of MAHA, therefore, does not seem to preclude a CAPS recurrence.

Another unusual aspect of the present case was that our patient developed a relapse with an atypical subacute course. She gradually developed fever, lung infiltration, thrombocytopenia, anemia, mucosal bleeding in the stomach and bladder, elevation of liver enzymes, acute kidney injury with hypertension and proteinuria, and palpable purpura over 1 month, while preliminary classification criteria (1, 13) state that manifestations of CAPS usually develop simultaneously or in <1 week. Indeed, data from the CAPS registry reveal that 175 of 176 patients (99%) fulfill this acute course criterion (1). A subacute course even over 1 month does not seem to preclude a second catastrophic event in APS patients if other possible diseases are excluded.

Treatment is always challenging if a CAPS patient is refractory to anticoagulation and corticosteroids (first-line therapies) and to the addition of plasma exchange and/or IVIg (second-line therapies) (12, 14). Although rituximab is recommended rather than cyclophosphamide for the treatment of refractory CAPS without systemic lupus erythematosus (12, 15), our patient was also refractory to rituximab and died. Eculizumab is another agent reported to be effective for CAPS treatment (7), but the cost is high and it is approved only for paroxysmal nocturnal hemoglobinuria. The administration of glucocorticoids and the plasma exchange were at least partially effective for fever, lung involvement, and liver enzyme elevation, so we speculate that anti-cytokine therapy such as anti-tumor necrosis alpha or interleukin-6 might have been effective for our patient, although there have been no reports using these agents for CAPS.

In conclusion, the lack of MAHA and a subacute course over a month are therefore insufficient to exclude a subsequent catastrophic event in APS or CAPS patients. The most effective third-line therapy for CAPS is still unresolved.

The authors state that they have no Conflict of Interest (COI).

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