“Possible Primary Antiphospholipid Syndrome”
with Concurrent Diffuse Alveolar Hemorrhaging
and Libman-Sacks Endocarditis Mimicking Catastrophic
Antiphospholipid Syndrome

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Abstract

Although antiphospholipid antibody syndrome (APS) is an autoimmune condition that is primarily characterized by arterial or venous thrombosis or pregnancy morbidity and the presence of antiphospholipid antibodies (aPL), recent reviews have introduced non-thromboembolic manifestations. We describe the case of a 58-year-old woman with vegetation on the aortic valve, whose initial presentation of APS abruptly developed into diffuse pulmonary hemorrhage. Despite consecutive plasma exchange procedures and the administration of corticosteroids and high-dose intravenous immunoglobulin, multiple brain infarctions developed, and the patient died of pneumonia. Although anecdotal, this case might serve as a useful example of the non-standard complications of fulminant APS.

Key words: antiphospholipid syndrome, diffuse alveolar hemorrhage, Libman-Sacks endocarditis, catastrophic antiphospholipid syndrome, multiple brain infarctions

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Introduction

Antiphospholipid syndrome (APS) is an autoimmune condition that is primarily characterized by arterial or venous thrombosis or pregnancy morbidity associated with the presence of antiphospholipid antibodies (aPL) (1). The primary form of APS is not associated with any significant features of other autoimmune diseases such as systemic lupus erythematosus. Other forms of APS are termed secondary APS. Although most of the clinical manifestations of APS have been attributed to the hypercoagulable state induced by aPL, the non-standard manifestations of APS, such as thrombocytopenia, cardiac valve disease, and diffuse pulmonary hemorrhage are relatively common and might be caused by biological abnormalities other than thrombosis (2).

Patients with the catastrophic variant of APS (CAPS) account for less than 1% of all patients with APS, and they often do not have a history of thrombosis. CAPS patients usually present with a life-threatening condition, and hence, CAPS is associated with a mortality rate of almost 50%. According to the preliminary classification criteria for CAPS, its main pathogenesis comprises multiple simultaneous vessel occlusions and the almost immediate onset of clinical manifestations (3). We describe a rapidly progressive case of possible APS that mainly displayed non-standard manifestations and closely mimicked the catastrophic variant.

Case Report

A 58-year-old Japanese woman was admitted to our hospital with rapidly progressive dyspnea. She appeared critically ill upon examination in the emergency room. Her vital signs were as follows: blood pressure, 122/68 mmHg; temperature, 37.1°C and heart rate, 68 beats per minute. She displayed 91% oxygen saturation while breathing ambient...
The patient was a hepatitis B carrier and had been pre-
scribed levodopa, amantadine hydrochloride, and cabergo-
line. She had also received deep brain stimulation to treat re-
fractory Parkinson’s disease. In addition, she had under-
gone an induced abortion due to a hydatidiform mole but had not had any miscarriages. Fresh frozen plasma exchange with anticoagulation by nafamostat mesilate was started, and lamivudine was administered through a gastric tube on hos-
pital day 1. On hospital day 2 ceftriaxone and ciprofloxacin were also administered after the aortic valve vegetation had been identified. Laboratory findings on that day showed rapidly decreasing platelet count of 51,000/mm$^3$ and prolonged APTT of 41.2 s. On hospital day 8, the results of a rheuma-
tological profile taken after admission revealed that she was negative for antinuclear, proteinase 3-antineutrophil cyto-
plasmic, myeloperoxidase-antineutrophil cytoplasmic, and anti-glomerular membrane antibodies. A lupus anticoagulant (LA) test, performed using the hexagonal phospholipid neutralization procedure, revealed a shortened coagulation time of 9.4 seconds, but other tests involving the aPL panel (tests for dilute Russell’s viper-venom time [dRVVT], anticardiol-
ipin IgG and IgM antibodies, and anti-β2-glycoprotein I antibody) were negative. Her serum surfactant protein D and KL-6 levels were elevated to 609.4 ng/mL and 676 U/mL, respectively, and her hepatitis B viral load was 3.3 log cop-
ies/mL. No blood cultures yielded bacterial growth indicat-
ing that antibiotics would not confer a benefit.

Primary antiphospholipid syndrome with diffuse alveolar damage and Libman-Sacks endocarditis was considered to be the most likely diagnosis. She received methylpredniso-
lone 1,000 mg/day for 3 days followed by 60 mg/day of prednisolone. A CT scan of her chest showed gradual im-
provement of the ground glass opacities, and her serum CRP and LDH levels decreased, although cardiac sonogra-
phy did not demonstrate a reduction in the size of the vege-
tation. She could not be removed from mechanical ventila-
tion because she did not regain consciousness even after the administration of sedative drugs was stopped. Right hemi-
paralysis developed on hospital day 20, and a brain CT scan revealed multiple brain infarctions (Fig. 3). The infusion of intravenous immunoglobulin (2 g/kg) over 5 days exerted no apparent benefit. She developed ventilator-associated pneu-
monia and died 33 days after admission.

**Discussion**

We described a case involving the abrupt development of concurrent diffuse pulmonary hemorrhaging and endocarditis followed by multiple brain infarcts that ultimately resulted in death. We believe that this patient had APS. The diagnos-
ic criteria for APS consist of vascular thrombosis and pregnancy-related morbidity, along with positivity for anti-
cardiolipin antibody or positive lupus anticoagulant findings. Nonetheless, the reported non-standard manifestations of APS are expanding to include diffuse pulmonary hemorrhaging, cardiac valve disease, thrombocytopenia, and nep-
thropathy (2). Although the precise mechanism of each symp-
The presence of LA in plasma is one of the most reliable indicators of APS. The best test for LA is the dRVVT, although no single test is 100% sensitive to all LA (7, 8). Moreover, seronegative APS involving the typical clinical manifestations has recently been advocated, and aPL positivity is not always necessary for a diagnosis of APS (9). Although the present patient produced a negative result on the dRVVT test, a confirmatory test using hexagonal phospholipid neutralization showed a more rapid coagulation time. According to the guidelines, LA needs to be demonstrated in plasma on two or more occasions at least 12 weeks apart for LA positivity to be confirmed (1). However, testing for aPL could not be repeated in this patient because of the rapid and fatal course of her condition. Nevertheless, the slightly prolonged aPTT on hospital day 2 and the positive result in the confirmatory test supported a diagnosis of APS.

Multiple organ involvement rapidly develops in patients with the CAPS variant of APS, and multiple thromboembolic occlusions are the most common histological finding. According to the CAPS registry, 72% of patients are female, (mean age: 37 years), and approximately half of them developed de novo CAPS (3). The present patient was a 58-year-old woman without a known history of APS who rapidly developed symptoms followed by multiple brain infarctions late in her clinical course. Although the patient’s main manifestations i.e., diffuse pulmonary hemorrhaging and endocarditis, were considered to be caused by mechanism(s) other than thromboembolism, these symptoms closely resembled those of CAPS, especially their rapid and lethal progression; however, the pathophysiology of her condition differed from that of typical CAPS.

Deane and West reported four patients with the unusual combination of diffuse alveolar hemorrhaging and pulmonary capillaritis without thrombosis in the setting of primary APS (4). All of them presented with acute respiratory illness and were positive for lupus anticoagulant accompanied by high titers of anticardiolipin antibody. Although they rapidly improved after high-dose corticosteroid treatment, three of them suffered recurrent pulmonary hemorrhaging, which was successfully managed with intravenous immunoglobulin. The present patient displayed similar symptoms, although her response to corticosteroid therapy was limited, and intravenous immunoglobulin did not confer any benefit. Moreover, none of these patients appeared to have manifestations of other coexisting pathologies such as cardiac valve vegetation.

Treatment was challenging in the present case because the patient was a hepatitis B carrier with cardiac valve vegetation. The initial therapy comprised seven daily plasma exchanges along with lamivudine and antibiotics. Methylprednisolone pulse therapy was not started until infectious disease was ruled unlikely. Early diagnosis and aggressive treatment are essential for rescuing patients from succumbing to CAPS. The highest recovery rate was achieved using a combination of anticoagulants, corticosteroids, and plasma exchange and/or intravenous immunoglobulin (3). Treatment of the most severe manifestations of APS probably requires a similar approach to that employed for CAPS (5, 7). The pulmonary hemorrhaging in the present patient only slowly improved, and the administration of high-dose corticosteroids from hospital day 8 did not reduce the size of the cardiac valve vegetation. In addition, the subsequent multiple brain infarctions interrupted her recovery. Intravenous immunoglobulin, which was added 24 days after admission, was not beneficial. No anticoagulation was performed because pulmonary hemorrhaging was the patient’s main manifestation.

In summary, APS probably involves a larger variety of manifestations than was previously thought. Early and aggressive intervention is warranted when non-standard, rapidly progressive manifestations develop in patients with suspected APS.

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

References

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