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Case Report

Catastrophic antiphospholipid syndrome post-Epstein-Barr virus infection: a case report

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Antiphospholipid syndrome (APS) is an autoimmune disease characterized by risks of venous or arterial thrombosis and pregnancy loss in the presence of antiphospholipid (aPL) antibodies.[1] Catastrophic Antiphospholipid Syndrome (CAPS), the most extreme variant of APS, is marked by accelerated multiorgans failure due to widespread microthrombi.[2] Although CAPS is a rare disease occurring in less than 1% of all APS,[1] disease fatality is as high as 50% if left untreated.[3] A registry created by the *European Forum on Antiphospholipid Antibodies* established four criteria[4] to diagnose CAPS (Table 1).

Table 1 – Criteria to define CAPS.

Involvement of ≥3 organs, systems and/or tissues
Manifestations developed simultaneously or <1 week
Confirmation by histopathology of small vessel occlusion in ≥1 organ/tissue
Lab confirmation of antiphospholipid antibodies presence

CAPS: Catastrophic antiphospholipid syndrome.

Despite these criteria, the very low incidence of CAPS and its acute presentation which mimics other diseases make CAPS a diagnostic challenge.[1] Therefore, detailed history taking, comprehensive physical exams, and wide ranges of differential diagnoses remain vital in diagnosing and treating CAPS.

Case presentation

A 27-year-old African female with no significant past medical history presented to the emergency room complaining of fever, diffuse joint pains, generalized weakness and sudden onset of gangrenous-appearing fourth and fifth digits of the left-hand. Six months before this presentation, she reportedly developed a severe headache and fever, followed by intermittent nonspecific rash, and diffused joints swelling and pain. She was diagnosed with acute EBV infection in the setting of elevated EBV IgM titers. Over the next few weeks, her symptoms persisted. Her family physician, suspecting an autoimmune disease, referred her to a rheumatologist who diagnosed her with post-infectious syndrome as the rheumatologic workup showed only elevated C-reactive protein and erythrocyte sedimentation rate.

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Table 2 – Labs on admission.

WBC Count (4.80–10.80 K/uL)	12.29
Neutrophil Count (1.40–6.50 K/uL)	10.06
Neutrophil % (42.2–75.2%)	81.8
Hemoglobin (12.0–16.0 g/dL)	8.9
C-Reactive Protein (0 – 0.40 mg/dL)	17.91

On admission, patient was ill-appearing, febrile, tachycardiac and hypotensive. Physical exam showed dry and dusky appearing left fourth and fifth digits with clear demarcation and a palpable left radial pulse. Patient was also anemic and leukocytic (Table 2), and chest x-ray showed pulmonary edema. Endocarditis was considered due to suspected sepsis associated with vascular phenomenon but was ruled out by transesophageal echocardiogram which failed to detect valvular vegetation. Suspicion for infections, specifically tropical diseases, remained high given the clinical presentation of sepsis and patient's history of being raised in the Ivory Coast. An infectious disease specialist tested for various tropical infections, but all tests came back negative. Patient continued to deteriorate with worsening of gangrenous digits.

Rheumatology and vascular surgery specialists ruled out rheumatological diseases and vasculitides. There was no Raynaud's phenomenon in the fourth and fifth digits to suggest scleroderma type process. There was a consideration for Adult-onset Still's disease (ASD) given hyperferritinemia of 21438 ng/mL, fevers, neutrophilic leukocytosis, myalgia, and negative antinuclear antibody and rheumatoid Factor; however, thrombotic microangiopathy in ASD is an extremely rare entity. While suspicion for autoimmune vasculitis was high, CT of upper extremities failed to show vascular wall changes to suggest vasculitis.

Extensive workups ruled out infections, rheumatological diseases and vasculitides. Patient continued to spike fever, and her hemoglobin levels were decreasing. Hematology was consulted for microcytic anemia. Initial suspected causes include hemophagocytic lymphohistiocytosis (HLH), paroxysmal nocturnal hemoglobinuria (PNH), anemia of chronic disease, and iron deficiency anemia due to menorrhagia. Bone marrow biopsy was performed by interventional radiology to rule out HLH. Meanwhile, CD55 and CD59 flow cytometry was conducted to rule out PNH. Patient also had aPL antibodies screening for her anemia, which included anticardiolipin antibody, lupus anticoagulant and anti-beta2-glycoprotein (GP)-1 antibody. After three days, her aPL antibodies screening showed negative anticardiolipin antibody and lupus anticoagulant. However, patient had abnormally elevated anti-beta2-GP1 IgM and IgG antibodies with titer values of >150 SMU (Normal: ≤20 SMU) and 53 SGU (Normal: ≤20 SGU) respectively, which led to a strong suspicion for APS.

Due to the high likelihood of CAPS, patient was immediately started on methylprednisone 1000 mg daily for three days. She was also started on a course of intravenous immunoglobulin (IVIG) 400 mg/kg daily for five days. In addition, patient was placed on a heparin drip. Simultaneously, skin biopsy of the left-hand fourth digit was performed, which showed microthrombus of the superficial dermis in the skin and confirmed the suspected diagnosis. Patient met the four criteria for CAPS. Specifically, she had: (1) signs of involvement in three organs: pulmonary edema, anemia and fingers necrosis; (2) acute digits ischemia one week prior to admission; (3) elevated anti-beta2-GP1 antibodies, which is lab confirmation of APS; and, (4) histopathological evidence of small-vessel occlusion in her left fourth digit.

After treatment initiation, patient's symptoms subsided with no further complaints of headaches, arthritis or fever. She was placed on long-term oral anticoagulation with warfarin and was discharged with steroid taper. Her digits could not be salvaged. Patient was asked to see a hematologist for follow-up and a plastic surgeon for amputation of her left fourth and fifth digits. Twelve weeks post-discharge, patient had a repeated test for aPL antibodies showing elevated anti-beta2-GP1 IgM antibodies of 117.3 SMU and IgG antibodies of 56.2 SGU that confirmed APS diagnosis.

Discussion

We described a 27-year-old woman who was diagnosed with CAPS after extensive hospital workups that excluded differential diagnoses such as infections, rheumatological diseases and vasculitides. She was started on high doses of steroid and completed a course of IVIG treatment. She was discharged on oral anticoagulation and asked to follow up outpatient for the amputation of her gangrenous left fourth and fifth digits.

CAPS can occur spontaneously; however, 60% of CAPS have precipitating factors which include infections, malignancies, surgeries, and medications.[5] Specific infections like syphilis, shigella, human immunodeficiency virus, hepatitis B or C, malaria and EBV have all been documented as triggering causes.[5] The time interval between exposure to a precipitating factor and CAPS development is not well-described; most studies reported that patients developed CAPS acutely from an exposure.[6] Dissimilar to previous reports, our patient had an EBV infection that occurred six months prior to her CAPS diagnosis, rendering her infection unlikely to be a primary precipitating factor in the diagnosis. Although a precipitating factor is unclear for our patient, it is interesting to note that she had elevated anti-beta2-GP1 antibodies, which is the lab confirmation of CAPS. Viral or bacterial infection can induce the production of anti-beta2-GP1 antibodies due to the antibodies cross-reacting with the bacterial and viral proteins via molecular mimicry.[5] These antibodies usually disappear once the acute infection has been resolved.[5] However, a few small studies have shown that these antibodies can last more than six months in a small number of patients, although their roles are unknown.[6] Therefore, a question of whether previous infections, like EBV infection in this case, can increase the risk of developing CAPS requires further investigation.[5]

Unfortunately, the pathogenesis for CAPS remains poorly understood. It is unclear why CAPS has such an aggressive course and predominantly affects small vessels compared to classic APS, which is more indolent and mainly affects large vessels. A possible explanation is that an insulting factor, such as an infection or stressful event, resulted in systemic inflammatory response syndrome leading to high levels of cytokines. This proinflammatory environment promotes prothrombic state that cause microthrombi affecting multiorgans, known as "thrombotic storm".[7] In fact, patients with CAPS have high

levels of cytokines and acute phase reactants compared to other variants of APS. Specifically, 71% of patients with CAPS have hyperferritinemia, characterized by serum ferritin values of >400 ng/mL in men and >300 ng/mL in women.[7] In the case of our patient, the serum ferritin level was significantly elevated to 21438 ng/mL suggesting the patient is undergoing a thrombotic storm seen in CAPS. While the proinflammatory state may explain why CAPS result in microthrombi and multiorgans failure, the reason why only a minority of APS patients develop CAPS is unknown at this time.

Regardless of whether precipitating factors are identified, diagnosing CAPS remains extremely difficult. The diagnostic criteria for CAPS (Table 1) was created to help recognize the disease and facilitate early treatment. Based on validation data, CAPS diagnostic criteria have a sensitivity of 90.3% and a specificity of 99.4%.[7] Despite positive validation, CAPS shares similarities with many syndromes in clinical practice, making it a diagnostic challenge. In our case study, the medical team first suspected sepsis because like CAPS, severe sepsis can result in multiorgan failure and microthrombotic events due to disseminated intravascular coagulation (DIC). Since CAPS is a form of APS affecting small blood vessels, having differential diagnoses of diseases causing microangiopathic hemolytic anemia can be helpful.[7,8] These include DIC, hemolytic uremic syndrome, thrombi thrombocytopenia, heparin-induced thrombocytopenia (HIT) and sepsis. Systematic review of systems and comprehensive physical exam with focus on APS history, recent drug exposure, infection and location of thrombosis can help eliminate some of these differential diagnoses. In our patient, understanding that she had no recent exposure to heparin make HIT unlikely.

Due to its rarity and high mortality rate, CAPS should be treated as quickly as possible when CAPS is suspected. Treatment include supportive care and medical therapy. Patient with CAPS can deteriorate quickly and will benefit from ICU monitoring. Triggering factors such as infection and malignancy need to be addressed and treated simultaneously.[8] Medical therapy mainly consists of anticoagulation, steroid, plasma exchange (PE) and/or IVIG. In an acute setting, unfractionated heparin is the anticoagulation of choice.[9] In addition to its main purpose of preventing clot formation, heparin also has anti-inflammatory properties as synergistic effect.[9] Once clinically stable, patient can transition to coumadin with a target INR between 2 and 3. Based on the CAPS Registry, the standard steroid treatment is methylprednisolone 500–1000 mg intravenously for three days, followed by oral prednisone 1 mg/kg per day until improvement.[1] PE and/or IVIG is part of the first line treatment for CAPS. Observational data show PE and/or IVIG are associated with improved clinical outcome with 20% decrease in mortality.[2] The main purpose of plasma exchange is to remove aPL antibodies and cytokines from patient's body.[9] On the other hand, IVIG overloads the body with immunoglobulins and blocks aPL antibodies and cytokines from eliciting their detrimental effects.[9] The choice between PE, IVIG or both are individualized, although IVIG is generally better tolerated. In our patient, IVIG was chosen because of its ease of implementation and safer profile.

Conclusion

This case illustrates the difficulty of diagnosing CAPS, which is a rare and life-threatening disease. It took workups from multi-subspecialties, a positive antibody test and a biopsy before the diagnosis of CAPS was made. Recognition of CAPS by understanding its criteria and identifying predisposing factors like infections can help improve patient outcomes via early therapy initiation.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Cervera R, Rodríguez-Pintó I, Espinosa G. The diagnosis and clinical management of the catastrophic antiphospholipid syndrome: a comprehensive review. J Autoimmun. 2018;92:1–11.
2. Rodriguez-Pintó I, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: the current management approach. Best Pract Res Clin Rheumatol. 2016;30(2):239–49.
3. Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, et al. European Forum on Antiphospholipid Antibodies. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum. 2006;54(8):2568–76.
4. Rodríguez-Pintó I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G, et al. CAPS Registry Project Group (European Forum on Antiphospholipid Antibodies). Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev. 2016;15(12):1120–4.
5. Mendoza-Pinto C, García-Carrasco M, Cervera R. Role of infectious diseases in the antiphospholipid syndrome (including its catastrophic variant). Curr Rheumatol Rep. 2018;20(10):62.
6. Sène D, Piette JC, Cacoub P. Antiphospholipid antibodies, antiphospholipid syndrome and infections. Autoimmun Rev. 2008;7(4):272–7.
7. Carmi O, Berla M, Shoenfeld Y, Levy Y. Diagnosis and management of catastrophic antiphospholipid syndrome. Expert Rev Hematol. 2017;10(4):365–74.
8. Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. Autoimmun Rev. 2010;10(2):74–9.
9. Ruffatti A, De Silvestro G, Marson P, Tonello M, Calligaro A, Favaro M, et al. Catastrophic antiphospholipid syndrome: lessons from 14 cases successfully treated in a single center. A narrative report. J Autoimmun. 2018;93:124–30.