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Case Report

Catastrophic antiphospholipid syndrome presenting with a stroke as a first presentation: case report

Ahmad Nouri [1,‡], Ameer Awashra [1,‡], Mohammad Alnees [2,3,*], Hadi Rabee [4], Alaa Shamlawi[4]

[1]Department of Medicine, Faculty of Medicine & Health Sciences, An-Najah National University, Nablus, Palestine
[2]Harvard Medical School Postgraduate Medical Education, Global Clinical Scholars Research Training program, Boston, United States
[3]Head of Palestinian Clinical Research Center, Bethlehem, Palestine
[4]Department of Internal Medicine, An-Najah National University Hospital, Nablus, Palestine

*Corresponding author. Mohammad Alnees, Harvard Medical School Postgraduate Medical Education, Global Clinical Scholars Research Training program, Boston, United States. Email: a2011z2012z2013@gmail.com
‡Ahmad Nouri and Ameer Awashra Equally distributed.

Abstract

Catastrophic Antiphospholipid Syndrome (CAPS), an autoimmune disease that causes multi-organ thromboses leading to their failure, is a rapidly developing form of antiphospholipid syndrome (APS). APS may be a primary disease or secondary to an autoimmune condition like Systemic Lupus Erythematosus (SLE). A 31-year-old male patient with unremarkable medical history presented with a sudden onset of left-sided body weakness including upper and lower extremities, frontal headache, and slurred speech. Diagnostic workup revealed diffuse ST elevation with elevated cardiac enzymes, elevated inflammatory markers, prolonged activated partial thromboplastin time (aPTT), hemolytic anemia, and intrarenal kidney injury. Further investigations confirmed the diagnosis of probable CAPS secondary to SLE, based on the simultaneous involvement of the brain, heart, and kidneys, along with the presence of positive antiphospholipid antibodies (aPL). The patient showed significant improvement in neurological functioning after treatment with Methylprednisolone, Hydroxychloroquine, Colchicine, and Rituximab.

Keywords: Critical care medicine; Neurology; Rheumatology; Catastrophic antiphospholipid syndrome

Introduction

Antiphospholipid syndrome (APS) is a multisystemic autoimmune disorder that can occur as a primary condition or secondary to other autoimmune diseases, such as Systemic Lupus Erythematosus (SLE). In some cases, APS may be the initial presentation of SLE. SLE is a chronic autoimmune disease characterized by periods of remission and relapse, affecting multiple systems throughout the body. It is also one of the most gender-differentiated autoimmune diseases, with a female-to-male ratio of 9:1 [1, 2].

APS is characterized by the presence of autoantibodies directed against phospholipid-binding proteins such as lupus anticoagulant (LAC), anticardiolipin (aCL), and/or anti-beta-2 glycoprotein 1 (aβ2GP1) antibodies. The presence of these antibodies is a key component of the diagnostic criteria, in addition to the presence at least one thrombotic event and/or pregnancy morbidity [2].

Catastrophic antiphospholipid syndrome (CAPS) is a rapidly progressing and severe form of APS, occuring in approximately 1% of APS patients. It is categorized as an autoimmune disease characterized by thromboses in multiple organ systems, leading to their failure [3].

Common manifestations of CAPS include thrombosis, renal and cardiac involvement, and neurological symptoms. CAPS may also present with complications in the pulmonary and gastrointestinal systems, as well as dermatologic abnormalities and hematologic issues [4].

We reports the critical nature and diagnostic challenges of a rare, highly morbid disorder in a 31-year-old male presenting with stroke symptoms. Moreover, this case is particularly rare given the patient's gender and the absence of any prior diagnosis of autoimmune diseases, including SLE.

Case presentation

A 31-year-old male presented to the emergency department (ED) with an acute onset of left-sided weakness including upper and lower extremities, which began approximately one hour prior, following a fall while seated. The patient reported a frontal headache and slurred speech, along with non-radiating, burning epigastric pain.

The patient had an unremarkable medical history, aside from recurrent episodes of left flank pain previously treated as renal colic at a urology clinic. For this, he had been prescribed a non-steroidal anti-inflammatory drug, his only medication. The patient also reported a smoking history of 18 pack-years but denied any alcohol or substance abuse.

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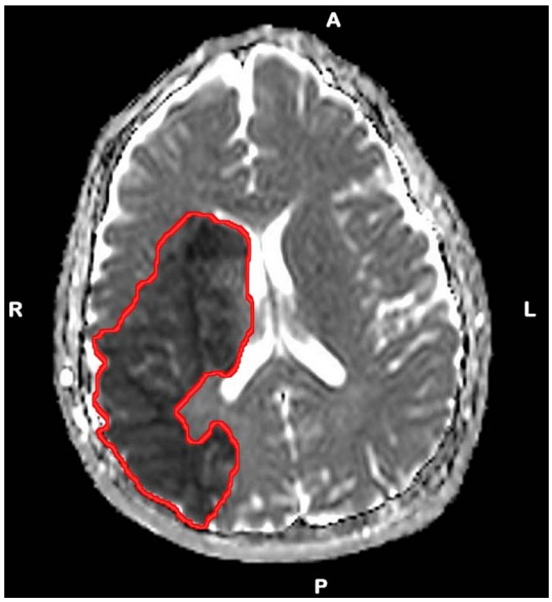

Figure 1. MRI demonstrates an apparent diffusion coefficient map of the brain, revealing ischemia in the right fronto-parietal–temporal lobes.

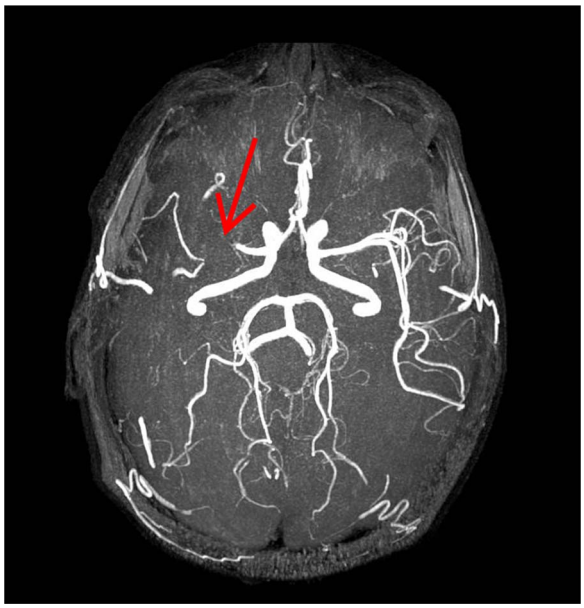

Figure 2. Axial MRA of the brain shows occlusion of the right middle cerebral artery.

The patient was conscious, alert, and oriented to time, place, and person, with hemodynamically stable and an oxygen saturation of 98% on room air. Neurologic examination showed non-fluent speech with intact comprehension and repetition. Sensation was preserved bilaterally; however, there was a marked reduction in power on the left side, with both upper and lower limbs scoring 1/5, and a muted Babinski sign on the left compared to the normal response on the right. Cranial nerve function was intact.

Initial laboratory results in the ED revealed elevated cardiac enzymes and normocytic anemia, with a hemoglobin level of 7 g/dl, a high reticulocyte count, and a low platelet count. Coagulation studies showed an elevated activated partial thromboplastin time (aPTT) with normal prothrombin time (PT) and international normalized ratio (INR). Evidence of intrarenal injury was noted, with a blood urea nitrogen (BUN) to creatinine ratio of 17:1. Additional findings included indirect hyperbilirubinemia, elevated inflammatory markers (C-reactive protein and erythrocyte sedimentation rate), normal serum electrolytes, and normal haptoglobin. The patient's baseline creatinine was 0.7 mg/dl. Urinalysis showed + 2 proteinuria and + 3 hematuria.

Diagnostic investigations included an electrocardiogram (ECG) that showed sinus rhythm with prolonged PR interval and diffuse ST-segment elevation, suggestive of myopericarditis. The echocardiogram revealed a Left ventricular ejection fraction of 60% and bi-atrial dilation. Cardiac catheterization showed non-obstructive coronary artery disease, indicating microvascular thrombosis. A CT scan showed a large acute nonhemorrhagic infarction in the right fronto-parietal–temporal lobes, along with multiple lacunar infarctions, confirmed by magnetic resonance imaging (MRI) (Fig. 1). Magnetic resonance angiography (MRA) revealed total occlusion of the middle cerebral artery (Fig. 2).

The patient was admitted to the intensive care unit (ICU), where additional laboratory investigations revealed schistocytes on blood smear, positive direct and indirect Coomb's test, increased ferritin, and a negative rheumatoid factor. Complement component C3 was decreased, and LAC was positive (ratio: 1.74). aCL was positive (26 IU/ml), while IgA and IgM β2GP1 antibodies were negative. Anti-nuclear antibodies (titer: 1:86) and anti-dsDNA antibodies (95.4 IU/ml) were also positive.

The patient received three units of packed red blood cells; two units were administered after the patient remained anemic following the first unit. The patient's condition dramatically improved after initiating treatment with Methylprednisolone, Hydroxychloroquine, Colchicine, and Rituximab.

Over the following 10 days, the patient exhibited further improvement with significant progress observed in both physical exam and laboratory results (Table 1). An ECG demonstrated regular sinus rhythm with no ST-segment elevation, but T wave inversion was noted in lead aVL. On the 12th day, the patient was discharged in stable condition with residual left-side weakness (1/5 in the upper limbs and 3/5 in the lower limbs) and normal strength on the right side. An ECG showed regular sinus rhythm with negative T waves in the anterior and inferior leads. An echocardiogram revealed normal findings, including a left atrial size of 20 mm (within the normal range of 20–40 mm).

At his last follow-up visit, 10 weeks after discharge, the patient remained stable and showed improvements in the strength of his left upper lower limb, which were 4/5 and 3/5, respectively. He continued to use crutches to assist with mobility while undergoing physiotherapy.

Thirteen weeks after discharge, the patient visited the rheumatology clinic, where the diagnosis of APS was confirmed through repeat laboratory tests. The results showed positive LAC (ratio: 1.85), as well as positive IgG aCL (46 IU/ml), IgM aCL (22 IU/ml), IgG aβ2GP1 (46 U/ml), IgA aβ2GP1 (39 U/ml), and IgM aβ2GP1 (35 U/ml) antibodies.

Discussion

Our 31-year-old male patient, previously healthy, presented with left-sided body weakness including upper and lower extremities and dysarthria, initially suggesting an acute ischemic stroke. In young individuals, the etiologies of stroke differ significantly from those in older populations. While atrial fibrillation and underlying cardiac conditions that predispose to cardiac thrombus or

Table 1. Laboratory test results and normal ranges.

Lab Test	1st Day	3rd Day	On Discharge	Normal Range	Unit
Blood Count					
Hemoglobin	7	10.8	12.1	13.5–17	g/dl
Hematocrit	21	30.6	35.4	43.5–53.7	%
MCV	90.2	91.4	90.6	80–100	fl
Platelet count	148	182	225	150–450	10^3/μl
Coagulation Profile					
PT	13.2	13.9	13.9	11–15	seconds
aPTT	44.8	43.0	38.8	25–35	seconds
INR	1.01	1.05	2.14	0.8–1.1	-
General Chemistry					
Sodium	136	137	139	135–145	mEq/l
Potassium	4.0	4.3	4.7	3.5–5.3	mEq/l
Chloride	105	105	104	98–100	mEq/l
BUN	25	20	21	6–20	mg/dl
Creatinine[a]	1.47	1.09	1.12	0.7–1.2	mg/ml
Hepatic					
Total Bilirubin	1.7	1.5	0.9	0.1–1.1	mg/dl
Direct Bilirubin	0.1	0.16	0.27	0.0–0.3	mg/dl
Others					
Troponin I	4.162	2.681	0.033	0–0.029	ng/ml
CRP	2.86	2.79	0.45	0–0.5	mg/dl
ESR	130	128	15	0–10	mm/hr
Haptoglobin	60	-	-	50–220	g/l
Ferritin	434	-	-	21–274	ng/ml
Complement C3	91	-	-	90–180	mg/dl

[a]The patient's baseline: 0.7 mg/ml.

arrhythmia are less common, other causes such as paradoxical embolism in the setting of a patent foramen ovale, chronic or recurrent infections, migraine with aura, APS, other inflammatory or autoimmune conditions, drug effects, and cancer must be carefully considered. APS, in particular, should be high on the differential diagnosis list in a young person presenting with acute ischemic stroke, as it is not an unusual cause in this demographic. The initial focus on more common conditions such as embolic or drug-induced causes should not overshadow the importance of considering APS early in the diagnostic process [5].

Diagnosing patients with abdominal pain is often complex, particularly when initial suspicions focus on common conditions like kidney stones. In this case, the previous suspicion of kidney stones complicated the diagnostic process. The abdominal pain reported by the patient may have arisen from thrombus formation in internal organs such as the kidneys, adrenal glands, spleen, intestines, mesentery, or pancreas, all of which can present with abdominal pain rather than being attributed to stones [6]. The age and sex of the patient as well as the spread of the disease throughout the body made the suspicion of APS more ambiguous during the initial diagnosis period.

A combination of clinical, laboratory, and imaging findings is required to diagnose CAPS. In 2003, specifically at the 10th International Congress on Antiphospholipid Antibodies, the definitive and probable criteria of CAPS were proposed (Table 2).

Based on the data presented in the previous table, the patient meets criteria 1, 2, and 4, indicative of a probable diagnosis of CAPS. The patient displays involvement of three distinct organs: the brain, with a confirmed stroke through imaging; the heart, evidenced by non-obstructive coronary artery disease suggestive of microvascular thrombosis [7]; and the kidneys, as reflected by a more than 50% increase in creatinine from the baseline [6] (baseline: 0.7 mg/mL; creatinine on presentation: 1.47 mg/ml). Furthermore, the sustained positivity of antiphospholipid antibodies both at the presentation and 12 weeks later aligns with criteria number 4.

It is imperative to conduct a follow-up assessment for the presence of aPL 12 weeks after the initial tests, as results obtained during the acute phase may yield falsely positive outcomes; because of harm to endothelial cells rather than the presence of pathogenic antibodies. Notably, aβ2GP1 was negative during the acute phase but turned positive 12 weeks later, attributable to consumption [6].

According to the American College of Rheumatology, aβ2GP1 and aCL antibodies are classified as moderate at 40–79 units and high at >80 units. This classification helps in understanding our patient's antibody profile, which shows LAC positivity with slightly elevated aCL and aβ2GP1 antibodies. This profile is common and can be influenced by anticoagulant use or inflammation. False-positive results for aPL tests can occur during infections, inflammatory syndromes, or anticoagulant treatment. Therefore, LAC testing should ideally be done in patients not on anticoagulants, as acute-phase responses can also affect test results [8].

Many factors may precipitate CAPS, with infections being the most common (46.7%), followed by malignancy (17.6%), surgery

Table 2. Preliminary classification criteria for CAPS.

Definitive criteria: Include all four criteria

1) "Evidence of involvement of three or more organs, systems, and/or tissues"
1) "Development of manifestations simultaneously or in less than one week"
1) "Confirmation by histopathology of small vessel occlusion in at least one organ or tissues"
1) Laboratory confirmation of the presence of antiphospholipid antibodies (LAC and/or aCL antibodies)

Probable CAPS

- All four criteria, except for only two organs, systems, and/or tissues involved
- All four criteria, except for the absence of laboratory confirmation owing to the early death of a patient never tested for antiphospholipid antibodies before the CAPS
- Criteria (1), (2), and (4)
- Criteria (1), (3), and (4) and the development of a third event between one week and one month after presentation, despite anticoagulation.

Modified from reference 7.

(16.8%), withdrawal of or sub-therapeutic anticoagulation (10.9%), obstetric complications, oral contraceptives (7%), trauma and flare of an autoimmune disease such as SLE [6].

CAPS represents a rare and intricate manifestation of APS, a complex condition involving both the adaptive and innate immune systems. The onset of CAPS typically involves the initiation of endothelial, immune, and platelet cell activation, followed by the inhibition of the protein C pathway and other anticoagulant pathways. Concurrently, fibrinolytic factors are suppressed, and eventually, the complement system is activated. The concept of a 'thrombotic storm' in CAPS suggests a genetic predisposition, with the presence of aPL acting as the 'first hit.' However, a 'second hit' from environmental factors, such as infections or surgeries, is necessary to trigger clot formation. CAPS is characterized by simultaneous local thrombosis and a systemic inflammatory response, involving excessive cytokine release (IL-1, IL-6, TNF). In classic APS, aPL binding induces intracellular changes and activates immune cells, creating a pro-thrombotic state. Endothelial cell activation, particularly through Toll-like receptor-4 and complement activation, contributes significantly to thrombosis in both APS and CAPS. Additional mechanisms proposed include oxidative stress and ADAMTS 13 deficiency [3, 4].

The treatment plan comprised a combination of medications aimed at preventing clot extension, inhibiting immune flares, and averting recurrence. Parenteral heparin, corticosteroids, and Rituximab were administered initially, with heparin used until the patient achieved an INR greater than 2. Subsequently, the patient was transitioned to warfarin for long-term anticoagulation management. Notably, Rituximab has been associated with a reduced rate of disease relapse [9].

Rituximab a B-cell-depleting therapy, has exhibited success in managing refractory SLE manifestations, often in conjunction with other therapies. According to a review of CAPS registry cases, 75% of Rituximab-treated patients experienced recovery from their episodes. Additionally, a pilot study focused on classic APS revealed Rituximab's favorable safety profile and potential efficacy against non-criteria APS manifestations [10].

Anticoagulation with heparin, aiming to halt ongoing clotting, prevent the formation of new clots, and leverage its anti-inflammatory effects, plays a critical role in the management of CAPS. While heparin does not directly dissolve existing clots, it prevents further thrombus formation and allows the body's natural fibrinolytic processes to break down existing clots. The noteworthy anti-inflammatory activity of heparin significantly contributes to its exceptional efficacy in CAPS. Moreover, heparin appears to impede the binding of aPL to their cellular targets, thereby mitigating the autoimmune response [6].

After resolving a CAPS flare crisis, a study demonstrated that the use of anticoagulants ensures some degree of health stability. Over a 5-year period, approximately 20% of patients experienced repeated thrombotic incidents, most of which occurred around the time of surgery [11]. Recent studies have showed a decrease in the mortality rates among CAPS patients from 53% to 33%, although this remains a high percentage [3]. Current investigations into APS suggest that Warfarin is more effective in preventing thrombosis compared to novel oral anticoagulants. Furthermore, the latter class of anticoagulants lacks established roles in the treatment of CAPS [10, 12].

The elevated aPTT measurement, which was over 40, led the medical team to avoid thrombolysis due to the increased risk of bleeding. In ischemic stroke management for CAPS patients, a high aPTT indicates a greater chance of bleeding, making thrombolysis less suitable. Additionally, plasmapheresis, a possible supportive therapy, was not available at our facility. As a result, the team followed the established protocol, focusing on anticoagulation to reduce the risk of clots while also minimizing bleeding complications [13].

It is important to know that about 50% of patients with CAPS have no previous history of APS [14]. In 62% of cases, there is observed central nervous system engagement, typically encompassing hypertensive encephalopathy, ischemic encephalopathy, stroke, and cerebral venous thrombosis. Following pulmonary involvement, neurological engagement emerges as the second most frequent presentation [15, 16].

Finally, it is essential to highlight that the patient was not entirely healthy due to his substantial smoking habit, amounting to 18 packs per year. Smoking is known to exacerbate autoimmune conditions and can increase the activity of lupus, leading to more severe symptoms and complications. The pro-inflammatory effects of smoking and its impact on immune modulation could have contributed to the patient's overall health status and possibly influenced the severity and presentation of his autoimmune disorder [17].

Conclusion

In this case of a 31-year-old male diagnosed with probable CAPS, the journey to diagnosis highlighted the intricate nature of this rare autoimmune disorder particularly in males. The patient's initial presentation with stroke symptoms prompted a thorough evaluation, considering a range of potential causes. The judicious

use of Rituximab, along with anticoagulation and a comprehensive multidisciplinary treatment approach, played a pivotal role in the patient's successful recovery.

Furthermore, this case serves as a reminder to healthcare providers about the importance of considering CAPS even before serological confirmation in individuals experiencing rapidly advancing thrombotic events. Timely diagnosis and intervention are crucial, as any delay can result in unfavorable clinical outcomes.

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Conflict of interest

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Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient's Himself for his anonymized information to be published in this article.

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