

# Erythrocytosis, embolism in a woman with antiphospholipid antibodies: A diagnostic challenge

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## Abstract

Systemic thromboembolism, along with acute multiorgan failure, should raise clinical suspicion for CAPS. Timely management, even in suspected cases, can have a significant impact on mortality.

## KEYWORDS

catastrophic antiphospholipid syndrome, Erythrocytosis, pulmonary embolism, stroke, thrombotic microangiopathy

## 1 | INTRODUCTION

The antiphospholipid syndrome (APS) is an autoimmune disorder associated with venous or arterial thrombosis and pregnancy morbidity (mostly fetal loss) and in the presence of antiphospholipid antibodies (aPL). The spectrum of APS-related vascular events ranges from a superficial thrombosis to life-threatening multiple organ system thromboses developing over a short period (catastrophic APS).<sup>1</sup> In 1992, the term "catastrophic" was first proposed by Asherson to describe the potentially life-threatening clinical course of the APS subset, based on analyses of 10 original patients.<sup>2,3</sup> After this initial description, the first comprehensive literature review of 50 patients with catastrophic antiphospholipid syndrome (CAPS) was published in 1998.<sup>1,3</sup> The significant difference between APS and CPAS is the predominant manifestation of CAPS as microangiopathy—that is, intravascular thrombosis affecting predominantly microcirculation rather than large peripheral or arterial involvement seen in typical APS.<sup>3,4</sup> The kidneys, lungs, CNS, and liver are most affected. Only about 1% of patients with APS develop CAPS.<sup>4,5</sup> However, this rare condition is associated with the mortality rate of 50 percent at the initial event, therefore warranting a high clinical suspicion of CAPS as a differential diagnosis and a low threshold to initiate appropriate treatment, even in suspected cases.

We present a case of a female with the predisposing pro-coagulant state due to chronic hypoxia-induced polycythemi, who initially presented with acute CVA and acute bilateral pulmonary embolism. However, was also found to have accompanied acute liver failure, renal failure, thrombotic microangiopathy (thrombocytopenia and hemolytic anemia with schistocytes), and severe coagulopathy along with high anticardiolipin antibody titers, raising the suspicion for possible superimposed CAPS.

## 2 | CASE PRESENTATION

57-year-old female was brought in by her son to the emergency department for an altered mental status of unknown duration. The patient has medical history significant for chronic polycythemia secondary to pulmonary hypoxia, chronic obstructive pulmonary disease (COPD), diabetes mellitus type II, hypertension, chronic hepatitis C (HCV). She has no prior surgeries. Patient had significant 20 pack year smoking history, however quit 10 years ago. Medications at the time of presentation included amlodipine and Ventolin. On examination, initial vitals were temperature 98.7, oxygen saturation 77 percent at room air, blood pressure 156/78 mm Hg, respiratory rate 24 breaths per minute, and pulse 80 beats per minute. She was alert but oriented to self and place only with a Glasgow coma scale of 15. She appeared comfortable and

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was noted to have scleral icterus. The rest of the physical examination was normal. The laboratory tests were prominent for erythrocytosis (hemoglobin and hematocrit 21 g/dL and 62% respectively), thrombocytopenia (platelet count  $54 \times 10^9/L$ ), conjugated hyperbilirubinemia (total and conjugated bilirubin 12 mg/dL and 10 mg/dL, respectively), transaminitis (AST/ALT 271 u/L/188/L), acute kidney injury (bun/cr 35mg/dL/1.6mg/L), coagulopathy (Pt/Inr25/2 seconds), and rhabdomyolysis (creatinine kinase 2233 u/L) (see Table 1 for basic laboratories).

Computed tomography (CT) of the head revealed acute versus subacute infarcts in the left cerebellar hemisphere and basal ganglia Figure 1. CT angiography of the chest showed intraluminal filling defects within subsegmental branches involving the left and right upper lobes consistent with bilateral pulmonary emboli Figure 2. It also showed patchy bilateral subpleural airspace opacities concerning underlying pulmonary infarct. There was a suggestion of the right ventricle (RV) strain due to the right atrium and RV dilation. Echocardiography with a bubble revealed a normal left ventricular ejection fraction of 63% but high pulmonary artery systolic pressure 102 mmHg and atrial septal defect-ostium secundum with a bidirectional shunt and severely enlarged right atrium and ventricle. Ultrasound abdomen was consistent with gallbladder sludge, possible congestive hepatopathy. Ultrasound Doppler of the bilateral lower extremity was negative for deep vein thrombosis.

Due to the findings of ischemic stroke and pulmonary embolism along with chronic polycythemia in the setting of possible Eisenmenger syndrome, a hypercoagulable state was suspected. The patient was admitted to the critical care unit, started on broad-spectrum antibiotics, intravenous fluids, and high flow oxygen. The decision was made to do therapeutic phlebotomy with the removal of 500 mL blood to maintain hematocrit less than 45%. Also, the patient was started on digoxin and intravenous furosemide to help with the diuresis. Anticoagulation therapy was not started due to severe coagulopathy. However, aspirin was started.

Further workup revealed worsening thrombocytopenia, coagulopathy, transaminitis, and low haptoglobin, elevated LDH along with blood smear showing schistocytes Figure 3 concerning for underline hemolytic anemia. At this point, our differential diagnosis included sepsis leading to multiorgan failure, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), heparin-Induced thrombocytopenia (HIT), Systemic lupus erythematosus (SLE) and vasculitis.

Septic workup, including blood, urine, and respiratory cultures, were negative. HIV serology, Rapid plasma reagin (RPR), antiplatelet factor 4 antibodies, serotonin release assay (SRA), and direct coombs antibodies (DAT) were negative. ADAMS 13 activity was normal. Hepatitis C virus antibody was positive with a viral load of 2480000 u/mL, complement levels (C3 and C4) were low 50mg/dL and 8mg/dL, respectively. However, cryoglobulins, antinuclear antibody (ANA), antiproteinase -3b (ANCA), anti-DNA antibody, anti-Jo antibody, antismooth muscle antibody, and antimitochondrial antibody were negative. Hypercoagulation workup, including Jak2V617F, were negative, and erythropoietin (EPO) levels were normal, ruling out polycythemia vera. Antibeta2 microglobulin antibodies ( $\alpha\beta 2GPI$ ) and lupus anticoagulant were negative. However, anticardiolipin (aCL) IgM and IgG were positive with a titer of > 150 u/ml and 113 u/ml, respectively (pertinent laboratories see Table 2).

Due to extremely high levels of antiphospholipid antibodies and multiorgan involvement, a diagnosis of catastrophic antiphospholipid antibody syndrome (CAPS) was strongly suspected. The patient was started on dexamethasone 20mg IV every 12 hours, intravenous immunoglobulins (IVIG) at a dose of 1g/kg daily for two days, along with plasma exchange daily for 5 days.

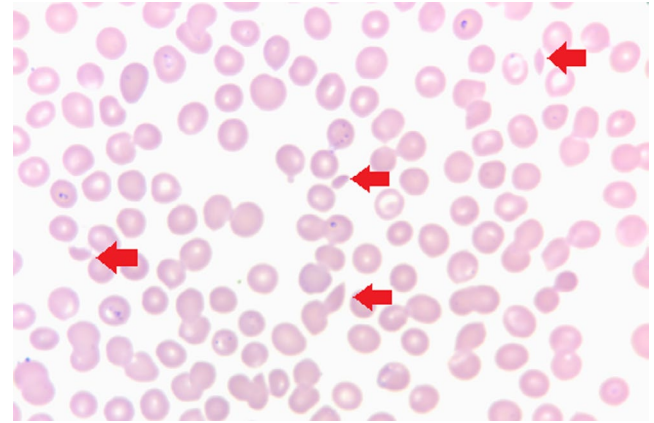
The seventh day into her admission, the patient's clinical course further deteriorated with worsening hypoxia; she was intubated and started mechanical ventilation. The patient experienced cardiac arrest with an initial rhythm of pulseless activity, and despite attempts at resuscitation following

**TABLE 1** Patient's basic laboratories trend over the hospital course

Laboratories	Base line (3 Y prior)	Date of admission	Day 3	Day 5	Day 7
Hg/Hct g/dL/%	20/60	21/62	18/55	16/48	15/43
WBC k/uL	13	11	8.3	12	23
Platelets k/uL	166	54	101	72	16
Bun/Cr mg/dL	14/0.6	35/1.6	32/1.2	35/1.2	25/1.5
AST/ALT u/L	77/44	277/188	144/107	129/104	335/118
Bilirubin total/ conjugated mg/dL	0.9/0.4	12/10	13/14	13/10	12.8/10
INR	0.8	1.8	2.02	2.06	2.10
PT/ PTT	11/26	21/31	24/35	24.8/32	25/37



**FIGURE 1** Computed tomography of the brain showing left cerebellar hemisphere ill-defined low attenuation abnormalities, suggestive of acute infarct



**FIGURE 3** Peripheral blood smear showing schistocytes

suffered pulmonary embolism and cerebrovascular events, along with the hematological manifestation of coagulopathy, thrombocytopenia, and hemolytic anemia. Given all of these laboratory and radiological findings, CAPS was suspected, and management with steroids IVIG and plasmapheresis was started. To confirm the definitive diagnosis of antiphospholipid syndrome, the patient was planned to get a repeat aCL titers in 12 weeks, but her clinical course worsened, and she expired.



**FIGURE 2** Contrast-enhanced computed tomography of the chest showing Intraluminal filling defects within subsegmental branches involving the right upper lobes consistent with pulmonary embolus

ACLS protocol, she succumbed to her underlying pathology and expired.

The patient was new in our system, and some parts of her medical history were unknown. The patient was found to have polycythemia secondary to either COPD or the intracardiac shunt (the possibility of Eisenmenger syndrome cannot be excluded). Her aCL titers were highly elevated,

### 3 | DISCUSSION

Catastrophic APS is the most severe complication of antiphospholipid syndrome and is characterized by end-organ damage due to small-vessel occlusion affecting at least three organ systems with laboratory confirmation of the presence of antiphospholipid antibodies. The diagnostic criteria are explained in Table 3<sup>[3,7]</sup>. The demonstration of APS's laboratory criteria (presence of lupus anticoagulant or >99th percentile titers of anticardiolipin or anti- $\beta_2$  glycoprotein I) is critical while diagnosing CAPS. Several criteria have been proposed to determine the presence of clinically significant APS profile, of which the revised Sapporo criteria is the most used. These criteria define high titer of inhibitors as >99th percentile or >40 g/L as the specificity of aCL and  $\alpha\beta_2$ GPI ELISA tests for APS-related clinical events increases with higher titers. As transient aPL positivity is common during infections (typically low titer aPL ELISA), documentation of persistently elevated antibodies (at least 12 weeks apart) is required for diagnostic purposes. Preferably, aPL test should be tested off anticoagulation as both false-negative and false-positive results can occur in anticoagulated patients.<sup>6-9</sup>

According to a review of 280 patient from the CAPS registry and a retrospective meta-analysis of 50 CAPS patients, the multiorgan involvement of CAPS typically manifests predominantly with renal failure (present in 71% of patients), respiratory failure (64%), and central nervous system involvement

**TABLE 2** Patient's pertinent laboratory values

Pertinent Laboratories	Laboratory values	Reference range
DRVVT screen (Lupus anticoagulant)	35	< = 45 sec
Beta-2-microglobulin serum	3.2	0.8-2.2 mg/L
B2 glycoprotein IgA	<9	< = 20
B2 glycoprotein IgM	<9	< = 20
B2 glycoprotein IgG	<9	< = 20
Cardiolipin Ab IgA	<11	
Cardiolipin Ab IgM	>150	
Cardiolipin Ab IgG	113	
Immunoglobulin G level, serum	1946	600-1640 mg/dL
D dimer	3723	0-230 ng/mL
fibrinogen	115	185-450 mg/dL
C3 complement	50	90.0-150.0 mg/dL
C4 complement	8.0	16- 47 mg/dL
Total hemolytic complement Assay	<13	31-60 U/mL
LDH	864	100-190 units/L
Haptoglobin	<10.0	30-200 mg/dL
ADAMTS13	94	68%-163% activity
JAK2 mutation	Not detected	Not detected
Erythropoietin Assay	9.7	2.6-18.5 mL U/ mL
Reticulocyte %	3.3	0.5-1.5
ANA	negative	Negative
Antiscleroderma 70	<1.0	<1.0 (negative)
SS-A Ab & SS-B ab	<1.0	<1.0 (negative)
Antibody to Jo-1	<1.0	<1.0 (negative)
Alpha-1 antitrypsin	147	83 - 199 mg/dL
Antimitochondrial Ab	Negative	Negative
Anti-DNA Ab	<1	<or = 4 (negative)
Cryoglobulin, QL	Not detected	Not detected
HCV RNA QN PCR	2 480 000	Target not detected (IU/ mL)

(62%). Most renal involvement patients demonstrated an overwhelming picture of renal microangiopathy, renal infarction, malignant hypertension, or laboratory evidence of glomerular damage (hematuria & proteinuria). Pulmonary involvement manifested predominately as ARDS followed by multiple pulmonary emboli, interstitial edema, or interalveolar hemorrhage. Major cerebral infarction, cerebral venous thrombosis, microinfarctions, retinal vascular involvement,

and less commonly status epilepticus were found as CNS manifestations. Liver involvement was described in 33% of the patients, and gastrointestinal involvement was seen in 25%. 94 percent of the patients had positive aCL titer, with the majority presenting high IgG titers as in our patient.<sup>3,4</sup>

Although precipitating factors remain unknown in most of the cases,<sup>2</sup> the most commonly identified provoking factors are infection and surgery, followed by drug ingestion (thiazide, captopril, OCPs), anticoagulation withdrawal, and obstetrics complications.<sup>3,5,10</sup> The proposed

**TABLE 3** Preliminary classification criteria for catastrophic antiphospholipid syndrome<sup>[3,7]</sup>

1. Evidence of involvement of three or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small-vessel occlusion
4. Laboratory confirmation of the presence of antiphospholipid antibodies (twice 12 weeks apart)

**Definite catastrophic antiphospholipid syndrome**

All four criteria present

**Probable catastrophic antiphospholipid syndrome**

All four criteria, except only two organs, systems, and/or tissues involved

All four criteria, except for the absence of laboratory confirmation of antiphospholipid antibodies

Criteria 1, 2, and 4

Criteria 1, 3, and 4, with the development of a third event more than 1 week but within 1 month of presentation, despite anticoagulation

**TABLE 4** Proposed pathogenic mechanisms in Catastrophic APS<sup>6</sup>**1. Cellular activation**

- Endothelial cell activation
- Immune cell activation
- Platelet activation

**2. Inhibition of anticoagulants**

- Inhibition of the protein C pathway
- Disruption of annexin A5 shield

**3. Inhibition of fibrinolysis**

- Inhibition of plasminogen activator inhibitor 1
- Blocking of  $\beta$ 2-glycoprotein I
- Blocking of annexin A2

**4. Complement activation**

- Endothelial cell activation by C5a and MAC
- Immune cell activation by C5a
- Platelet activation by C3a and MAC
- Inhibition of fibrinolysis by C5a

pathogenic mechanisms of antiphospholipid antibodies can be arbitrarily divided into four interrelated groups: 1) cellular activation, 2) inhibition of anticoagulants by disrupting protein C pathway, 3) inhibition of fibrinolysis, and 4) complement activation Table 4. Antiphospholipid antibodies stimulate endothelial cells, immune cells, and platelets by reducing the activity of endothelial nitric oxide synthase resulting in impaired vasodilation, further promoting platelet aggregation.<sup>11</sup>

Activation of coagulation cascade along with inhibition of protein C & fibrinolysis leads to acute thrombotic microangiopathy (TMA) resulting in microangiopathic hemolytic anemia and thrombocytopenia, which are the most predominant hematological manifestations of CAPS. However, due to overlapping features, it is critical to rule out other TMAs, such as sepsis, hemolytic uremic syndrome (HUS), TTP, DIC, HIT, HELLP syndrome, and SLE vasculitis, to establish a definitive diagnosis of CAPS.<sup>6,12</sup> According to studies by Asherson et al and Cervera et al, the most common hematological manifestations of CAPS were DIC, thrombocytopenia (<100,000/uL), and hemolytic anemia with schistocytes.

Our patient had chronic erythrocytosis, most likely secondary to COPD and Eisenmenger syndrome induced hypoxia. Initial presentation of simultaneous arterial and venous thrombosis, including bilateral pulmonary embolism and CVA, raised concerns for thromboembolic events due to underline erythrocytosis-induced hyperviscosity, leading to prompt initiation of phlebotomy. Later, JAK 2 mutation was negative, and EPO was normal, ruling out polycythemia vera. Polycythemia vera is known to be associated with thromboembolic events; however, the causative relationship between elevations of hematocrit in patients without a myeloproliferative neoplasm and venous thromboembolic events (VTE) remains questionable. A retrospective case-control study demonstrated that VTE events did not occur more frequently in patients with secondary polycythemia than in those without after a median follow-up of five years.<sup>13,14</sup> In a UK study of 7,346 men, an increased risk of stroke was not seen at higher hematocrit levels ( $\geq 51\%$ ) in normotensive men but was apparent in hypertensive individuals.<sup>15</sup> In the Framingham study, hematocrit was associated with an increased risk of stroke, but this association disappeared in multivariate analysis when smoking, a well-established risk factor for stroke, was accounted for.<sup>16</sup> In conclusion, the evidence suggests that secondary polycythemia per se is not an independent risk factor for VTE.

Moreover, acute and simultaneous deterioration of multiple organs, including the brain, lungs, liver, kidneys, and hematological evidence of microangiopathy, cannot be explained by merely underline severe polycythemia. Other possible TMA, including autoimmune vasculitis, TTP, and HIT, were ruled out. Infections and anticoagulation can

cause false-positive aCL, but titers are usually low. In our patient, aCL titers were obtained in the absence of anticoagulation, and infections are less likely to cause such high titers. Unfortunately, due to our patient's short hospital course, we were unable to repeat the aCL titers, and no biopsy or autopsy was performed to provide the histopathological evidence of small-vessel occlusion. Despite lacking the definitive CAPS diagnostic criteria in our patient, it was highly suspicious, and the patient was started on IVIG, steroids, and plasmapheresis.

CAPS carries a dismal prognosis. According to Cervera et al, 44 percent died at the time of the catastrophic APS event. However, the higher recovery rate was achieved by the combination of anticoagulants plus corticosteroids plus rapid reduction of aPL titers using plasma exchange (PE) and intravenous immunoglobulins (IVIG) (69% versus 54%).<sup>1,3,4</sup> Another study showed that the recurrence rate in untreated patients is 44-55% after the first vascular event and approaches zero in patients treated with high-intensity warfarin.<sup>1</sup> In the case of refractory or relapsing CAPS, new treatment modalities have been suggested, including rituximab, defibrotide, and eculizumab (terminal complement inhibitor).<sup>17</sup>

## 4 | CONCLUSION

Even though our case does not fulfill the definitive diagnostic criteria of Catastrophic APS, an acute catastrophic manifestation of more than three organs (brain, lungs, liver, kidney along with severe thrombocytopenia, hemolytic anemia & severe coagulopathy) along with high isolated aCL IgG and IgM titers (in the absence of anticoagulation) makes the diagnosis of CAPS highly likely in our patient. Our case report emphasizes that high clinical suspicion and awareness are required to diagnose this rare but potentially life-threatening entity. Anticoagulation, steroids, and rapid reduction of aPL titers using IVIG and plasmapheresis remain the mainstay of treatment. Timely initiation of these managements, even in suspected cases, can have a significant impact on mortality.

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## CONFLICTS OF INTEREST

In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## AUTHORS CONTRIBUTION

AS: contributed to original draft preparation and manuscript editing. AH: contributed to original draft preparation and manuscript editing. MM: contributed to manuscript editing. AH: contributed to conception of design and manuscript editing.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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