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Antiphosphatidylserine Antibody as a Cause of Multiple Dural Venous Sinus Thromboses and ST-Elevation Myocardial Infarction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 48
Final Diagnosis: Antiphospholipid syndrome
Symptoms: Chest pain • confusion • seizure-like activity
Medication: —
Clinical Procedure: Endovascular venous suction thrombectomy
Specialty: Hematology

Objective: Rare disease

Background: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by antibodies directed against phospholipids on plasma membranes. Through unclear mechanisms, APS confers hypercoagulability. APS may cause recurrent thromboses in the arterial and venous vasculature. We report a case of primary APS resulting in cerebral venous thrombosis and ST-elevation myocardial infarction (STEMI) for which only antiphosphatidylserine (aPS) IgM antibody was positive after extensive investigation.

Case Report: A 48-year-old male was admitted after a witnessed generalized seizure with subsequent confusion. Imaging demonstrated thrombosis of multiple central nervous system (CNS) sinuses, including the superior sagittal sinus and bilateral transverse sinuses. The patient was heparinized with aggressive hydration, which proved inadequate, prompting endovascular thrombectomy. Three months later, despite anticoagulation therapy, the patient developed a STEMI when International Normalized Ratio (INR) was 1.8. Echocardiogram (ECHO) and PAN CT scan were normal. Initial coagulation studies demonstrated normal anticardiolipin antibody, prothrombin time, partial thromboplastin time, and platelet count. Outpatient coagulation studies revealed normal antithrombin III, protein C/S, hemoglobin electrophoresis, homocysteine, anti-β2 glycoprotein 1 antibodies, and D-Dimer. Factor V Leiden, JAK 2 mutation, prothrombin gene mutation, and tests for paroxysmal nocturnal hemoglobinuria (PNH) were negative. A positive phosphatidylserine IgM was detected. The patient was continued on warfarin (10 mg daily) with a target INR of 3.0–3.5 and clopidogrel (75 mg daily).

Conclusions: Despite extensive investigation, this patient only showed evidence of elevated aPS IgM antibodies, likely contributing to his CNS venous sinus thromboses and STEMI. It is important to screen for antiphosphatidylserine antibodies in cases of unprovoked thrombosis when standard thrombophilia analysis is unrevealing. This will assist in identifying pathogenicity and help prevent recurrence of subsequent thromboses.

MeSH Keywords: Antiphospholipid Syndrome • Intracranial Thrombosis • Phosphatidylserines • Thrombophilia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/909698

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Background

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder that results in a hypercoagulable state characterized by recurrent venous and/or arterial thrombosis [1]. Antiphospholipid antibodies are directed against proteins that bind to anionic phospholipids on plasma membranes [2]. APS can be characterized as a primary or secondary disorder and is more frequently seen in women, particularly those who have pregnancy-related complications such as miscarriage, stillbirth, or preterm delivery [3]. APS may contribute to an increased frequency of stroke or myocardial infarction (MI), especially in younger individuals [3]. Laboratory classification of APS requires the presence of at least one of the following: lupus anticoagulant, moderate to high levels of anticardiolipin antibodies (aCL), and/or moderate to high levels of anti-β_2 glycoprotein 1 antibodies (Anti-β_2GP1) [3]. Anticardiolipin antibody testing should include cardiolipin and β_2GP1, as well as the individual isotypes IgG, IgM, and IgA. While various risk factors can contribute to the formation of a venous thromboembolism (VTE), it is important to keep APS in the differential diagnosis, especially when thrombosis is unprovoked. Here, we report an uncommon case of primary APS resulting in cerebral venous thrombosis and STEMI, for which only aPS IgM antibody was positive after an extensive workup.

Case Report

A 48-year-old white male was taken to the emergency room after his family witnessed a generalized seizure and noted subsequent prolonged confusion and agitation in February 2017. Glasgow coma scale (GCS) was 13 upon admission. Computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance venography (MRV) demonstrated thrombosis of multiple CNS sinuses. MRI demonstrated left temporal lobe edema and small linear hemorrhages (Figure 1). MRV and conventional angiography demonstrated cerebral venous thrombosis of multiple CNS sinuses including a vertebral artery occlusion of unknown chronicity and bilateral transverse sinus thrombosis, as well as straight sinus and superior sagittal sinus thrombosis (Figure 2). The patient was placed on levetiracetam, systemic heparin, and aggressive hydration without difficulty, but suffered progressive clinical worsening requiring endovascular mechanical venous suction thrombectomy, resulting in good angiography effect (Figure 3). The initial coagulation workup was completed and demonstrated normal aCL, prothrombin time (PT), and activated partial thromboplastin time (APTT).

The patient denied any past medical history or surgical history prior to the thrombotic event. He denied a history of tobacco

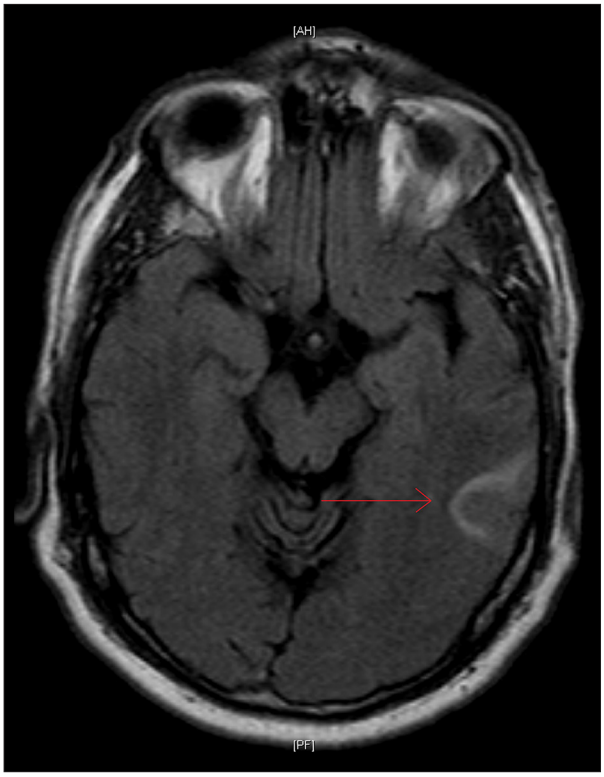

Figure 1. Axial FLAIR MRI reveals hyperintensity consistent with left temporal lobe edema (arrow) and small linear hemorrhages.

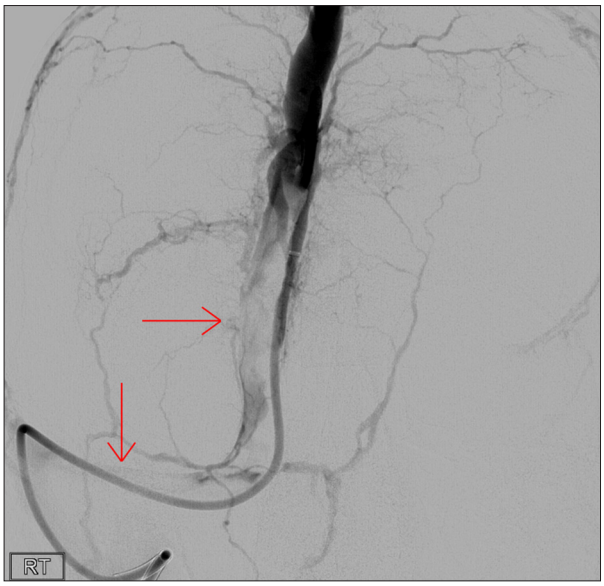

Figure 2. Contrast-enhanced coronal MRV demonstrating extensive superior sagittal sinus thrombosis (horizontal arrow) affecting the right transverse sinus (vertical arrow).

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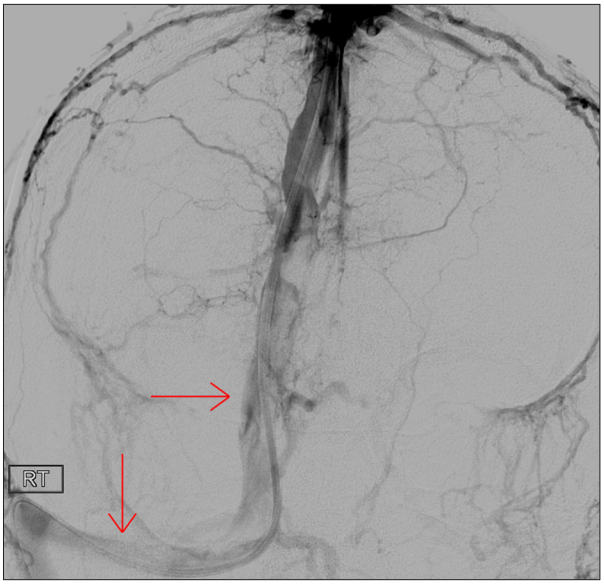

Figure 3. Coronal MRV contrast injection revealing improved drainage through superior sagittal sinus (horizontal arrow) and transverse sinus (vertical arrow) after venous sinus aspiration thrombectomy.

and illicit drug use. He did report drinking two 12-ounce cans of beer per month.

His family history was unremarkable for familial thrombotic tendency or autoimmune disease. His maternal uncle reportedly had polycythemia vera, his paternal grandfather had prostate cancer, and his maternal grandmother had bone cancer.

The patient was discharged 6 days after admission on warfarin, enoxaparin, and levetiracetam with an appointment to follow up with hematology to begin an outpatient thrombophilia workup.

While undergoing an outpatient workup, in May 2017, just 3 months after his initial presentation, he developed burning retrosternal chest pain with radiation to the left arm. An electrocardiogram (EKG) showed sinus rhythm with inverted T waves inferiorly, which proved to be a ST-elevation myocardial infarction (STEMI); simultaneously, International Normalized Ratio (INR) revealed a level of 1.8. Intravenous heparin was commenced. Echo showed normal left ventricular systolic function with middle inferior hypokinesis. Coronary angiography indicated evidence of obstructive coronary artery disease with 50% stenosis in the left circumflex artery, 30% stenosis in the distal left anterior descending artery, and 40% stenosis in the proximal left anterior descending artery. The patient was discharged 5 days after admission on enoxaparin 120 mg subcutaneous injection twice daily, clopidogrel 75 mg daily, atorvastatin 40 mg daily, and lisinopril 10 mg daily.

At his outpatient hematology follow-up, physical examination revealed normal vital signs. He was obese with a body mass index (BMI) of 31.4kg/m^2.

The neck examination was normal, showing supple without lymphadenopathy. The skin examination was normal, with no heliotrope rash, malar rash, acrocyanosis, or livedo reticularis. Bilateral heart and lung examination results were normal. No carotid bruits were noted. The abdomen was soft, nontender, and non-distended with no hepatosplenomegaly. The neurological examination was normal. Distal pulses were palpable and lower extremities were without edema or cyanosis.

A bilateral lower-extremity venous Doppler was negative. A PAN CT scan was done to rule out underlying malignancy and was negative.

Laboratory studies included a general hematology analysis, which was within normal limits with the exception of a low platelet count (120×10^3/uL), which recovered to 159×10^3/uL within 2 months. Studies showed a white blood cell count of 6.0×10^3/uL and a normal hemoglobin of 14.0 g/dL.

His general chemistry results were normal.

Based on past thrombotic and embolic events, despite anticoagulation therapy, a full hypercoagulability workup was completed, including protein C, protein S, antithrombin III, factor V Leiden, D-dimer, fibrinogen, flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH), homocysteine, hemoglobin electrophoresis, factor VIII, factor X, complement, plasminogen activator inhibitor (PAI) screen, JAK2 mutation detection, prothrombin gene mutation screen, antiphospholipid antibodies, and beta-2 glycoprotein 1 antibodies (Table 1). General coagulation tests prior to warfarin initiation showed normal prothrombin time (PT: 10.5 s), International Normalized Ratio (INR) 1.0, normal activated partial thromboplastin time (APTT: 28.5 s), and negative D-dimer of <0.20 mg/L FEU. Protein C, protein S, antithrombin III, fibrinogen, homocysteine, complement levels, and hemoglobin electrophoresis were normal. Factor VIII activity was just slightly above the normal range, while factor X was low. He lacked factor V Leiden and prothrombin gene mutation. JAK2 and PAI genotype were normal. Flow cytometry was negative for PNH. Cardiolipin antibodies were normal (IgG: <9; IgM: 13; IgA: <9). Beta-2 glycoprotein 1 antibodies were normal (IgG: <9; IgM: <9; IgA: <9). Of note, his phosphatidylserine antibodies (IgM) were significantly positive, with a value of 45. Phosphatidylserine antibodies IgG and IgA were normal (IgG: 1; IgA: 1).

The patient was continued on clopidogrel (75 mg daily) and transitioned from enoxaparin (120 mg, twice per day) to warfarin (10 mg daily) with a target INR of 3.0–3.5.

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Table 1. Hypercoagulability profile.

Result	Value/result	Units	Range
Prothrombin time (PT)	10.5	Seconds	9.1–12.0
International normalized ratio (INR)	1.0		0.8–1.2
Partial thromboplastin time (APTT)	28.5	Seconds	24.0–33.0
Protein C – functional	117	%	73–180
Protein S, total	120	%	60–150
Antithrombin III activity	94	%	75–135
Factor V Leiden mutation	Negative		Negative
D-Dimer	<0.20	mg/L FEU	0.00–0.49
Fibrinogen	291	mg/dL	193-507
Flow cytometry PNH*	No evidence of PNH		No evidence of PNH
Homocysteine	11.7	umol/L	0.0–15.0
Hemoglobin solubility**	Negative		Negative
Factor VIII activity	168	%	56–163
Factor X activity	15	%	76–183
Complement, total	56	U/ml	42–60
PAI-1 activity	5G/5G***		
JAK2 mutation inhibitor	Negative		Negative
Prothrombin gene mutation	Negative		Negative
Anticardiolipin Ab, IgG	<9	U/ml	0–15
Anticardiolipin Ab, IgM	13	U/ml	0–12
Anticardiolipin Ab, IgA	<9	U/ml	0–11
Beta-2 glycoprotein I Ab, IgG	<9	GPI IgG units	0–20
Beta-2 glycoprotein I Ab, IgM	<9	GPI IgM units	0–32
Beta-2 glycoprotein I Ab, IgA	<9	GPI IgA units	0–25
Antiphosphatidylserine IgG	1	GPS IgG	0–11
Antiphosphatidylserine IgM	45	MPS IgM	0–25
Antiphosphatidylserine IgA	1	APS IgA	0–20

* Peripheral blood specimen; ** normal adult hemoglobin present; *** homozygous for 5G insertion allele which is associated with the lowest PAI-1 activity.

Discussion

Phosphatidylserine is a negatively charged phospholipid that is a component of the cellular membrane. This phospholipid acts as a procoagulant when activated by collagen, thrombin, or antibodies, resulting in a hypercoagulable state [2]. While phosphatidylserine is not the most common antiphospholipid antibody (aPL), it serves as a significant antigenic target in APS [4]. Antiphospholipid syndrome is characterized by a prothrombotic state that can occur in both venous and arterial vasculature [5].

The most common aPLs include lupus anticoagulant, aCL, and anti-β_2GP1 [4]. These aPLs react with phospholipids and proteins on the venous and arterial vasculature, ultimately resulting in thrombosis [4]. β_2GP1 is the most common of these antibodies and is found in the vast majority of seropositive APS patients [4].

The most common sites of thrombosis consist of cerebral arterial vasculature and the lower-extremity venous system [5]. The clinical presentation of APS most commonly includes pulmonary embolism (PE), deep venous thrombosis (DVT), and/or thrombosis in the arterial system [3]. The initial presentation may or may not be associated with dermatologic manifestations such as livedo reticularis and a heliotrope rash [3].

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In women of child bearing age, obstetric complications such as miscarriage and stillbirth may be the initial presentation of APS [3]. Thrombosis is the most common initial presentation and is typically diagnosed by CT, MRI, MRV, or Doppler ultrasound to confirm a thrombotic event in the brain, chest, abdomen, or deep veins of the lower extremities.

The differential diagnosis when encountering a patient with thrombophilia can be extensive. Malignancy may initially present with thrombotic tendencies and should be ruled out with imaging. Homocystinemia, antithrombin III deficiency, protein C or S deficiency, factor V Leiden mutation, and prothrombin gene mutation should be considered in patients who exhibit thrombophilia [6]. Atherosclerotic vascular disease should also be ruled out in patients presenting with prothrombotic tendencies. The workup for a hypercoagulable state should investigate both inherited and acquired conditions that may contribute to a procoagulant state [6].

The diagnosis of APS is primarily based on the detection of antiphospholipid antibodies in a patient's serum and evidence of thrombosis [7]. Triple positivity of lupus anticoagulant, anticardiolipin antibodies, and beta-2 glycoprotein 1 antibodies create the highest risk of thromboembolic events [7]. Deficiencies in protein C, protein S, and antithrombin should be explored, as well as mutations, including factor V Leiden, prothrombin, and plasminogen inhibitor genes [6]. Antibodies directed against phosphatidylserine should also be considered when initial APS studies are negative [7]. Recent studies have demonstrated a significant association between aPS and APS, and seronegative APS patients have been found to be positive for aPS [8,9].

The mainstay of treatment for thrombotic events associated with APS primarily consists of anticoagulation [10]. In certain circumstances aspirin and heparin may be used, but warfarin is the most commonly prescribed anticoagulant for treatment of APS [10]. Recent research emphasizes the importance of indefinite anticoagulation for patients who have had a thrombotic event, due to the high recurrence risk [10].

The patient discussed in this case report is a prime example of a seronegative APS patient who tested positive only for aPS after an extensive thrombophilia workup. This patient did not have any significant risk factors that would have contributed to his thrombophilia. He denied recent hospitalization, immobilization, and smoking, showed no evidence of malignancy, and had no personal or family history of clotting disorders. The patient's mild obesity and positive phosphatidylserine IgM were the only apparent contributing factors. Of note, a recent case report described multiple etiologies in a lower-extremity DVT, including significantly positive phosphatidylserine IgG antibodies, which demonstrates the importance of this as a risk factor for thrombosis [11]. At 1-year follow-up, the patient had not developed any autoimmune or collagen vascular diseases. This study suggests further investigation into the possibility of phosphatidylserine antibodies in individuals with clinical symptoms related to thrombosis with an exhaustive, unrevealing clinical workup.

Conclusions

It is important to consider other uncommon causes for thrombophilia, such as APS. Laboratory testing should include the common disorders that result in thrombophilia, but if results are unrevealing, further workup is necessary. Antiphosphatidylserine antibodies should be considered if there is a high index of suspicion for a hypercoagulable state in patients who have a pan-negative standard thrombophilia workup.

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Institution where work was done

Abington Hematology Oncology Associates, Philadelphia, PA.

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