Secondary antiphospholipid syndrome at a young male

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Abstract

Background: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by recurring venous and/or arterial thrombosis and the presence of circulating antiphospholipid antibodies. APS occurs as a primary condition or secondary to other autoimmune disorders, mainly systemic lupus erythematosus (SLE). The diagnosis of APS is made on the basis of suggestive clinical findings and the presence of one or more of the following antiphospholipid antibodies (LAC, aCL antibody or aβ2GPI antibody present on two or more occasions, at least 12 weeks a part). A clinically significant aPL profile has been detected in approximately 30 % of patients with SLE.

Case presentation: We are presenting a rare case of a 23 years old male with complaints of dyspnea, retrosternal discomfort, fatigue, general weakness, joint pain over a period of 3 months. The patient reported a single syncopal episode, 3 months prior to admission as his first clinical manifestation. He was at first diagnosed with Thrombocytopenia in 2007 and Systemic Lupus Erythematosus (SLE) in 2020. During his hospitalization, the patient experienced recurrent headaches, dizziness and episodes of elevated blood pressure (170/100 mmHg), as well. Moreover, laboratory and imaging examinations showed bilateral pulmonary thromboembolism and positive Anticardiolipin antibodies, positive ANA, positive SSA & SSB.

Conclusion: Given the lack of typical clinical findings in the early stages of the disease, establishing a diagnosis of APS can be challenging. Although APS is one of the most common thrombocytophilias, unfortunately, it remains underdiagnosed. Clinicians should investigate for the presence of antiphospholipid antibodies, as early diagnosis may influence the course of the disease.

Keywords: *Antiphospholipid syndrome, SLE, Male*

Background

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by a state of hypercoagulability potentially resulting in thrombosis of all segments of the vascular bed [1].

The syndrome is characterized clinically by recurrent venous and/or arterial thromboembolic events, or pregnancy morbidity. In addition to these clinical manifestations, the sine qua non for the syndrome is the persistent presence of a unique collection of autoantibodies that target specific phospholipid-binding proteins [2]. Antibodies against β2-glycoprotein I (aβ2GPI) and cardiolipin (aCL), together with the functional assay lupus anticoagulant (LAC), are the three

laboratory tests considered in the revised criteria for the diagnosis of the syndrome [3].

Currently, we use the classification criteria for antiphospholipid syndrome (APS) formulated during the consensus conference in Sapporo and revised in Sydney [4].

The classification criteria for definite APS are met when at least one clinical criteria (thrombosis or pregnancy morbidity) is present in association with one laboratory criterion (LAC, aCL antibody or aβ2GPI anti- body present on two or more occasions, at least 12 weeks a part), and thrombosis should be confirmed by objective validated criteria [3, 5].

However, there are several clinical manifestations not included in the classical revised criteria of APS such as thrombocytopenia, hemolytic anemia, cardiac valve disease, renal microangiopathy, livedo reticularis, neurologic disturbances, leg ulcers and amaurosis fugax [6] that are common features in APS patients and as stated by Miyakis et al., they can be classified as "non-criteria features of APS".

Prevalence of the aPL in the general population ranges between 1 and 5%. However, only a minority of these individuals develop the APS. Some estimates indicate that the incidence of APS is around 5 new cases for 100,000 persons for year and the prevalence around 40–50 cases for 100,000 persons [7].

Although the ontogeny of these pathogenic antibodies has not been fully elucidated, some evidences suggest the involvement of both genetic and environmental factors. The ability of aPL to induce a procoagulant phenotype in APS patients plays a central role in the development of typical arterial and venous thrombotic manifestations of the disease. Inflammation serves as a necessary link between this procoagulant phenotype and actual thrombus development. Recent evidence indicated a role for abnormal cellular proliferation and differentiation in the pathophysiology of APS, especially in those patients with pregnancy morbidity and other more atypical manifestations that have no identifiable thrombotic cause [8].

The APS can be found in patients with no clinical or laboratory evidence of another definable condition ("primary" APS), or it may be associated with other diseases ("secondary" APS).

Renal involvement in primary APS is primarily characterized pathologically by noninflammatory occlusion of a broad spectrum of renal blood vessels, ranging from glomerular capillaries to the main renal artery and vein [9,10,11-14].

Involved arteries and arterioles often have a thrombotic lesion, resulting in reactive intimal mucoid thickening, subendothelial fibrosis, and medial hyperplasia [9].

Affected glomerular capillaries reveal thrombi with associated mesangiolysis, mesangial interposition along the glomerular capillary wall, and electron lucent areas in the subendothelial space.

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Focal atrophy of the cortex in association with interstitial fibrosis may be observed, presumably resulting from tissue ischemia.

Renal disease in antiphospholipid syndrome associated with systemic lupus erythematosus — Patients with lupus and aPL commonly have a history of systemic thrombosis, fetal loss, neurologic disorders, and thrombocytopenia [15,16,17]. In patients with lupus, the principal laboratory features that correlate with the presence of high titers of immunoglobulin G (IgG) aPL are thrombocytopenia, the presence of a false-positive Venereal Disease Research Laboratory (VDRL) test for syphilis (fluorescent treponemal antibody [FTA] negative), and a prolonged activated partial thromboplastin time (aPTT) [15,10,18]. Renal disease in this setting may result from microthrombi and/or deposits of immune complexes.

Here, we describe a case of a young man who was diag- nosed with antiphospholipid syndrome (APS) with early complex and unusual manifestations.

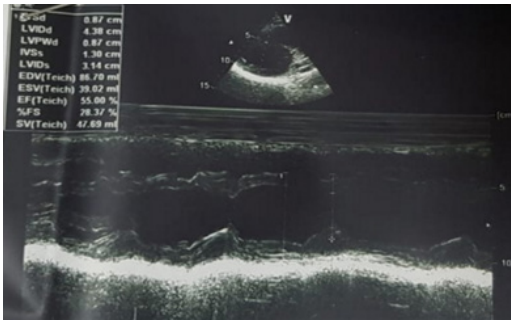
Case presentation

A 23-years old man presented to the Emergency Department on September 2019 with a 3-month history of dyspnea, retrosternal discomfort, fatigue, general weakness and joint pain. His personal medical history was significant for a single episode of syncope 3 months prior to his presentation. In 2007 he was diagnosed with Thrombocytopenia, hospitalized for 1 week with a platelet count of 98,000/ mm3. He was treated with a daily dose of Prednisone 10 mg, however he reported poor treatment compliance. In March 2020 he was diagnosed with Systemic Lupus Erythematosus (SLE) and was prescribed Hydroxychloroquine (HCQ) 200 mg/d p.os and Prednisone 5 mg/d p.os. He continued not to adhere to the prescribed therapy. He had no known allergies and his family history was unremarkable.

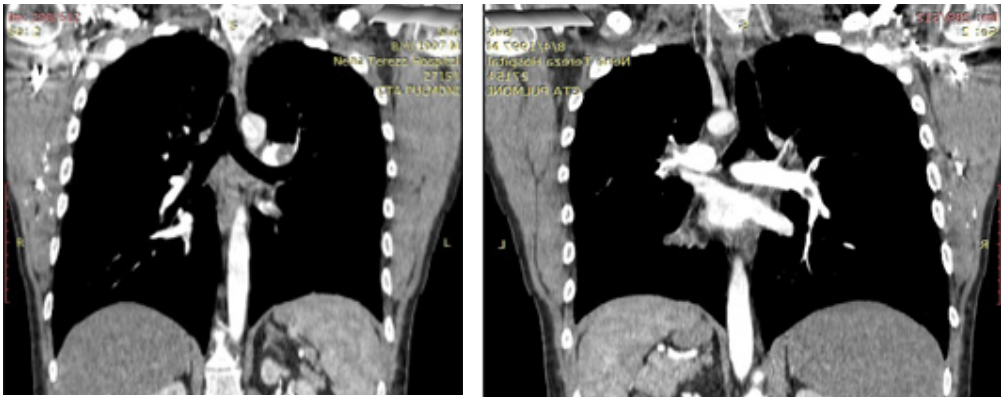
Following his admission to the Department of Internal Medicine, the physical examination showed:

- Normal body temperature,
- HR 91 per min & BP 170/110 mmHg
- Bilateral vesicular respiration, RR 26 per min, SpO2 96%
- No edema

Multiple imaging studies were scheduled. A transthoracic ultrasound and an abdominal ultrasound, were both normal. Subsequently, a chest CT revealed bilateral pulmonary embolism (PE).



Echocardiography



Chest CT Angiography

A Complete Blood Count analysis showed: WBC 8500/mm3 (n.v 4000-10000), HGB 14.9 g/dl (n.v 11.0-16.5), RBC 4.99x 106/mm3 (n.v 4.2-6.1 x 106), HCT 41.6% (n.v 35.0-50.0), MCV 83 (n.v 80-97), MCH 29.9 (n.v 26.5-33.5), PLT 154x103 (n.v 150-400);

Laboratory findings were as follows: prothrombin time (PT)— INR 1.1 (n.v. < 1.2), activated Partial Thromboplastin Time (aPTT) 87 (n.v. < 1.20), Amylase 108 U/L (n.v. 29–100), Alanine aminotransferase ALT 101 U/L (n.v. 0–45), Aspartate aminotransferase AST 68 U/L (n.v. 0–35), C-Reactive-Protein (CRP) 3.46 mg/L (n.v. 1.1-8), Serum Urea 19 mg/dl (n.v 10-43), Creatinine 0.8 mg/dl (n.v 0.5-1.2), Potassium 4.8 mmol/l (n.v 3.5-5.1), Sodium 138 mmol/l (n.v 136-146), Chloride 108 mmol/l (n.v 101-109), Blood glucose 84 mg/dl (n.v 74-106), Bilirubin 0.8 mg/dl (n.v 0.5-1.2),

Lipid profile: Cholesterol 280 mg/dl (n.v 140-220) and Triglyceride 154 mg/dl (n.v 50-150); Ferritin 213.1 ng/ml (n.v 22-275).

Urine analysis: Albumin 25 mg/; RBC 1-2/mm (0-5); WBC 2-3mm (0-5);

Proteinuria 1.2 g/day.

Microbiological tests (i.e. Manthoux, Quantiferon, CMV, EBV, HIV, HBV, HCV, VDRL) were all negative.

Neoplastic markers: CEA 0.89 (n.v <5); AFP 1.2 (n.v <20); CA 19-9 25.1 (N);

Workup for autoimmune diseases revealed elevated levels of IgG Anti-Cardiolipin 75.5 u/ml (<10), IgM Anti-Cardiolipin 10.1 U/mL (<10); ENA Screen 8.8 (<0.8), RF 20.6 UI/ml (<20) with positive Antinuclear antibody (ANA), Anti-RO 52, Anti-SS-B and Anti-SS-A, whereas, Anti ds-DNA was negative.

Treatment

The patient was put on bed rest and was started on anticoagulation therapy with Enoxaparin 6000 UI bid initially, along with Prednisolon 25 mg/d IV, Perindopril/ Amlodipine 4/10 mg/d and Atorvastatin 20 mg/d. Two days later, he was switched to Warfarin 3 mg p.os, followed up with INR. On the 6th day, INR was 2.3, so Enoxaparin was discontinued. Hydroxychloroquine (HCQ) 200 mg/d p.os was added to his regimen, in addition to the anticoagulation therapy with Warfarin.

In a 3 month follow-up, the patient was asymptomatic. During the physical examination, HR 91 bpm, BP 120/75 mmHg, bilateral vesicular respiration, SpO2 96%, were noted. Maintenance therapy with oral anticoagulation and hydroxychloroquine was continued.

Discussion and conclusions

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the occurrence of venous and/ or arterial thrombosis and the presence of circulating antiphospholipid antibodies [19]. Single or multiple thrombi in veins, arteries and the microvasculature may give rise to a diverse clinical picture. While deep vein thrombosis, particularly of the lower limbs, is the most frequently reported clinical manifestation (39%), thrombocytopenia (30%), livedo reticularis (24%), stroke (20%), pulmonary embolism (14%), heart valve lesions (10%), epilepsy (7%), myocardial infarction (6%), leg ulcers (5%) and amaurosis fugax (5%) may also occur and they are classified as "non-criteria features of APS" [20].

The average age of primary APS patients has been reported to be about 35–40 years and the disease is more common in women than in men. In this report we describe a rare case of a young male who presented with a 13 year history of a wide spectrum of clinical manifestations involving multiple organs, in whom a diagnosis of APS was initially missed.

Dyspnea and syncope were presenting symptoms. In patients with pulmonary embolism of the main or lobar pulmonary arteries, dyspnea or tachypnea occurred in 92% of cases. Conversely, acute PE may be a frequent finding in patients presenting with syncope (17%), even in the presence of an alternative explanation. [21].

In APS, pulmonary embolism disease occurs in approximately 14% of the patients [22] The pathogenesis of pulmonary embolism in APS may show wide variability, but common complications of the pulmonary system involve pulmonary thromboembolism and its associated sequelae, such as infarction and PH. [23] aPLs are associated with thrombosis; a 2GP1 antibodies are not only a marker of thrombophilia, but moreover contribute to hypercoagulability. PE may be the first manifestation of APS. Cervera et al. [24] prospectively examined the morbidity and mortality in 1,000 APS patients over a 10-year period. They found that 14.1% of patients had PE at initial diagnosis and incidence of new PE was 3.5% over the 10-year follow-up. PE-associated mortality occurred in 5.4% of the patients. [24]

The mainstay of treatment for acute thromboembolism in a patient with antiphospholipid syndrome (APS) is anticoagulation. Typically, this involves heparin overlapped with warfarin followed by indefinite warfarin therapy in most patients. The rationale for indefinite anticoagulation therapy is the high rate of recurrent thrombosis, although the number of risk-stratified studies is limited. Following initial interventions for an acute thrombosis, we suggest anticoagulation with warfarin rather than a direct oral anticoagulant (DOAC; eg, apixaban, dabigatran, edoxaban, rivaroxaban) based on the lack of data regarding efficacy and safety of the DOACs in APS patients. Due to its autoimmune nature, immunomodulatory agents for the treatment of APS have been proposed [25]. However, there is a lack of high-quality data to guide practice and there is no good-quality evidence to support the use of specific immunomodulatory agents. We often add hydroxychloroquine (HCQ) and statins for patients with recurrent thrombosis despite adequate anticoagulation and we often use rituximab for patients with hematologic manifestations of APS (eg, thrombocytopenia) or a thrombotic microangiopathy (TMA) picture. (See 'Thrombocytopenia' above.) Statins can be used as an additional treatment in difficult-to-treat APS patients. Limited data suggests that statins may have a beneficial effect in APS patients by reducing proinflammatory and prothrombotic markers [25-29]. However, there is insufficient data to recommend the routine use of statins in patients with APS in the absence of hyperlipidemia.

Based on the patient's medical history, laboratory and imaging findings, an autoimmune disorder was among the top differential diagnosis. The autoimmune profile revealed the presence of β2GPI antibodies, aCL antibodies and LAC. In these circumstances, due to the presence of multiple specific "non-criteria features

of APS", namely thrombocytopenia, and bilateral pulmonary embolism (Bilateral PE), along with the persistence of elevated levels of aPL 3 months apart and the presence of an associated autoimmune disease (LES), a diagnosis of secondary APS was made.

Thrombocytopenia, as a primary manifestation of APS, has a prevalence of approximately 20 to 40% [30]. It has been suggested that antiphospholipid antibodies bind to the phospholipids in the platelet membrane, thus participating in the process of platelet destruction, that ultimately leads to thrombocytopenia. However, the specific role the aPL plays in this process, is yet to be proven. Immunosuppressive therapy appears to be effective in patients with APS-associated thrombocytopenia [31]; indeed, a short cycle of intravenous prednisolone resulted in a significant increase in platelet count in our patient.

Considering his age, sex and unspecific symptoms our patient presented a diagnostic challenge. Though APS is one of the most common thrombocytophilias, its often goes undiagnosed. The lack of prophylactic measures, puts patients in a significant risk of serious complications including pulmonary embolism, infarction and pulmonary hypertension, that can turn out to be fatal.

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