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Case Report

Intra-cardiac thrombus in antiphospholipid antibody syndrome: An unusual cause of fever of unknown origin with review of literature

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ABSTRACT

Classically, antiphospholipid antibody syndrome (APS) presents with recurrent episodes of vascular thrombosis and abortions. For APS to present as fever of unknown origin (FUO) is a rare phenomenon. We present an interesting case of FUO who on workup was found to have primary APS with right atrial thrombus and chronic pulmonary thromboembolism (PTE). Fever resolved completely with anticoagulation therapy and surgical removal of the intra-cardiac thrombus. Although rare, APS should be considered in any case of FUO with prolonged activated partial thromboplastin time and/or thrombocytopenia. We also take this opportunity to briefly review 28 cases of APS with intra-cardiac thrombus reported to date in the medical literature.

<**Learning objective:** Primary antiphospholipid antibody syndrome (APS) presenting as fever of unknown origin (FUO) is rare. APS should be kept in the differential diagnosis in any case of FUO with prolonged activated partial thromboplastin time or thrombocytopenia. Intra-cardiac thrombus is more frequently associated with primary APS as compared to secondary APS.>

Introduction

Antiphospholipid antibody syndrome (APS) commonly presents with thrombotic events, pregnancy morbidity, and recurrent pregnancy loss [1]. APS presenting as fever of unknown origin (FUO) is rare. To date, there are only a few case reports that have described FUO as presenting manifestation of APS [2]. Intra-cardiac thrombus and pulmonary thromboembolism (PTE) are life-threatening thrombotic events of APS, but asymptomatic presentation of intra-cardiac thrombus with PTE is rare [3].

Case report

A 41-year-old man presented with 4-months history of high-grade fever, 38.8–40 °C, associated with chills and rigor, 1–2 episodes per month. Each episode used to last for 1–2 days followed by spontaneous resolution of symptoms. During this time, he also had significant loss of appetite with weight loss of ~15 kg. There was no other history to suggest localization. On evaluation he was febrile, normotensive with tachycardia (heart rate – 100/min) no tachypnea, and was maintaining room air oxygen saturation of 97%. He had average build (body mass index – 21.70 kg/m^2), grade-I pan-digital clubbing and there was no palpable lymph node or hepatosplenomegaly. Cardiovascular examinations revealed a systolic click at 3rd inter-costal space, near left parasternal area with no appreciable variation of intensity during respiration and there was no definitive thrill or murmur. Other systemic examinations were essentially normal. Clinically, differential diagnosis of sub-acute bacterial endocarditis, tuberculosis, human immunodeficiency virus (HIV) infection, occult malignancy, lymphoma, or any autoimmune phenomena were considered. Investigations revealed thrombocytopenia (25×10^9/L) with normal hemoglobin (Hb-13.5 g/dL) and total leucocytes count (TLC-7×10^9/L). Blood and urine cultures were sterile multiple times. Chest X-ray showed mild broncho-vascular

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prominence on the right side and montoux skin test was not reactive. Tests for HIV, hepatitis B virus surface antigen and anti-hepatitis C virus core immunoglobulin M were also negative. Serum procalcitonin, galactomannan, β-D-glucan were not elevated and fungal serology was negative. Coagulogram suggested persistently elevated activated partial thromboplastin time (aPTT) (55–59 s). Electrocardiography showed sinus tachycardia with S1Q3T3 pattern and right ventricular hypertrophy. Trans-thoracic followed by trans-esophageal echocardiography (TEE) showed no evidence of infective endocarditis, but incidentally detected a right atrial (RA) mass of 3.2 cm × 2.0 cm, attached to inter-atrial septum (IAS) by a stalk, prolapsing into the right ventricle (RV) causing tricuspid regurgitation (TR) (Fig. 1A and Supp. Video 1). RA was dilated with raised RV systolic pressure (RVSP) of 85 mmHg and normal left ventricular (LV) function. Subsequently contrast-enhanced computed tomography of the chest and abdomen was done which showed chronic PTE involving bilateral descending pulmonary artery (PA) and a hypodense filling defect in RA with central calcification suggestive of myxoma or thrombus. In addition there was a patchy peripheral opacity at the right upper lobe lung suggestive of infarct. In the view of unprovoked PTE and prolonged aPTT with no evidence of malignancy and infection, a strong possibility of APS was considered. Subsequently he was found to be positive for lupus anticoagulant (LA). IgG anti-cardiolipin antibody (aCL) and IgG anti-β2 glycoprotein I (aβ2GP I) were elevated in high titers, 119 GPLU/ml and 97 U/ml respectively by enzyme-linked immunosorbent assay method. Tests for antinuclear antibody (ANA) and anti-dsDNA were negative; C3 and C4 were normal. Hemolytic workup, direct Coomb test and paroxysmal nocturnal hemoglobinuria (PNH) workup were also negative.

Supplementary Video 1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jccase.2016.07.005.

For persistence of thrombocytopenia manual platelet count was done, which showed giant platelets. Bone marrow biopsy showed normo-cellular to slightly hyper-cellular marrow with intense megakaryocytic hyperplasia and focal clustering, with no lymphoid aggregates, granulomas, or metastatic deposit. Its culture was sterile for bacteria, mycobacterium, and fungus. We concluded that primary APS with PTE and RA mass with immune thrombocytopenia was the cause of FUO. For immune thrombocytopenia oral prednisolone was started at 1 mg/kg/day. Platelet count gradually improved and anticoagulation was started with fondaparinux 7.5 mg/day once platelet count increased to $>50 \times 10^9$/L. As RA mass was prolapsing into the RV, there was high chance of outflow obstruction. Hence, he underwent surgical excision to prevent life-threatening complications. During the surgery it was found that there were two large, firm to hard masses, 3 cm × 3 cm each in RA, arising from IAS and RA wall one each, with multiple vegetations over the tricuspid valve leaflets (Figs. 1B and 2A, B). Histopathological examination (HPE) confirmed thrombus with central calcification (Supp. Fig. S1) and cultures were sterile. Post-operatively, the patient was continued with moderate intensity anticoagulation (international normalized ratio of 2–3) with warfarin, steroid was gradually tapered off as thrombocytopenia resolved and sildenafil was added for pulmonary arterial hypertension (PAH). IgG aCL and IgG aβ2GP I were persistently elevated in high titer even after 12 weeks, thereby fulfilling the criteria for APS. Repeat 2D echocardiography after 2 months and 6 months showed no recurrence of thrombus with RVSP of 52 mmHg and there was no recurrence of fever.

Supplementary Fig. 1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jccase.2016.07.005.

Discussion

APS is diagnosed in the presence of persistently elevated one or more antiphospholipid (APL) antibody (LA, aCL, aβ2GP I) on two or more occasions at least 12 weeks apart along with presence of one or more episodes of vascular thrombosis or recurrent pregnancy loss [4]. Our patient had vascular thrombosis in the form of PTE and RA thrombus in the presence of persistently elevated high titer of IgG aCL and IgG β2GP I, which were reconfirmed 12 weeks later. There was no evidence of secondary causes of APS such as systemic lupus erythematosus (SLE), autoimmune hemolytic anemia (AIHA), and PNH. There is increased risk of intra-cardiac thrombosis in APS with SLE, LA and high levels of aCL antibody [5]. In a retrospective study it has been shown that venous thrombosis with PTE is more frequent with positive LA activity; however, coronary, cerebrovascular, and peripheral arterial events are more common with elevated levels of aCL antibody [6]. Recurrent thrombotic events are well known in APS. A 5-year prospective study showed that the median time to a recurrent thrombotic event is shorter in patients with high titer of aCL antibody and intra-cardiac thrombus [7].

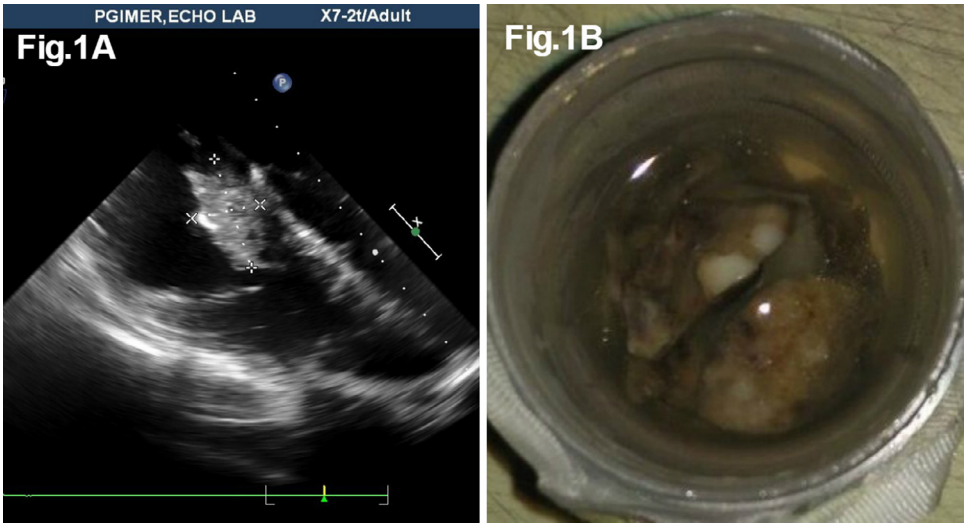

Fig. 1. (A) Trans-esophageal echocardiography showing a single large right atrial (RA) mass (3.2 cm × 2.0 cm) attached to inter-atrial septum by a stalk. (B) Post-operative picture of the excised RA mass.

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