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Received Date: 20 January, 2019; Accepted Date: 23 January, 2019; Published Date: 31 January, 2019  

Abstract  

Background: HIV is commonly associated with positive antiphospholipid antibodies and lupus anticoagulant (LA) assay, but association with clinical evidence of thrombosis is not well established. To our knowledge, we are the first to describe concurrent Pulmonary Embolism (PE), ischemic stroke due to paradoxical embolism, and renal infarction occurring in the presence of Patent Foramen Ovale (PFO) and HIV-related Antiphospholipid syndrome (APS).  

Clinical Presentation: This article reports a 60-year-old male with pertinent past medical history of HIV presented to the ER with left-sided weakness, slurred speech and left facial droop. Patient was highly suspected of ischemic stroke and given tPA. The CT angiogram (CTA) head and neck was negative, but revealed bilateral PE, later confirmed by CTA chest. This was determined to be an unprovoked PE. CTA chest also revealed large left renal infarction, later confirmed by renal radioisotope scan. Repeated EKG showed atrial flutter, and TTE with bubble study revealed a 3 mm PFO. Hypercoagulability work-up revealed LA.  

Conclusion: Clinical significance of aPL antibodies, positive LA assay in HIV infection remains unclear. Yet, several case-reports, including our own, describe major thrombotic events, including PE, CVA and renal infarction. We can conclude, that screening for APS in HIV patients, especially those with intracardiac shunts, followed by proper anticoagulation, may prevent life-threatening thrombotic events.  

Introduction & Background  

Introduction  

Antiphospholipid syndrome (APS) is an autoimmune disease, which occurs as a primary condition, or in the setting of another autoimmune or rheumatic disease and is characterized by venous or arterial thrombosis and pregnancy morbidity in the presence of antiphospholipid (aPL) antibodies against B2-glycoprotein I and antiprothrombin, and/or positive Lupus Anticoagulant test [1]. HIV is commonly associated with positive aPL antibodies and LA assay, but association with clinical evidence of thrombosis is not well established and has been described only in casereports [2].  

Patent Foramen Ovale (PFO) is a congenital cardiac lesion that may persist into adulthood with prevalence of 22.6 percent. Most of the patients with PFO are asymptomatic, however, paradoxical embolic events, including, most commonly, ischemic stroke and, less frequently, myocardial infarction and renal infarction, are potential manifestations of the disease.  

Paradoxical emboli originate in the systemic venous circulation and enter arterial circulation via PFO, atrial or ventricular septal defect [3,4]. To our knowledge, we are the first to describe concurrent pulmonary embolism (PE), ischemic stroke, and renal infarction occurring in the presence of PFO and HIV-related APS.
Case presentation

60 y.o Male with past medical history of HIV (compliant with HAART, CD4 count 599), HTN, CKD and Asthma presented to ER with left-sided weakness, slurred speech and left facial droop. The patient had been in his usual state of health until 2 hours prior to arrival, when he reportedly suddenly felt the left side of his body becoming weak. On examination, the patient was alert and well oriented. The blood pressure was elevated (160/110), the heart rate was 101 beats per minute, and saturation was 97% on room air. Patient presented with mild dysarthria, left facial paresis, left arm and leg plegia with decreased tone; right Babinski was negative, left mute.

Patient did not report any recent prolonged immobilization, surgery or other risk factors for thrombosis. Medication review did not reveal any procoagulant medications. Stroke code was activated, emergent CT scan of the head and CT angiogram of the head and neck did not show ischemic or hemorrhagic CVA, or any significant arterial occlusion. Neurology evaluated the patient and based on high clinical suspicion of stroke, and no absolute contraindications, recommended to proceed with tPA. Patient was admitted to medical ICU for close monitoring of neurological status and for tight BP control. One hour later the radiologist on call contacted the ICU team and reported that CT angiogram of the head and neck also revealed b/l pulmonary embolism (PE). CT angiogram of the chest was performed and confirmed right upper and lower lobe large pulmonary emboli and left upper and lower lobe moderate pulmonary emboli without right ventricular strain. Patient did not report any recent prolonged immobilization, surgery or other risk factors for thrombosis, therefore this PE was considered unprovoked. Another finding on CT angiogram of the chest was large left renal infarction, later confirmed with renal radioisotope scan.

Repeated troponins went up from normal level to 5, and creatinine went up from 1.3 (baseline) to 5.05. Patient reported flank and diffuse abdominal pain; abdominal examination was benign. Patient was started on IV unfractionated heparin with close PTT monitoring. Repeated EKG showed atrial flutter, and transthoracic echocardiogram with agitated saline injection (bubble study) revealed 3 mm PFO. Venous doppler of the legs did not reveal any signs of deep venous thrombosis. Cardiology and Cardiothoracic surgery evaluated the patient, but did not proceed with any emergent intervention, and recommended atrial-flutter ablation and PFO closure after stabilization of his condition. Radioisotope renal scan was performed and showed that left kidney contributes only 6% to overall renal funcitoning. TTE was performed and did not reveal any intracardiac thrombi. Hypercoagulability work-up was sent, and Lupus anticoagulant (LA) test came back positive.

Patient was monitored in ICU setting for three days, remained stable with significant improvement of neurological and renal functions, and was transferred to telemetry, started on apixaban and discharged home with outpatient follow up with cardiology, cardiothoracic surgery and hematology. Patient went to hematology clinic in 12 weeks, LA assay was repeated and remained positive.

Review

HIV-related antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease, which occurs as a primary condition, or in the settings of another autoimmune or rheumatic disease and is characterized by venous or arterial thrombosis and pregnancy morbidity in the presence of antiphospholipid (aPL) antibodies against β2-glycoprotein 1 and antcardiolipin, and/or positive Lupus Anticoagulant (LA) test [5]. At least one clinical and one laboratory criteria must be met for diagnosis of APS, according to revised Sapporo APS Classification Criteria. These should include one or more episodes of venous, arterial, or small vessel thrombosis and/or pregnancy morbidity (clinical criteria), and presence one or more of the aPL antibodies and/or Lupus anticoagulant activity on two or more occasions at least 12 weeks apart (laboratory criteria) [6]. APS is most commonly associated with SLE with prevalence 30% [7], but there are other less common conditions with proven association, including malignancy, medications, and infections [8-10]. In this case, we have a patient with unprovoked multiple thromboembolic events, and we sent aPL antibodies and LA test as part of the hypercoagulability work-up. Rheumatological work-up (including ANA, RF, c-ANCA and p-ANCA) was sent and came back negative. Patient has known HIV, compliant with HAART with recent CD4 count of 599. HIV infection has been recognized as a prothrombotic condition, with 10 times increased incidence of thrombosis, compared to the general population [11-13]. There is robust evidence of association between aPL antibodies, positive LA essay and HIV infection, but there is little clinical evidence of thrombosis or hematologic manifestation of APS [14-16]. Despite it being distinctively rare, HIV-related APS cases with isolated ischemic stroke, PE, and testicular thrombosis were described in literature [17-19]. To our knowledge, we are the first to describe concurrent PE, ischemic stroke and renal infarction occurring in one patient.

Pulmonary embolism, patent foramen ovale and cryptogenic stroke

Given the presence of bilateral PE, the thromboemboli most likely originated from the systemic venous circulation, and then traveled via the PFO to the systemic arterial circulation (paradoxical embolism), which lead to ischemic stroke and renal artery infarction. PFO is the most common lesion causing intracardiac right-to-left shunting [20]. Evaluation for intracardiac shunts is usually indicated as part of the routine ischemic stroke work-up, and TTE or TEE with agitated saline injection ("bubble study") is considered as a standard diagnostic modality. TEE is more sensitive for diagnosis of the potential source of the cardiac
emboli, such as LV or intraPFO thrombus. Transcranial Doppler (TCD) could be an alternative to TEE, it is noninvasive and could be performed at the bedside, however, TCD can only detect the presence of a right-to-left shunt, it cannot verify the location [21].

In our patient, ischemic stroke was the initial presentation, and bilateral PE was accidentally discovered on the CT angiogram of the head and neck as part of the stroke work-up. Given the absence of identified cardioembolic or carotid source and its non-lacunar type, this stroke fits into the category of cryptogenic stroke. According to the TOAST classification, cryptogenic stroke is an ischemic CVA that is not related to cardioembolic event, large artery atherosclerosis, or small artery disease [22].

Presence of DVT was not found on the venous doppler study of the legs. However, despite having high sensitivity to detect proximal DVT (94.2%), sensitivity of the doppler study for distal DVT has shown to be significantly lower (63.5%) [23]. There is a statistically significant correlation however between cryptogenic stroke and pelvic DVT [24], which could be identified using MRI venogram. Later in the clinical course of the patient, he was found to have lone atrial flutter, which has proven association with embolic stroke, but given presence of the large-to-moderate bilateral PE and PFO, and absence of intracardiac thrombus on TEE, paradoxical embolism is more likely in our case.

Multiple case-control studies and one meta-analysis have shown statistically significant association between PFO and cryptogenic stroke [25]. In the PFO-ASA and PFO in Cryptogenic Stroke studies, 37 and 39 percent of the patients, respectively, were noted to have PFO [26,27]. Another study showed that patients with PFO also had significantly higher incidence of peripheral arterial embolism (15% versus 0% in control group, P<0.001) [28].

The 10-point Risk of Paradoxical Embolism Score was developed to estimate the probability for PFO to be incidental or pathogenic in cryptogenic stroke. Notably, PFO prevalence was found to be increased from 23% in patients with score 0 to 3 to 73% in those with 9 to 10 points [29,30].

**Antiphospholipid syndrome, paradoxical embolism and renal infection**

Renal infection is distinctively rare, in a study of almost 250,000 patients seen in Emergency Departments over four years, only 17 (0.0017%) were diagnosed with renal infection [31]. A large case-series study involving 483 patients has been performed, and the major sources of renal infection were identified as cardioembolic events, traumatic injury and hypercoagulable state [32]. In the same study APS was identified as a cause of the infarction in 4 patients (0.008%). However, no evident cause could be found in 30.1% of the patients. Atrial fibrillation and cardiogenic emboli were reported as the most common cause in this and other case-series studies [33,34]. Renal infarction has unspecific presentation with flank and/or diffuse abdominal pain, nausea and fever, mimicking nephrolithiasis and pyelonephritis, and quite often remains undiagnosed for several days after the admission. Elevated lactate dehydrogenase has been described as a distinctive marker, which can help differentiate renal infarction from nephrolithiasis and pyelonephritis [35]. Contrast-enhanced CT scan is the modality of choice in diagnosis of the renal infarction with 80% sensitivity, radioisotope renal scan has sensitivity of 97%, and ultrasound of only 11% [29].

Intravenous anticoagulation followed by oral warfarin is the preferred initial regimen, with further options of switching to non-vitamin K antagonist oral anticoagulants (NOACs), depending on renal function and other comorbidities [33,35]. In our patient we have renal infarction in the setting of APS and concurrent PE and cryptogenic stroke with paradoxical emboli through PFO. Isolated renal infarction cases caused by paradoxical embolism have been described in case-reports, but none of them, to our knowledge, presented with APS and concurrent stroke and PE [36,40].

APS nephropathy is another pattern of pathological lesions involving the kidneys of patients with APS. Notchy and al, studied renal biopsies of patients with primary APS and described for the first time APS nephropathy. They defined APS nephropathy as a renal small vasculopathy with at least one finding consistent with: acute thrombosis, chronic arterial or arteriolar lesions [41]. It is not clear whether APS nephropathy is secondary to thrombotic events or inflammatory responses or both. There is a lack of evidence supporting the exclusive or complete effectiveness of anticoagulant therapy in the treatment of APS nephropathy. Medications targeting inflammatory response such as anti-CD20 Ruxitumab or anticomplement C5 Ecluzimab have been used successfully as well [42,43].

**Conclusions**

HIV infection has been established as a prothrombotic state, with 10 times increased incidence of thrombosis. HIV infection is commonly associated with aPL antibodies and positive LA essay, however, association with clinically significant APS is not well understood. Evidence of thrombosis in the setting of HIV-associated APS has been described in several case reports. LA assay and aPL antibodies are not routinely checked in patients with HIV, given unknown clinical significance of these tests. However, as we decribed, HIV-related APS in the presence of PFO, or other intracardiac shunts, could present as multiple potentially life threatening thrombotic events, including paradoxical emboli, causing ischemic stroke and renal infarction. It might be prevented by screening for APS in HIV patients with PFO or other intracardiac shunts, and proper initiation of anticoagulation. More studies on this subject, including case-controls and clinical trials, are needed to provide statistically significant evidence of morbidity and mortality reduction with routine testing and initiation of anticoagulation for APS in HIV patients with intracardiac shunts.
References


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