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Case Report

Concurrent Pulmonary Embolism with Paradoxical Embolic Stroke and Renal Infarction in The Setting of Patent Foramen Ovale and HIV-Related Antiphospholipid Syndrome: Case Report and Review of The Literature

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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 anticardiolipin, 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 stablilization of his condition. Radioisotope renal scan was performed and showed that left kidney contributes only 6% to overall renal fuctioning. 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 I and anticardiolipin, 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 hypercoaguability 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 infaction [31]. A large case-series study involving 483 patients has been performed, and the major sources of renal infarction 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 fibrilation 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 infartion 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 pathogical 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 thromobitic 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 Rutiximab 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 asscociated 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

1. Chaturvedi S, McCrae KR (2017) Diagnosis and management of the antiphospholipid syndrome. Blood Rev 31: 406-417.
2. Leder AN, Flansbaum B, Zandman-Goddard G, Asherson R, Shoenfeld Y (2001) Antiphospholipid syndrome induced by HIV. Lupus 10: 370-374.
3. Purvis JA, Morgan DR, Hughes SM (2011) Prevalence of patent foramen ovale in a consecutive cohort of 261 patients undergoing routine "coronary" 64-multi-detector cardiac computed tomography. Ulster Med J 80: 72-75.
4. Giovanni Fazio, Giovanni Ferro, Giuseppe Barbaro, Kalil Fattouch, Filippo Ferrara, et al. (2010) Patent Foramen Ovale and Thromboembolic Complications. Current Pharmaceutical Design 16: 3497-3502.

5. Cecilia Beatrice Chighizola, Tania Ubiali, Pier Luigi Meroni (2015) Treatment of Thrombotic Antiphospholipid Syndrome: The Rationale of Current Management-An Insight into Future Approaches. Journal of Immunology Research 2015: 20.
6. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, et al. (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome. Journal of Thrombosis and Haemostatsis 4: 295-306.
7. Taraborelli M, Leuenberger L, Lazzaroni MG, Martinazzi N, Zhang W, et al. (2016) The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus 25: 1365-1368.
8. Vassalo J, Spector N, de Meis E, Rabello LS, Rosolem MM, et al. (2014) Antiphospholipid antibodies in critically ill patients with cancer: a prospective cohort study. J Crit Care 29: 533-538.
9. Dlott JS, Roubey RA (2012) Drug-induced lupus anticoagulants and antiphospholipid antibodies. Curr Rheumatol Rep 14: 71-78.
10. Asherson RA, Cervera R (2003) Antiphospholipid antibodies and infections. Ann Rheum. Dis 65: 388-393.
11. Dobbs MR, Berger JR (2009) Stroke in HIV infection and AIDS. Expert Review of Cardiovascular Therapy 7: 1263-1271.
12. Aima A, Ahonkhai, MD, Kelly A. Gebo, MD, MPH, Michael B. Streiff, MD, Richard D. Moore, MD, MHS, and Jodi B. Segal, MD, MPH (2008) Venous Thromboembolism in Patients With HIV/AIDS A Case-Control Study. J Acquir Immune Defic Syndr 48: 310-314.
13. Michele Bibas, Gianluigi Biava, Andrea Antinori (2011) HIV-Associated Venous Thromboembolism. Mediterr J Hematol Infect Dis 3: e2011030.
14. Damien Sène, Jean Charles Piette, Patrice Cacoub (2008) Antiphospholipid antibodies, antiphospholipid syndrome and infections. Autoimmunity Reviews 7: 272-277.
15. Gisele Zandman-Goddard, Yehuda Shoenfeld (2002) HIV and autoimmunity. Autoimmunity Reviews 1: 329-337.
16. Cervera R, Asherson RA, Acevedo M, Gomez-Puerta J, Espinosa G, et al. (2004) Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Annals of the Rheumatic Disease 63: 1312-1317.
17. Sabiha Shahnaz MD, Grishma Parikh MD, Adriana Opran MD.: Antiphospholipid Antibody Syndrome Manifesting as a Deep Venous Thrombosis and Pulmonary Embolism in a Patient with HIV. The American Journal of the Medical Sciences 327: 231-232.
18. Leder AN1, Flansbaum B, Zandman-Goddard G, Asherson R, Shoenfeld Y (2001) Antiphospholipid syndrome induced by HIV. Lupus 10: 370-374.
19. Ramos-Casals M, Cervera R, Lagrutta M, Medina F, García-Carrasco M. et al. (2004) Clinical Features Related to Antiphospholipid Syndrome in Patients with Chronic Viral Infections (Hepatitis C Virus/HIV Infection): Description of 82 Cases. Clinical Infectious Diseases 38: 1009-1016.
20. Meissner I, Whisnant JP, Khandheria BK, Spittell PC, O'Fallon WM, et al. (1999) Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. Stroke Prevention: Assessment of Risk in a Community. Mayo Clin Proc 74: 862-869.
21. Blersch WK, Draganski BM, Holmer SR, Koch HJ, Schlachetzki F, et al. (2002) Transcranial duplex sonography in the detection of patent foramen ovale. Radiology 225: 693-699.
22. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, et al. (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Stroke 24: 35-41.
23. Steve Goodacre, Fiona Sampson, Steve Thomas, Edwin van Beek, Alex Sutton (2005) Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. BMC Med Imaging 5: 6.
24. Cramer SC, Rordorf G, Maki JH, Kramer LA, Grotta JC, et al. (2004) Increased pelvic vein thrombi in cryptogenic stroke: results of the Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) study. Stroke. 35: 46-50.
25. Handke M, Harloff A, Olschewski M, Hetzel A Geibel A (2007) Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 29: 2262-2268.
26. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, et al. (2002) Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. Stroke 33: 706-711.
27. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP (2002) Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study (PICSS). Circulation 105: 2625-2631.
28. Stavros Konstantinides, Annette Geibel, Wolfgang Kasper, Manfred Olschewski, Liane Blümel, et al. (1998) Patent Foramen Ovale Is an Important Predictor of Adverse Outcome in Patients with Major Pulmonary Embolism. Circulation 97: 1946-1951.
29. Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, et al. (2013) An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke 13: 619-625.
30. Thaler DE, Ruthazer R, Weimar C, Mas JL, Serena J, et al. (2014) Recurrent stroke predictors differ in medically treated patients with pathogenic vs. other PFOs 15: 221-226.
31. Jai Radhakrishnan, MD MS (2018) Renal infarction. UpToDate. Waltham, MA: UpToDate Inc.
32. Oh YK, Yang CW, Kim YL, Kang SW, Park CW, et al. (2016) Clinical Characteristics and Outcomes of Renal Infarction. Am J Kidney Dis 67: 243-250.
33. Hazanov N, Somin M, Attali M, Beilinson N, Thaler M, et al. (2004) Acute renal embolism. Forty-four cases of renal infarction in patients with atrial fibrillation. Medicine. Baltimore 85: 292-299.

34. Antopolsky M, Simanovsky N, Stalnikowicz R, Salameh S, Hiller N, et al. (2012) Renal infarction in the ED: 10-year experience and review of the literature. Am J Emerg Med 30: 1055-1060.
35. Bourgault M, Grimbert P, Verret C, Pourrat J, Herody M, et al. (2013) Acute renal infarction: a case series. Clin J Am Soc Nephrol 8: 392-398.
36. Iwasaki M1, Joki N, Tanaka Y, Hara H, Suzuki M, et al. (2011) A suspected case of paradoxical renal embolism through the patent foramen ovale. Clin Exp Nephrol 15: 147-150.
37. Oleksandr Khoma, Aravind Suppiah, David Martin (2016) Case report: Renal infarction by paradoxical embolism through the patent foramen ovale as an unusual cause of post-operative abdominal pain after sleeve gastrectomy. Int J Surg Case Rep 26: 47-49.
38. Valerie M Lopez, Jonathan Glauser (2010) A case of renal artery thrombosis with renal infarction. J Emerg Trauma Shock 3: 302.
39. Saeed K (2012) Renal infarction. Int J Nephrol Renovasc Dis 5:119-123.
40. Hyemin Jeong, Hyun Woo Lee, Ji Young Joung, Yoon Young Cho, Dongmo Je, et al. (2012) Kidney Res: Clin Pract. Renal infarction caused by paradoxical embolism through a patent foramen ovale 31: 196-199.
41. Tektonidou MG (2018) Antiphospholipid Syndrome Nephropathy: From Pathogenesis to Treatment. Front Immunol 9: 1181.
42. Rodríguez-Pintó I, Cervera R, Espinosa G (2015) Rituximab and its therapeutic potential in catastrophic antiphospolipid syndrome. Ther Adv Musculoskelet Dis 7: 26-30.
43. Sciascia S, Radin M, Yazdany J, Tektonidou M, Cecchi I. et al. (2017) Expanding the therapeutic options for renal involvement in lupus: eculizumab, available evidence. Rheumatol Int 37: 1249-1255.

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