

Repeated renal infarction in native and transplanted kidneys due to left ventricular thrombus formation caused by antiphospholipid antibody syndrome

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Abstract: Antiphospholipid syndrome can be a feature of several underlying conditions, such as lupus, but it can also occur idiopathically. Diagnosis usually comes after investigation of recurrent venous or arterial thromboses, emboli, or hypertension/proteinuria where the kidney is involved and is usually confirmed by laboratory testing. We describe a case of a man with a myocardial infarction who developed mural thrombus in an akinetic left ventricular segment but then who recurrently embolized first to one of his native kidneys and then later to a transplanted kidney. Although the clinical behavior was typical of antiphospholipid syndrome, it took numerous laboratory assays over many years until finally the problem was confirmed and life-long warfarin therapy instituted.

Keywords: antiphospholipid therapy, emboli, infarction, kidney, kidney transplant

Renal transplantation is the cornerstone of successful management of severe progressive loss of kidney function. There are, however, many potential threats to longer term allograft survival.¹ We describe a case unique in the literature of recurrent embolic infarction of the kidney (both native kidney and then allograft) in a subject with von-Hippel-Lindau (VHL) syndrome. The discovery of antiphospholipid antibodies many years later finally explained this most unusual clinical course.

Case

In 1990, a 37-year-old man with VHL syndrome and diabetes mellitus presented with chest pain and was found to have sustained a large anterolateral transmural myocardial infarction that was treated with intravenous streptokinase followed by coronary angioplasty. A transthoracic echocardiogram (TTE) at that time showed a left ventricular (LV) aneurysm with mural clot for which he was anticoagulated with warfarin for 6 months.

He subsequently underwent a total right native nephrectomy for VHL-related renal cell carcinoma in 2001. By June 2003 his renal function had deteriorated significantly, he had experienced flank pain, and had developed nonvisible hematuria. An abdominal MRI scan revealed several splenic infarcts, and his left native kidney, previously with a normal smooth outline (except for a superficial cyst, part of the VHL constellation of renal changes), now had a scarred and shriveled appearance consistent with multiple infarcts (Figure 1A and B). TTE revealed a dilated and akinetic apical septum, apex, and

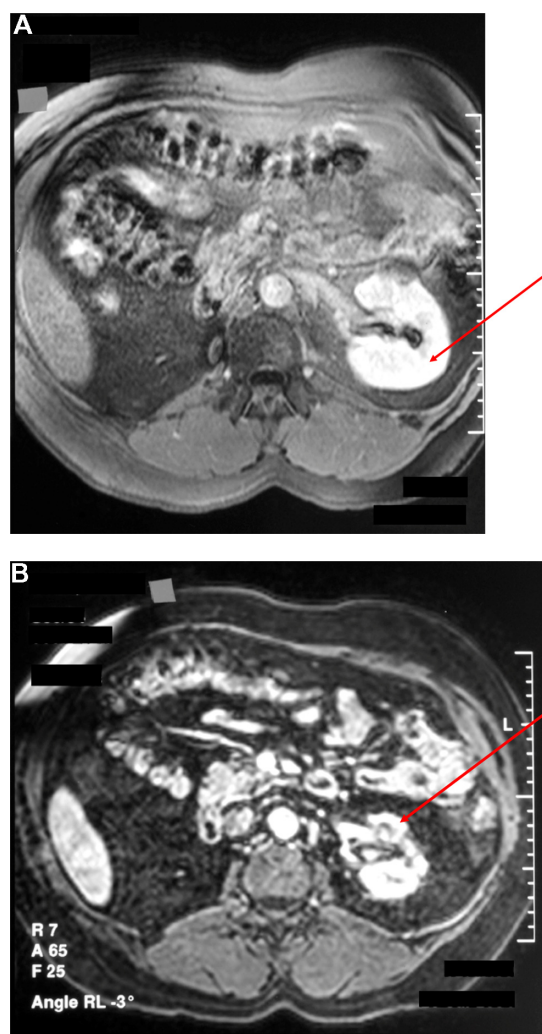


Figure 1 Abdominal MR scans. (A) January 2003 axial, fat-suppressed, T1-weighted, contrast-enhanced MR image showing normal, left, native, renal parenchyma (and a small superficial renal cyst) (arrow). (B) July 2004 axial, fat-suppressed, T1-weighted, contrast-enhanced MR image showing scarred left native kidney after embolic infarction (arrow).

Abbreviations: MR, magnetic resonance; CT, computed tomography.

inferior walls, with a mildly aneurysmal apical inferior segment. However, no LV thrombus was seen at that stage (but no other potential embolic focus was identified). He was placed on warfarin once again, and a thrombophilia screen sent at this time revealed the possible presence of a lupus anticoagulant on the activated seven lupus anticoagulant assay and dilute Russell's viper venom time (DRVVT) with correction testing, but this was not demonstrated on further mixing studies. A trans-esophageal echocardiogram (TOE) performed later once again revealed no obvious thrombus but a thin, akinetic, LV apex.

As his renal function deteriorated further, an unrelated living donor kidney transplant was performed in April 2004. As part of the work-up for this, a TTE revealed a similar appearance as the previous TOE, only now with evidence of

left atrial dilatation. A myocardial perfusion scan was also carried out pre-operatively that confirmed the previous large myocardial defect but no evidence of reversible ischemia.

Some years later in June 2009 he underwent a native left nephrectomy for renal cell carcinoma, and as part of his pre-operative work-up, a further TTE was performed that again showed no evidence of thrombus but a dilated LV cavity with mildly impaired systolic function (ejection fraction 45%) and biatrial enlargement. Once again warfarin was withdrawn for the nephrectomy; after careful consideration it was decided not to restart warfarin.

In November 2010 the patient presented with an acutely painful, pale, cold, and pulseless left leg and acute kidney injury to the allograft. A computed tomography (CT) angiogram disclosed filling defects in the left distal common, proximal, superficial, and profunda femoral arteries (Figure 2), consistent with emboli or focal thrombus. Similar filling defects were seen in the proximal anterior tibial artery, the tibioperoneal trunk, and peroneal and posterior tibial arteries. It also revealed clear-cut infarcts in the parenchyma of the transplant kidney (Figure 3), with filling defects visible in a few distal intrarenal branches of the left renal artery. A left femoral embolectomy was undertaken with good results. A thrombophilia screen was repeated, which showed both a prolonged DRVVT and diluted, activated, partial thromboplastin time, in keeping with the presence of a lupus anticoagulant; however, immunoglobulin (Ig)G and IgM anti- $\beta(2)$



Figure 2 2011 maximum intensity projection coronal oblique reformat MDCT angiogram showing embolus lodged at the left CFA bifurcation (arrow).

Abbreviations: MDCT, multidimensional computed tomography; CFA - common femoral artery.

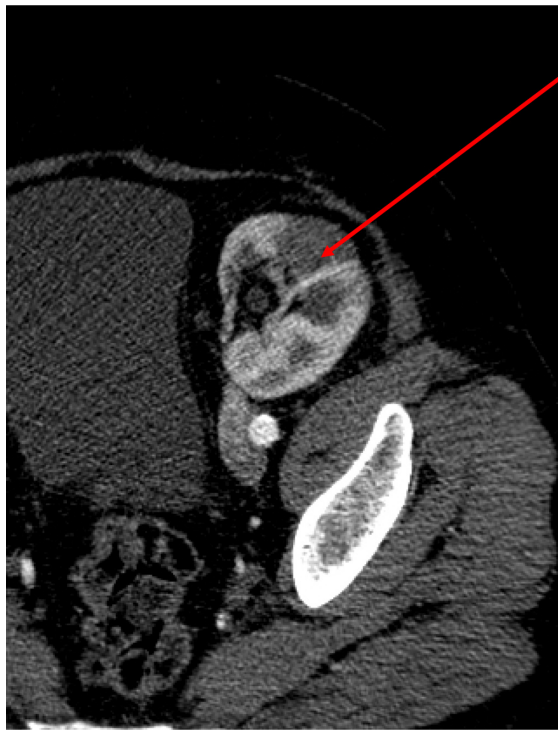


Figure 3 2011 axial contrast-enhanced MDCT showing nonenhancing infarcted segment of renal transplant cortex (arrow).

Abbreviation: MDCT, multidimensional computed tomography.

glycoprotein I (anti- β 2GPI) antibodies were normal. He was restarted on warfarin. A repeat TTE revealed normal left ventricular size, an aneurysmal apex with mildly impaired systolic function, and a large mobile pedunculated thrombus at the left ventricular apex; LV thrombus and the aneurysm were also shown on a CT scan of his chest performed at this time (Figure 4A and B).

A subsequent (2012) repeat thrombophilia screen finally revealed a sustained, elevated, anti-IgM anti- β 2GPI anticardiolipin antibody titer of 9.8 (normal < 7 MPLU/mL). He has since been reviewed by cardiology and thrombophilia teams who recommended that he should remain on warfarin sine die with repeat echocardiograms every 3 years. The case timeline is shown as Figure 5.

Discussion

Emboic disease affecting native or transplanted kidneys can involve cardiac sources (endocarditis, patent foramen ovale, mitral valve disease, atrial fibrillation, LV mural thrombus), aortic, or iliac vessel sources, including spontaneous or postinstrumentation cholesterol embolization syndrome and malignancy.² Antiphospholipid antibody syndrome can lead to micro-emboli and vasculopathy in native renal arteries and also in renal transplants.³ Renal transplant infarction

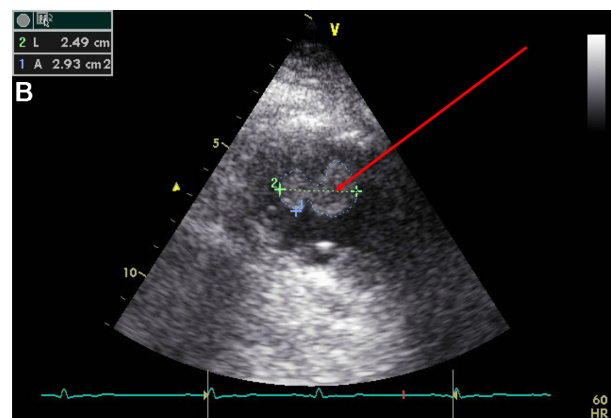
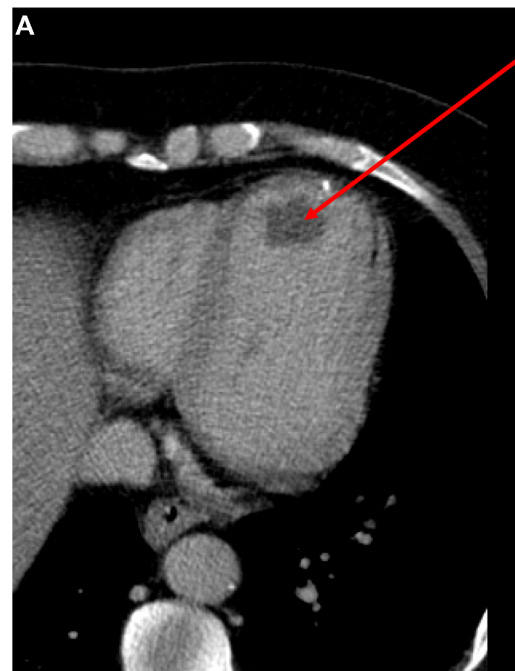


Figure 4 CT chest and echocardiogram. (A) October 2010 contrast-enhanced axial oblique multidetector CT image showing thinning and calcification in the wall of the LV aneurysm and mural thrombus (arrow). (B) 2-D echocardiogram showing pedunculated LV mural thrombus in the aneurysmal segment (arrow).

Abbreviations: CT, computed tomography; LV, left ventricle; 2-D, two dimensional.

can also occur with thrombosis or occlusion of the allograft artery or vein.

This patient's first vasculopathic problem was with an anterior myocardial infarction with LV aneurysm formation with adherent mural thrombus (in 1990). This was not uncommon in the prethrombolytic era,⁴ although this patient was in fact thrombolized, and then underwent cardiac intervention in the form of a coronary artery angioplasty. The LV aneurysm did not require surgical intervention, and as the patient was placed on warfarin therapy for some months, there was no peripheral embolization from the cardiac mural thrombus. The natural history of intracardiac mural thrombi is

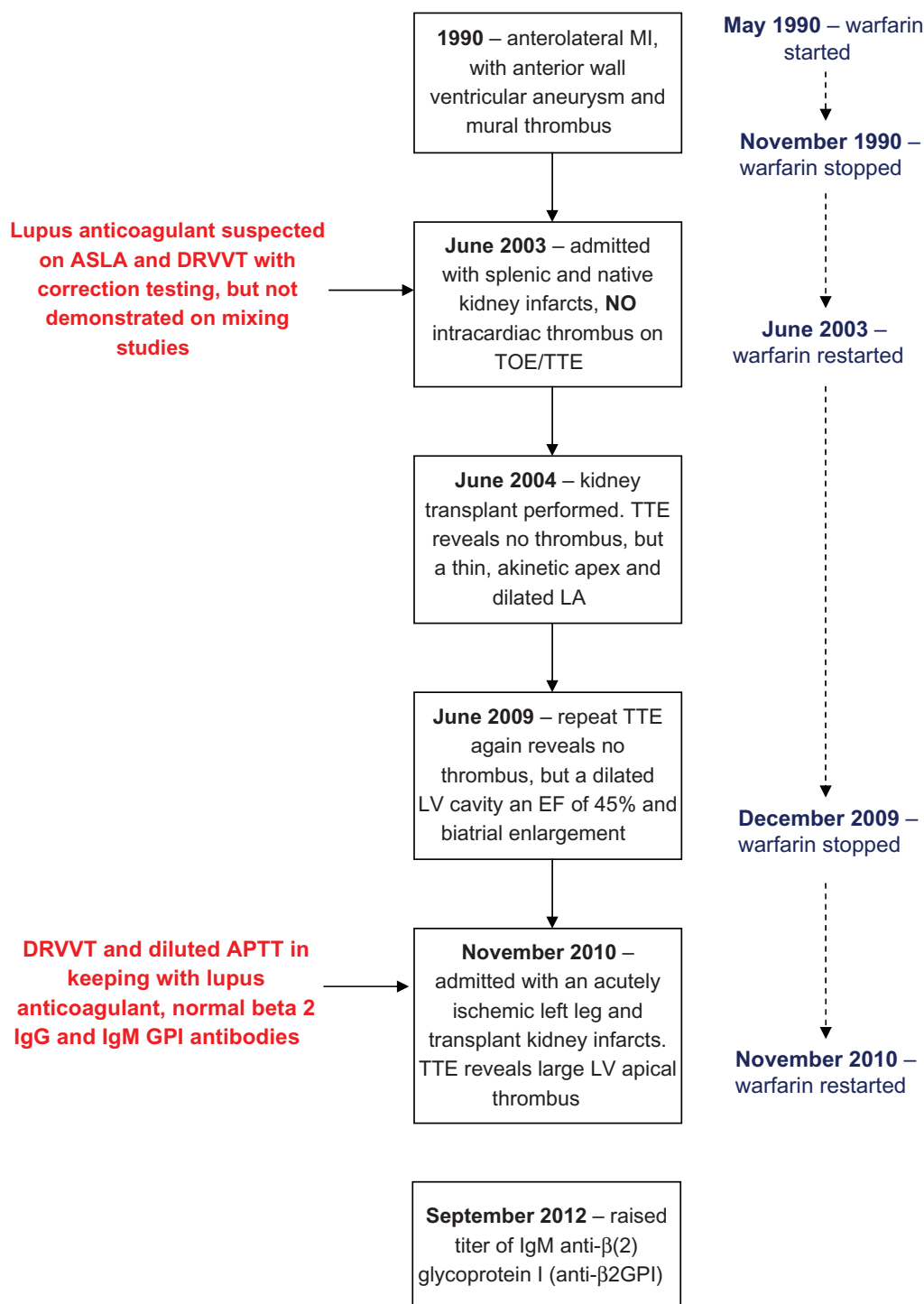


Figure 5 Case clinical timeline.

Abbreviations: ASLA, activated seven lupus anticoagulant; DRVVT, dilute Russell's viper venom time; APTT, activated partial thromboplastin time; TTE, transthoracic echocardiogram; TOE, transesophageal echocardiogram; LA, left atrium; LV, left ventricular; EF, ejection fraction; IgG, Immunoglobulin G; IgM, Immunoglobulin M; GPI, glycoprotein I.

for patients to undergo organization within weeks to months, at which point the risk of embolization becomes very low, allowing anticoagulants to be stopped,^{4,5} as in this case.

Thirteen years later there was an episode of flank pain, hematuria, and acute kidney injury, which proved on imaging to

be related to embolic infarcts in his remaining kidney. Although at that stage no cardiac (or other) source for these events was identified, it was presumed that the source of the emboli would have been the LV aneurysm; he was re-anticoagulated with warfarin. Tests for antiphospholipid antibodies at this

point were inconclusive. Six years later, now the recipient of a well-functioning renal allograft, the remaining native kidney was removed, again for lesions with malignant potential. Warfarin was discontinued for this surgery, and once again within a year a further severe episode of peripheral clot embolization occurred; this time with demonstrable pedunculated LV mural thrombus. In this episode the emboli travelled widely, including to his transplanted kidney, causing some acute kidney injury once again as well as causing blockage of an iliac artery. This was successfully dealt with by interventional radiology and achieving anticoagulation by administration first of heparin and then warfarin. Further attempts to clarify the coagulopathy have (in 2012) disclosed the presence of raised titers of IgM anti- β 2GPI antiphospholipid antibodies. There is no current or past clinical or serological evidence of any underlying autoimmune disease, such as systemic lupus erythematosus, connective tissue disorder, or vasculitis.

This case is unique in having a recurrent cardiac cause for LV apical mural thrombus with embolization first to the (by then) single native kidney and later in a discrete episode to a transplanted kidney. The propensity for the LV apical aneurysm to develop recurrent fresh thrombosis must, we presume, be a result of a “second hit” in the form of hypercoagulability secondary to development of antiphospholipid antibodies. This double hit explains the timing and nature of his subsequent problems – it could only come about after the withdrawal of warfarin for other reasons. Late embolization from LV aneurysms with preserved LV systolic function (as here) is very unusual because an existing clot organizes and is not replenished.^{4,5} In this case, only in the absence of warfarin was it possible for the antiphospholipid antibodies to cause coagulation in the abnormal aneurysmal LV mural segment (Figure 5).

There have been many important laboratory advances in the description and characterization of anticardiolipin and antiphospholipid antibodies used to diagnose this rare condition over the last two decades;^{6,7} modern techniques in a reference laboratory (such as ours) are currently very sensitive and specific,^{6,8} so it is no surprise that these tests have only become “positive” at a later stage in this clinical sequence. Among the many different assays that can be employed where there is suspicion of antibody-mediated thrombophilia, there are assays or tests for lupus anticoagulant (LA), anti-cardiolipin, anti- β 2GPI, solid phase antiprothrombin, anti-phosphatidylserine/prothrombin (aPS/PT), and anti-phosphatidylethanolamine antibodies.⁸ It is now thought that a combination of LA, anti- β 2GPI, and aPS/PT testing improves the diagnostic power and helps in stratifying

the risk for each patient, according to their anti-phospholipid antibodies (aPL) profile.⁸ The significance and management of such antibodies in renal dialysis and transplanted patients remains uncertain however; many patients on dialysis can be shown to have these antibodies, but only in a minority is there evidence of any serious clinical consequences.⁹

The care of (renal) transplant patients remains challenging and requires a skilled multiprofessional team, dedicated time and resources, and constant vigilance about the development of new conditions and complications over the ensuing years. Good clinical event archiving and consistency are also assets in this regard. Repeating the search on several occasions for the underlying coagulopathy, including waiting for more sensitive laboratory assays to become available, finally aided the correct management of this patient.

Conclusion

The diagnosis of antiphospholipid syndrome can be difficult and take several attempts and possibly more than one laboratory. If it seems clinically likely, keep trying to demonstrate the antibodies over time.

Disclosure

The authors have no relevant disclosures with respect to potential conflicts of interest.

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