

Coexistence of the Antiphospholipid Syndrome and Abdominal Aortic Aneurysm

Martine Szyper-Kravitz MD¹, Arie Altman MD PhD¹, Jozélio Freire de Carvalho MD², Francesca Bellisai MD³, Mauro Galeazzi MD³, Yael Eshet MD⁴ and Yehuda Shoenfeld MD^{1*}

¹Center for Autoimmune Diseases and Department of Medicine B, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

²Rheumatology Division, Sao Paulo University Medical School, Brazil

³Rheumatology Unit, University of Siena, Italy

⁴Department of Radiology, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Israel

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Abstract

The antiphospholipid syndrome is characterized by recurrent fetal loss, venous and/or arterial thrombosis, and thrombocytopenia associated with elevated titers of lupus anticoagulant and anticardiolipin antibodies. Although thrombosis is the characteristic vascular involvement in APS, the development of vascular aneurysms in patients with APS has been reported. We describe four patients with established APS who developed abdominal aortic aneurysm, and review the literature on previous published cases of arterial aneurysms developing in patients with APS. In addition, we discuss the possible pathophysiological association between APS and the development of this vascular abnormality.

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The antiphospholipid syndrome was defined by G. Hughes in 1983 [1] as a clinical condition characterized by recurrent fetal loss, venous and/or arterial thrombosis, and thrombocytopenia associated with elevated titers of lupus anticoagulant and anticardiolipin antibodies. APS was originally described in patients with systemic lupus erythematosus, and only later was considered a syndrome on its own (primary APS) [2]. APS can affect almost every organ and system in the body, leading to the suggestion that the syndrome be renamed “systemic APS” [3]. Intensive research in the last decade has greatly advanced our understanding of the role of antiphospholipid antibodies in the hypercoagulable state characteristic of APS [4,5]. However, although the characteristic vascular involvement in APS is thrombosis, some authors have described the development of vascular aneurysms in patients with APS [6-9]. As lifelong anticoagulation remains the main therapy in APS, the development of vascular aneurysms may expose patients to an increased risk of rupture and fatal hemorrhage.

We present four patients with established APS who developed abdominal aortic aneurysm, and review the literature on previous published cases of arterial aneurysms coexisting with APS. In addition the pathophysiology of this possible association is discussed.

Patient Descriptions

Patient 1

In October 2006 a 45 year old man was hospitalized for investigation of fever, left flank pain and gross hematuria that lasted for 2 weeks. His complete blood count was remarkable only for anemia; hemoglobin level was 13.2 g/dl. Chemistry results were within the normal range. Repeated blood and urine cultures were negative. His blood was negative for hepatitis B and human immunodeficiency virus. Bone marrow biopsy was unremarkable and cultures were sterile. D-dimer levels were elevated, and tests for thrombophilia revealed that he was positive for LAC, and had elevated titers of aCL antibodies (immunoglobulin M > 120 MPL IgG > 120 GPL). Further serological evaluation indicated that he was negative for antinuclear and antineutrophil cytoplasmic antibodies. Deep vein thrombosis was diagnosed by Doppler ultrasonography, and a chest and abdominal computed tomography angiography disclosed multiple emboli in the lungs, spleen and kidneys, and an infra-renal aortic aneurysm of 28.7 mm. No valvular or intracardiac thrombi were seen on trans-esophageal echocardiography. Treatment with low molecular weight heparin was begun but later switched to coumadin. The patient was discharged asymptomatic and without fever. At a follow-up visit in our outpatient clinic 6 weeks after discharge he was asymptomatic. This time, his serum was tested for a panel of antibodies, and he was positive for aCL, anti-phosphatidylserine and anti-beta-2 glycoprotein-I. Based on the clinical presentation of DVT and multiple emboli, and the elevated titers of aCL antibodies found on two occasions 6 weeks apart, the diagnosis of APS was established. In March 2007, he was admitted to the surgical department with severe abdominal pain, predominant in the left lower quadrant. On admission the patient was afebrile, hemodynamically stable, and had an international normalized ratio of 3. Abdominal CT angiography disclosed an enlarged fusiform aneurysm of 46.1 mm outpouching latero-posteriorly

LAC = lupus anticoagulant
Ig = immunoglobulin
aCL = anticardiolipin
DVT = deep vein thrombosis

* Incumbent of the Laura Schwartz-Kipp Chair for Autoimmunity, Tel Aviv University.
APS = antiphospholipid syndrome

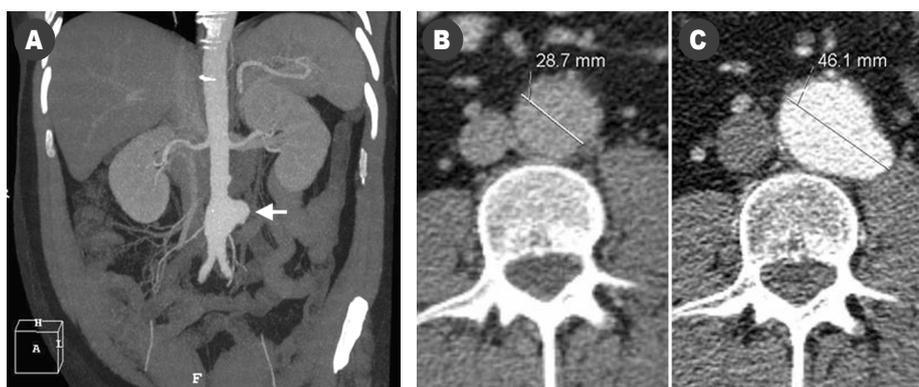


Figure 1. Saccular aneurysm in a 45 year old patient with APS (case 1). **[A]** Coronal reformation of a CT angiography shows a saccular aneurysm of the infra-renal abdominal aorta, extending to the left. Axial CT images performed a year before **[B]** and immediately after **[C]** the presentation of symptoms show a fusiform aneurysm outpouching latero-posteriorly into a new saccular aneurysm, pressing against the left psoas muscle

into a new secular aneurysm, pressing against the left psoas muscle [Figure 1]. At this time, LAC and aCL antibodies were not detected. Aneurysmectomy was performed successfully, and after an uneventful recovery he was discharged on anticoagulant treatment. Three months later, on routine follow-up, elevated titers of LAC and aCL were observed. He continues follow-up.

Patient 2

A 51 year old Hispanic woman with a prolonged history of systemic arterial hypertension, heavy smoking, and prolonged oral contraceptive use was admitted to the hospital in September 2003 with left foot ischemia and livedo reticularis. Anticoagulation with heparin was administered, and lumbar sympathectomy followed by repeated arterial bypass was performed due to refractory ischemia and thrombosis of the bypass vessel. Her lipid profile was elevated and simvastatin was introduced. Thrombophilia screening revealed a persistent positive LAC (tested twice with an interval of 4 months), and she was negative for aCL. Levels of antithrombin III, C and S proteins were normal, and her blood was negative for cryoglobulin and ANCA. Serologies for HIV, and hepatitis B and C virus were negative. Warfarin therapy was initiated, and she was followed in the outpatient clinic. In May 2005 she was asymptomatic and had a normal physical examination. A cerebral magnetic resonance imaging angiography (performed as part of a scientific study) revealed a bilobular aneurysm on the bifurcation of the left middle cerebral artery, which was confirmed by digital arteriography showing an aneurysm of 9 mm with a neck of 6 mm. The fundoscopic examination was normal. She underwent neurosurgical correction of the aneurysm without neurological sequelae. Four days after surgery, enoxaparin was initiated followed by warfarin and she had an uneventful recovery. She continued her follow-up in the outpatient clinic without additional clinical events. In April 2006 an abdominal

aorta dilatation was found on Doppler ultrasonography, and abdominal CT angiography confirmed an infra-renal fusiform aneurysm of 3.4 cm diameter with an extension of 6.0 cm. The patient is being followed regularly by the vascular department physicians who perform serial ultrasonography every 6 months.

Patient 3

A 48 year old woman was diagnosed with APS in 1992 after she had experienced recurrent pregnancy losses, two episodes of DVT, and elevated titers of aCL and LAC. Even though she was treated with heparin, aspirin and intravenous immunoglobulin, she did not achieve a successful pregnancy,

and had two more pregnancy losses. In 2005 abdominal ultrasonography disclosed enlargement of the aorta, and CT angiography confirmed the presence of an aneurysm below the renal arteries, measuring 27 mm in diameter and involving a tract of 58 mm. Further evaluation including echocardiography and carotid and vertebral Doppler was normal. She is currently being followed by serial sonography every 6 months. Her latest laboratory tests are remarkable only for a moderate thrombocytopenia of 80,000 platelets/mm³ without anemia or leukopenia, and the presence of aCL antibodies, IgG 90 GPL (normal value < 10), and anti- β 2GPI antibodies IgG type.

Patient 4

In 1989 a 67 year old man was diagnosed with APS after he experienced recurrent deep vein thromboses and an episode of massive pulmonary thromboembolism. The patient was found to be positive for LAC and treatment with coumadin was started. A year later he developed acute upper gastrointestinal bleeding and an inferior vena cava filter was inserted. In 2005 the patient had an acute ST-elevation extensive posterolateral wall myocardial infarction. Coronary angiography revealed a 50% stenosis of the left main and additional triple vessel disease was demonstrated. He was treated conservatively. In the same year, the patient was admitted for evaluation of abdominal pain. Abdominal CT scan revealed an AAA, not demonstrated in the angiography performed in 1989 for the IVC filter insertion. The aneurysm, measuring 4.5 cm in diameter, was between the inferior mesenteric artery and the aortic bifurcation [Figure 2, arrow].

Discussion

In this report four patients with established APS who developed abdominal aortic aneurysm are presented. Patient 2 also devel-

ANCA = anti-neutrophil cytoplasmic antibodies
HIV = human immunodeficiency virus

β 2GPI = beta-2 glycoprotein-I
AAA = abdominal aortic aneurysm
IVC = inferior vena cava

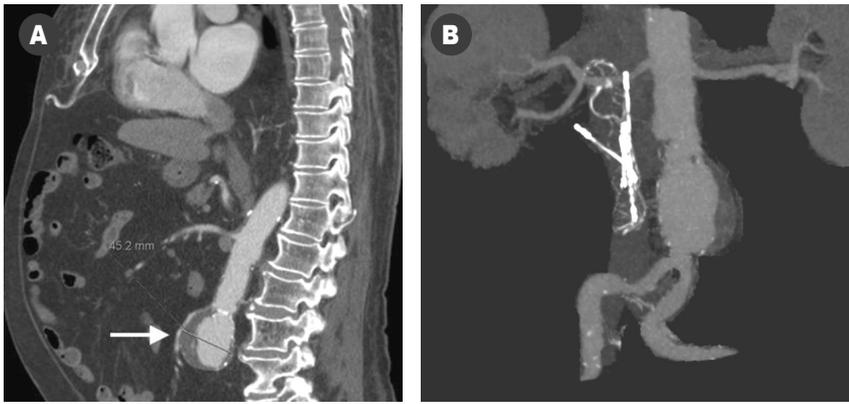


Figure 2. AAA in case 4. **[A]** Sagittal reformation of multidetector CT angiography shows abdominal aortic aneurysm between the inferior mesenteric artery and the aortic bifurcation measuring 4.5 cm in diameter (arrow). **[B]** AAA and inferior vena cava filter side by side (case 4). Maximum intensity projection (MIP) image demonstrates an inferior vena cava filter adjacent to the aortic aneurysm.

Table 1. Patients with APS and vascular aneurysms

Source	N	Gender	Age (yrs)	Artery involved	aPL Abs	APS history	Outcome
Present report	1	M	45	AAA	LAC, aCL IgM & IgG	DVT, PE, splenic and kidney infarcts	Alive
Present report	2	F	51	Lt MCA, AAA	LAC, aCL	Lt leg ischemia, livedo reticularis	Alive
Present report	3	F	48	AAA	LAC, aCL, anti-β2GPI	Recurrent abortions (x 7) DVT (x 2)	Alive
Present report	4	M	70	AAA	LAC	DVT, recurrent PE	Alive
Szpak et al. [6]	5	F	34	Carotid, and MCA	aPL		Dead
Vancheri et al. [16]	6	F	42	Hepatic	LAC, aCL IgM & IgG	Recurrent abortions, CVA, ITP	Alive
Koutoulidis et al. [8]	7	F	38	Splenic, hepatic, renal	aCL	Recurrent abortions	Dead
Chung et al. [7]	8	M	20	Pulmonary	aCL	PE	Alive
Dongola & Foord [17]	9	M	31	Jejunal, pancreatic, superior mesenteric, renal	LAC, aCL	DVT, recurrent PE	Dead

PE = pulmonary embolism, MCA = middle cerebral artery, ITP = immune thrombocytopenia purpura

oped an aneurysm on the bifurcation of the left middle cerebral artery. Primary APS classically presents with arterial and venous thrombotic events, and vascular aneurysms have rarely been reported. In contrast, several cases of APS have been described in association with vasculitis in patients who developed vascular aneurysms, such as polyarteritis nodosa [10,11], Takayasu's arteritis [12], giant cell arteritis [13], and Behçet's syndrome [14]. In these cases, the aneurysm was attributed to the vasculitic process. In the four cases presented here, the patients lacked clinical or serological features compatible with an established vasculitis syndrome. On the other hand, three of our four patients also lacked the classical risk factors for AAA, such as male preponderance, older age, hypertension and smoking [15].

We reviewed the literature and found several patients with apparently primary APS who developed vascular aneurysms [Table 1]. Szpak et al. [6] described a 34 year old woman with primary APS,

as well as intracranial aneurysm and thrombotic small vessel vasculopathy, who died of hemorrhage secondary to aneurysm rupture. At the postmortem evaluation the patient lacked features of SLE or other autoimmune disease, and biopsies of the aneurysm walls disclosed dysplastic changes compatible with arterial fibromuscular dysplasia of the carotid and middle cerebral artery. Vancheri and colleagues [16] described a 42 year old APS patient who presented with acute abdomen secondary to a ruptured aneurysm of the common hepatic artery. Histology of the aneurysmal wall showed marked fibrosis involving the full mural thickness, and focal destruction of the internal elastic lamina with infiltration of plasma cells and neutrophils at the rupture site. Chung et al. [7] reported a 20 year old male who in a 2 year period developed recurrent pulmonary emboli and multiple venous thromboses. He was found to harbor antiphospholipid antibodies. Pulmonary angiography disclosed saccular aneurysm and fusiform dilatations in the pulmonary vasculature. Open lung biopsy showed vascular thrombi and focal necrosis without evidence of vasculitis. Koutoulidis and co-authors [8] described a 38 year old APS patient who developed multiple visceral aneurysms affecting the splenic, hepatic and both renal arteries. After 3 years, and despite supportive treatment, the patient died of multi-organ failure. Postmortem examination confirmed the presence of splanchnic aneurysms without evidence of rupture. Dongola and team [17] presented a 31 year old male, who during a period of 2 years developed postoperative DVT and recurrent episodes of pulmonary emboli, with the presence of LAC and aPL. Eight

years later, he developed acute abdominal bleeding which led to his death. At postmortem evaluation multiple aneurysms were found at the pancreatic and renal arteries, with multiple infarcts and emboli within the kidneys. All his arteries were abnormally dilated and tortuous. Although the patient had angiographic features compatible with polyarteritis nodosa, Takayasu's arteritis and fibromuscular dysplasia, histological examination showed no evidence of vasculitis. Together with the four new cases presented here a total of nine cases have been published [Table 1]. Except for our patient # 4, all the patients were young, with a mean age of 38.5 years. Five aneurysms developed in women and four in men, and five patients had an isolated aneurysmatic vessel, while four patients had multiple aneurysms, two of them involving

SLE = systemic lupus erythematosus
aPL = antiphospholipid antibodies

multiple splanchnic arteries. Three young patients died, two of them due to aneurysmal rupture and fatal bleeding, and all cases of death occurred in patients with multi-vessel involvement.

The possible association of APS with vascular wall abnormalities such as aneurysms merits a cautious discussion. On the one hand, these two entities may share pathogenetic features, and antiphospholipid antibodies may be involved in the development of arterial wall abnormalities. aPL have been shown to trigger activation of endothelial cells, monocytes and platelets [18], and to up-regulate the synthesis of mediators active on vessel tone regulation [19]. By causing endothelial perturbation, aPL may alter the balance between vessel wall dilatation and constriction [20]. Furthermore, vasculopathy and APS may be inherently associated [21]. Studies have demonstrated that aPL can enhance factors remodeling the artery wall, such as metalloproteinase 9, which degrades elastin in the vessel wall and was found to have a pivotal role on the induction of aneurysms in experimental models [22]. Interestingly, elevated levels of MMP-9 have been found in the sera of SLE patients harboring aPL [23], highlighting a possible link between aPL and aneurysm induction. On the other hand, because the treatment of APS is lifelong anticoagulation, it may impose an increased risk for fatal hemorrhage on patients with vascular aneurysm.

Several authors have suggested that beyond the classical presentation, the APS has multiple faces and various complications [24]. We suggest that vascular aneurysms can be an additional vascular presentation or complication of this syndrome. This possible association raises diagnostic and therapeutic dilemmas. Should patients with APS be screened for vascular aneurysm?

With this report we aim to raise awareness of these unusual manifestations, so that physicians caring for APS patients will have a high index of suspicion for these complications and will evaluate patients with the relevant clinical presentations accordingly.

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Correspondence: Dr. Y. Shoenfeld, Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel.

Phone: (972-3) 530-2652

Fax: (972-3) 535-2855

email: shoenfel@post.tau.ac.il

MMP = metalloproteinase

A half-truth is a whole lie

Yiddish proverb