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CASE REPORT

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Severe hypertension associated with multiple intrarenal microaneurysms in a patient with systemic lupus erythematosus and antiphospholipid antibodies

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Abstract A 26-year-old Japanese woman with systemic lupus erythematosus (SLE) developed severe hypertension and an increased active renin concentration (ARC), ischemic colitis, and splenic infarction. She had antiphospholipid antibodies (APA), multiple intrarenal microaneurysms, and multiple stenoses of the mesenteric arteries. Combination therapy with antihypertensive agents, aspirin, warfarin, and corticosteroids (30 mg daily) controlled her abdominal symptoms and hypertension. Multiple intrarenal microaneurysms in SLE with APA may be the cause of severe hypertension and elevated serum ARC.

Key words Active renin concentration (ARC) · Antiphospholipid antibodies (APA) · Hypertension · Microaneurysm · Systemic lupus erythematosus (SLE)

Introduction

Antiphospholipid antibodies (APA) are autoantibodies directed against phospholipids, and they induce a variety of organ disorders in association with arterial or venous thrombosis (antiphospholipid syndrome, APS). APS- or APA-associated systemic hypertension is not common, but is sometimes accompanied by renal artery thrombosis, renal thrombotic microangiopathy, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura (TTP)-like syndrome.[1] We treated a patient with APA-positive systemic lupus erythematosus (SLE), who had severe systemic hypertension along with an increased serum active renin concentration (ARC). She had multiple intrarenal microaneurysms and ischemic changes in her other organs. Here, we review previous reports of APA-related hypertension with increased serum ARC, including our case.

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Case report

In July 1996, a Japanese woman developed polyarthralgia and visited Keio University Hospital. Because she had leukocytopenia (2500/mm^3), antinuclear antibodies ($\times$1280, diffuse and speckled pattern), a false-positive serological test for syphilis, and an increased serum level of anti-DNA antibodies (Ab), she was diagnosed as having SLE. In November 1996, she developed a high fever, lower abdominal pain, and watery diarrhea. High titers of serum anti-DNA Ab ($>$300 IU/ml) and hypocomplementemia indicated an active phase of SLE. After prednisolone (PSL, 30 mg daily) was started, her abdominal symptoms and fever promptly disappeared with a normalization of her serum anti-DNA Ab. In 1998, however, while she was taking 7 mg PSL daily, similar symptoms with an increased anti-DNA Ab concentration (132 IU/ml) reappeared. Serum anticardiolipin antibodies were also increased (42.3 U/ml (normal $<$ 10)). She was successfully treated with an increased dose of PSL (30 mg daily) again. Her blood pressure had been normal until this time. In June 1999, her lower abdominal pain and diarrhea recurred without fever. Because an increased dose of PSL (20 mg daily) was not effective in controlling her symptoms, she was admitted to our hospital in August 1999. She had no history of pregnancy, and her mother had been diagnosed as having APS.

On admission, severe hypertension (176/128 mmHg) and lower abdominal tenderness were observed. There was no evidence of scleroderma. The laboratory findings were as follows: erythrocyte sedimentation rate (ESR), 8 mm/h; white blood cell counts (WBC), 11 600/mm^3; hemoglobin (Hgb), 13.5 g/dl; platelet count, 36.1 $\times$ 10^6/ml; activated partial thromboplastin time (APTT), 20.1 s; prothrombin time $>$ 100%; fibrinogen degradation products (FDP), 115 ng/ml

(normal); antithrombin-III (AT-III), 106 mg/dl (normal); D-dimer, 0.8 μg/dl (normal); negative for lupus anticoagulant; serum albumin, 2.9 g/dl; blood urea nitrogen (BUN), 10.7 mg/dl; creatinine, 0.5 mg/dl; normal liver function test; creative protein (CRP), 3.30 mg/dl. Repeated urine tests including urinary sediment were always normal, and creatinine clearance was 96.8 ml/min. Immunological test results were as follows: IgG, 2140 mg/dl; IgA, 528 mg/dl; IgM, 444 mg/dl; C3, 59 mg/dl (normal, 60–80 mg/dl); C4, 12 mg/dl (normal, 20–35 mg/dl); negative cryoglobulin; immune complex, 15 μg/ml (anti-C3d, normal < 13 μg/ml); negative myeloperoxidase-antineutrophil cytoplasmic autoantibodies (MPO-ANCA); strongly positive antinuclear antibodies (×1280, diffuse and speckled pattern); anti-DNA Ab, 31.3 IU/ml (normal < 10 U/ml); anti-cardiolipin Ab, 26.0 U/ml (normal < 10 U/ml); anti-β2-glycoprotein I (β2GPI) Ab < 1.2 U/ml (normal < 3.5 U/ml). It is of interest that both her serum active renin concentration (ARC) (152.9 pg/ml; normal range, 3.6–36.2 pg/ml) and aldosterone (379 pg/ml; normal range, 50–200 pg/ml) were increased. Funduscopy performed by an ophthalmologist showed hypertensive retinopathy. An abdominal computed tomography (CT) scan showed splenic infarction (Fig. 1A). Colonoscopy showed intestinal ulcers on both transverse and descending colons (Fig. 1B). Selective abdominal angiography was performed. Multiple stenoses, occlusions, or collateral arteries were recognized in the superior and inferior mesenteric arteries (Fig. 2A). In addition, while both renal arteries were completely normal, multiple microaneurysms in the interlobular arteries were observed bilaterally (Fig. 2B). A brain MRI, abdominal echography, an upper gastrointestinal series, and pulmonary perfusion scintigraphy were normal.

After hospitalization, the dose of PSL was increased to 30 mg daily, and the antihypertensive drugs labetalol hydrochloride and enalapril maleate were started. Her blood pressure and abdominal symptoms, however, were not well controlled. Active lupus signs had disappeared, and the acute-phase reactants were completely normal. A renal biopsy specimen, which was taken 3 weeks after admission, showed no evidence of abnormal cell proliferation, vasculitis, or thrombosis in glomeruli or tubules. Immunofluorescence staining was not performed. After warfarin and low-dose aspirin therapy were started, the patient's blood pressure had completely normalized and her abdominal symptoms had resolved. A follow-up abdominal CT scan and colonoscopy showed that the splenic infarction and the intestinal ulcers had disappeared. She is currently taking 12 mg PSL and aspirin, without any active lupus signs, hypertension, or abdominal discomfort.

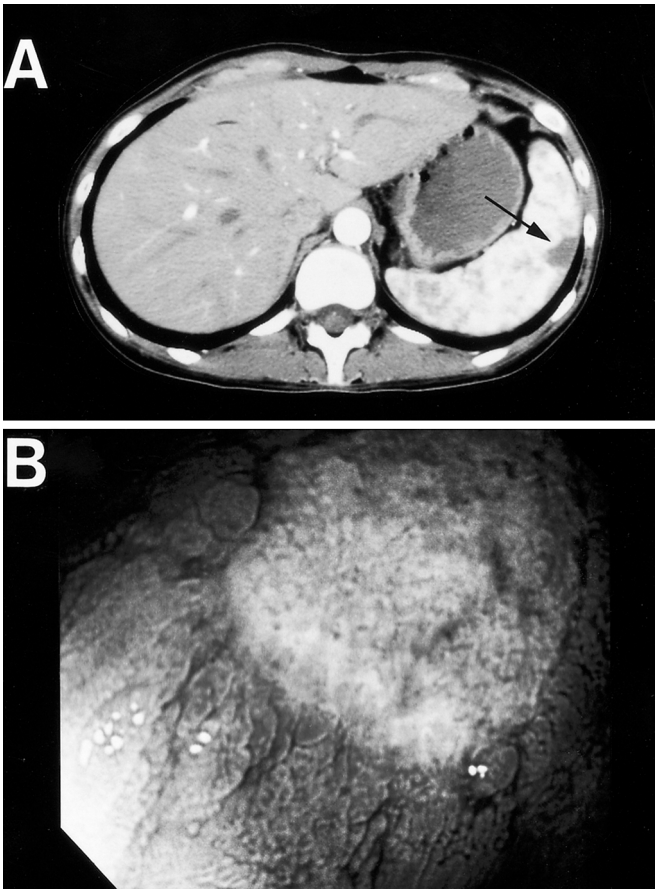

Fig. 1. The findings of an abdominal computed tomography (CT) scan and colonoscopy. **A** Splenic infarction was detected (*arrow*) in the CT scan. After treatment with prednisolone (PSL) (30 mg daily), warfarin, and low-dose aspirin was initiated, this ischemic change disappeared. **B** Active ulcers were observed in the transverse and descending colons

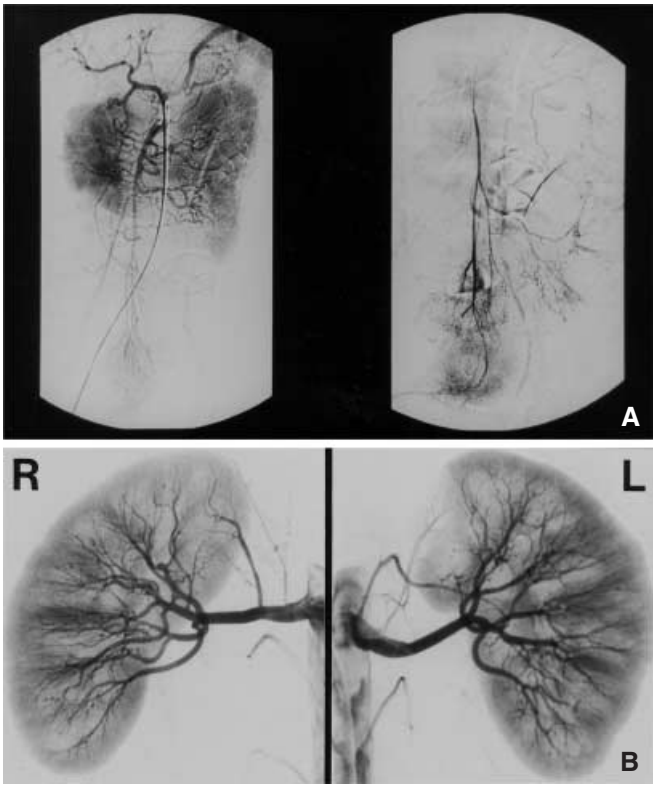

Fig. 2. Selective angiography. **A** Superior and inferior mesenteric arteries. Severe stenosis and occlusion in peripheral arteries of both mesenteric arteries were observed. **B** Renal arteries. Both renal arteries were intact, but multiple intrarenal microaneurysms were observed bilaterally in the lobular arteries.

Table 1. Hypertension associated with increased serum renin concentration in patients with APA

	Age (years)/ Sex	Diagnosis	APA	Renal dieases	Treatments	Reference
1	13 / F	SLE + APS	BFP, LA, aCL	Renal artery thrombosis	CS, CY, WAR, PE, PTA	Ostuni et al. 1990[3]
2	35 / F	APS	BFP, aCL	Renal artery stenosis, renal infarction	CS, HEP, WAR, PTA	Asherson et al. 1991[4]
3	10 / M	APS	BFP, LA	Thrombotic microangiopathy	CS, ACEI, WAR	Inam et al. 1991[5]
4	30 / F	APA positive	BFP, aCL	Renal artery stenosis	ACEI, PTA	Rossi et al. 1992[6]
5	22 / F	APS	LA, aCL	Renal infarction	WAR	Sonpal et al. 1993[7]
6	40 / F	APS	LA, aCL	Thrombotic microangiopathy	CS, ACEI, ASA	Hamidou et al. 1995[8]
7	49 / F	SLE + APS	BFP, LA, aCL	Renal artery stenosis	CS, HEP, ASA, WAR, PTA	Serino et al. 1996[9]
8	13 / F	APS	LA, aCL	Renal artery occlusion, thrombotic microangiopathy	Urokinase, ASA, WAR	Ohtomo et al. 1998[10]
9	35 / F	SLE + APS	BFP, LA, aCL	Renal artery stenosis	CS, ACEI, ASA, acenocumarol	Remondino et al. 2000[11]
10	26 / F	SLE + APA	BFP, aCL	Multiple microaneurysms	CS, ASA, WAR	This paper

SLE, systemic lupus erythematosus; APA, antiphospholipid antibodies; APS, antiphospholipid syndrome; BFP, a false-positive serological test for syphilis; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; CS, corticosteroids; CY, cyclophosphamide; WAR, warfarin; PE, plasma exchange; PTA, percutaneous transluminal angioplasty; HEP, heparin; ACEI, angiotensin converting enzyme inhibitor; ASA, aspirin

Discussion

APA induce several renal disorders such as renal vein thrombosis, renal artery occlusion, renal infarction, thrombotic microangiopathy, or glomerular thrombosis in association with lupus nephritis.[2] The association between systemic hypertension and renal manifestations in patients with APA has been also discussed.[1] However, the mechanisms of systemic hypertension in APA-positive patients may be complicated, and not all APA-positive patients with renal involvement develop systemic hypertension. In our patient, serum ARC was significantly increased, suggesting renovascular hypertension (RVH). Ostuni et al.[3] reported the case of a 13-year-old girl with RVH who had renal artery thrombosis in association with APS. After this first report of APS-related RVH, other patients with different types of APA-related RVH[4–11] have been described (Table 1). Rossi et al.[6] describe a 30-year-old woman who had RVH with APA-associated renal artery stenosis. Some recent studies have indicated that renal thrombotic microangiopathy, which is characterized by progressive renal insufficiency, proteinuria, and hypertension, plays an important role in APS-related nephropathy and systemic hypertension.[3,8,10] Renal infarction has been also reported as a cause of severe systemic hypertension along with increased serum ARC.[4,7]

To the best of our knowledge, this is the first report of a patient with SLE and/or APA who had severe hypertension in association with multiple intrarenal microaneurysms. This case also showed vasculopathy in splenic and mesenteric arteries. Superior mesenteric artery aneurysms, in which multiple thromboses but not vasculitis were involved, have been reported in SLE.[12] In addition, cerebral aneurysms occurring at atypical sites in patients with SLE were previously identified as lupus vasculitis.[13] Although the possible relationships between SLE, vasculitis, and aneurysm development are intriguing, high-dose steroid therapy should be selected for lupus vasculitis. On the other hand, APA-related vasculopathy has also been recognized.[14–18] Dongola and Foord[14] reported the case of an APS patient who had multiple aneurysms in mesenteric and renal arteries with no evidence of vasculitis. They concluded that the moderate-sized aneurysm could have been caused by APA. There are several reports of polyarteritis nodosa associated with APA.[15–18] Almeshari et al.[15] reported the case of a patient who had acute renal failure in association with renal vasculitis. However, some patients have been successfully treated with aspirin or anticoagulation therapy, suggesting that thrombosis was mainly involved in their renal vasculitis. Therefore, although treatment with warfarin and low-dose aspirin seemed more effective than PSL, vasculitis may have been involved in the pathophysiology of multiple aneurysms in our case.

In our patient, autoantibodies to structurally altered β2GPI, which are thought to be associated with thrombosis in SLE,[19] were not detected. Anti-β2GPI antibodies were more specific, but are less sensitive for onset of cardiovascular accident than anticardiolipin Ab (specificity 74% vs. 61%; sensitivity 41% vs. 51%).[20] This patient was not diagnosed as having APS according to the Sapporo criteria,[21] but her renal manifestations and systemic hypertension seemed to be mainly associated with APA. We suggest that this patient's findings may be rare, but they should be considered in patients with severe hypertension, an increased serum ARC, and APA.

References

1. Asherson RA, Khamashta MA, Hughes GRV. Hypertension and the antiphospholipid syndrome. Clin Exp Rheum 1993;11:465–7.
2. Asherson RA, Kant KS. Antiphospholipid antibodies and the kidney. J Rheumatol 1993;20:1268–72.

3. Ostuni PA, Lazzarin P, Pengo V, Ruffatti A, Schiavon F, Gambari P. Renal artery thrombosis and hypertension in a 13-year-old girl with antiphospholipid syndrome. Ann Rheum Dis 1990;49:184–7.
4. Asherson RA, Noble GE, Hughes GR. Hypertension, renal artery stenosis and the "primary" antiphospholipid syndrome. J Rheumatol 1991;18:1413–5.
5. Inam S, Sidki K, Al-Marshedy A-R, Judzewitsch R. Addison's disease, hypertension, renal and hepatic microthrombosis in "primary" antiphospholipid syndrome. Postgrad Med J 1991;67:385–8.
6. Rossi E, Sani C, Zini M, Casoli MC, Restori G. Anticardiolipin antibodies and renovascular hypertension. Ann Rheum Dis 1992;51:1180–1.
7. Sonpal GM, Sharma A, Miller A. Primary antiphospholipid antibody syndrome, renal infarction and hypertension. J Rheumatol 1993;20:1221–3.
8. Hamidou MA, Moreau A, Jego P, Testa A, Banisadr F, Buzelin F, et al. Captopril and aspirin in treatment of renal microangiopathy in primary antiphospholipid syndrome. Am J Kidney Dis 1995; 25:486–8.
9. Serino R, Osajima A, Hiroshige K, Anai H, Tanaka H, Kabashima N, et al. Renovascular hypertension associated with antiphospholipid antibodies in a woman with systemic lupus erythematosus (in Japanese). Nippon Jinzo Gakkai Shi 1996;38:417–22.
10. Ohtomo Y, Matsubara T, Nishizawa K, Unno A, Motohashi T, Yamashita Y. Nephropathy and hypertension as manifestations in a 13-year-old girl with primary antiphospholipid syndrome. Acta Paediatr 1998;87:903–7.
11. Remondino GI, Mysler E, Pissano MN, Furattini MC, Basta MC, Presas JL, et al. A reversible bilateral renal artery stenosis in association with antiphospholipid syndrome. Lupus 2000;9:65–7.
12. Ko S-F, Hsien M-J, Ng S-H, Wong H-F, Lee T-Y, Lee C-M. Superior mesenteric artery aneurysm in systemic lupus erythematosus. Clin Imaging 1997;21:13–16.
13. Kelly RE, Stokes N, Reyes P, Harik SI. Cerebral transmural angiitis and ruptured aneurysm. A complication of systemic lupus erythematosus. Arch Neurol 1980;37:526–7.
14. Dongola NA, Foord KD. Angiographic features associated with antiphospholipid syndrome. Br J Radiol 2000;73:1215–18.
15. Almeshari K, Alfurayh O, Akhtar M. Primary antiphospholipid syndrome and self-limited renal vasculitis during pregnancy: case report and review of the literature. Am J Kidney Dis 1994;24:505–8.
16. Norden DK, Ostrov BE, Shafritz AB, Von Feldt JM. Vasculitis associated with antiphospholipid syndrome. Semin Arthritis Rheum 1995;24:273–81.
17. Dasgupta B, Almond MK, Tanqueray A. Polyarteritis nodosa and the antiphospholipid syndrome. Br J Rheumatol 1997;36:1210–12.
18. Schoonjans R, Van Vlem B, Wewers S, De Keyser F, Praet M, Versieck J, et al. Polyarteritis nodosa and the antiphospholipid syndrome. Clin Rheumatol 1996;15:410–13.
19. Tsutumi A, Matsuura E, Ichikawa K, Fujisaku A, Mukai M, Kobyashi S, et al. Antibodies to β2-glycoprotein I and clinical manifestations in patients with systemic lupus erythematosus. Arthritis Rheum 1996;39:1466–74.
20. Lockshin MD. Antiphospholipid syndrome. In: Ruddy S, Harris ED Jr, Sledge CB, editors. Textbook of rheumatology. 6th ed. Philadelphia: WB Saunders; 2001. p. 1145–52.
21. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Ware Branch D, Piette J-C, et al. International consensus statement on preliminary classification criteria for defining antiphospholipid syndrome. Report of an international workshop. Arthritis Rheum 1999;42: 1309–11.