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## Renal artery thrombosis in a pediatric case of systemic lupus erythematosus without antiphospholipid antibodies

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**Abstract** A 13-year-old Japanese boy with an 11-month history of systemic lupus erythematosus (SLE) without antiphospholipid antibodies (APAs) suddenly developed severe hypertension, associated with fever and generalized seizures, and mild abdominal pain. Emergency abdominal computed tomography (CT) confirmed left renal artery thrombosis, and a renal scintiscan revealed reduced blood flow to the left kidney. Promptly instituted intravenous anticoagulant therapy was not effective for controlling the infarction-reduced renal arterial blood supply. Moreover, he developed stupor due to central nervous system (CNS) lupus a week after the occurrence of the hypertensive episode. Finally, a percutaneous transluminal angioplasty successfully relieved the occlusion of the left renal artery at its origin. The CNS lupus was also successfully treated with intravenous methylprednisolone pulse therapy combined with intrathecal methotrexate and dexamethasone. Although it is well known that SLE patients with APAs have a high incidence of thrombotic complications, to date, renal artery thrombosis has rarely been reported in young patients. This APA-negative SLE patient unusually manifested renal thrombosis associated with CNS lupus.

**Keywords** Antiphospholipid antibodies · Central nervous system lupus · Renal artery thrombosis · Systemic lupus erythematosus

### Introduction

Arterial and venous thromboses are sometimes seen in patients of systemic lupus erythematosus (SLE) with antiphospholipid antibodies (APAs) [1]. However, renal

artery thrombosis causing renal artery occlusion has rarely been seen reported, even in SLE patients with APAs. To our knowledge, this is the first report describing renal artery thrombosis in pediatric-onset APA-negative SLE. Moreover, the patient developed unusual manifestations of renal artery thrombosis associated with central nervous system (CNS) lupus with a flare of SLE.

### Case report

A 13-year-old Japanese boy with an 11-month history of APA-negative SLE with lupus nephritis (WHO class IVb) was transferred to Hirosaki University Hospital in June 2004 because of sudden-onset generalized seizures. Prior to this episode, his disease activity had been successfully controlled with low-dose prednisolone (PSL), 15 mg (0.3 mg/kg) per day, mizoribine (MZR), an angiotensin-converting enzyme inhibitor (ACE inhibitor) and d-lazep dihydrochloride, following induction therapy of high-dose PSL. Most recent results of immunological examinations were as follows: serum C3, 77 mg/dl (normal, 79–152 mg/dl); serum C4, 17 mg/dl (normal, 16–38 mg/dl); serum hemolytic complement activity (CH50), 41.2 U/ml (normal, 23–46 U/ml); serum antinuclear antibody (ANA), 1:1,280 (normal, <1:20); serum anti-double stranded DNA (dsDNA) antibody, 58 IU/ml (by ELISA, normal, <12.0 IU/ml). He complained of mild abdominal pain, nausea and diarrhea, which were attributed to some viral infection prior to the exacerbation.

On admission, his temperature was 38.2°C and pulse rate was 154/min. Blood pressure was markedly elevated to 224/144 mmHg. There were no signs of endocarditis, such as positive blood culture, heart murmur, chest pain, embolic phenomena (Roth spots, Osler nodes, petechiae) and electrocardiogram abnormalities. The laboratory study results were as follows: white blood cell (WBC) count, 13,030/ $\mu$ l; red blood cell (RBC) count,  $581 \times 10^4$ / $\mu$ l; hemoglobin level, 16.7 g/dl; hematocrit, 46%; platelet count, 118,000/ $\mu$ l; erythrocyte sedimentation rate (ESR), 42 mm/h; prothrombin time (PT), 11.5 s (normal, 10.0–12.5 s); activated partial thromboplastin time (aPTT), 31.8 s (normal, 25.0–35.0 s); serum fibrinogen, 417 mg/dl (normal, 200–400 mg/dl); serum level of fibrin degradation products, 5.7  $\mu$ g/ml (normal, <5.0  $\mu$ g/ml); serum anti-thrombin III (ATIII) activity, 92% (normal, 80–120%); serum total protein, 7.4 g/dl; serum albumin, 4.4 g/dl, blood urea nitrogen, 16 mg/dl; serum creatinine, 1.0 mg/dl; serum total cholesterol, 280 mg/dl; serum aspartate transaminase, 18 U/l; serum alanine transaminase, 25 U/l; serum  $\gamma$ -glutamyl transferase, 19 U/l; serum alkaline phosphatase, 599 U/l; serum sodium, 139 mmol/l; serum potassium, 4.1 mmol/l; serum chloride, 97 mmol/l; serum creati-

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**Fig. 1 a** Abdominal computed tomography showing hypodense areas in the upper and middle segment of the left kidney. **b** Aortography of renal arteries showing occlusion of the left artery at 1 cm from the origin



nine kinase, 425 U/l; blood glucose, 234 mg/dl; serum C-reactive protein, 0.8 mg/dl; serum ammonia, 101  $\mu$ g/dl.

The results of immunological examinations were as follows: serum IgG, 1,170 mg/dl (normal, 751~1,560 mg/dl); serum IgA, 268 mg/dl (normal, 82~453 mg/dl); serum IgM, 40 mg/dl (normal, 46~304 mg/dl); serum C3, 67 mg/dl (normal, 79~152 mg/dl); serum C4, 24 mg/dl (normal, 16~38 mg/dl); serum hemolytic CH50, 33.7 U/ml (normal, 23~46 U/ml); serum ANA, 1:2,560 (normal, <1:20); serum anti-dsDNA antibody, 70 IU/ml (by ELISA, normal, <12.0 IU/ml). The serum was negative for APAs (by ELISA), anti- $\beta$ 2-glycoprotein I antibodies (by ELISA) and lupus anticoagulant (by the following method: first, aPTT was used as a screening test. Then, corrigibility of aPTT was examined by the mixing of the patient's plasma with an equal volume of normal plasma. Dilute Russell viper venom time and a kaolin clotting time were not examined.), which was confirmed by repeated examinations more than six times during the clinical course. Serum protein S activity was 91% (by EIA, normal, 65~135%). Serum protein C activity was 163.0% (by latex photometric immunoassay, normal, 70~140%).

Laden factor V mutations were not tested, because the possibility of a positive result for Laden factor V mutations in the Japanese is quite low. Test results for anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Urinalysis showed a urinary specific gravity of 1.034, pH 7.0, protein 493 mg/dl, many RBC sediments and 16 WBC sediments per high-power field, with a sterile culture. The urinary  $\beta$ 2-microglobulin level was elevated to 771  $\mu$ g/dl (normal <30  $\mu$ g/dl).

Cranial computed tomography (CT) showed a slightly hypodense area in the left occipital region. Initial cranial magnetic resonance imaging (MRI) showed a high signal intensity area in the left occipital region on T2-weighted images. Although ultrasonography (US) and intravenous pyelography at the time of renal biopsy performed in October 2003 had revealed normal-sized kidneys, renal US showed a small and poorly perfused left kidney. Abdominal CT revealed a hypodense area in the upper and middle segment of the left kidney, suggestive of left renal infarction (Fig. 1a).

After a tentative diagnosis of hypertensive encephalopathy due to renal infarction, anti-hypertensive therapy with an ACE inhibitor, angiotensin II receptor blocker (ARB) and calcium channel blocker, and anticoagulation therapy with heparin and urokinase were started. Although the patient recovered his consciousness on the following day, mild abdominal pain and moderate hypertension persisted. The T2-signal abnormalities had disappeared at the second cranial MRI performed 6 days after the episode.

A week after this episode, the patient suddenly developed high fever and became stuporous again. A third cranial MRI revealed diffuse high signal intensity areas bilaterally in the cerebral deep white matter, cerebellum, basal ganglia, thalami and brainstem, on T2-weighted images. The results of cerebrospinal fluid (CSF) examination were as follows: cells, 10/3 c.mm; protein, 48 mg/dl; glucose, 79 mg/dl; chloride, 121 mmol/l, IgG index, <0.85; IL-6 activity, 248 pg/ml (normal, 10~30 pg/ml); IL-8 activity, 592 pg/ml (normal, <10 pg/ml).

A week after the first episode selective arteriography of the renal arteries was performed, which revealed complete occlusion of the left renal artery from its origin (Fig. 1b), while some blood flow to the lower pole of the kidney was provided by collateral small vessels. Percutaneous transluminal angioplasty successfully restored the renal blood flow, and the hypertension was gradually resolved with this procedure. The CNS lupus was successfully treated with intravenous methylprednisolone pulse therapy, combined with 10 mg intrathecal methotrexate, and 8 mg dexamethasone. Sequential lumbar puncture confirmed a progressive and dramatic decrease in the CSF concentrations of IL-6 and IL-8.

Although the patient recovered completely without any neuropsychiatric sequelae within 4 months after the episode, slight atrophy of the left kidney persisted, which was confirmed by abdominal CT and  $^{99m}$ Tc dimercaptosuccinic acid renoscintigraphy. The glomerular filtration rate, as estimated by renography, decreased to 38 ml/min per 1.73m<sup>2</sup> in the left kidney. Serum creatinine remained at 0.6 mg/dl. Repeat test results for APAs and lupus anticoagulant in the blood remained negative.

## Discussion

It is well known that APA-positive SLE patients have a high incidence of thrombotic complications. With regard to other factors predisposing to thrombosis in cases of SLE, besides APA, hypercoagulability caused by corticosteroid treatment itself, hypertension, hyperlipidemia, and vasculitis have been considered [2]. Rajagopalan et al. previously reported that heightened endothelial apoptosis might be an important factor in the development of atherothrombosis in SLE [3]. With regard to renal thrombosis in SLE, venous thrombosis, rather than arterial thrombosis, has been reported usually [1], and even if renal artery involvement is present, it is usually detected in small arteries. In the literature, SLE patients who presented with renal thrombosis usually showed APA positivity [4, 5, 6, 7, 8, 9, 10]. To our knowledge, only one, adult, APA-negative case of SLE with thrombotic occlusion of the renal artery has been reported [2]. Thus, we believe that this case report is the first of a pediatric patient with APA-negative SLE who developed renal artery occlusion.

Our patient that had developed sudden-onset severe hypertension had never been detected to have hypertension at regular monthly check-ups prior to this episode. Since the hypertension was severe, renal hypertension was initially considered. Abdominal CT revealed left re-

nal infarction. It has been reported that renal artery occlusion is rarely encountered, partly because the synthesis of large amounts of nitric oxide and PGI<sub>2</sub> by the mesangial cells may counter the effects of platelet activation, preventing the development of thrombosis within the glomerular capillaries [11]. Although the activity of the disease had been successfully controlled with 15 mg PSL per day, MZR [12], an ACE inhibitor and dilazep dihydrochloride, our patient suddenly developed renal artery thrombosis with very severe hypertension. Furthermore, he developed CNS lupus concomitantly with the renal artery infarction. It has been reported that the presence of APAs is strongly associated with thrombotic CNS events. However, our patient was detected to have neither APAs nor lupus anticoagulant in his serum.

Although dilute Russell viper venom time and a kaolin clotting time were not examined, the fact that the aPTT was normal indicated that the patient was negative for APAs. Cranial MRI revealed diffuse high signal intensity areas bilaterally in the cerebral deep white matter, cerebellum, basal ganglia, thalamus and brainstem on T2-weighted images, suggestive of some vasculitic inflammation/vasculopathy. Based on the clinical course, aggressive immunosuppressive therapy, consisting of intravenous methylprednisolone pulse therapy and intrathecal methotrexate and dexamethasone, was initiated, which successfully controlled the CNS lupus. Taken together, large- and medium-vessel vasculitis due to lupus flare, as well as hemo-concentration due to pre-existing enterocolitis, might explain the unusual turn of events in our patient, although this remains speculative.

In conclusion, this case report underscores the fact that even pediatric patients with APA-negative SLE may develop renal artery thrombosis. Thus, SLE patients should be kept under close observation, with special attention paid to the development of thrombotic events.

## References

1. Soltesz P, Veres K, Lakos G, Kiss E, Muszbek L, Szegedi G (2003) Evaluation of clinical and laboratory features of antiphospholipid syndrome: a retrospective study of 637 patients. *Lupus* 12:302–307
2. Suwabe H, Moriuchi J, Hoshina Y, Iwata Y, Ishikawa Y, Arimori S (1993) Renal and cerebral infarctions in a patient with systemic lupus erythematosus without antiphospholipid antibodies (in Japanese). *Ryumachi* 33:335–340
3. Rajagopalan S, Somers EC, Brook RD, Kehrer C, Pfenninger D, Lewis E, Chakrabarti A, Richardson BC, Shelden E, McCune WJ, Kaplan MJ (2004) Endothelial cell apoptosis in systemic lupus erythematosus: a common pathway for abnormal vascular function and thrombosis propensity. *Blood* 103:3677–3683
4. Asherson RA, Derksen R, Harris EN, Hughes GRV (1987) Chorea in systemic lupus and lupus-like disease: association with antiphospholipid antibodies. *Semin Arthritis Rheum* 16: 253–259
5. Ostuni PA, Lazzarin P, Pengo V, Ruffatti A, Schiavon F, Gambari P (1990) Renal artery thrombosis and hypertension in a 13 year old girl with antiphospholipid syndrome. *Ann Rheum Dis* 49:184–187
6. Arnold MH, Schriber L (1988) Splenic and renal infarction in systemic lupus erythematosus: association with anti-cardiolipin antibodies. *Clin Rheumatol* 7:406–410
7. Ames PRJ, Cianciaruso B, Bellizzi V, Balletta M, Lubrano E, Scarpa R, Brancaccio V (1992) Bilateral renal artery occlusion in a patient with primary antiphospholipid antibody syndrome: thrombosis, vasculitis or both? *J Rheumatol* 19:1802–1806
8. Hernandez D, Dominguez ML, Diaz F, Fernandez ML, Lorenzo V, Rodriguez A, Torres A (1996) Renal infarction in a severely hypertensive patient with lupus erythematosus and antiphospholipid antibodies. *Nephron* 72:298–301
9. Remondino GI, Mysler E, Pissano MN, Furattini MC, Basta MC, Prsas JL, Allievi A (2000) A reversible bilateral artery stenosis in association with antiphospholipid syndrome. *Lupus* 9:65–67
10. Kuzmanovska DB, Sahpazova EM, Grujovska SJ, Trajkovski Z (2004) Renal infarction in a child with systemic lupus erythematosus. *Pediatr Nephrol* 19:685–687
11. Raij L (1993) Nitric oxide and the kidney. *Circulation* 87:26–29
12. Tanaka H, Tsugawa K, Tsuruga K, Suzuki K, Nakahata T, Ito E, Waga S (2004) Mizoribine for the treatment of lupus nephritis in children and adolescents. *Clin Nephrol* 62:412–417