



# A case of IgA nephropathy with deep venous thrombosis in the mesentery and lower extremities

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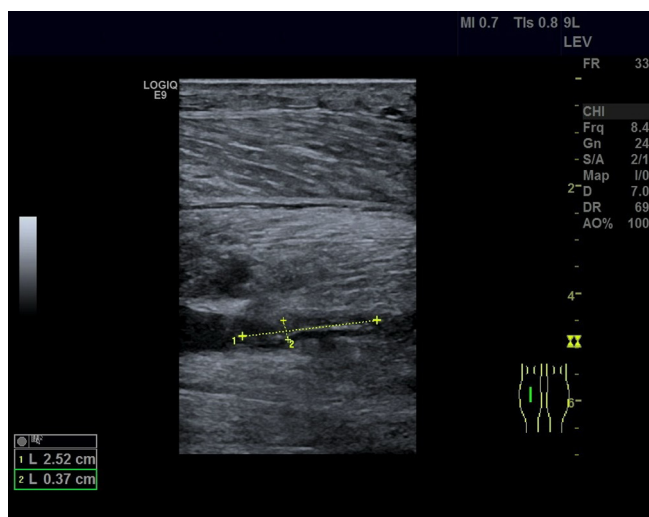
## Introduction

IgA nephropathy (Berger disease) is a disorder in which there is prominent IgA deposition in the glomerular mesangial area, and is the most common type of primary glomerulonephritis (1), receiving more and more attention (2-8). With diverse clinical manifestations, it has its own characteristic type of glomerular mesangial lesions (9). IgA nephropathy accounts for 45.2–58.2% of primary glomerulonephritis in China and 1/3 of cases in other countries in Asia, as well as 20% in Europe and 10% in the United States. This significant difference in prevalence may be caused by differences in the indications for a renal biopsy between Asia and the United States. IgA nephropathy is associated with an increased risk of deep venous thrombosis (DVT) (10), mostly involving the renal veins and the lower extremities, and sometimes the portal vein and vena cava. Superior mesenteric vein thrombosis is rare. We present a case of IgA nephropathy with deep venous thrombosis of the superior mesenteric vein and both lower extremities. The patient gave informed consent according to the World Medical Association Declaration of Helsinki.

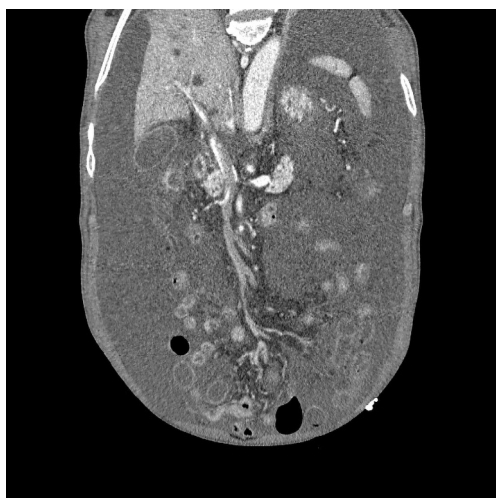
## Case presentation

The patient, a 52-year-old male, was diagnosed as having DVT of the lower extremities in another hospital because of a 10-day history of swelling, pain, and restricted range of motion of the lower extremities. He was transferred to the Department of Vascular Surgery in our hospital for further evaluation. The physical examination showed non-

pitting edema and pain involving both lower extremities slightly relieved with elevation, and obvious pain while walking. On the second hospital day, the patient had gradually increasing abdominal pain and occasional diarrhea, accompanied by fever up to 39 °C. There was tenderness and mild guarding in the umbilical area, with no rebound tenderness, and no hyperactive bowel sounds. The laboratory and imaging results: blood: WBC  $17.6 \times 10^9/L$ , 80% neutrophils; blood coagulation: fibrin (origin) degradation product: 7.90  $\mu g/mL$ ; D-dimer: 1.20  $\mu g/mL$ , fibrinogen concentration: 14.02  $\mu mol/L$  (normal range, 5.8–11.8  $\mu mol/L$ ), prothrombin time: 15.2 s (normal range, 11–13 s), PT normalized ratio: 1.3; globulin ratio: 0.96, albumin: 27.4 g/L, alanine aminotransferase: 52.4 U/L; review of blood routine examination: WBC:  $26.5 \times 10^9/L$ , 96; urinalysis: occult blood: 10/ $\mu L$  1+, leukocytes: 28.8/ $\mu L$ , crystallization examination: 0.1/ $\mu L$ ; stool routine examination: color: yellow, occult blood: positive, qualitative state: semi-liquid. An ultrasound (US) of the lower extremities (*Figure 1*) was positive for DVT in the muscular calf veins; a contrast-enhanced CT of the abdomen (*Figure 2*) suggested superior mesenteric vein thrombosis and intestinal necrosis. In the evening of the same day, he was transferred to a higher-level hospital. After treatment with anticoagulation, antibiotics for intestinal necrosis detumescence and detumescence and rehydration for >20 days, his condition was improved, with no abdominal pain, and improvement of the swelling and pain in both lower extremities. However, when he returned to the Department of Vascular Surgery of our hospital

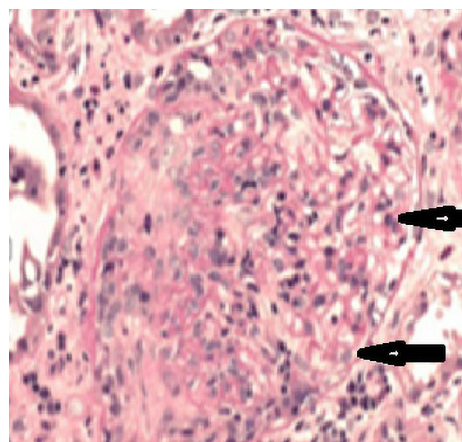


**Figure 1** Ultrasound shows leg intermuscular vein ectasia in lower extremities with scattered thrombus.



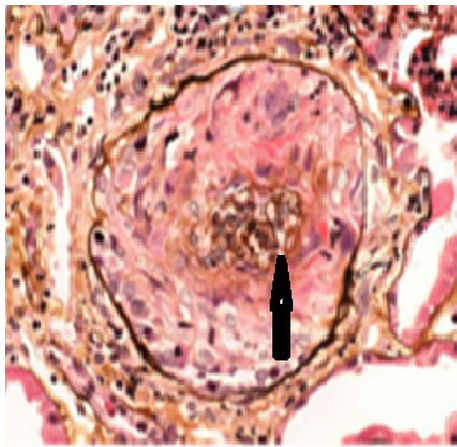
**Figure 2** Contrast-enhanced CT with coronal reconstruction shows superior mesenteric vein thrombosis.

to continue the treatment, abdominal pain, diarrhea, and swelling in both lower extremities reappeared. Membranous nephropathy was suspected. He was transferred to the Department of Nephrology. His GFR: left kidney 22.02 mL/min; right kidney: 24.23 mL/min (normal value is 40–60 mL/min). A renal biopsy was performed, with three core samples acquired. Global sclerosis appeared in one glomerulus, spherical cellular crescents were found in three glomeruli, and segmental cellular crescents were found in eight glomeruli. The glomerular capillary loop was

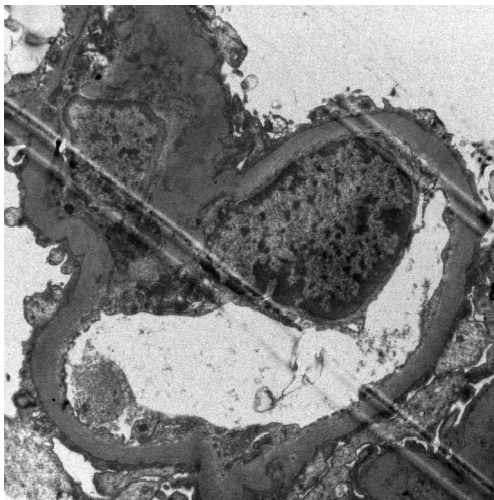


**Figure 3** PAS staining (x400) shows negative PLA2R. The arrows display mild glomerular mesangial matrix hyperplasia.

obstructed under pressure and was necrotic. The remaining glomeruli were normal in size, with about 80–100 cells/glomerulus, 2–3 mesangial cells/mesangial area (slight elevation), mild mesangial matrix hyperplasia, opening of capillary loops, normal basement membranes, and renal capsular adhesions involving some glomeruli. Masson staining was negative. Severe tubulointerstitial lesions were noted, with unclear tubular structures, diffuse tubular epithelial cell edema and degeneration, and necrosis and detachment in certain cells. Protein casts were seen, and there was diffuse infiltration of the interstitium by neutrophils, lymphocytes, and eosinophils. The arteriolar walls were thickened slightly, with intimal hyperplasia. No hyaline degeneration was seen. No thrombosis was seen in the vessel lumen, and no obvious inflammatory cell infiltration was seen in the vessel wall. Immune-combined Periodic Acid-Schiff stain (PAS) staining (Figure 3) and Periodic Acid-Silver Methenamine stain (PASM) staining (Figure 4) suggested that PLA2R was negative and Ig isoforms were negative. Under electron microscopy, there was glomerular capillary loop mesangial matrix hyperplasia, electron-dense deposits in the mesangial area (arrow, Figure 5), an even basement membrane, no obvious electron-dense deposits on the epithelial medial or endothelial sides of the basement membrane, and foot process fusion of epithelial cells and cytoplasmic shedding. Necrosis and exfoliation were seen in certain renal tubular epithelial cells, but no electron-dense deposits were found around the tubular basement membrane. Combined with immunofluorescence findings (Figure 6), we diagnosed IgA nephropathy (mesangial proliferative glomerulonephritis with crescent



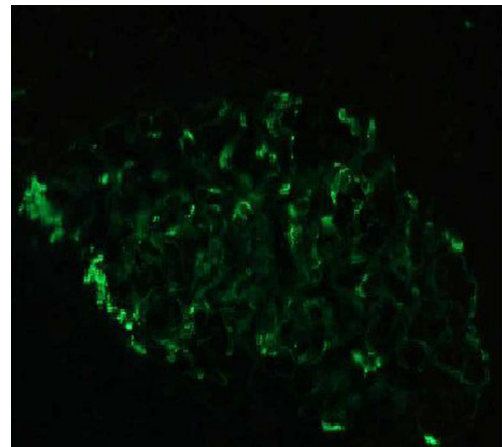
**Figure 4** PASM staining (×400) shows negative Ig subtype. The arrow displays glomerular sclerosis.



**Figure 5** Electron microscopy shows there was glomerular capillary loop mesangial matrix hyperplasia, electron-dense deposits in the mesangial area, but no obvious electron-dense deposits on the epithelial medial and endothelial sides of the basement membrane, and foot process fusion of epithelial cells and cytoplasmic shedding. Necrosis and exfoliation were seen in certain renal tubular epithelial cells.

formation), Hass IV type, M0E0S0T2 (Oxford, 2009) (total number of glomeruli: 15, endothelial cell proliferation: 0, crescent: 11, global sclerosis: 1, and segmental sclerosis: 0).

The patient was administered a single pulse of 500 mg methylprednisolone, and calcium supplements and gastrointestinal protection were given for symptomatic



**Figure 6** Immunofluorescence (×400) shows IgA nephropathy. IgA and C3 are present in the mesangial area as massive diffuse fluorescent deposits.

supportive treatment. After 3 days, he was significantly improved. He was switched to methylprednisolone tablets 52 mg/day. The patient was discharged after 2 days and was followed as an outpatient, with regular adjustments of the methylprednisolone dose.

## Discussion

### *Clinical diagnostic signs of IgA nephropathy*

The clinical manifestations of IgA nephropathy mainly include mild painless hematuria and/or proteinuria, or signs of more serious renal damage, such as acute and chronic renal failure, in which the clinically most common feature is microscopic hematuria with or without proteinuria (11–14). Approximately 40–50% of patients show paroxysmal hematuria; most patients have intermittent or persistent mild to moderate proteinuria, and only about 5% of patients have proteinuria at nephrotic syndrome levels (15). The incidence of nephrotic syndrome in children and adolescents is significantly higher. The Clinical Guidelines of the Chinese Medical Association for Kidney Diseases (16) point out that although there is no characteristic pattern in the clinical manifestations and laboratory examinations of IgA nephropathy, IgA nephropathy should be suspected if the following symptoms occur: (I) upper respiratory tract infection or tonsillitis attacks with gross hematuria at the same time for at least 1 week, disappearing or decreasing after infection control; (II) hematuria with or without



proteinuria; (III) high serum IgA levels.

### ***Key points for pathological diagnosis of IgA nephropathy***

IgA nephropathy is a pathologic diagnosis requiring a renal biopsy. Under light microscopy, the most prominent feature of IgA nephropathy is the widening of the mesangial area that results from the proliferation of mesangial cells and mesangial matrix. Immunofluorescence examination shows that a large amount of IgA is present in the mesangial area in the form of massive or granular diffuse deposits, which may be accompanied by the deposition of IgG and IgM. Sometimes, the deposits may extend to the capillary wall. The vast majority of cases are associated with C3 deposition and IgG and IgM deposition of the same magnitude as the IgA distribution, but the C1q and C4 are negative. Masson staining shows that the red IgA, IgG, and IgM deposits are mainly distributed in the mesangial area, mostly in spot or plaque shape, occasionally in short linear collections, and are accompanied by enlargement of the blue mesangial area, namely, increased matrix. Electron microscopy electron-dense deposits in all mesangial areas, indicating that the lesions are diffuse, and a small number of electron-dense material deposits can be seen occasionally under the endothelium or epithelium, especially in critically ill patients. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines point out that all patients with renal biopsy-proven IgA nephropathy should undergo secondary pathogenesis identification (17-21). Common secondary glomerular diseases including lupus nephritis, Henoch-Schönlein purpura nephritis, hepatitis B nephritis, as well as liver cirrhosis, inflammatory bowel disease, and human immunodeficiency virus (HIV) nephropathy should be identifiable by the glomerular IgA deposits.

The study of pathological grading for IgA nephropathy has developed from more emphasis on quantitative classification, usually including Lee's grading and Haas's grading, which divide it into grades I, II, III, IV and V from light to severe based on the severities of glomerular and tubulointerstitial lesions. In 2009, the International IgA Nephropathy Network and the Renal Pathology Society jointly published the Oxford Classification of IgA Nephropathy, focusing on levels of mesangial cell proliferation (M), segmental glomerulosclerosis (S), intra capillary cell hyperplasia (E) and tubular atrophy/interstitial fibrosis (T). Through a series of evidence-based studies, the Oxford Classification Group suggested that renal M, S, E and T lesions detected on renal biopsy are closely related to

indicators such as 24-hour urinary protein quantification, blood pressure levels, and glomerular filtration rate (GFR), and can be used to evaluate the prognosis of patients with IgA nephropathy (22). Strictly formulated with full consideration for repeatability, Oxford's pathological classification system is currently the most rigorous and scientific classification method and is considered to have good clinical utility.

### ***Mechanism of IgA nephropathy with thrombosis***

Venous thrombosis is mainly caused by aggregation of fibrin and red blood cells, and the main components of arterial thrombosis are platelets and a small amount of fibrin. Venous thrombosis is more clinically common. Factors that are currently recognized to promote thrombosis include vascular endothelial cell damage, hypercoagulable state, and hemodynamic changes (23,24). Immune complexes and autoantibodies in patients with anti-IgA nephropathy can cause vascular endothelial damage with subsequent collagen exposure and that can initiate endogenous and exogenous coagulation pathways. Exogenous tissue factor plays an important role in the formation of a hypercoagulable state that is the result of multiple pathophysiological changes (25). IgA nephropathy complicated by DVT in both lower extremities is rare, and simultaneous mesenteric venous thrombosis is rarer (26). Studies found that IgA nephropathy causes significant microvascular damage (27-30), and IgA patients are more prone to arteriosclerosis than healthy people of the same age group.

### ***Treatment progress in IgA nephropathy***

An effective individualized treatment plan is developed according to the histopathological type and grade found in the renal biopsy. Obvious inflammatory cell infiltration, proliferation of mesangial cells, and formation of cellular crescents are indications for using immunosuppressive agents. For patients with simple hematuria IgA nephropathy, the KDIGO guidelines do not recommend tonsillectomy or antiplatelet drug treatment due to insufficient evidence. Whether to adopt more aggressive initial immunosuppressive treatment regimens for patients with IgA nephropathy and the setting of treatment timing and program for severe IgA nephropathy patients with initial poor renal function is subject to the development of large-scale randomized controlled trials and large data

analyses.

In summary, the clinical manifestations of IgA nephropathy are diverse, such as extensive DVT, abdominal pain, anemia, and proteinuria in this patient. The conditions were treatment-resistant. After a multi-disciplinary consultation, the renal physician suggested the possibility of membranous nephropathy, so a renal biopsy was performed (31), and accurate pathological grading, definitive diagnosis of IgA nephropathy, and effective treatment followed (32-34). It is difficult to diagnose or clarify IgA nephropathy, so multi-disciplinary consultations should be organized. Renal biopsy is necessary for the pathological diagnosis, and CT angiography and MR angiography are the gold standards for the diagnosis of thromboembolism in CT and MRI examinations.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Informed Consent:* The patient gave informed consent according to the World Medical Association Declaration of Helsinki.

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