AJKD
Case Report

A Case of Phospholipase A_2 Receptor–Positive Membranous Nephropathy Preceding Sarcoid-Associated Granulomatous Tubulointerstitial Nephritis

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We report the case of a 29-year-old man with membranous nephropathy that was associated with a sarcoidosic granulomatous tubulointerstitial nephritis, but was without an apparent calcium metabolism disorder. Corticosteroid treatment was associated with remission of nephrotic syndrome. We discuss the relationship between membranous nephropathy and sarcoidosis based on the close appearance of the 2 diseases and the detection of phospholipase A_2 receptor in glomerular immune deposits.
Am J Kidney Dis. 57(1):140-143.

INDEX WORDS: Causality; membranous nephropathy; renal sarcoidosis.

Sarcoidosis is a relapsing multisystemic disorder characterized by noncaseating granulomas of unknown cause. Granuloma formation results from an interaction between $CD4^+$ T cells and antigen-presenting cells.[1-3] The disease affects people of all racial and ethnic groups and occurs at all ages, with the incidence peaking at age 20-39 years.[3] Diagnosis requires a biopsy specimen and clinical exclusion of other causes of granulomatous inflammation.[2,4]

Renal involvement occurs in 4%-22% of cases,[5] primarily related to calcium metabolism disorders.[1,3,4,6] Granulomatous tubulointerstitial nephritis represents the second main nephropathy and usually is shown by acute renal failure with systemic manifestations.[1,2,5,7] Although rare, different glomerulopathies have been reported, including membranous nephropathy (MN), focal segmental sclerosis, immunoglobulin A (IgA) nephropathy, and crescentic glomerulonephritis.[2,4,8,9] Corticosteroids are the standard of treatment.[6,10]

We report a case of atypical sarcoidosis, with initial MN presentation followed by granulomatous ureteral involvement and tubulointerstitial nephritis with systemic manifestations. We discuss the association between MN and sarcoidosis.

CASE REPORT

A 29-year-old white man was admitted for nephrotic syndrome. He reported dyspnea with effort for 2 months, with lumbar pain and peripheral edema for 2 weeks. Physical examination showed temperature of 38.1°C and blood pressure of 152/64 mm Hg. A full blood cell count showed results in the reference range, except for mild lymphopenia with lymphocyte count of 800 cells/μL. Blood chemistry tests showed increased serum creatinine level (1.7 mg/dL [150 μmol/L], corresponding to estimated glomerular filtration rate of 51 mL/min/1.73 m^2 [0.85 mL/s/1.73 m^2], calculated using the isotope-dilution mass spectrometry [IDMS]-traceable 4-variable Modification of Diet in Renal Disease [MDRD] Study equation), decreased serum albumin level (1.35 g/dL [13.5 g/L]), and increased C-reactive protein level (23 mg/L). Urinalysis showed heavy proteinuria with protein excretion of 8.84 g/g of creatinine, of which 67% was albumin. There was no hematuria or leukocyturia. Antinuclear antibody, hepatitis B and C, and human immunodeficiency virus test results were negative. A chest radiograph showed left-sided pleural effusion with lung infiltrate; 1,100 mL of transudate was evacuated. Ventilatory-perfusion scintigraphy showed segmental pulmonary embolism of the right lobe. On ultrasound, kidney size was enlarged, with heights of 13 and 14 cm for the right and left kidneys, respectively. Kidneys were of normal shape and echogenicity. There was no dilation of the pelvicalyceal system. Kidney biopsy showed typical MN with granular deposits of polytypic IgG without complement (Fig 1A). No interstitial lesion was seen. On treatment with an angiotensin-converting enzyme inhibitor, statin, diuretics, and anticoagulant, the patient's condition improved. Serum creatinine level decreased to 1.4 mg/dL (125 μmol/L).

The patient was admitted 3 months later for macroscopic hematuria, abdominal pain, and vomiting. Values for full blood cell count, serum creatinine, and albuminemia were unchanged. Serum calcium concentration was low (86 mg/L [2.15 mmol/L]), as well as urine calcium concentration (0.72 mg/dL [0.18 mmol/L]). Serum 25-hydroxyvitamin D (9.0 ng/mL [22.5 nmol/L]; reference range, 7-30 ng/mL [17.5-74.9 nmol/L]) and 1,25-dihydroxyvitamin D levels (3.0 pg/mL [7.8 pmol/L]; reference range, 17-67 pg/mL [44.2-174.2 pmol/L]) were low. Parathyroid hormone level was within the reference range (26 pg/mL [26 ng/L]; reference

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Received May 1, 2010. Accepted in revised form September 13, 2010. Originally published online November 18, 2010.

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0272-6386/$36.00
doi:10.1053/j.ajkd.2010.09.015

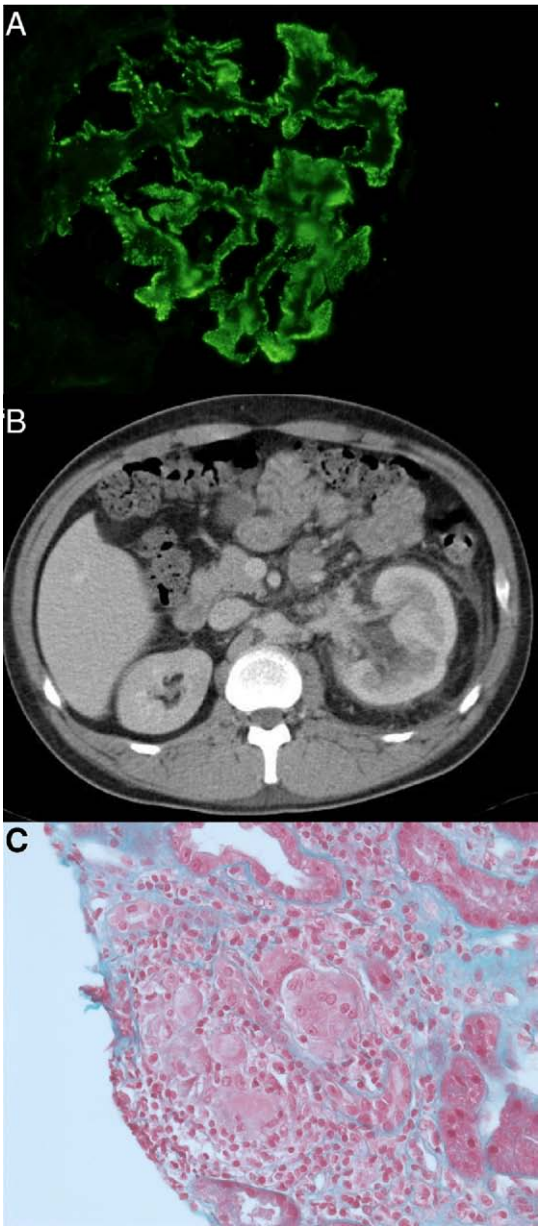

Figure 1. (A) Immunofluorescence study shows subepithelial granular deposits of immunoglobulin G. (Original magnification, ×100.) (B) Abdominal computed tomographic scan shows an enlarged left kidney with perirenal and periureteral infiltration (arrows). (C) Granulomatous tubulointerstitial nephritis characterized by interstitial noncaseating granuloma with multinucleated giant cells, surrounded by resident lymphocytes. (Hematoxylin and eosin staining; original magnification, ×60.)

range, 8-79 pg/mL [8-79 ng/L]). Serum electrophoresis showed polyclonal hypogammaglobulinemia (γ-globulin, 300 mg/dL [3 g/L]). Urinalysis showed nephrotic-range proteinuria (protein excretion, 5.1 g/g of creatinine), microscopic hematuria (red blood cells, 2 $\times 10^5$/mL), and leukocyturia (white blood cells, 2 $\times 10^5$/mL). Computed tomography (CT) of the abdomen confirmed the enlarged left kidney and showed perirenal and periureteral infiltration (Fig 1B). Urine was drained through a double-J catheter.

Two months later, the patient reported nycturia, buccal sicca syndrome, weight loss, and a decrease in visual acuteness. CT of the thorax showed bilateral hilar and mediastinal non-necrotizing lymph nodes with pleural thickening and subpleural lymph nodes. Serum creatinine level was 1.2 mg/dL (105 μmol/L; estimated glomerular filtration rate, 77 mL/min/1.73 m^2 [1.3 mL/s/1.73 m^2], serum albumin level was 2.9 g/dL (29 g/L), and the patient was still heavily proteinuric (protein excretion, 2.7 g/g of creatinine). Serum angiotensin-converting enzyme level was increased (67 U/L; reference range, 8-52 U/L). The optic fundus had bilateral papillary edema with venous stasis and tortuosity, probably caused by optic neuritis. CT of the brain and magnetic resonance imaging results were normal. Bronchial biopsy had negative results; however, cytopunction of mediastinal lymph nodes showed epithelioid and gigantocellular granulomas. Bronchoalveolar lavage showed T $CD4^+$ lymphocytosis, with a $CD4^+$; $CD8^+$ ratio of 10. A diagnosis of sarcoidosis was made. A second kidney biopsy performed to guide immunosuppression therapy showed granulomatous tubulointerstitial nephritis associated with granular subepithelial deposits of IgG (+++), IgM (++), C3 (+) and C1q (+++) (Fig 1C).

As with adult idiopathic MN,[11] with both kidney biopsies, we found M-type phospholipase A_2 receptor (PLA_2R) in immune deposits, assessed using affinity-purified rabbit antibodies specific for PLA_2R (Atlas antibodies AB; www.atlasantibodies.com; Fig 2A-C). Anti-PLA_2R antibodies, mostly IgG4 and, to a lesser extent, IgG1, were detected in serum using Western blot (Fig 2D and F) and immunoprecipitation (Fig 2E) at the initial diagnosis and second presentation, but disappeared during remission.

Corticosteroid therapy, initiated at a dosage of 1 mg/kg of body weight daily for 2 months and then tapered over 1 year, promptly improved the patient's condition. Complete remission of nephrotic syndrome occurred after 4 weeks of treatment. On control CT performed 6 months later, hilar and mediastinal lymph nodes had disappeared. One year later, visual acuteness and optic fundus normalized, but partial perirenal and periureteral infiltration remained. Serum creatinine level stabilized at 1.2 mg/dL (107 μmol/L).

DISCUSSION

We report a case of PLA_2R-positive MN preceding granulomatous tubulointerstitial nephritis in a patient with sarcoidosis. The diagnosis of renal involvement in sarcoidosis is a key issue because renal outcome depends on early specific treatment. Hypercalciuria is present in up to half the patients with sarcoidosis, with overt hypercalcemia found in only 10%.[1,3,4,6] The hypocalcemia observed in our patient was caused by hypoalbuminemia and a low 1,25-dihydroxyvitamin D level resulting from vitamin D–binding protein deficiency induced by nephrotic syndrome.[12]

Granulomatous tubulointerstitial nephritis shown by acute renal failure is the second most frequent renal presentation of sarcoidosis.[4,8] The prevalence of tubulointerstitial nephritis varies from 15%-40% in patients with renal sarcoidosis, but tubulointerstitial nephritis may be clinically silent.[6,7] The prevalence of kidney failure ranges from 0.7%-4.3%.[6] Kidney failure also can be linked to enlarged retroperitoneal lymph nodes causing bilateral hydronephrosis.[2,5] Urethral, ureteral, or bladder obstruction caused by sarcoid inflammation is rare.[4] We assume that the periureteral infiltration observed on CT of the abdomen was granulomatous inflammation.