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Case Report

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Possible Link between IgA Nephropathy and B-cell Acute Lymphoblastic Leukemia

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Abstract

IgA nephropathy (IgA-N) is the most common glomerulonephritis type globally. IgA-N is usually accepted as a kidney disease; however, IgA-N has been reported with infections, autoimmune diseases, and malignancies in the literature. In this report, we present a case of a 33-year-old man diagnosed with IgA nephropathy first and then with B-cell acute lymphoblastic leukemia (B-ALL). He was admitted to our hospital with complaints of nausea, vomiting, fatigue, and headache. Laboratory investigations revealed increased levels of blood urea nitrogen and creatinine, hypercalcemia, anemia, and thrombocytopenia. Kidney biopsy was performed, and IgA nephropathy was detected. Atypical lymphocytes and erythroblasts were present in the peripheral blood smear. Bone marrow biopsy was performed and demonstrated B-ALL. Kidney function tests normalized after 1 month of chemotherapy, including steroid treatment with intravenous fluid administration. In conclusion, it has been speculated that IgA nephropathy is associated with B-ALL.

Keywords: Immunoglobulin A nephropathy, hypercalcemia, leukemia

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INTRODUCTION

IgA nephropathy (IgA-N) was first described by Berger and Hinglais in 1968. The disease is currently the most common reason of primary glomerulopathy in many developed countries. Patients may present at any age; however, it usually presents in the second and third decades of life. Diagnosis is usually based upon histopathological evaluation of the kidney biopsy (1, 2). The major findings on light microscopy are mesangial hypercellularity and matrix expansion. The characteristic findings observed on immunofluorescence microscopy are dominant or co-dominant mesangial deposits of IgA, either alone with IgG or IgM, or with both IgG and IgM. In some patients with IgA-N and rapid kidney function decline, segmental necrosis with or without crescent formation is usually observed (3). It is usually asymptomatic or with mild symptoms and is diagnosed by detecting microscopic hematuria during routine screening of subjects. Ninety percent of the patients present with recurrent episodes of gross hematuria or microscopic hematuria with mild proteinuria. Less than 10% of patients present with nephrotic syndrome or an acute, rapidly progressive glomerulonephritis characterized by edema, hypertension, and acute kidney failure (1, 4).

Otherwise, it has been reported that IgA-N can be associated with some clinical conditions including cirrhosis; celiac disease; HIV infection; and malignancies (2) including lymphoma, renal cell carcinoma, and cancers of the gastrointestinal system (5-7). The occurrence of IgA-N is thought to be a course of paraneoplastic syndrome. Paraneoplastic IgA-N has been rarely reported in patients with acute leukemia (8-10).

In this case report, we present a patient with kidney dysfunction, hematuria, hypercalcemia, anemia, and thrombocytopenia diagnosed with IgA-N and B-cell acute lymphoblastic leukemia (B-ALL) by kidney and

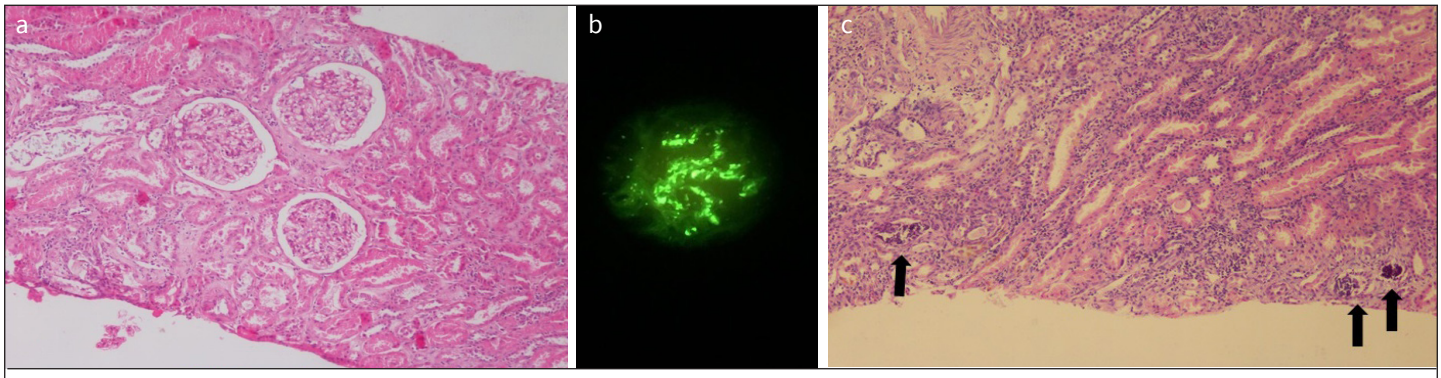

Figure 1. a-c. a) Light microscopy (H&E ×400) demonstrates hypercellularity in glomeruli and increased mesengial matrix. b) Immunofluorescence microscopy (×400) demonstrates the deposition of IgA, predominantly within mesangial regions of glomeruli. c) Light microscopy (H&E X 100) demonstrates calcified materials in the tubule lumen of a medulla section.

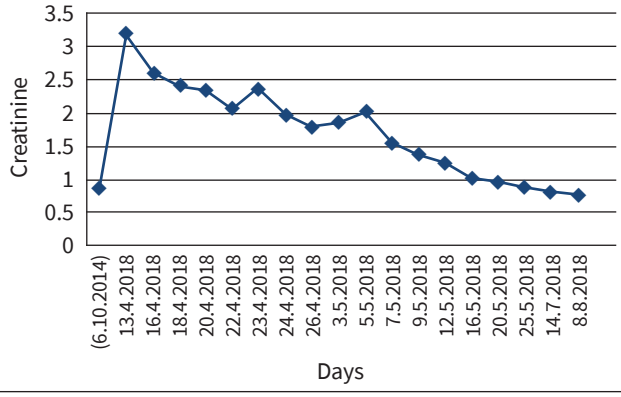

Figure 2. Serum creatinine levels of the patient during follow-up.

bone marrow biopsy, respectively. The patient's kidney function and hypercalcemia was normalized after chemotherapy.

CASE PRESENTATION

A 33-year-old man, admitted to hospital in April 2018 with nausea, vomiting, and headache for 2 weeks, was referred to our nephrology department due to the detection of kidney dysfunction. The patient had no known chronic diseases including diabetes mellitus and hypertension. On physical examination, his blood pressure, body temperature, and heart rate were within the reference range. There were no abnormalities in the systemic physical examination, except mildly dry oral mucosa. Skin turgor and tonus were normal. Routine laboratory tests showed the following: serum white blood cells (WBC) 4580 µl/mm^3, neutrophils 1730, hemoglobin 11 g/dL, platelets 86,000, MCV 81, erythrocyte sedimentation rate 79 mm/h, C-reactive protein 10.4 mg/dl, sodium 137 mmol/L, potassium 3.4 mmol/L, calcium 12.02 mg/dL, phosphorus 4.2 mg/dL, blood urea nitrogen (BUN) 44.8 mg/dL, serum creatinine 3.1 mg/dL, serum albumin 4.5 g/dL, and serum total protein 7.2 g/dL. Liver function parameters were within the reference range. Urinalysis showed urine red blood cell count was 25/HPF and urinary protein excretion was 0.22 g/day. During follow-up, it reached 0.8 g/day. Antinuclear antibody, anti-dsDNA, anti-streptolysin O, anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody, anti-HBs, and anti-HCV were all negative. Complement factors C3 and C4 were within the reference range. Serum and urine protein electrophoresis were negative for monoclonal gammopathy. Serum IgA level was 155 mg/dL (reference range: 45-380). Atypical lymphocytes, erythroblasts, polychromasia, anisocytosis, tear cell were observed in the peripheral blood smear without any schistocytes. The PTH level was 9 pg/mL (reference range: 15-65). Anemia, thrombocytopenia, hypercalcemia, and elevated levels of BUN and creatinine were detected in the laboratory studies.

Kidney biopsy was performed and light microscopy showed up to three glomeruli in serial sections. There was a slight mesangial cell increase in the glomeruli. Calcified materials were observed in tubular lumen of some of the medulla sections. Immunofluorescence microscopy showed global, diffuse mesengial staining with IgA and C3 in six glomeruli. There was no crescent formation in the glomeruli (Figure 1). Bone marrow biopsy was performed and light microscopy showed 95% cellularity. Mature cells decreased in every three series. Common diffuse lymphoid cells were seen in all areas. Immunohistochemically, CD5 was positive, CD20 pale positive, CD23 negative, CYCLIN D1 negative, Tdt pale positive, CD2 positive, and PAX5 diffusely positive (B-cell lymphoblastic leukemia).

The patients who were diagnosed with common acute lymphoblastic leukemia were subjected to the German multicenter ALL chemotherapy protocol phase 1 and phase 2. After 3 months, the patient's kidney function improved as BUN 17.2 mg/dL,

Main Points

- Paraneoplastic IgA nephropathy is increasing due to the increase in cancer cases worldwide.
- IgA nephropathy could be a harbinger of cancer development.
- Physicians should be alert for the leukemia development and on the occasion of anemia, thrombocytopenia with IgA nephropathy.

serum creatinine 0.72 mg/dL) (Figure 2), and bone marrow flow cytometry reported that there were no group of cells associated with B-ALL (remission) in August 2018.

DISCUSSION

In this report, we presented a patient with acute kidney failure, anemia, thrombocytopenia, and hypercalcemia who was first diagnosed with IgA nephropathy and then with B-cell lymphoblastic leukemia. He was treated with fluid administration, steroids, and specific chemotherapy. Kidney dysfunction and hypercalcemia were successfully improved in a month.

IgA nephropathy cases have been reported to be associated with neoplasms such as non-Hodgkin's lymphoma, monoclonal IgA gammopathy, and carcinomas of the lung and colon (1, 11). However, the close association between malignancies and IgA-N was not completely understood, and it has been widely accepted that paraneoplastic immune changes might be responsible. There are several factors associated with the development of IgA nephropathy including genetic factors, adhesion molecules on mononuclear cells, and abnormal IgA glycosylation (9, 11, 12). Chromosome aberrations have been demonstrated by a genome-wide linkage analysis in families with IgA-N that suggests a genetic factor plays a role in the occurrence of the disease. Moreover, abnormal glycosylation in the hinge region of IgA1 subclass is associated with the development of circulating immune complexes and its accumulation in the mesangium. These accumulations may induce the release of growth factors, cytokines, and adhesion molecules, which result in inflammation, proliferation of mesangial cells, and sclerosis (11, 13). Understanding the role of adhesion molecules and B-cell defect is important to establish treatment modalities such as bone marrow transplantation and neutralizing antibodies (12, 13). Authors searching for an upstream immunologic abnormality have suggested that abnormal T-lymphocyte function drives the increased IgA production by B cells (12). This association suggests that a B-cell defect is involved in the pathogenesis of IgA nephropathy and B-ALL. Motoyama et al. (8) reported a patient with acute lymphocytic leukemia and IgA nephropathy. Treatment of the malignancy did not provide the remission of IgA nephropathy, which suggests that the IgA nephropathy with malignancies could be seen as a coincidence. However, Iwata et al. (9) and Park et al. (10) reported cases of IgA nephropathy and leukemia. The remission of IgA nephropathy has been achieved by bone marrow transplantation in both cases. In line with these cases, successful treatment of B-ALL induced the remission of IgA-N in our case. This case presented with hypercalcemia and kidney function decline first, and then leukemia was diagnosed during the investigation of possible causes of kidney dysfunction. We speculate that the reason of severe kidney injury is possibly multifactorial. Many factors might contribute to kidney dysfunction, including hypercalcemia, prerenal azotemia, acute tubular injury, and mesangial hypercellularity due to IgA nephropathy. The PTH level was 9 pg/mL (reference range: 15-65). Therefore, we believe that this occurred due to paraneoplastic hypercalcemia. There was no crescent formation on the histopathological examination of the kidney specimen, but calcified material was detected in medulla sections. We considered that hypercalcemia and IgA nephropathy may be seen in patients with leukemia as a paraneoplastic syndrome.

On the other hand, the patient also presented with anemia and thrombocytopenia but leukocytes were within the reference range. Hence, the examination of peripheral blood smear is important in patients with abnormal complete blood count results even if the leukocyte count is normal. Anemia and thrombocytopenia are more common in B-ALL. However, it has been reported that the WBC count may be low, normal, or high; the WBC count is <10,000/[micro]L in 50% and >50,000/[micro]L in 20% of the patients (14, 15).

CONCLUSION

Paraneoplastic IgA nephropathy is increasing in the past decades due to the longevity of humans and increasing incidences of cancer. Thus, physicians should be alert about patients with IgA nephropathy with hematologic disturbances due to its possible association with leukemia.

Informed Consent: Written informed consent was received from the patient who participated in this case.

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Conflict of Interest: The authors have no conflict of interest to declare.

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