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IgA Nephropathy may be a Disease Related to Crohn's Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Authors GHK and YNK wrote the protocol, and wrote the first draft of the manuscript. Authors SG, SYK, JWY and HSS managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

IgA nephropathy (IgAN) is the commonest form of glomerulonephritis worldwide and 15–30% of patients will ultimately develop end-stage renal failure. IgAN can be primary (in most cases) or secondary (associated with seronegative arthritis, cirrhosis, coeliac disease, vasculitis, HIV), but is rarely associated with Crohn's disease (CD). We describe a case of 22 year-old man with CD associated with IgAN. After the patient underwent surgical resection of right colon due to suspected colon tumor, CD was diagnosed. 5 years after right hemicolectomy, microscopic hematuria was developed and a renal biopsy had revealed IgAN (type III). Patients with CD who present with hematuria more commonly have urological complications, but the possibility of renal parenchymal disease should also be considered.

Keywords: IgA nephropathy; Crohn's disease; hematuria.

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1. INTRODUCTION

IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis worldwide [1]. Clinical features vary from asymptomatic hematuria to nephrotic syndrome [1,2]. Prognosis is also varied. Two-thirds of patients experience a stable course, while the remainder progress to end-stage renal failure [3]. This disease is generally isolated but sometimes occurs in association with extra-renal disorders, such as liver disorders or mucosal inflammation of the gastrointestinal tract [4,5].

Crohn's disease (CD) is a systemic disease that involves not only enterocolon but also other entire organs. Urinary complications, such as urolithiasis, ureteral obstruction, and enterovesicular fistulas, are seen in up to 25% of patients; however, renal parenchymal disease has rarely been reported [6,7].

IgAN associated with Crohn's disease is very rare. Only ten cases have been reported worldwide [8-12]. We report a case of a 22 year-old man with IgAN in association with Crohn's disease.

2. CASE REPORT

A 22-year-old man was admitted to the nephrology ward of our institution with proteinuria and microhematuria. He had a five-year history of Crohn's disease, proven by surgical resection and histology. He had initially presented to another hospital due to lower abdominal pain and weight loss. CT scan revealed a differential diagnosis of cecal tumor or inflammatory bowel disease. He was then transferred to our hospital for further evaluation. Colonoscopy was performed and revealed several linear, transverse ulcers with raised, indurated margins and pseudopolyps in the cecum and proximal ascending colon 70 to 90 cm from the anal verge (AV). There was also a 3.5 x 4.5-cm movable, round, firm mass noted 95 cm from the AV (Fig. 1A).

Hemicolectomy was performed due to concern for cecal tumor (Fig. 1B). Direct visual inspection revealed an edematous and thickened mucosal surface of the right colon with focal abscesses in the pericolic fat. A distinct solid mass was not seen. No noncaseating granulomas were observed, but full-thickness neutrophilic and lymphocytic infiltration, focal abscesses, and fibrosis were observed on the biopsy specimen. Crohn's disease was suspected. Tuberculosis (TB) polymerase chain reaction (PCR) was found to be negative, and tuberculosis was excluded.

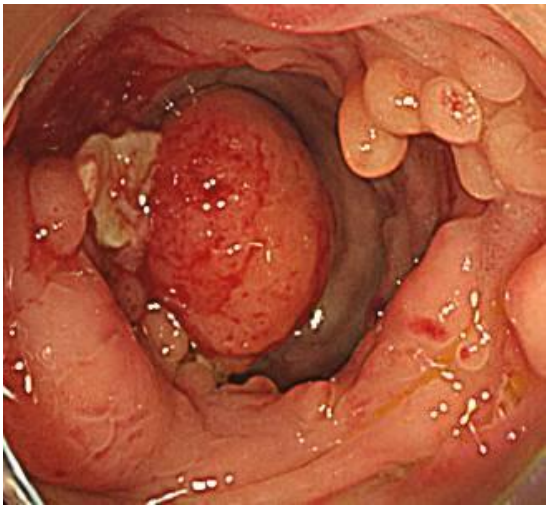

Fig. 1A. Colonoscopy showed there was also a 3.5 x 4.5-cm movable, round, firm mass noted 95 cm from the anal verge

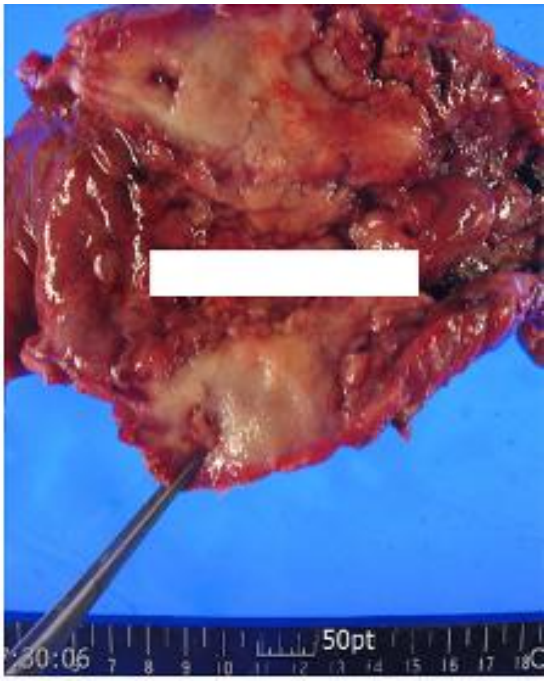

Fig. 1B. Direct visual inspection revealed an edematous and thickened mucosal surface of the right colon with focal abscesses in the pericolic fat

The disease showed good response to treatment with daily oral azathioprine, mesalazine, and

bimonthly infliximab administered at the gastroenterology outpatient clinic. Although he experienced an episode of hematochezia 15 months after diagnosis, the remission state was maintained without diarrhea, abdominal pain, or extragastrointestinal symptoms.

During regular urinary follow-up examinations in Dec 2013 and Feb 2014, 1(+) proteinuria by dipstick method and microscopic hematuria was noted. The patient was referred to us via the urology department and was admitted for renal biopsy.

On admission, he was taking daily azathioprine 50 mg and mesalazine 4,000 mg.

He was normotensive and afebrile with an unremarkable physical examination.

Chest and abdominal radiography was normal. Laboratory data showed hemoglobin level of 12.7 g/dL, platelet count of 261,000/uL, white blood cell count of 4,340/uL with 62.7% neutrophils, 22.0% lymphocytes, 12.2% monocytes, and 2.1% eosinophils. Serum creatinine was 0.74 mg/dL, and BUN was 10.8 mg/dL. Serum total protein was 6.1 g/dL, albumin 3.6 g/dL, sodium 139 mEq/L, potassium 4.0 mEq/L, chloride 112 mEq/L, uric acid 5.7 mg/dL, AST 11 IU/L, ALT 6 IU/L, total bilirubin 0.55 mg/dL, and alkaline phosphatase 55 IU/L. Prothrombin time (PT) and partial thromboplastin time (PTT) were normal. Urinalysis at the time showed no proteinuria, 5-10 red blood cells, and 1-4 white blood cells per high-power field (HPF). Urine culture showed no growth. Twenty-four-hour urine collection revealed creatinine 90.6 mg/dL and total protein 135 mg/day. Estimated glomerular filtration rate (GFR) by modification of diet in renal disease (MDRD) equation was >120 mL/min. Serum and urine protein electrophoresis showed no M-peak. Further laboratory tests revealed increased serum IgA of 507.8 mg/dL (40-350 mg/dL), complement component 3 (C3) levels of 116 mg/dL (82-170 mg/dL), and complement component 4 (C4) levels of 28.4 mg/dL (12-36 mg/dL). C-reactive protein (CRP) was <0.4 mg/L, and testing for antinuclear antibody, rheumatoid factor, antineutrophilic cytoplasmic antibody were all negative. Serologic tests for hepatitis B and C and HIV were also negative.

Renal ultrasound showed normal-sized kidneys with regular contours and no sign of obstruction. A left kidney percutaneous biopsy was performed. Light microscopy contained eleven glomeruli, none of which were globally sclerosed. The mesangium showed rare mild increase in matrix with mild hypercellularity. There was less than 3% early interstitial fibrosis and a few patches of tubular atrophy. The arterioles were unremarkable (Fig. 2). Immunofluorescence examination included five glomeruli in every section, which showed intense (+++) and moderate (++) granular staining for IgA and C3 in the mesangium (Fig. 3). Electron microscopy showed increase in mesangial matrix and some mesangial electron-dense deposits. The above-mentioned findings on light microscopy and immunofluorescence are consistent with the diagnosis of IgAN (HAAS 3).

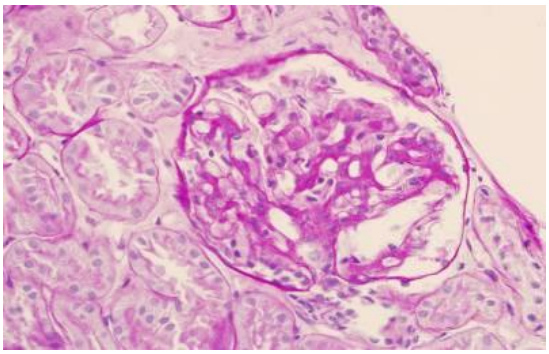

Fig. 2. Light microscopy showed mesangial proliferation

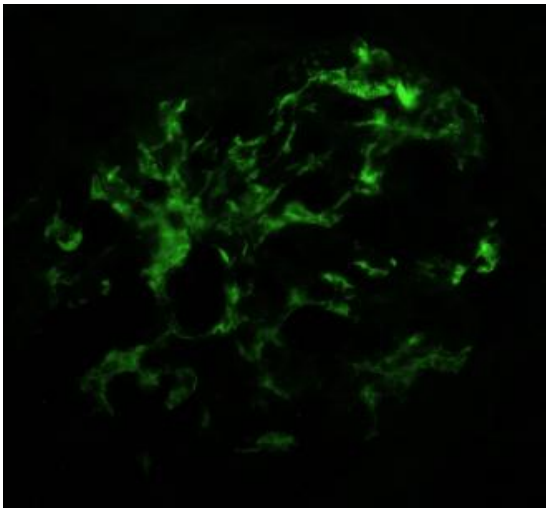

Fig. 3. Immunofluorescence examination showed intense (+++) granular staining for IgA in the mesangium

Biopsy follow-up was uncomplicated, and the patient was discharged. Omega-3 poly-unsaturated fatty acids were prescribed at a daily

dose of 3 g. Angiotensin-converting enzyme (ACE) inhibitors were avoided because of nonsignificant proteinuria. At last follow-up visit nine months after initial presentation, the patient remained asymptomatic with normal blood pressure, no proteinuria, and 16-20 RBC /HPF on urinalysis. Renal function remained stable with serum creatinine at 0.68 mg/dL and CrCl at >120 mL/min/1.73 m2.

3. DISCUSSION

The pathogenesis of the association between Crohn's disease and IgAN is not yet clear; however, some common features are observed in both diseases and suggest that the two conditions have a similar etiology.

One possible etiology is the transfer of antigen through intestinal mucosa. Antibody stimulation through the intestine has been noted as an important cause of IgAN.

Increased permeability of the intestinal mucosa caused by intestinal inflammation leads to an increase in the inflow of bacterial antigens and IgA. This results in deposition of immune complexes in the glomeruli [5]. In Crohn's disease, inflammation of the intestinal mucosa increases the absorption of antibodies and bacteria and provokes a rise in serum levels of IgA and IgG with the development of immune complexes [13-15].

In addition, Barratt et al. [16] suggested that a systemic antibody response to mucosal infection of Helicobacter pylori may play an important role in the onset and progression of IgAN.

Meanwhile, other researchers suggested that mononuclear plasma cells in tonsils or salivary glands, rather than intestinal mucosa, are the major source of excess circulating IgA that deposits in the glomeruli [17,18].

Another shared characteristic is the abnormal immune response of T cells. The increased IgA production associated with altered T cell activation has been proposed both in IgAN and CD patients [19,20]. Furthermore, various inflammatory cytokines produced by activated T cells may induce IgA production in the bone marrow and lymphoid tissues [21,22].

Treatments acting directly on these inflammatory mediators in IgAN and CD patients have been proposed. The use of TNF-specific antibody is an effective treatment in up to 60% of CD patients, and monoamine oxidase inhibitors have been proposed as a treatment for IgAN because increasing the intracellular monoamine level results in inhibition of TNF production [23,24].

Third, IgAN and CD have the same genetic basis. IgAN is associated with the human leukocyte antigen (HLA)-DR1 allele, and CD is associated with the HLA-DR1/DQw5 alleles. Thus, patients with the HLA-DR1 allele have a higher risk of both diseases [25].

We can, therefore, estimate that there will be a close link between the clinical courses of IgAN and CD. There are reports that the onset of CD occurred when IgAN recurred, or that the onset of IgAN occurred when CD worsened. Both diseases tended to be improved by immune-suppressant or surgical therapies [25,13,26].

On the other hand, there are cases in which the onset of CD occurred while kidney function was well maintained [12,27].

In our case, it seems that the activity of both diseases was not associated because IgAN occurred while CD was stable. More research is needed on the relationship between the two diseases.

4. CONCLUSION

When a patient with CD is suspected to have abnormal renal function, the possibility of renal parenchymal disease such as IgAN should be considered.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Since data from the literature, only, were used for description, ethical approval is not applicable to this paper. This study is not against the public interest. All authors hereby declare that all description have been performed in accordance with the ethical standards. laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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