Crohn’s Disease Complicated by Granulomatous Interstitial Nephritis, Choroidal Neovascularization, and Central Retinal Vein Occlusion

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Abstract

Extraintestinal manifestations of Crohn’s disease are common. Granulomas may occur in different tissues in Crohn’s disease, although kidney granulomas are extremely rare. Although ocular complications of Crohn’s disease are infrequent, most ocular manifestations include iritis, uveitis, episcleritis, scleritis, and conjunctivitis. Central retinal vein occlusion has been reported in a few patients with Crohn’s disease. The choroidal neovascularization is related to inflammatory disorders such as panuveitis, sarcoidosis. We report a patient with Crohn’s disease complicated by granulomatous interstitial nephritis, choroidal neovascularization, and central retinal vein occlusion.

Key words: central retinal vein occlusion, choroidal neovascularization, Crohn’s disease, granulomatous interstitial nephritis

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Introduction

Crohn’s disease (CD) is a systemic inflammatory disease which primarily involves the intestine, but potentially affects many organs such as the kidney and eye. Kidney involvement is rare, including secondary amyloidosis, tubulointerstitial nephritis (TIN), calcium oxalate stones and their complications (1-4). Two case reports in the literature state that granulomatous interstitial nephritis is also a renal manifestation of CD (5, 6). Thromboembolic events are a well-known complication of CD (7). However, central retinal vein occlusion (CRVO) is rarely seen in CD (8, 9). Choroidal neovascularization (CNV) is associated with inflammatory diseases such as sarcoidosis and panuveitis (10). Here, we present a case of CD complicated by granulomatous interstitial nephritis, CNV, and CRVO.

Case Report

A 43-year-old man was admitted to hospital because of renal dysfunction. The patient was first hospitalized for diarrhea that lasted for approximately one month in January 1999. The patient’s complaint had repeated intermittently from 1992. Stool examinations, which were performed for parasites and/or its ovum, were negative and gaita culture, which was performed to exclude bacterial causes of diarrhea, were also negative. In microscopic examination of stool, abundant leucocytes were observed. A perianal abscess and fistula orifice was seen in the rectal inspection. In rectosigmoidoscopy, it was observed that loss of vascularity, ulcers, and nodular protuberances began from 20 cm in the sigmoid colon. These lesions extended distally and endoscopic biopsy specimens were taken from these lesions showed that the mucus content was decreased in surface epithelium and in gland epithelium of lamina propria. Inflammatory cell infiltration which also contained neutrophils and
In the endoscopic colon biopsy specimen, non-caseous epithelioid granuloma formation containing multinucleated giant cells was seen. The arrow shows granuloma in the colon (Hematoxylin and Eosin staining 400× magnification) (A). In the endoscopic duodenum biopsy specimen, the granuloma formation consisted of epithelioid histiocytes in two areas. The arrow indicates the granuloma (Hematoxylin and Eosin staining 100× magnification) (B). The renal biopsy specimen shows severe interstitial nephritis with non-caseous epithelioid granuloma formation containing multinucleated giant cells. The arrow indicates the granuloma formation (Hematoxylin and Eosin staining 200× magnification) (C).

eosinophils was seen between glands. In three areas, it was observed that non-caseous granuloma formation consisted of epithelioid histiocytes. One of these granuloma formations contained multinucleated giant cells (Fig. 1A). These findings were indicative of Crohn’s disease. The patient started treatment with oral mesalamine (Salofalk) plus oral steroid. However, the patient’s intestinal symptoms intermittently recurred and he intermittently received mesalamine and steroid. In June 2003, he was rehospitalized for non-bloody diarrhea. On rectosigmoidoscopy, minimal colitis was found. The stool examination was normal. An upper GIS endoscopy was performed. Endoscopic duodenal biopsy specimens revealed villous atrophy and mucosal glands with a decreased number of goblet cells. Inflammatory cell infiltration including abundant neutrophils was seen between glands. These neutrophils infiltrated into the surface epithelium and glands. In two areas, it was observed that granuloma formation consisted of epithelioid histiocytes (Fig. 1B). The diagnosis was reported to be Crohn’s disease. Finally, the patient was admitted to hospital because of renal dysfunction in April 2006. He had no gastrointestinal symptom related to CD and did not use 5-ASA preparation for approximately two years. On admission, physical examination showed no abnormality. The laboratory evaluation revealed anemia (hemoglobin level, 11.5 g/dL) and impaired renal function (serum creatinine level, 2.6 mg/dL and creatinine clearance, 32.6 ml/min). He had non-nephrotic proteinuria (660 mg/day) without hematuria or leukocyturia. White blood cell (WBC) count was 8.45×10^9/L and eosinophilia was not detected. Platelet count was 103×10^9/L. Renal ultrasonography showed kidneys of nearly normal size without any finding of obstruction. Renal biopsy revealed severe chronic TIN with non-caseous epithelioid granuloma formation containing multinucleated giant cells (Fig. 1C). No deposit was observed on immunofluorescence evaluation.

We performed examinations to exclude other possible causes of renal granuloma formation. Serum calcium, chest radiography, and the serum angiotensin-converting enzyme level were found to be normal. Brucella serology was negative. Urine samples were negative for acid-resistant bacilli. Urine cultures were negative for tuberculosis. Tuberculin skin test was negative. The Ziel-Nielsen staining for mycobacteria in biopsy samples was negative. Serum complement and immunoglobulin levels were normal and no autoantibody was detected. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were moderately elevated. This patient was diagnosed as having renal involvement of CD and oral prednisolone (1 mg/kg/day) was initiated. His serum creatinine level decreased to 2.1 mg/dL after three weeks.

Two months later, he experienced decreased visual acuity in the right eye while receiving prednisolone 32 mg a day. He had no gastrointestinal complaint related with CD. The patient was referred to ophthalmology for detailed evaluation. On ophthalmologic examination, visual acuity was 0.2 in the right eye. The examination of the left eye was normal. Fluorescein angiogram showed a choroidal neovascularization lesion on his right eye (Fig. 2A). He refused treatment with intravitreal steroid injection. Photodynamic therapy with verteporfin was applied to his right eye. Visual acuity increased to 0.7 at the fourth treatment week.

At the next follow-up, eight weeks later, he experienced blurred vision and redness in the right eye while his serum creatinine level was still 2.1 mg/dL, proteinuria decreased into normal range (130 mg a day) and he was receiving prednisolone 16 mg a day. He had also no gastrointestinal complaint related to CD. Visual acuity was 0.1 in his right eye. The examination of the right eye revealed CRVO characterized by widespread hemorrhage on retina. Because he rejected fluorescein angiogram, it was not performed. The evaluation including antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), lupus anticoagulant, anticardiolipin antibodies, antithrombin III activity, protein
C and S activity, homocysteine level, activated protein C resistance, and prothrombin mutation were performed to determine the etiology of CRVO. No abnormality was found related to the above-mentioned tests. Plasma lipid levels were normal. CRP and ESR were moderately elevated. Serum fibrinogen level was found to be elevated (fibrinogen was 608.69 mg/dL, range 146-380 mg/dL). The CRVO was considered to be associated with hypercoagulation condition and as an extraintestinal manifestation of CD. We started anticoagulation with warfarin to a target of INR of 2.0-3.0. The prednisolone was tapered and withdrawn at 6 months after the determination of granulomatous interstitial nephritis.

At 5 months after development of CNV, visual acuity was 0.6 in right eye and fluorescein angiogram revealed regression of CNV and development of shunt vessel on the optic disc, which is a sequel of CRVO (Fig. 2B).

**Discussion**

Renal manifestations of CD are rare. The most frequent renal manifestations are calcium oxalate stones and their complications (4). Chronic TIN is another common finding. The most frequent cause of chronic TIN among patients with CD is 5-ASA preparations-related nephritis (2, 3, 11). However, Izzedine et al reported four patients who had TIN without granuloma at the diagnosis of CD and did not use 5-ASA preparations and suggested that primary TIN could also be an extraintestinal renal manifestation of CD (12).

Granulomatous chronic interstitial nephritis has been reported in patients with CD. In the literature, there are three cases with granulomatous chronic interstitial nephritis and CD. These cases were defined as renal involvement of CD. Archimandritis and Weetch reported that a patient with CD with coexisting granulomatous interstitial nephritis. This patient’s impaired renal function was improved by proctocolectomy and then a second renal biopsy revealed atrophy of renal tubules, and local interstitial fibrosis, but no granuloma formation was found. These authors suggested that renal granuloma was a manifestation of CD (5). Baumer et al reported another patient with CD complicated with granulomatous interstitial nephritis. This patient had received mesalazine because of intestinal symptoms related with CD. At 19 months after withdrawal of mesalazine, a renal biopsy was performed because of impaired renal function. Renal biopsy showed granulomatous interstitial nephritis. Because serum creatinine level remains elevated despite treatment with corticosteroid and azathioprine, second renal biopsy was performed. The second biopsy also showed granulomatous tubulointerstitial nephritis as similar to the first biopsy. These authors suggested that granulomatous interstitial nephritis was probably related to CD, but not related to the use of 5-ASA-preparation (6). Mahmood et al reported two patients with renal microgranuloma formation. The first patient had CD and used sulfasalazine. The second patient had acute renal allograft rejection. These authors suggested that non-specific inflammatory tubular destruction should be considered as a cause of renal microgranuloma formation (13).

In these small series, which included three patients with CD and granulomatous interstitial nephritis, one patient’s renal functions were improved by proctocolectomy, thus steroid treatment had not been necessary for renal granuloma (5). In the other two patients, renal function was not recovered by corticosteroid treatment (6, 13). However, steroid treatment improved renal functions in the present patient.

The 5-ASA preparations are frequently used for treatment of patients with CD. Epidemiological studies have shown that patients taking 5-ASA preparations have an increased risk of renal disorder (14). It is well known that 5-ASA preparations such as mesalazine may cause TIN without granuloma. In patients with TIN and inflammatory bowel disease, withdrawal of 5-ASA preparations results in the recovery of renal function in 85% of patients (2). However, it is unclear whether they can cause granulomatous TIN. It is also controversial whether kidney granulomas are extraintestinal involvement of CD or a result that is triggered by chronic interstitial inflammation. A patient with granulomatous TIN reported in the literature did not use 5-ASA preparations (5). In the patient reported by Baumer et al, granulomatous interstitial nephritis was found at 19 months after cessation of mesalazine (6). These authors suggested that

![Figure 2. The choroidal neovascularization is shown in the late phase fluorescein angiogram. The arrow indicates the choroidal neovascularization (A). The fluorescein angiogram shows the regression of choroidal neovascularization and the optiociliary shunt vessels on the optic disc as a sequel to central retinal vein occlusion. The arrow indicates the optiociliary shunt vessels (B).](image-url)
granulomatous interstitial nephritis probably related to CD but not related to use of 5-ASA-preparation as similarly Archimandritis and Weetch’opinion. In another patient with granulomatous TIN, there was no information about time of 5-ASA medication (13). The present patient had not used 5-ASA preparation for approximately two years when granulomatous interstitial nephritis appeared. We thereby consider that granulomatous interstitial nephritis may be a renal manifestation of CD.

In CD, the retinal vascular disorders may have been associated with the immune character of the disease or probably with changes in vascular tissue or with hypercoagulation conditions (15). Igarashi et al reported that CRVO related to optic disk vasculitis induced by Crohn’s disease and corticosteroid treatment inhibits the development of CRVO (9). The latter mechanism does not appear to be possible in the present patient because he had been receiving corticosteroid for treatment of granulomatous interstitial nephritis when CRVO developed. The tendency for thrombosis in CD is well known. However, the mechanisms explaining the tendency of thrombosis in CD are not well explained. It was reported that the causes such as hyperfibrinogenemia, protein C and S deficiency, antithrombin III deficiency, high plasminogen activator inhibitor levels have been accused for the tendency to thrombosis in CD (8). We have commented that CRVO may be a consequence of the hypercoagulation status which is sometimes observed in Crohn’s disease. In the present patient we investigated the coagulation system to determine the hypercoagulation conditions including antiphospholipid syndrome, antithrombin III deficiency, protein C and S deficiency, hyperhomocysteinemia, activated protein C resistance which is also called factor V Leiden disease, prothrombin gene mutation, also called factor II mutation, hyperfibrinogenemia, and thrombocytosis and determined hyperfibrinogenemia. We considered that hyperfibrinogenemia which is a hypercoagulation status may be a possible cause of CRVO in the present patient. As for other extraintestinal complications such as renal granuloma, the occurrence of thrombosis in CD is usually associated with the activation of disease (5, 8, 16). In the present patient, CRVO and renal granuloma developed while CD was in remission in terms of intestinal symptoms. However, inflammation markers such as CRP and ESR were moderately elevated. Also fibrinogen, which is an inflammation marker, was elevated. Even if CD was in remission in terms of intestinal symptoms, an inflammation condition persisted when CRVO and renal granuloma developed in the patient.

The most ocular manifestations of CD include iritis, uveitis, episcleritis, scleritis, and conjunctivitis (17). To the best of our knowledge, our patient is the first patient with CD complicated by CNV. The most common cause of CNV in older patients is age-related macular degeneration. In younger patients (<50 years), however, CNV may occur as a secondary manifestation of many inherited and acquired disorders including angioid streaks, high myopia, and trauma. The possible inflammatory causes of the CNV such as panuveitis, sarcoid retinchoroiditis, candida retinchoroiditis, toxocariasis, serpinginous choroidopathy, presumed ocular histoplasmosis syndrome, rubella, toxoplasma, and syphilis and the other causes of the CNV including disruption of Bruch’s membrane such as choroidal rupture, angioid streaks, chroidal tumors, and retinal pigment epithelium membrane alterations such as idiopathic central serous chorioretinopathy, idiopathic parafoveal capillary telangiectasis were excluded via medical history, physical examination and the findings of fluorescein angiogram in the patient. CNV is also related to inflammatory disorders (10). Active inflammation may result in to CNV (10, 18). When CNV developed in the present patient, inflammation markers such as CRP and ESR were normal. In other words, active inflammation had not been presented. Furthermore, to the best of our knowledge, CNV is not associated with hypercoagulation status. In this patient, whether or not the development of CNV was associated with CD is unclear.

Finally, this patient is of particular interest because granulomatous TIN, CNV, and CRVO have not been reported to arise together at the same time or at different times during the course of CD.

References


