CASE REPORT

Interstitial nephritis associated with ulcerative colitis in monozygotic twins

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SUMMARY

Although renal impairment is a rare complication of ulcerative colitis (UC), interstitial nephritis can occur as an idiosyncratic reaction to 5-aminosalicylate (5-ASA) treatment for UC. Monozygotic twins developed UC at ages 49 and 51, and they were separately treated at different medical institutes. They did not know that they had the same disease and were treated with the same drug (5-ASA). During the course of 5-ASA treatment, renal impairment diagnosed as interstitial nephritis occurred in both. Granulocyte/monocyte adsorption was initiated, UC remission was achieved and renal function deterioration subsided in both. Drug or treatment responses may be concordant in monozygotic twins with UC. Careful review is important before treatment to avoid serious adverse events.

BACKGROUND

Inflammatory bowel disease (IBD) is a chronic, relapsing, immunologically mediated gastrointestinal disorder that consists of ulcerative colitis (UC) and Crohn's disease (CD). The identification of genetic determinants has provided insight into the pathogenesis of IBD. We report monozygotic twin sisters who developed UC within 6 months. Both responded to pharmacological intervention and achieved remission.¹ The onset and severity of UC were similar for both sisters. Compared with the general population, first-degree relatives of patients with IBD are at 10-fold increased risk for the same disease. This strongly suggests that these disorders have a genetic cause.² Both renal and urinary involvement and urinary involvement occur in 4–23% of patients with IBD.³ The most common manifestations are kidney stones, enterovesical fistula and ureteral obstruction.⁴ Parenchymal kidney disease complicated by IBD is rare, but a study of kidney biopsy specimens from patients with IBD has been reported.⁵ IgA nephropathy is the most common diagnosis (24%), followed by interstitial nephritis (19%) and arterionephrosclerosis (12%). 5-Aminosalicylates (5-ASA) is the standard therapy for acute relapse of IBD and is used as maintenance therapy during remission. A systematic review of case reports of interstitial nephritis cases either currently or previously treated with 5-ASA has been published. Forty-six cases have been described, with a reported incidence rate of 0.26% per patient-year.⁶ We describe here monozygotic twins with UC who developed renal impairment during treatment.

CASE PRESENTATION

Case 1

A woman aged 48 years was admitted to the hospital in May 2013 with lower abdominal pain, diarrhoea and anorexia. UC involving the whole colon was diagnosed based on the results of the colonoscopy and intestinal biopsy. Treatment involving 2400 mg mesalazine daily was started and remission was achieved. She was referred to us in August 2014 with an increased serum creatinine (SCr) level (figure 1). Her high creatinine level (>2.0 mg/dL) and female sex indicated a high risk for bleeding complications;⁷ therefore, a renal biopsy was avoided. Interstitial nephritis was assumed based on increased α -1 microglobulin (α 1MG) and β -2 microglobulin (β 2MG) levels instead of biopsy.⁸ An angiotensin receptor blocker was prescribed and dietary therapy was started. In October 2014, gall stones and cholecystitis were diagnosed and a laparoscopic cholecystectomy was performed. Two doses of cefazolin were administered during the operative period and no non-steroid anti-inflammatory drugs were prescribed. Her renal function deteriorated after surgery. Although no uraemic symptoms appeared, an arteriovenous fistula developed, providing a smooth transition from chronic kidney disease to end-stage renal disease.

Case 2

A woman aged 51 years was admitted to the hospital in October 2015 with a 6-month history of intermittent diarrhoea (figure 2). Before treatment, her SCr level was 0.88 mg/dL and she had no abnormal urinalysis findings. A daily dose of 750 mg mesalazine was prescribed and her SCr level remained stable. Three months after initiation of mesalazine, a mild to moderate flare was diagnosed; therefore, the mesalazine dosage was increased to 1500 mg daily. One week later, her condition worsened (C reactive protein (CRP), 14.79 mg/dL; SCr, 1.83 mg/dL). Clinical remission could not be achieved and a hypersensitive reaction to mesalazine was suspected; therefore, the drug was discontinued. Antiflatulence treatment and acetaminophen were administered and her general condition improved (CRP, 1.58; SCr, 1.65 mg/dL). After symptomatic remission, she received no medication for UC; her SCr level remained unchanged (1.58–2.11) during the subsequent 3 months. She was hospitalised for further diagnostic and therapeutic evaluations because of renal impairment in May 2016. At that time, it was discovered that she and the patient described in Case 1 are monozygotic twins.

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Figure 1 Temporal profiles of Case 1. 1. Time course of serum creatinine and C reactive protein.

Figure 2 Temporal profiles of Case 2. 2. Time course of serum creatinine and C reactive protein.

INVESTIGATIONS

In Case 1, the SCr level increased to 5.14 mg/dL; serum electrolyte concentrations and CRP were normal. Ultrasonography showed small kidneys (right: 85×40 mm; left: 87×40 mm), but no evidence of obstruction or renovascular anomalies was found. Increased echogenicity of the renal parenchyma was found in both kidneys. Urine protein was 0.3 g/gCr, and no casts or red cells were found with microscopy. Urinary β 2MG and α 1MG excretion levels were increased (38 700 μ g/L and 110.8 mg/gCr, respectively); *N*-acetyl- β -D-glucosaminidase (NAG) remained normal (5.0 U/gCr). Antinuclear antibody (ANA) was 160 (homogeneous and speckled), but antidouble-stranded DNA (anti-dsDNA) antibody and antineutrophilic cytoplasmic antibodies (ANCA) were negative. In Case 2, CRP and SCr were 0.74 and 1.60 mg/dL, respectively, and urinary β 2MG and α 1MG excretion levels were increased (15 300 μ g/L and 66.4 mg/gCr, respectively); NAG remained normal (3.6 U/gCr) in May 2016. ANA, anti-dsDNA antibodies and ANCA were negative. Renal ultrasonography demonstrated kidneys with a normal size and shape. Renal biopsy revealed marked lymphocyte infiltration and moderate interstitial fibrosis with mild tubular atrophy (figure 3). Glomeruli appeared with a mild increase in the mesangial matrix. No crescent formation was found in the specimen. Immunofluorescence indicated no specific findings. The overall findings were consistent with a diagnosis of tubulointerstitial nephritis. Cases 1 and 2 had human leucocyte antigen (HLA) haplotype *DRB1*090102*.

Figure 3 Renal biopsy specimen from Case 2. (Left) Acute interstitial nephritis with diffuse fibrosis and tubular atrophy. The glomerulus is preserved (periodic acid-Schiff, original magnification ×40). (Right) Interstitial infiltration by mononuclear cells composed predominantly of lymphocytes and eosinophils (H&E, original magnification ×100).

DIFFERENTIAL DIAGNOSIS

The cause of renal impairment in both cases could have been nephrotoxicity induced by 5-ASA. Another cause of renal impairment could have been hereditary predisposition or extra-intestinal manifestation of UC.

TREATMENT

In Case 1, despite mesalazine, a mild to moderate UC flare was diagnosed in March 2015; therefore, the drug was stopped. Steroid therapy and granulocyte/monocyte adsorption (GMA)

were proposed to the patient after mesalazine was discontinued. The patient rejected pharmacological therapy and GMA was started, which included Adacolumn with a duration of 120 min and a blood flow rate of 30 mL/min. Ten weekly sessions of GMA were performed. In Case 2, renal biopsy showed active chronic tubulointestinal nephritis; therefore, prednisolone 30 mg/day was started. GMA was considered for remission maintenance because she had diabetes mellitus and steroid therapy caused concerns regarding worsening glucose tolerance. Moreover, GMA was effective treatment for disease control in her twin sister. Therefore, it was performed in the same way as in Case 1 and her symptoms markedly improved. Prednisolone was tapered to 10 mg/day in August 2016 and remission was maintained. Urinary β 2MG and α 1MG levels were improved in August 2016 (931 μ g/L and 22.04 mg/gCr, respectively).

OUTCOME AND FOLLOW-UP

In Case 1, clinical remission was achieved and maintained. The SCr level gradually decreased to 4.79 mg/dL by May 2016. In Case 2, the SCr level was maintained between 1.86 and 1.96 mg/dL.

DISCUSSION

Interstitial nephritis is a rare complication that developed in monozygotic twins with UC. Genetic factors definitively contribute to the cause of UC. This has been highlighted in a twin study performed in Sweden⁹ that demonstrated a stronger hereditary factor in CD compared with UC among monozygotic twins, with a concordance rate of 50.0% for CD and 18.8% for UC. Monozygotic twin concordance was significantly higher than dizygotic twin concordance for UC (14–19% vs 0–5%, respectively) in major European studies conducted in Sweden,⁹ Denmark¹⁰ and the UK.¹¹ When UC occurs in families, the susceptibility rate of extraintestinal manifestation may be higher in siblings. Satsangi *et al*¹² revealed clinical patterns of familial IBD by studying 380 patients, including 82 CD–CD pairs and 69 UC–UC pairs. Eleven twin pairs were identified. The concordance rates for sex, age of onset, disease type, disease extent, extraintestinal manifestations and smoking habits at diagnosis were 65.2%, 62.5%, 100%, 68.6%, 88.9% and 82.5%, respectively. In the present study, both of the reported twins had gall stones and renal impairment as extraintestinal manifestations. The HLA system is an important determinant of disease susceptibility and behaviour in UC. *HLA-DRB1*09* is a popular DRB1 allele in the Japanese, with an allele frequency of 0.1238, which corresponds to the common HLA-DR antigen DR9.¹³ Although *HLA-DRB1*09* was not significantly associated with overall UC rates, it has been reported that the allele frequency of *HLA-DRB1*09* is significantly higher in patients with UC diagnosed at age 40 or older.¹⁴ The onset of UC in the reported twins occurred at ages 48 and 51, respectively. 5-ASA is widely used as IBD treatment. A British epidemiological study reported that among the 19025 5-ASA users with IBD, the incidence rate of renal disease was 0.17 cases per 100 patients per year.¹⁵ 5-ASA was the possible cause of interstitial nephritis in these cases. A genome-wide association study identified a suggestive association with 5-ASA-induced nephrotoxicity in the HLA region ($p=4\times 10^{-9}$; OR, 3.1), and 30% of cases recovered completely after drug withdrawal, with 15 out of 151 patients requiring permanent renal replacement therapy.¹⁶ Although the aetiology of UC is still not fully understood, increased and activated myeloid lineage leucocytes (granulocytes and monocytes) are potentially significant factors in the exacerbation and perpetuation of IBD because they release inflammatory cytokines.

Accordingly, selective depletion of myeloid cells by GMA has been used as a non-pharmacological treatment strategy for patients with UC. GMA was effective in Case 1, and the course of treatment was helpful as a therapeutic choice in Case 2. Remission was maintained and renal impairment was attenuated in both patients.

Learning points

- ▶ Nephrotoxicity in monozygotic ulcerative colitis (UC) twins is rare.
- ▶ Adverse effects of or responses to some drugs and UC itself may be concordant in monozygotic twins; therefore, familial history is important when choosing treatment.
- ▶ However, patients might not know that their siblings have UC or how they were treated by other healthcare providers; therefore, it is important to perform an indepth review.

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