Crescentic IgA nephropathy after administration of human monoclonal interleukin-12/23p40 antibody in a patient with Crohn's disease: a case report

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Received: 20 October 2019 / Accepted: 13 February 2020 / Published online: 25 February 2020
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Abstract

Ustekinumab (UST), an interleukin (IL)-12/IL-23-blocking monoclonal antibody, is a novel therapeutic option for Crohn's disease (CD). We describe a 24-year-old man with CD who showed an abrupt decline in renal function after administration of UST. Twenty-nine months previously, the patient was diagnosed with CD, and abnormal urinalysis findings in health checkup were coincidentally found at that time. Three months previously, treatment for CD was switched from infliximab to UST because of therapy-resistant severe diarrhea and bloody stools. A single dose of UST (260 mg) was initially intravenously administered, followed by single subcutaneous administration (90 mg) 2 months later. Thereafter, the patient exhibited rapid renal dysfunction with significant urinary abnormalities, although his gastrointestinal symptoms had completely disappeared. He was admitted to our hospital for further examination and treatment. Renal pathologic findings were compatible with crescentic glomerulonephritis consisting of almost fibro-cellular crescents. Immunofluorescent study showed IgA and C3 deposition in the glomerular mesangial area and IgA subclass staining revealed predominant IgA1 with concomitant mild IgA2 deposition. Furthermore, galactose-deficient IgA1 (Gd-IgA1) was also positive in the mesangial area. In addition, serum-Gd-IgA1 level was moderately increased. UST treatment was stopped and he responded to intensive steroid therapy with a parallel reduction of serum creatinine and Gd-IgA1 levels without flare of gastrointestinal symptoms. To our knowledge, this is the first case of immunoglobulin A nephropathy (IgAN) in patient with CD that might be aggravated by UST treatment. We presume that inhibition of IL-12/23 signaling with UST may cause to form crescentic IgAN by enhancing Gd-IgA1 production.

Keywords Crohn's disease (CD) · Galactose-deficient IgA1 (gd-IgA1) · Immunoglobulin A nephropathy (IgAN) · Ustekinumab (UST)

Introduction

Interleukin (IL)-12 and IL-23 (IL-12/23) are closely related inflammatory cytokines with important roles in the modulation of T-helper (Th) 1 and Th17 cell subsets [1]. Ustekinumab (UST), a human monoclonal antibody that binds to

the p40 subunit of IL-12/23 [2], is anticipated to be a novel therapeutic option for immune-mediated disease. UST is approved for treatment of moderate-to-severe plaque psoriasis in Europe, the United States, and Japan, and it has demonstrated efficacy in Crohn's disease (CD) and psoriatic arthritis without causing renal impairment [1–3].

Immunoglobulin (Ig) A nephropathy (IgAN) is the most common glomerulonephritis (GN) and is a principal cause of chronic kidney disease [4]. In terms of the pathogenesis of IgAN, several studies that investigated aberrant IgA1 O-glycosylation indicated that galactose-deficient IgA1 (Gd-IgA1) plays a pivotal role in the progression of IgAN [5, 6]. Significant elevations in serum Gd-IgA1 levels and high levels of glomerular Gd-IgA1 deposition were identified in patients with IgAN [7–9]. Furthermore, the recently

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proposed multi-hit theory of IgAN states that overproduced Gd-IgA1 and autoantibodies against Gd-IgA1 subsequently form circulating immune complexes, resulting in glomerular mesangial deposits followed by accelerated nephritis [6, 10]. Thus, Gd-IgA1 is considered as a critical pathogenic factor in IgAN.

Herein, we describe a patient with CD who showed severe renal dysfunction after administration of UST. To the best of our knowledge, this is a first case report of UST-related crescentic IgAN in CD with serum Gd-IgA1 elevation and glomerular Gd-IgA1 deposition. We will discuss its rarity and developmental mechanism. Especially, we will focus on whether IgAN in the present case was Gd-IgA1-related primary IgAN or CD-related IgAN (CD-IgAN) and if crescentic IgAN was caused by administration of UST or not.

Case report

A 24-year-old man was admitted to our hospital in December 2018 with rapid decline of renal function. He had been healthy after birth and abnormal urinalysis findings had not been found during annual health checks. However, he had been suffering from abdominal pain, severe diarrhea, bloody stools, and weight loss since May 2016. He was diagnosed as ileocolic type of CD in June 2016. Additionally, mild degree of proteinuria and hematuria by dipstick urinalysis were coincidentally found on health checkups in July 2016, but no further examinations were performed because his renal function was within normal limits; serum creatinine (Cr) level was 0.8 mg/dL and estimated glomerular filtration rate (eGFR) was 102 mL/min/1.73 m², respectively. He did not have a history of alcohol consumption, smoking, or surgery. His family medical history was unremarkable. After diagnosis of CD, his gastrointestinal symptoms were treated with oral administration of mesalazine (3000 mg/day) and monthly administration of infliximab (IFX) (6 mg/kg). However, severe diarrhea, persistent bloody stools, and weight loss were not controlled and his renal function exhibited mild abnormalities at that time; serum Cr level was 1.1 mg/dL and eGFR was 74 mL/min/1.73 m². The degree of proteinuria and hematuria at that time was unidentified since gastroenterologist for him had not assessed urinary analysis during the period for IFX therapy against CD. Accordingly, treatment was switched from IFX to UST at end of August 2018. A single dose of UST (260 mg) was initially intravenously administered, followed by single subcutaneous administration (90 mg) 2 months later. Thereafter, the patient's renal function rapidly deteriorated with abnormal urinary findings by dipstick urinalysis, although his gastrointestinal symptoms disappeared. He was admitted to our hospital for further examination and treatment for his renal complications.

On admission, his temperature was 36.1 °C, his pulse rate was 74 beats per minute, and his blood pressure was 138/98 mmHg. Findings of a physical examination were unremarkable. Tonsillar swelling and skin lesions, such as butterfly rash or purpura, were not detected. Laboratory tests showed the following: white blood cell count, 5100/μL; erythrocyte count, 444 × 10⁴/μL; hemoglobin, 12.8 g/dL; hematocrit, 41.2%; platelet count, 15.9 × 10⁴/μL; erythrocyte sedimentation rate, 12 mm/h; total protein, 8.4 g/dL; albumin, 4.5 g/dL; blood urea nitrogen, 31.2 mg/dL; Cr, 2.6 mg/dL; eGFR, 27.9 mL/min/1.73 m²; total cholesterol, 158 mg/dL; C-reactive protein, <0.1 mg/dL; IgG, 1903 mg/dL; IgA, 529 mg/dL; and IgM, 83 mg/dL. Serum complement levels were within normal limits. Anti-nuclear antibody (×160, homogeneous and speckled) and anti-single-stranded DNA (11.8 U/mL; normal range <7.0 U/mL) were mildly positive, but anti-double-stranded DNA, anti-Ro, anti-La, or anti-Sm antibodies were not detected. Likewise, anti-glomerular basement membrane antibodies and anti-neutrophil cytoplasmic antibodies were absent. Serum hepatitis B surface antigen and anti-hepatitis C virus antibody findings were negative. A 24-h urine collection showed 0.8 g of protein. The urinary sediment contained five to nine red blood cells per high-power field. Cr clearance was 30.3 mL/min. Urinary markers for tubulointerstitial injury showed *N*-acetyl-β-D-glucosaminidase, 8.3 U/L (normal range <7.0 U/L); β2-microglobulin, 648 μg/L (normal range <200 μg/L); and α1-microglobulin, 29.5 μg/mL (normal range <8 μg/mL).

On day 3 after admission, a percutaneous renal biopsy was performed to obtain a definitive diagnosis. A total of 21 glomeruli were available, 3 of which showed global sclerosis. Additionally, of the 21 glomeruli, 2 were cellular crescents, and 9 were fibro-cellular crescents. Light microscopic examination of the glomeruli showed crescentic GN that consisted of almost fibro-cellular crescents (Fig. 1a, d). Those crescents appeared to develop in a similar period and patchy tubular damage with mononuclear cell infiltration was detected around fibro-cellular crescents (Fig. 1b). Immunofluorescence microscopy revealed significant depositions of IgG, IgA (Fig. 2a), C3 (Fig. 2b), and fibrinogen (Fig. 2c) in the glomerular mesangial area; κ and λ were also deposited in the mesangial area. No deposits of IgM or C1q were seen. In terms of IgA subclasses on glomerulus, assessed by immunohistochemical staining with mouse anti-human IgA1 or IgA2 antibody (IgA1: Southern Biotech, #9130-01, 1:4000 antibody dilution) (IgA2: Southern Biotech, #9140-01, 1:4000 antibody dilution), IgA1 was predominantly positive in the mesangium with concomitant mild IgA2 deposition (Fig. 2d, e). Electron microscopy revealed electron-dense deposits in the para-mesangial region.

Based on these pathological findings, we diagnosed the patient with crescentic IgAN. To investigate the

Fig. 1 Light microscopy findings. The glomerulus exhibited crescentic glomerulonephritis that consisted of almost fibro-cellular crescents (a) (periodic acid–Schiff [PAS] stain; original magnification $\times 200$). Patchy cell infiltration around the glomerulus was evident (b) (PAS stain; original magnification $\times 100$). The glomerulus showed typical fibro-cellular crescent (c) (PAS stain; original magnification $\times 400$) and fibrinoid necrosis (d) (Masson trichrome stain; $\times 400$)

Fig. 2 Immunostaining findings. Immunofluorescence showed intense mesangial staining for IgA (a), moderate mesangial staining for C3 (b), and intense mesangial staining for fibrinogen (c) (original magnification $\times 400$). Immunohistochemical analysis revealed intense

deposition of IgA1 (d) and mild deposition of IgA2 (e) on the mesangial area (original magnification $\times 400$). Immunohistochemical staining with KM55 showed intense mesangial deposition of Gd-IgA1 (f) (original magnification $\times 400$)

pathogenesis of glomerular IgA deposition in the present case, we examined glomerular Gd-IgA1 deposition and

serum Gd-IgA1 level using anti-human Gd-IgA1-specific monoclonal antibody (KM55) [8]. Glomerular-Gd-IgA1

deposition was evident by immunohistochemical staining with KM55, as previously reported, [9] (Fig. 2f). Serum-Gd-IgA1 levels measured by ELISA with KM55 [8, 9] was 15.3 $\mu\text{g/mL}$, which was increased compared to data in our recent report [9]. Therefore, we considered that the diagnosis of the patient was crescentic IgAN associated with Gd-IgA1 after administration of UST.

The treatment with oral corticosteroids (prednisolone [PSL], 30 mg/day) was started for the patient on the 8th hospital day, and then intensive immunosuppressive therapy was performed: high-dose methylprednisolone (500 mg/day for 3 days for three courses) followed by oral PSL at an initial dose of 30 mg on alternate days (Fig. 3). Subsequently, PSL was gradually reduced, and administration of UST was not resumed. In addition, to preserve residual renal function, administration of mesalazine was ceased, and low-dose losartan (25 mg/day) was started (Fig. 3) after confirming the absence of any flare in gastrointestinal symptoms and

improvement of renal function. Consequently, this intensive therapy resulted in a favorable outcome. Serum-Cr levels decreased from 2.8 to 1.6 mg/dL and eGFR increased from 24.8 to 47.4 mL/min/1.73 m^2 , which correlated with a decrease in urinary protein from 1.2 to 0.3 g/gCr, serum IgA from 529 to 306 mg/dL, and serum Gd-IgA1 level from 15.3 to 7.8 $\mu\text{g/mL}$ (Fig. 3). No severe adverse effects of the steroid therapy were detected. In addition, no relapse of gastrointestinal symptoms occurred.

Discussion

According to randomized clinical trials of UST therapy for CD [11, 12], the population of patients with one or more adverse events and patients who discontinued treatment because of an adverse event was small. So far, several side effects of UST therapy, including serious infections,

Fig. 3 Clinical course and treatment of the patient. *eGFR* estimated glomerular filtration rate, *HPF* high-power field, *IFX* infliximab, *IgA* immunoglobulin A, *i.v* intravenous, *mPSL* methylprednisolone, *PSL* prednisolone, *s.c* subcutaneous, *sCr* serum creatinine, *U-RBC* urinary red blood cells, *UP* urinary protein, *UST* ustekinumab. *Treat-

ment with oral prednisolone (30 mg/day) was started, and then intensive steroid therapy was performed: high-dose methylprednisolone (500 mg/day for 3 days for three courses) followed by oral prednisolone at an initial dose of 30 mg on alternate days

low-grade fever, weight loss, complication of skin cancer or prostate cancer, lung inflammation, and reversible posterior leukoencephalopathy syndrome have been reported [3, 11, 12]. However, to the best of our knowledge, no case of renal insufficiency associated with UST treatment has been reported.

In the present case, Gd-IgA1 was positive in the mesangial area. According to recent reports, including ours, glomerular Gd-IgA1 deposition was specific to patients with IgAN and Henoch–Schönlein purpura nephritis, whereas staining for glomerular Gd-IgA1 was very faint in patients with other kidney diseases such as membranous nephropathy, lupus nephritis, hepatitis C virus-related nephritis, and minimal change disease [7, 9]. Therefore, immunopathological features in the present case indicated that the patient might have usual primary IgAN, that is, Gd-IgA1-related IgAN. In addition, age-inappropriate global sclerosis seen in the present case might be attributable to the influence of primary IgAN that developed several years ago. Meanwhile, IgAN is recognized as a representative extraintestinal manifestation of inflammatory bowel disease, and CD-IgAN is not uncommon [13, 14]. Thereby, the present case may be also regarded as CD-IgAN when considering the time for appearance of abnormal urinalysis findings.

Regarding the features of CD-IgAN, Ambruzs et al. [14] reported that IgAN was the most frequent renal complication in patients with CD. They described that clinical and pathologic findings in CD-IgAN are usually paralleled with the activity of CD [14]. Moreover, intriguing research by Wang et al. [15] showed that the interaction between abnormal immune response in intestinal mucosa is critical in the pathogenesis of CD-IgAN. In the present case, rapid renal dysfunction was observed despite the complete disappearance of gastrointestinal symptoms after administration of UST, which makes it difficult to explain that his abrupt renal disorder was due to the aggravation of CD-IgAN. Moreover, in contrast to Western countries, there have not been many reports about CD-IgAN from Asian countries, including Japan, that are known to have a high prevalence rate of IgAN [16]. Also, none have reported the glomerular Gd-IgA1 deposition in patients with CD-IgAN. Therefore, it might be plausible that the patient's rapid renal disorder was due to the activation of latently progressed usual primary IgAN rather than CD-IgAN. However, further detailed analysis focusing on the distinction between CD-IgAN and primary IgAN is necessary and it is desirable to elucidate the association of Gd-IgA1 with the pathogenesis of CD-IgAN.

Remarkably, pathologic findings in the present case showed crescentic IgAN, which is relatively rare phenotype. Jennette [17] reported that 12 out of 853 patients with IgAN showed rapidly progressive crescentic GN. Crescentic IgAN is usually defined as the presence of crescents in more than 50% of the glomeruli, and it often

presents as rapidly progressive GN [18]. In accordance with a previous report, such crescentic IgAN comprised various phases of crescents including cellular, fibro-cellular, and fibrous types [18]. In contrast, the present case consisted of almost fibro-cellular crescents, which appeared to develop in broadly similar phase, suggesting that severe glomerular capillaritis occurred nearly simultaneously after the specific trigger. Therefore, we presume that preexisting primary IgAN might have been abruptly exacerbated in the form of crescentic GN by the administration of UST.

With regard to the possibility of mesalazine-related renal disorder, validation of its diagnosis is low when considering the distribution of tubulointerstitial lesions. Usually, the characteristic finding of mesalazine-associated renal disorder is considered to be diffuse interstitial nephritis [13, 14], whereas the present case exhibited patchy tubulointerstitial damage around fibro-cellular crescents. Furthermore, the main lesions of this patient's renal disorder are thought to be crescentic GN rather than tubulointerstitial nephritis. Thus, the present case is unlikely to be a mesalazine-associated renal disorder.

In general, Th1 and Th17 cells-mediated inflammatory cytokines such as IL-12/23 are essential in the progression of CD [1, 19]. Also, Th2 abnormality with activation of IL-4 is reported to partially affect the pathogenesis of CD [20]. Similarly, abnormal T-cell-mediated immunity is related to the pathogenesis of IgAN by affecting the aberrant IgA1 galactosylation process [21]. In a recent review by Ruszkowski et al. [21], IgAN was usually characterized by higher proportions of circulatory Th2, not Th1. It was reported that Th2-related IL-4 amplifies Gd-IgA1 formation by altering terminal glycosylation of secreted IgA1 in an experimental *in vitro* study [22]. Therefore, we speculate as follows: administration of UST optimized Th1-dominant immune abnormalities, leading to a state of relative Th-2 dominance. Such brash alteration of T-cell subpopulations, pharmacologically induced by UST, might cause crescentic IgAN via amplifying Gd-IgA1 formation. However, accumulation of similar cases and further analysis are needed to elucidate the relationship between crescent formation and rapid Gd-IgA1 production. Also, detailed analysis is indispensable to clarify Th2-mediated mechanism for Gd-IgA1 formation in patients with IgAN.

In conclusion, we report a rare case of crescentic IgAN in CD after administration of UST. Based on clinicopathologic findings, we presumed that preexisting primary IgAN was abruptly exacerbated via enhancing Gd-IgA1 production due to UST-induced modification of T-cell immunity. Thus, a definitive diagnosis based on renal biopsy might be necessary in case that physicians consider UST therapy to patients with severe CD exhibiting abnormal urinalysis findings.

Acknowledgements We greatly appreciate the excellent technical assistance provided by Ms. Tomoko Suzuki.

Compliance with ethical standards

Conflict of interest Y. Wada received Speakers Bureau from Mitsubishi Tanabe Pharma Corporation and T. Shibata has received research funding from Mitsubishi Tanabe Pharma Corporation, although the funder played no role in the present case of the manuscript.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient described in the present case.

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