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CASE REPORT

Active flare of IgA nephropathy during long-term therapy with anti-tumor necrosis factor-α antibody drugs for Crohn's disease: three case reports and literature review

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Abstract

In recent years, increasing numbers of reports have described new onset or active disease flare of IgA nephropathy (IgAN) during administration of TNF-α inhibitor (TNFi) therapy for chronic inflammatory diseases. Crohn's disease (CD) is the most common indication for TNFi therapy in this clinical setting, but the underlying etiology of IgAN in such patients remains unclear. We report our experience with three patients who developed acute worsening of preexisting urinalysis abnormalities and kidney dysfunction approximately 2 to 6 years after TNFi administration for CD. Kidney biopsies at the time of kidney disease flare revealed IgAN in two patients and IgAN complicated by acute tubulointerstitial nephritis in one patient. The CD and IgAN in all three patients were successfully managed with additional corticosteroid therapy and tonsillectomy without discontinuing TNFi therapy. The clinical course of our patients and similar patients described in the literature suggests that TNFi therapy for CD is associated with a relatively high risk for new onset or disease flare of IgAN. This report discusses the possible involvement of Th1/Th2 imbalance on the immunological background of CD or IgAN.

Keywords Tumor necrosis factor-α · Crohn's disease · IgA nephropathy · Corticosteroid · Tonsillectomy

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis and a significant cause of end-stage kidney disease worldwide. Although its etiology has not been fully elucidated, involvement of abnormal mucosal immunity in the upper respiratory and intestinal tracts has been postulated. Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the mucosa of the intestinal tract. Ulcerative colitis (UC) and Crohn's disease (CD) are two representative types of IBD, and antibody drugs targeting tumor necrosis factor-α (TNF-α) are effective and well-established treatment options for both UC and CD. Notably, numerous reports have described IgAN complicated with IBD, suggesting an etiologic link between the two [1–3].

With the widespread and long-term use of TNF-α inhibitor (TNFi) therapy, various adverse events have become evident. New onset or acute exacerbation of subclinical or previously diagnosed IgAN has been reported as an adverse event associated with TNFi therapy, CD being more common than UC as a background disease [4–8]. We report three cases of acute exacerbation of IgAN during TNFi therapy for CD. The IgAN was successfully treated with corticosteroids and tonsillectomy without discontinuation of TNFi therapy, which was effective for maintaining remission of CD.

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Case report

Case 1

A man in his 40 s was referred to our hospital because hematuria and proteinuria had been found during his medical check-up. Because the urinalysis abnormalities were relatively mild, kidney biopsy was not performed. After approximately 20 months of outpatient visits, the patient reported frequent diarrhea, which had been present before identification of his abnormal urinalysis results. Colonoscopy showed a typical cobblestone appearance consistent with colonic CD. Treatment of CD was initiated by administration of infliximab (IFX) every 8 weeks. The clinical course of CD remained stable for several years with IFX therapy, but an acute increase in microscopic hematuria and proteinuria and worsening of kidney function were observed approximately 6 years after initiating the therapy (Fig. 1a). A kidney biopsy revealed diffuse proliferative glomerulonephritis along with mesangial and paramesangial IgA deposits, consistent with IgAN (Table 1, Fig. 2a, b). Corticosteroid therapy was administered for 6 months, including 3 consecutive days of methylprednisolone 500 mg/body/day pulse therapy at months 1, 3, and 5, followed by oral prednisolone at 0.5 mg/kg body weight every other day [9]. He had not taken corticosteroids for CD before this. After 6 months of corticosteroid therapy, the patient underwent tonsillectomy to treat his IgAN. His urinary findings gradually improved, and he eventually reached complete remission. The CD remained in remission throughout the clinical course after initiation of IFX therapy.

Case 2

A man in his 30 s had been noted to have abnormal urine test results since high school. He was diagnosed with CD in his late 20 s and started treatment with adalimumab 6 years later. He was referred to our hospital because of a gradual decline in kidney function found at his annual check-ups. A kidney biopsy revealed focal and segmental mesangial and endocapillary hypercellularity with cellular and fibrous crescents. Approximately 30% of the glomeruli showed global glomerulosclerosis, and tubulointerstitial injury was present in 30% of the cortical region identified in the biopsy specimen. Immunostaining showed that the glomeruli were positive for IgA and C3, consistent with IgAN (Table 1, Fig. 2c, d). The patient received 6 months of corticosteroid treatment. He had not previously received corticosteroid therapy for CD. One month after completion of the regiment, tonsillectomy was performed to treat the IgAN, after which the hematuria and proteinuria gradually improved. The CD remained in remission throughout the clinical course after initiation of adalimumab therapy (Fig. 1b).

Case 3

A man in his 20 s had been diagnosed with CD approximately 3 years previously upon investigation of a perianal abscess. At that time, kidney dysfunction was already evident based on a serum concentration of creatinine of 1.48 mg/dL. One year after diagnosis of CD, he underwent a seton procedure and began IFX therapy, which dramatically improved his gastrointestinal symptoms. However, urinalysis revealed hematuria and proteinuria, and his creatinine concentration increased to 1.69 mg/dL. Mesalazine-induced tubulointerstitial nephritis was suspected, and discontinuation of mesalazine resulted in a transient improvement of kidney function. Three years later, his kidney function further deteriorated. A kidney biopsy showed diffuse mesangial proliferative glomerulonephritis and tubulointerstitial nephritis (Table 1, Fig. 2e, f). He was diagnosed with IgAN complicated by tubulointerstitial nephritis, and corticosteroid therapy was administered for 6 months. He had not received corticosteroid therapy for CD before. After tonsillectomy was performed to treat the IgAN, the hematuria resolved and the proteinuria showed a decreasing trend. The CD remained in remission throughout the clinical course after initiation of IFX therapy (Fig. 1c).

Discussion

This report has described three patients who developed acute exacerbations of IgAN during long-term TNFi therapy for CD. All patients showed a relatively good clinical course of IgAN following corticosteroid therapy and tonsillectomy. Notably, continuation of TNFi therapy may have maintained remission of CD in all three patients. Our findings suggest that the combination of corticosteroid therapy and tonsillectomy may be a promising therapeutic option for the treatment of acute exacerbation of IgAN during TNFi therapy.

TNFi therapy is reportedly associated with increased risk of developing autoimmune diseases, including vasculitis, lupus-like syndromes, and psoriatic skin changes [10–12]. IgAN was recently reported as one such adverse event (Table 2) [4–8, 13–19]. We consider that all three patients described in the present report developed flares of latent IgAN because all patients showed hematuria and proteinuria prior to initiation of TNFi therapy. In addition, their kidney biopsies showed concomitant chronic sclerotic lesions and active glomerulonephritis, further supporting the occurrence of IgAN flare (Fig. 2). Notably, among all cases reported to

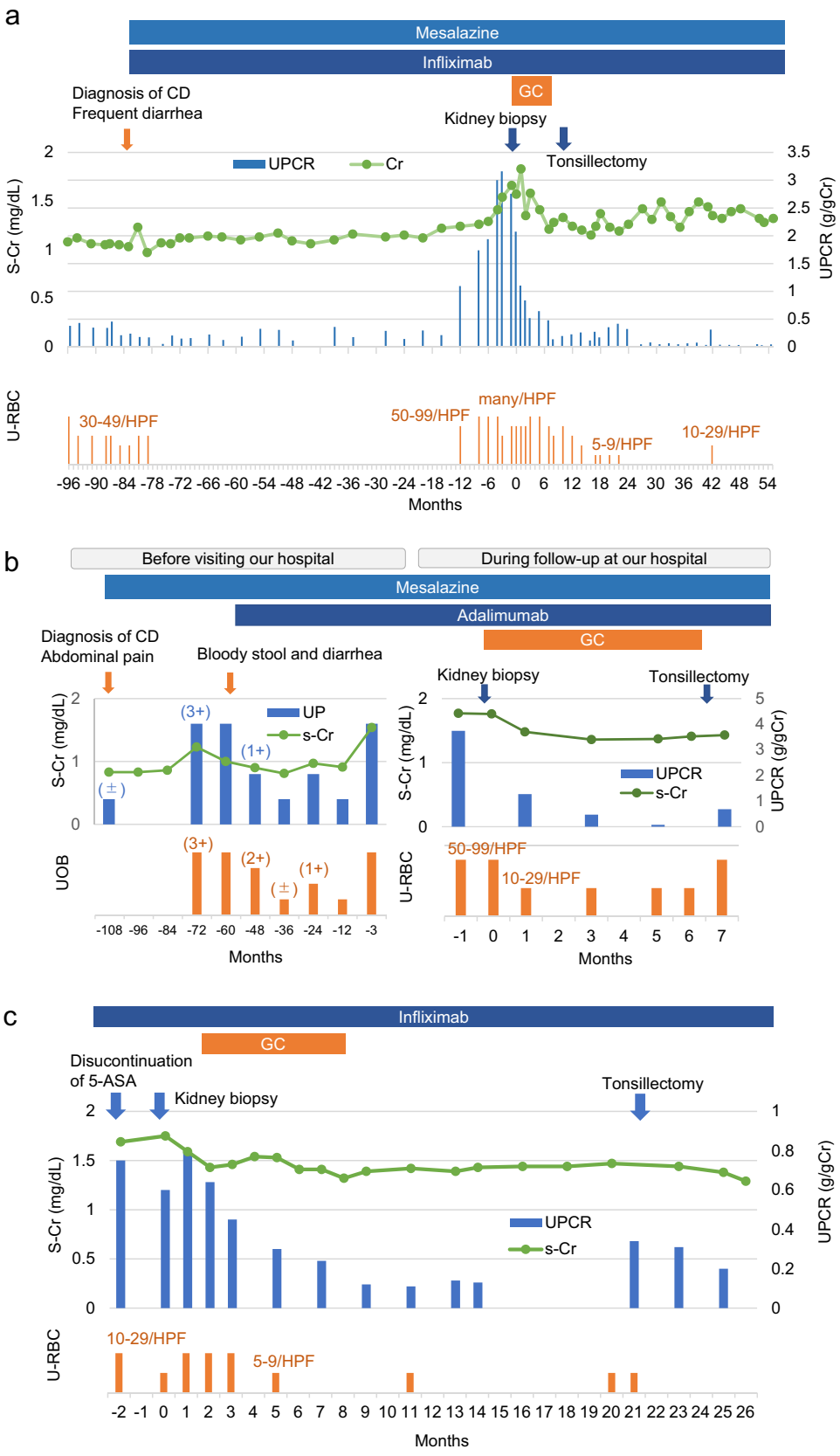

Fig. 1 Clinical course of patients. **a** Case 1 during follow-up at our hospital. **b** Case 2 in a periodic medical check-up before the visit to our hospital (left panel) and during follow-up at our hospital (right panel). **c** Case 3 during follow-up at our hospital. *CD* Crohn's disease; *Cr* creatinine; *GC* glucocorticoid; *HPF* high-power field; *RBC* red blood cell; *S-Cr* serum creatinine; *UOB* urinary occult blood; *UP* urine protein; *UPCR* urine protein-to-creatinine ratio; *U-RBC* urine red blood cells; *5-ASA* 5-aminosalicylic acid

Table 1 Laboratory findings, kidney biopsy histopathological findings, and treatments of the three patients

	Case 1	Case 2	Case 3
Physical findings at kidney biopsy			
Height (cm)	175	170	174
Body weight (kg)	65	58.2	62.5
Blood pressure (mmHg)	127/74	117/69	118/76
Laboratory findings at kidney biopsy			
WBC count (cells/μL)	6000	6300	5300
BUN (mg/dL)	22	20	17
Creatinine (mg/dL)	1.57	1.86	1.59
eGFR (mL/min/1.73 m^2)	40	35.2	44.9
Total protein (g/dL)	6.2	6.5	7.6
Albumin (g/dL)	3.2	3.5	4.4
IgG (mg/dL)	952	876	2299
IgA (mg/dL)	399	613	413
C3 (U/L)	95	104	141
Antinuclear antibody	40	< 40	< 40
MPO-ANCA	< 1.0	< 1.0	< 1.0
PR3-ANCA	< 1.0	< 1.0	< 1.0
Anti-GBM antibody (U/mL)	N/A	N/A	< 2.0
Cryoglobulin	N/A	(−)	(−)
Proteinuria (g/gCr)	3.2	4.33	0.6
Hematuria (RBCs/HPF)	50–99	50–99	5–9
Kidney biopsy findings			
Light microscopy			
Renal histopathological diagnosis	MsPGN	MsPGN	TIN with MsPGN
Oxford classification	M1E0S1T1C0	M0E1S1T1C1	M1E0S1T1C0
Immunostaining (PAP)			
Mesangial and paramesangial area	IgA +, IgM +, C3 +, C1q +	IgA + + +, IgM +, C3 +, C1q +	IgA +, IgM ±, C3 ±, C1q +
Glomerular capillary spaces	−	−	−
Electron microscopy			
EDDs			
Mesangial and paramesangial area	−	+ +	+
Glomerular capillary spaces	−	−	−
Mesangial interposition	+	−	−
Foot process effacement	60%	30%	5%
Therapies			
Discontinuation of TNFi	−	−	−
Therapies for IgAN	mPSL pulse + oral PSL	mPSL pulse + oral PSL	mPSL pulse + oral PSL
Tonsillectomy	+	+	+
RASI	Losartan	Losartan	Losartan
Therapies for CD	IFX 700 mg q8W Mesalazine 3000 mg/day	ADA 40 mg qW Mesalazine 3000 mg/day	IFX 300 mg q8W
Last follow-up			
Creatinine (mg/dL)	1.32	1.43	1.38
Albumin (g/dL)	4.0	3.8	4.5
Proteinuria (g/gCr)	0.05	0.68	0.2
Hematuria (RBCs/HPF)	1–4	50–99	1–4
Follow-up period (months)	55	7	25

ADA Adalimumab; *Anti-GBM* anti-glomerular basement membrane; *ARB* angiotensin II receptor blocker; *BUN* blood urea nitrogen; *CD* Crohn's disease; *EDD* electron-dense deposit; *HPF* high-power field; *IgA* immunoglobulin A; *IgAN* immunoglobulin A nephropathy; *IgG* immunoglobulin G; *IFX* infliximab; *MsPGN* mesangial proliferative glomerulonephritis; *MPO-ANCA* myeloperoxidase anti-neutrophil cytoplasmic antibody; *mPSL* methylprednisolone; *N/A* not available; *PAP* peroxidase–antiperoxidase; *PR3-ANCA* proteinase-3 anti-neutrophil cytoplasmic antibody; *PSL* prednisolone; *qW* every week; *q8W* every 8 weeks; *RASI* renin–angiotensin system inhibitors; *RBC* red blood cell; *TNFi* tumor necrosis factor-alpha inhibitor; *WBC* white blood cell; *5-ASA* 5-aminosalicylic acid

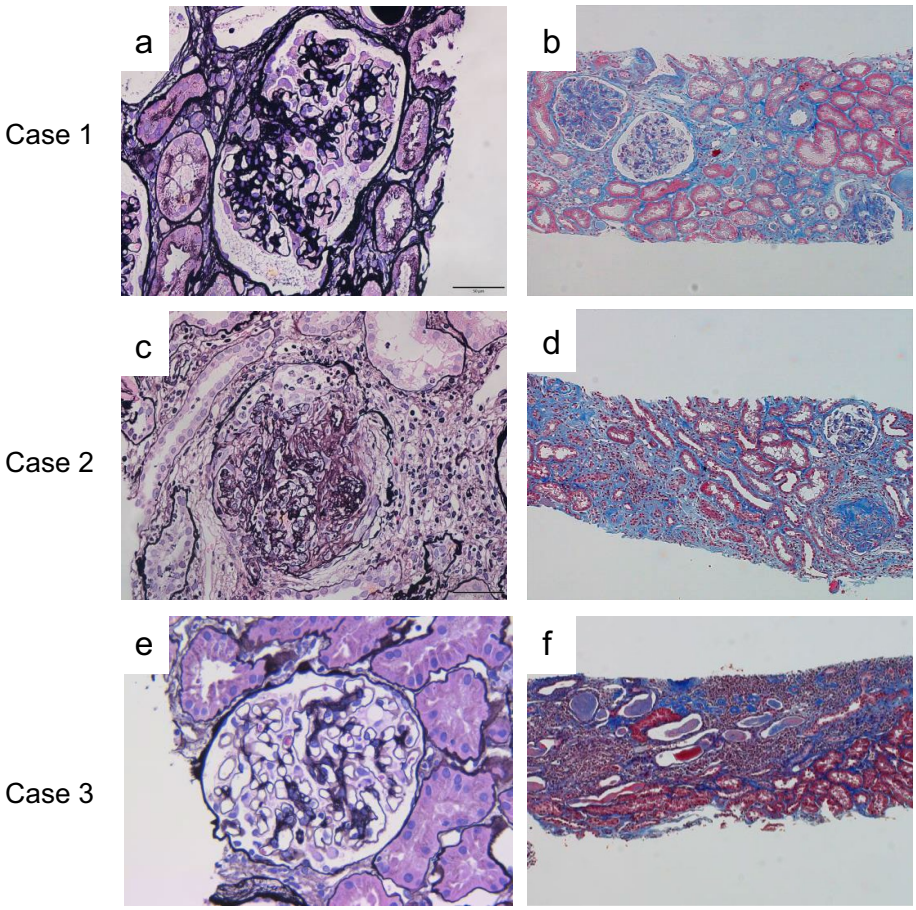

Fig. 2 Kidney biopsy findings. **a** Light microscopic findings in case 1; the glomeruli exhibit moderate mesangial hypercellularity and adhesion. Periodic acid methenamine silver (PAM) stain (×400 original magnification). **b** Lower-magnification view in case 1 showing segmental sclerosis and interstitial fibrosis with tubular atrophy. Masson's trichrome stain (×100 original magnification). **c** Light microscopic findings in case 2; the glomeruli have cellular crescents, segmental sclerosis, and mononuclear cell infiltration in the endocapillary and extracapillary areas. PAM stain (×400 original magnification). **d** Lower magnification view in case 2 showing global sclerosis and interstitial fibrosis with tubular atrophy. Masson's trichrome stain (×100 original magnification). **e** Light microscopic findings in case 3; the glomeruli have mild mesangial hypercellularity. PAM stain (×400 original magnification). **f** Lower magnification view in case 3 showing global sclerosis, interstitial fibrosis with tubular atrophy, and interstitial inflammation. Masson's trichrome stain (×100 original magnification)

date (including ours), CD was the primary disease for which TNFi therapy was administered in 19 (66%) of 29 patients. In a Japanese study, the incidence of IgAN in patients with IBD, including suspected cases of IgAN, was significantly higher in patients with CD (11/207, 5.3%) than UC (2/220, 0.9%) [20]. This suggests that the immunopathological background of IgAN is more closely aligned with CD than UC. Lee et al. reported a case of IgAN complicated by CD, which was diagnosed as primary IgAN based on positive immunostaining with the galactose-deficient IgA1-specific monoclonal antibody (KM55 mAb) [21]. Consequently, certain patients might have primary IgAN and could potentially benefit from the combination of tonsillectomy and steroid pulse therapy (TSP). In addition to CD, there have been reports on the emergence or exacerbation of IgAN during TNFi therapy for conditions such as ankylosing spondylitis, psoriasis, and rheumatoid arthritis. Nevertheless, no apparent differences in clinical parameters, such as the duration of TNFi treatment or renal function at the onset of IgAN, were identified (Table 2).

A previous study showed that TNFi therapy may be associated with new-onset IgA vasculitis in patients with IBD, with a median onset time of 31.5 months after TNFi initiation [22]. A report from Mayo Clinic showed that the mean duration of TNFi therapy in eight patients with TNFi-associated vasculitis was 34.5 months [23]. These patients with vasculitis as well as the patients shown in Table 2 (including our patients), who were diagnosed with IgAN at a median of 36 months after initiation of TNFi therapy, are consistent in terms of the duration of time from TNFi initiation to IgAN onset or disease flare. This suggests that it may take several years before TNFi-associated IgAN becomes clinically

Table 2 Literature review of patients showing new onset or disease flare of IgA nephropathy during treatment with TNFα inhibitors

Refs.	Age/sex	Underlying disease	TNFi	Prior to initiation of TNFi		Kidney features at biopsy diagnosis					Kidney biopsy findings		Management and outcome at final observation								
				IgAN diagnosis	Urinalysis abnormality	TNFi administration (months)	sCr (mg/dL)	eGFR	Proteinuria (g/gCr or g/day)	Hematuria	Cellular or fibrocellular crescent	MEST-C	Follow-up (months)	TNFi discontinuation	Corticosteroid for IgAN	Tonsillectomy for IgAN	Treatment for underlying disease	sCr (mg/dL)	eGFR	Proteinuria (g/gCr or g/day)	Kidney outcome
[4]	34/F	CD	IFX	Yes	Yes	0	1.6	N/A	1.92	Yes	N/A	N/A	5.8	No	No	No	IFX	1.28	N/A	< 0.5	Improvement
[5]	39/F	CD	ADA	No	No	48	1.7	37	0.56	Yes	No	N/A	12	Yes	No	No	IFX	1.29	52	0.04	Improvement
[6]	19/F	CD	IFX	No	N/A	36	N/A	N/A	N/A	Yes	N/A	N/A	N/A	Yes	No	No	VDZ	N/A	N/A	N/A	N/A
	74/M	CD	ADA	No	N/A	11	1.22	N/A	N/A	Yes	N/A	N/A	24	Yes	No	No	No	N/A	N/A	N/A	Death
	45/M	CD	ADA	No	N/A	48	1.81	N/A	N/A	Yes	N/A	N/A	N/A	Yes	No	No	VDZ	1.57	N/A	N/A	Improvement
[7]	33/M	CD	ADA	No	Yes	84	1.8	44	4.34	980×10^6/L	Yes	M1E1S1T1C1	48	Yes	mPSL pulse	No	VDZ	1.07	N/A	< 0.03	Improvement
[8]	42/M	CD	IFX	No	N/A	N/A	N/A	58	0.63	Yes	No	M1S1E0T0C0	36	No	No	N/A	N/A	N/A	53	0.55	Stable
	45/M	CD	IFX	No	N/A	N/A	N/A	54	1.42	Yes	No	M0S1E0T0C0	60	No	No	N/A	N/A	N/A	9	1.96	ESKD-KT
	23/M	CD	IFX	No	N/A	N/A	N/A	69	0.64	No	No	M1S1E0T1C0	62.2	No	No	N/A	N/A	N/A	64	0.3	N/A
	46/M	CD	IFX	No	N/A	N/A	N/A	78	6.72	No	No	M0S0E0T0C0	36	No	No	N/A	N/A	N/A	80	0.8	N/A
	51/M	CD	IFX	No	N/A	N/A	N/A	52	2.3	No	No	M0S1E0T1C0	60	N0	No	N/A	N/A	N/A	30	0	N/A
	61/M	CD	IFX/ADA	No	N/A	N/A	N/A	98	0.11	Yes	No	M0S0E0T0C0	24	No	No	N/A	N/A	N/A	91	0	N/A
	27/F	CD	IFX	No	N/A	N/A	N/A	63	2.21	Yes	No	M1S1E0T1C0	61.9	No	Yes	N/A	N/A	N/A	52	0.5	N/A
	32/F	CD	ADA/IFX	No	N/A	N/A	N/A	59	7.97	Yes	Yes	M1S1E1T0C1	84	No	Yes	N/A	N/A	N/A	94	0.05	N/A
	21/F	CD	IFX	No	N/A	N/A	N/A	81	0.71	Yes	No	M0S0E0T0C0	264	No	Yes	N/A	N/A	N/A	44	0.53	N/A
	38/M	CD	IFX	No	N/A	N/A	N/A	77	0.8	No	N/A	N/A	180	No	Yes	N/A	N/A	N/A	69	0.44	N/A
Other disease																					
[13]	49/M	AS	IFX	Yes	Yes	9.3	3.4	N/A	9.4	N/A	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	ESKD-HD
[14]	61/M	PsO	ADA	No	No	18	3.22	N/A	11.9	> 100/HPF	Yes	N/A	20	Yes	Yes	No	No	1.27	N/A	4.6	Improvement
[15]	56/M	PsO	IFX	N/A	N/A	9	1.13	73	N/A	N/A	No	N/A	27	Yes	No	No	UST	N/A	95	0.82	Stable
[16]	37/M	AS	IFX	No	No	36	1.23	68.4	1.75	100,000/mL	No	N/A	6	No	No	No	No	N/A	N/A	N/A	Stable
[17]	52/M	AS	IFX	Yes	Yes	48	1.6	34.1	1.08	N/A	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	Stable
	46/M	AS	IFX	Yes	Yes	17	N/A	N/A	> 2.0	N/A	N/A	N/A	N/A	No	No	No	MTX, CyA	N/A	N/A	< 1.0	Improvement
[18]	41/M	RA	ADA	No	No	59	1.55	54.8	2.25	20–30/HPF	No	M1E0S1T2C0	48	Yes	Yes	No	RTX, BALI	N/A	42.2	1.9	Stable
	35/F	RA	GLM	No	No	36	0.69	112.8	0.47	N/A	No	M1E1S1T2C0	24	Yes	PSL. CPA	No	RTX, AZA	N/A	73.3	0.09	Improvement

Table 2 (continued)

Refs.	Age/sex	Underlying disease	TNFi	Prior to initiation of TNFi		Kidney features at biopsy diagnosis					Kidney biopsy findings		Management and outcome at final observation								
				IgAN diagnosis	Urinalysis abnormality	TNFi administration (months)	sCr (mg/dL)	eGFR	Proteinuria (g/gCr or g/day)	Hematuria	Cellular or fibrocellular crescent	MEST-C	Follow-up (months)	TNFi discontinuation	Corticosteroid for IgAN	Tonsillectomy for IgAN	Treatment for underlying disease	sCr (mg/dL)	eGFR	Proteinuria (g/gCr or g/day)	Kidney outcome
	59/F	RA	ADA	No	N/A	70	0.92	68	4.55	N/A	No	M1E1S1T2C0	N/A	Yes	Yes	No	RTX	N/A	65	0.13	Improvement
[19]	28/F	GPP	IFX	No	Yes	< 36	0.87	N/A	3.04	> 100/HPF	Yes	M1E0S1T0C1	5	Yes	mPSL pulse	Yes	SCK	0.7	N/A	0.2	Improvement
Present cases																					
Case 1	40 s/M	CD	IFX	No	Yes	79	1.57	40	3.20	50–99/HPF	No	M1E0S1T1C0	55	No	Yes	Yes	IFX	1.32	47	0.05	Improvement
Case 2	30 s/M	CD	ADA	No	Yes	24	1.86	35.2	4.33	50–99/HPF	Yes	M0E1S1T1C1	7	No	Yes	Yes	ADA	1.43	46.9	0.68	Improvement
Case 3	30 s/M	CD	IFX	No	Yes	36	1.59	44.9	0.6	5–9/HPF	No	M1E0S1T1C0	25	No	Yes	Yes	IFX	1.38	51.4	0.2	Improvement

ADA Adalimumab; *AS* ankylosing spondylitis; *AZA* azathioprine; *BALI* baricitinib; *CD* Crohn's disease; *CPA* cyclophosphamide; *CyA* cyclosporin; *eGFR* glomerular filtration rate estimated with the CKD-EPI formula and expressed in mL/min/1.73 m^2; *ESKD* end-stage kidney disease; *GLM* golimumab; *GPP* generalized pustular psoriasis; *HD* hemodialysis; *IgAN* immunoglobulin nephropathy; *IFX* infliximab; *KT* kidney transplantation; MEST-C according to the Oxford classification; *mPSL* methylprednisolone; *N/A* not available; *PSL* prednisolone; *PsO* psoriasis; *RA* rheumatoid arthritis; *Ref.* reference; *RTX* rituximab; *SCK* secukinumab; *sCr* serum creatinine; *TNFi* anti-tumor necrosis factor-alpha inhibitor; *UST* ustekinumab; *VDZ* vedolizumab

evident. However, we cannot rule out the possibility that our three patients developed a relapse of the natural course of IgAN independent of TNFi therapy.

There is currently no practice guideline on whether TNFi therapy should be discontinued for TNFi-target diseases such as CD when IgAN or other complications occur. Singh et al. reported a case of TNFi-associated IgAN in which discontinuation of TNFi therapy resulted in decreased proteinuria but recurrence of CD, and both CD and IgAN improved when TNFi therapy was resumed [5]. In another study, one-third of patients discontinued TNFi therapy because of post-IBD remission relapse after 1 year [24]. Furthermore, in a Korean study, more than 60% of patients with CD developed relapse 5 years after discontinuation of TNFi therapy [25]. Based on these previous studies, we continued TNFi therapy in our patients to balance the treatments of CD and IgAN.

CD and IgAN may have overlapping etiological factors, including increased intestinal mucosal permeability, elevated levels of mucosal IgA, T cell dysfunction, and susceptibility genes, such as HLA-DR1. Thus, when the two diseases coexist, their disease states are often perceived to be concurrent. However, in our three cases, IgAN flared while CD remained in remission. We hypothesized that TNFi, a shared factor among our three cases, induced a Th1/Th2 imbalance, leading to the discrepancy between IgAN and CD disease status. According to the "hygiene hypothesis," IgAN is more likely to develop when T helper 2 (Th2) cytokines predominate over Th1 cytokines. Excessive activity of T cells, particularly the Th2, T follicular helper (Tfh), Th17, and Th22 subpopulations, is reportedly involved in the etiology of IgAN [26]. An overactive Th1 response has been observed in the inflamed mucosa and serum of IBD patients [27]. Because TNF-α is a crucial component in the Th1 cytokine cascade, chronic blockade of TNF-α may induce Th2 dominance of cytokines [28]. In our patients, the combination of corticosteroid therapy and tonsillectomy was effective for attenuating the acute deterioration of kidney function and was well tolerated without worsening CD. Tonsillectomy has long been performed to treat IgAN, particularly in Japan, and recent studies have shown that the combination of tonsillectomy and corticosteroid pulse therapy provides better kidney disease outcomes than corticosteroid pulse therapy alone [29]. However, tonsillar lymphocytes in patients with IgAN have been shown to exhibit polarity toward a Th2 response [30], and tonsillectomy can reportedly increase susceptibility to CD [31]. This may further support the hypothesis that Th1/Th2 imbalance is involved in the predominance of CD or IgAN (Fig. 3). Further case studies and research are essential to substantiate this hypothesis.

In conclusion, we experienced three cases of acute exacerbation of IgAN during long-term treatment of CD. These exacerbations were effectively attenuated by the combination of corticosteroid pulse therapy and tonsillectomy without discontinuing TNFi therapy, while CD remained in remission. Our cases together with similar cases reported previously suggest that among chronic inflammatory diseases, CD is the most likely underlying disease to cause acute exacerbation of latent or previously diagnosed IgAN during TNFi therapy. Therefore, such patients' urinary indices and kidney function should be carefully monitored. Further case information and clinical studies are needed to clarify the etiology of IgAN in patients with IBD.

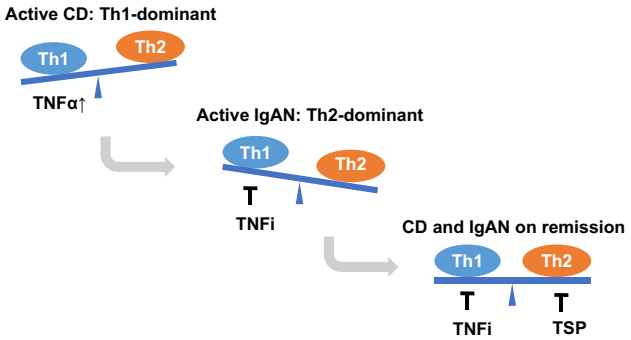

Fig. 3 Hypothesis regarding Th1/Th2 balance in CD and IgAN for our three patients. CD is a Th1-dominant disease and is closely associated with TNF-α activation. Long-term administration of TNFi therapy may have tilted the patients toward Th2 dominance and increased susceptibility to IgAN, a Th2-dominant disease. TSP is thought to suppress Th2. Combining these two treatment strategies (i.e., TNFi therapy and TSP) may have balanced the disease activity of CD and IgAN. *CD* Crohn's disease; *IgAN* immunoglobulin nephropathy; *Th1* type 1 helper T cells; *Th2* type 2 helper T cells; *TNFi* TNF-alpha inhibitor; *TSP* tonsillectomy and steroid pulse therapy

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This study did not conduct any tests on any human participants or animals.

Informed consent Informed consent was obtained from all individual participants involved in the study.

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