

Effect of infliximab on inflammatory bowel disease with Takayasu arteritis

— Case series and review of the literature —

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Abstract

Takayasu arteritis (TA) and inflammatory bowel disease (IBD) are chronic inflammatory disorders. The mechanisms underlying these diseases are not precisely known, but tumor necrosis factor alpha (TNF- α) is considered to have an important role in the pathophysiology of both TA and IBD. Simultaneous occurrence of both TA and IBD is rare. Our first case was a 42-year-old woman with TA and inflammatory bowel disease unclassified. The patient was refractory to treatment with an immunomodulator, and infliximab (IFX) was started. After starting IFX, clinical remission was achieved and maintained for 2 years. The second case was a 34-year-old woman with TA accompanied by Crohn's disease. Because her abdominal symptoms relapsed despite treatment with an immunomodulator, IFX was started. Both diseases were well controlled for 2 years by scheduled maintenance therapy with IFX. Relapse of the TA required increased doses of IFX at shorter intervals, which relieved her symptoms.

From literature we identified and our cases, there were nine cases for which IFX was effective. They may demonstrate the efficacy of IFX for IBD with TA and emphasize the role of TNF- α in the pathophysiology of them.

Keywords

Takayasu arteritis • Inflammatory bowel disease • Tumor necrosis factor alpha • Infliximab

Introduction

Takayasu arteritis (TA) is a chronic inflammatory vasculitis of unknown etiology that affects the large vessels, predominantly the aorta and its main branches. Vessel inflammation leads to wall thickening, fibrosis, stenosis, and thrombosis formation. Various ischemic symptoms appear depending on the affected arteries, such as chest, limb, and abdominal pain [1, 2].

Although TA has been associated with other autoimmune diseases, such as glomerulonephritis, systemic lupus erythematosus, juvenile idiopathic arthritis, anterior uveitis, sarcoidosis, and Sweet's syndromes, the coexistence of TA and inflammatory bowel disease (IBD) is rare [1-3].

The pathogenesis of both TA and IBD remains unclear. A common pathomechanism between the two diseases, however, is conceivable, because treatment with anti-tumor necrosis factor alpha (TNF- α) antibody often leads to a favorable clinical outcome of TA and IBD [4-7].

Several case reports have demonstrated the therapeutic effects of anti-TNF- α antibody in IBD with TA [6-10]. We herein report our two cases of IBD with TA successfully treated with infliximab (IFX) and discuss previously published reports of the efficacy and safety of IFX treatment for IBD with TA.

Case Report

Case 1

A 42-year-old woman suffering from TA with severe arterial stenosis was followed as an outpatient at the Department of Cardiovascular Medicine, Kyoto University Hospital. In April 2007, she complained of recurrent abdominal pain with hematochezia. Colonoscopic findings revealed multiple ulcerations from the ileocecal region to the ascending colon. Contrast-enhanced computed tomography revealed stenosis of the superior mesenteric artery root. We considered that her abdominal symptoms were due to ischemia of the superior mesenteric artery. Percutaneous transcatheter angioplasty of the superior mesenteric artery was performed but did not relieve her symptoms. Colonoscopic findings after percutaneous transcatheter angioplasty revealed no significant change. Although her colonoscopic findings mimicked ulcerative colitis (UC), the involved areas were inconsistent with UC (Fig. 1). Histological findings of biopsy specimens from colonic mucosa revealed chronic inflammatory features with no characteristic features of UC and Crohn's disease (CD). Fecal culture was negative for pathogenic microbes. Intranuclear inclusion body of cytomegalovirus was not detected in biopsy specimens. Contrast-enhanced computed tomography did not reveal any abnormality of her small intestine. Therefore, she was diagnosed with inflammatory bowel disease unclassified (IBDU) accompanied by TA. Administration of prednisolone (PSL) and mercaptopurine did not

ameliorate her symptoms, and therefore IFX treatment was initiated. Following treatment with IFX, her abdominal symptoms subsided and clinical remission of her IBD was maintained by scheduled maintenance therapy with IFX. She was successfully tapered off the PSL and contrast-enhanced computed tomography revealed no new vascular lesions.

Case 2

A 34-year-old woman presented with anterior neck pain. Physical examination showed bruit of left carotid artery on auscultation. Contrast-enhanced computed tomography revealed stenoses of left carotid artery, aortic arch, celiac artery and superior mesenteric artery. These clinical and imaging findings met the criteria of TA described in the Japanese Circulation Society guideline. Therefore, she was diagnosed with TA and treated with oral administration of PSL. She complained of worsening diarrhea and body weight loss under the treatment with PSL 10 mg/day. Colonoscopy revealed multiple ulcerations at the terminal ileum. Histologic findings of biopsy specimens obtained from the ulcerative lesions indicated noncaseating granuloma and led to a diagnosis of CD. She was started on 2250 mg/day mesalazine and 50 mg/day azathioprine (AZA) with continued PSL at 10 mg/day. Although her abdominal symptoms subsided for 7 months after combined treatment with mesalazine and AZA, her symptoms recurred. Double-balloon enteroscopy revealed discontinuous longitudinal ulcers from the distal ileum to

the ileocecal valve (Fig. 2). Because her CD disease activity was not controlled with conventional therapies, treatment with IFX was initiated. After starting 5 mg/kg of IFX, clinical remission of her CD was rapidly achieved and treatment with PSL could be tapered off completely. Although she exhibited no symptoms related to CD by a scheduled maintenance therapy with IFX for 2 years, laboratory data revealed gradually increasing serum C-reactive protein (CRP) levels. The uptake of fluorodeoxyglucose in the thoracic aorta wall in positron emission tomography suggested that the increased serum CRP levels were associated with TA activity (Fig. 3a). The dose of IFX was increased (from 5 mg/kg to 10 mg/kg) and the dosing interval was shortened (from every 8 weeks to every 6 weeks) to normalize the CRP levels. The uptake of fluorodeoxyglucose in the thoracic aorta wall in positron emission tomography disappeared and double-balloon enteroscopy revealed the disappearance of multiple ulcerations in the distal ileum (Fig. 3b).

Characteristics and outcomes of the 9 patients with IBD and TA treated with anti-TNF- α agents

Including our 2 cases, there have been a total of 9 cases (8 women, 1 man) with IBD and TA successfully treated with anti-TNF- α agents (Table 1). There were seven cases with CD, one case with UC, and one case with IBDO. IBD preceded TA in 4 of the 9 cases and TA preceded IBD in

our 2 cases. In the remaining 3 cases, IBD and TA were simultaneously diagnosed. Mean age at definitive diagnosis of both IBD and TA was 28 years (median 28 years, range 16-49 years). PSL was administered in all 9 cases and immunomodulators such as AZA, 6-mercaptopurine, and methotrexate were administered in 7 cases before treatment with IFX was initiated. In 8 of 9 cases, the clinical symptoms subsided following the administration of IFX and scheduled maintenance therapy with IFX. In the remaining 1 case, IFX was switched to adalimumab (ADA) because of an allergic reaction to IFX and the patient's clinical symptoms disappeared after switching to ADA. In 5 of 9 cases, PSL was completely tapered after treatment with the anti-TNF- α was initiated.

Discussion

Based on the clinical outcome of our 2 cases, IFX was effective for achieving clinical remission of IBD concomitant with TA. Additionally, IFX treatment inhibited the progression of TA. These findings indicate the possibility that TNF- α is mainly involved in the pathophysiology of IBD concomitant with TA.

The simultaneous occurrence of IBD and TA is considered rare [3, 8]. Reports on IBD concomitant with TA have increased recently, however, although the reason for this is unclear [3, 7-13]. Until now, there have been 56 IBD cases concomitant with TA including our two cases,

and the majority of cases were treated with corticosteroid therapy [3, 6-13].

Treatment with corticosteroids is effective for patients with both IBD and TA, but long-term use of corticosteroids is not necessarily favorable because of the related side effects [1, 2, 14]. Therefore, treatment with immunomodulators is usually started to control inflammation from both diseases as well as other autoimmune diseases. Administration of anti-TNF- α antibody has been considered in recent cases that failed to respond to conventional treatment, including immunomodulators [5-7].

IFX treatment was administered in only a total of 9 of 56 cases, including our 2 cases [6-10]. Only one case required switching from IFX to ADA due to an allergic reaction related to IFX. In all cases, the symptoms of both IBD and TA were ameliorated by treatment with IFX or ADA. These data suggest that anti-TNF- α treatment for IBD concomitant with TA might lead to a clinically favorable outcome compared with other inflammatory diseases. In fact, in our case 2 presented here, exacerbated inflammation of TA during scheduled maintenance therapy with IFX was reduced by increasing the dose and administration interval of IFX. Notably, PSL could be completely tapered off in 5 of 9 cases after starting anti-TNF- α treatment.

HLA analysis revealed that HLA-B52 and DR2 are common genetic factors that predispose to TA and UC [13]. In contrast, there is no clear association between a common HLA genotype shared by both CD and TA, although both diseases are granulomatous in nature with an integral

cell-mediated autoimmune component in the pathogenesis of these two diseases [3, 15]. Both IBD and TA share common features of autoimmune origin. In addition, TNF- α is thought to induce mucosal inflammation in IBD patients and the granulomatous process in the vessel walls of patients with TA. It is therefore likely that treatment with anti-TNF- α agents will be useful in abrogating the immunoinflammatory features of coexisting TA and IBD.

On the other hand, there are some reports of patients with IBD developing TA despite IFX treatment [11, 12]. Because a subpopulation of patients with IBD also has TA subclinically, it is not surprising that TA would appear during treatment for IBD. The mechanism underlying the appearance of TA in IBD patients treated with anti-TNF- α agents, however, is unclear. In addition, because the present study is limited in that previous cases report a short-term follow-up, we cannot comment on the long-term efficacy and safety of IFX treatment, especially when it is necessary to increase the dose and administration interval.

In conclusion, this review of previous cases reports and our cases may demonstrate the efficacy of anti-TNF- α treatment for patients with coexisting IBD and TA, and provide support for treatment with anti-TNF- α agents in cases refractory to conventional therapies. Further follow-up studies with a greater number of patients are required to assess the long-term efficacy and safety of anti-TNF- α therapy.

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Figure legends

Figure 1

Colonoscopy image showing mimicked UC, including friability of mucosa with erythema and ulcerations from the terminal ileum to the ascending colon.

Figure 2

Double-balloon enteroscopy image showing the longitudinal ulcerations in the distal ileum.

Figure 3

a. Positron emission tomography image showing the uptake of fluorodeoxyglucose in the thoracic aorta wall. (*arrow*)

b. Positron emission tomography image showing the disappearance of fluorodeoxyglucose in the thoracic aorta wall. (*left panel*)

Double-balloon enteroscopy image showing the disappearance of multiple ulcerations in the distal ileum. (*right panel*)

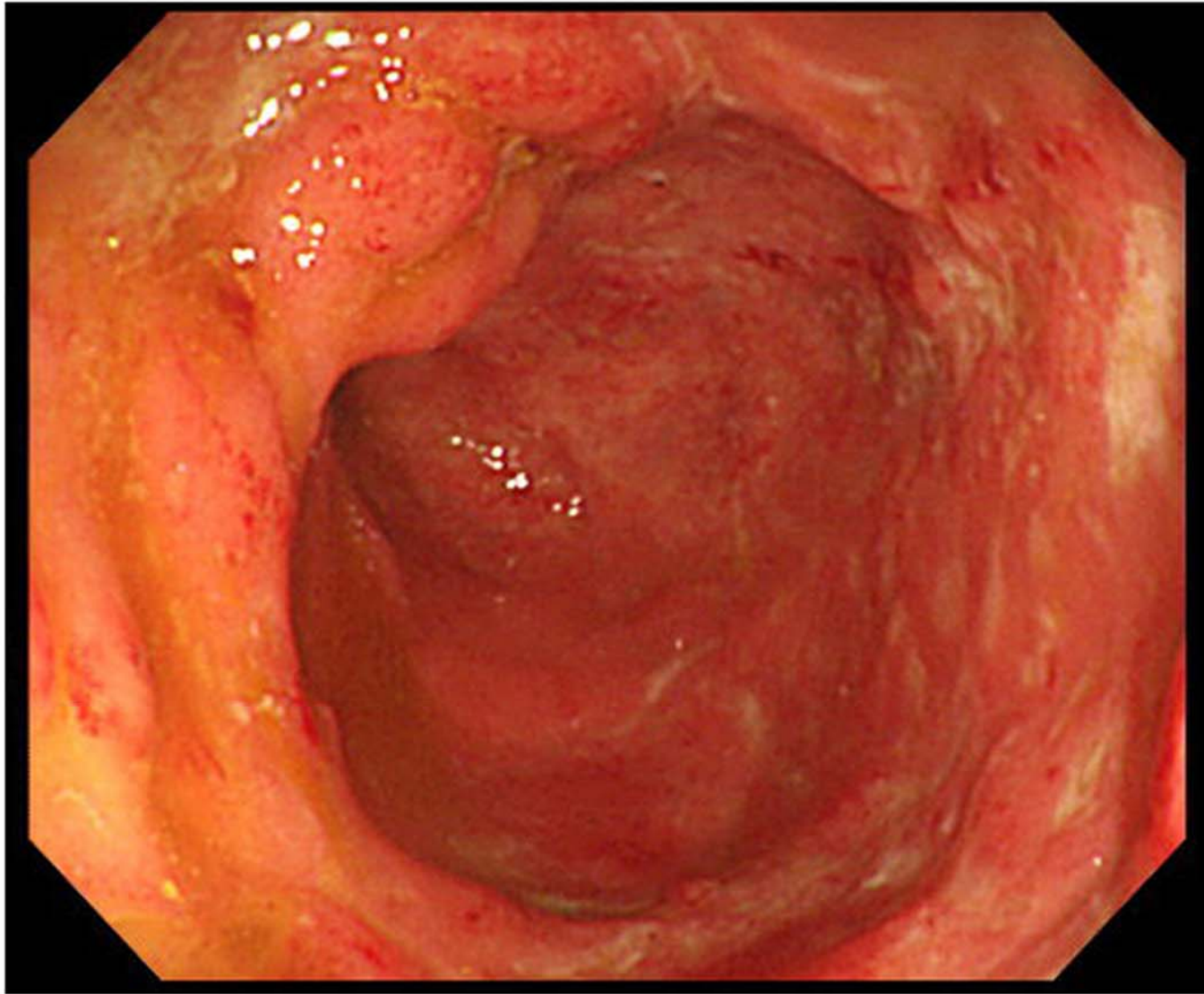


Figure 1

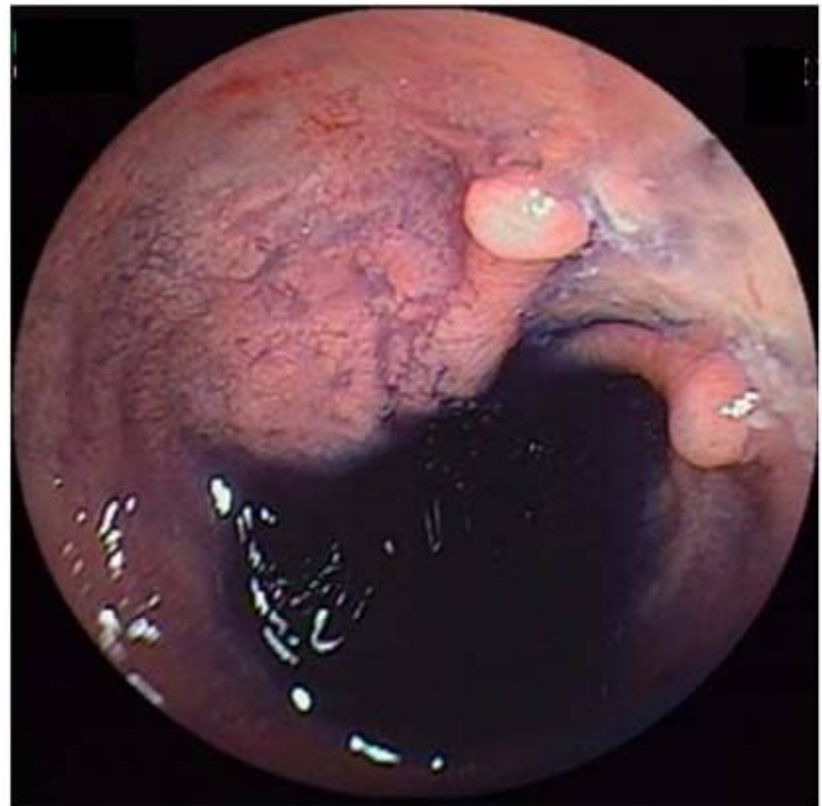
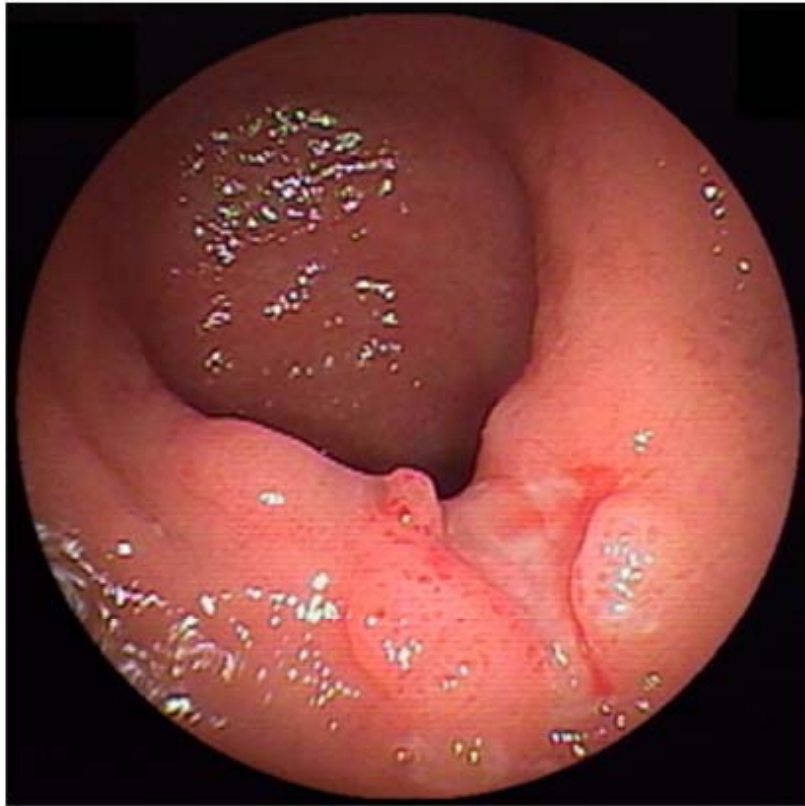


Figure 2

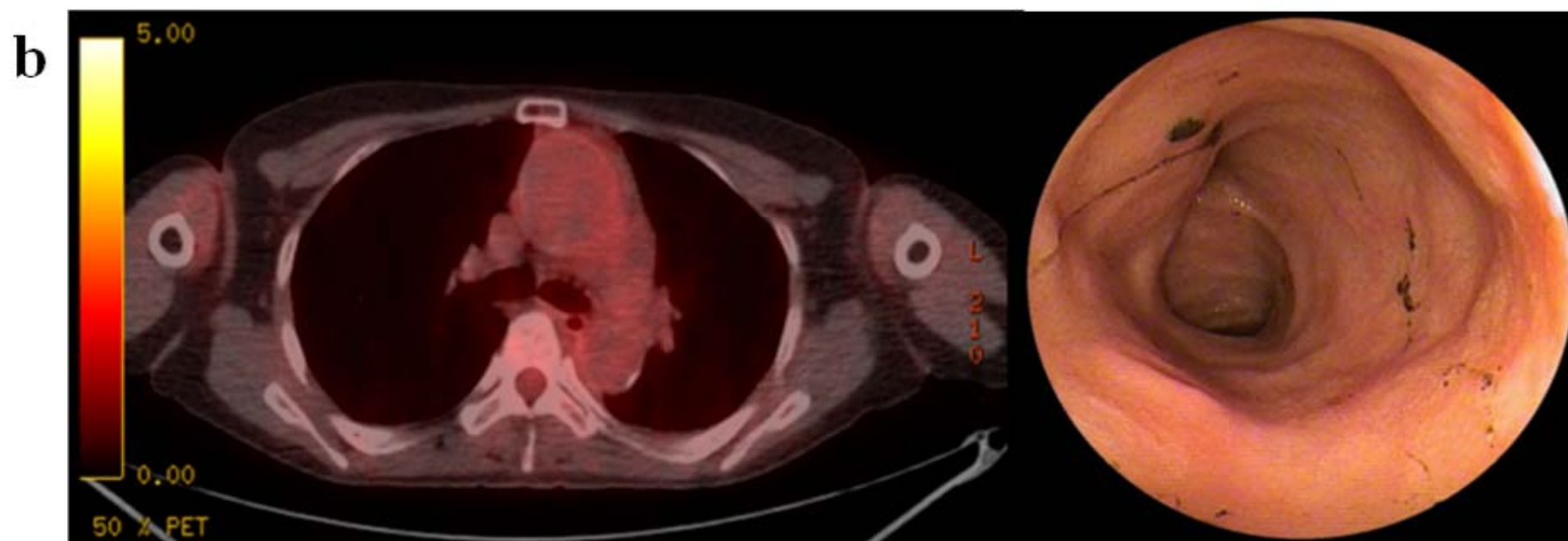


Figure 3

Table

Table 1 9 cases reports of IBD with TA treated successfully by IFX.

Author	Year	Gender	Age at diagnosis.		Therapy	PSL	Reference
			IBD	TA			
Kellermayer	2008	F	12 (CD)	17	PSL, 5-ASA, 6-MP, IFX	discontinuation	8
Judah	2009	F	24 (CD)	24	PSL, IFX	discontinuation	9
		F	30 (CD)	49	PSL, antibiotics, 6-MP, IFX	unknown	
		F	30 (CD)	30	PSL, AZA, IFX, ADA	discontinuation	
Calderon	2010	F	17 (CD)	20	PSL, 5-ASA, MTX, AZA, IFX	unknown	6
Ratuapli	2010	M	16 (CD)	16	PSL, MTX, AZA, IFX	discontinuation	10
Gecse	2011	F	20 (UC)	30	PSL, sulfasalazine, IFX	unknown	7
Our case	2012	F	37 (IBDU)	31	PSL, 6-MP, IFX	discontinuation	
		F	28 (CD)	22	PSL, 5-ASA, AZA, IFX	continuation	

IBDU: inflammatory bowel disease unclassified, PSL: prednisolone, AZA: azathioprine,

6-MP: 6-mercaptopurine, MTX: methotrexate, IFX: infliximab,

ADA: adalimumab, 5-ASA: mesalazine