

## Takayasu's Arteritis in a Patient with Crohn's Disease: An Unexpected Association during Infliximab Therapy

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### Abstract

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We report a 20-year-old woman with Crohn's disease (CD) who developed anterior neck pain while being treated with the anti-tumor necrosis factor (TNF)- $\alpha$  monoclonal antibody, infliximab. She showed no symptoms suggestive of active CD except for tenderness along the left common carotid artery with marked increases in serum TNF- $\alpha$  and inflammatory reactions. Based on thickened walls of large vessels with enhancement effects on computed tomography, she was diagnosed as having associated Takayasu's arteritis (TA), which was successfully treated with corticosteroid. Even if CD is controlled by infliximab, other autoimmune disorders, such as TA, may develop as a complication.

**Key words:** Takayasu's arteritis, Crohn's disease, tumor necrosis factor, infliximab

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### Introduction

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Crohn's disease (CD) is an autoimmune disorder characterized clinically by recurrent involvement of the gastrointestinal tract, particularly the terminal ileum and colon, and pathologically by granulomatous fibrosing inflammation. CD sometimes accompanies other autoimmune inflammation, such as polyarthritis and uveitis, in which Takayasu's arteritis (TA) is also included (1-15). Inflammatory cytokines, such as tumor necrosis factor (TNF)- $\alpha$ , are considered to play an important role in the pathogenesis of TA as well as CD (16, 17), and the anti-TNF- $\alpha$  therapy has been reported to show beneficial therapeutic effects in both disorders (18-21). Here, we describe a patient with CD, who developed TA while being treated with the anti-TNF- $\alpha$  monoclonal antibody, infliximab. As the activity of CD was being well controlled by infliximab, the appearance of TA was completely unexpected in this patient. We review the literature of TA associated with CD, and focus upon the pathogenesis.

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### Case Report

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A 16-year-old Japanese woman developed continuous watery diarrhea with no precipitating cause or significant family history. She was diagnosed as having CD in our hospital based on characteristic endoscopic findings of the colon, such as the cobblestone appearance and longitudinal ulcer (Fig. 1). CD was well controlled by 5-aminosalicylic acid (5-ASA), prednisolone and azathioprine. Nevertheless, the dose of prednisolone could not be tapered to less than 15 mg/day because of recurrence of CD. At the age of 19 the CD exacerbated soon after reducing the dose of prednisolone to 10 mg/day. The doses of 5-ASA and azathioprine were 3,000 mg/day and 50 mg/day, respectively. She started to receive infliximab at a dose of 5 mg/kg every 8 weeks. As clinical symptoms ascribable to CD quickly improved, prednisolone and azathioprine were tapered off in the subsequent 6 months. At the age of 20 she became aware of anterior neck pain and general malaise with intermittent low-grade fever approximately 1 month after the 7th administration of infliximab. The dose of 5-ASA was 2,250 mg/day. These symptoms gradually worsened, and she was admitted

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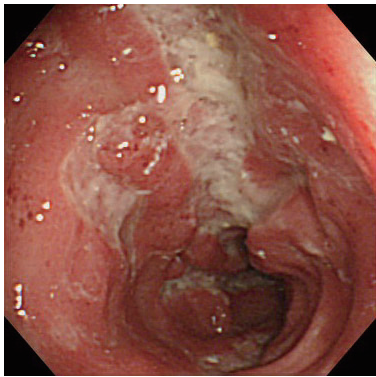
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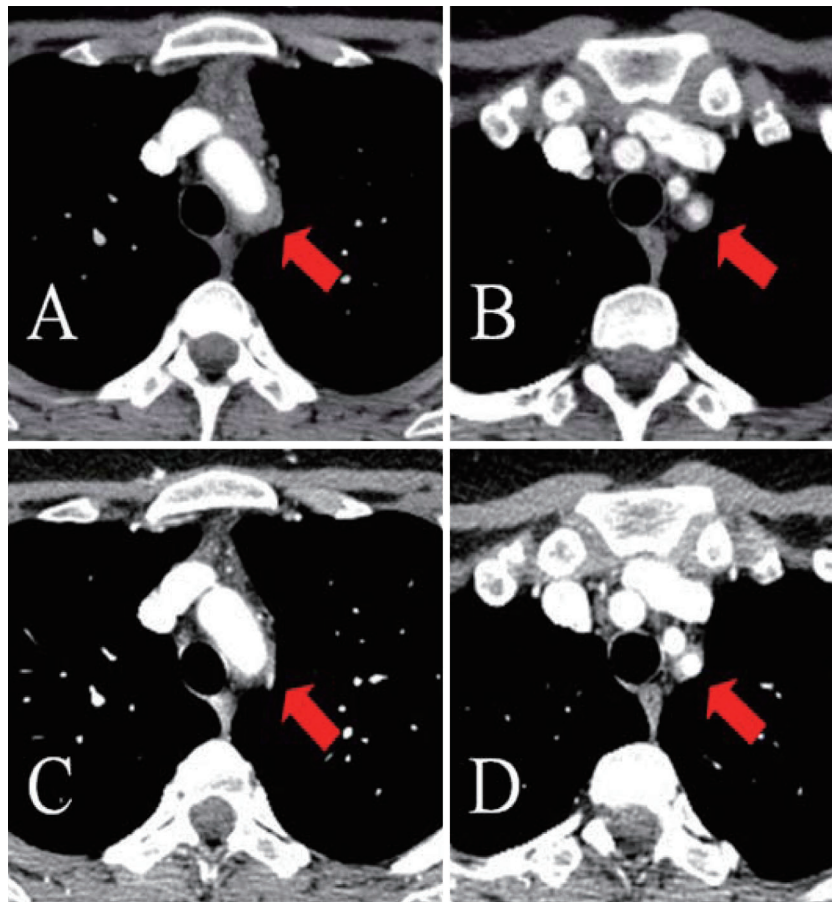
to our hospital.

On admission, physical examination showed cervical tenderness along the left common carotid artery and decreased pulse pressure in the left radial artery. Blood pressure was 98/63 mmHg and 80/0 mmHg in the right and left brachial arteries, respectively. Her body temperature was 36.6°C, and there was no bruit in any part of her body, including the neck and left subclavian area, or abnormal findings in the



**Figure 1.** Small-bowel endoscopy demonstrates longitudinal ulcers typical of Crohn's disease.

abdomen and perineal region suggestive of active CD, such as tenderness and accentuated bowel sounds. She had no skin lesions or tender joints. Neurological findings, including fundus oculi, were unremarkable. Routine laboratory tests demonstrated slight anemia (hemoglobin 9.2 g/dL, normal 10.7-15.3 g/dL) with increases in C-reactive protein (CRP, 7.48 mg/dL, normal <0.1 mg/dL), erythrocyte sedimentation rate (ESR, 97 mm/h, normal 3-15 mm/h) and IgG (2,552 mg/dL, normal 870-1,700 mg/dL). Hematology showed normal counts of WBC (5,220/ $\mu$ L, normal 3,040-8,720/ $\mu$ L) but a slight increase in stab cells (11%, normal 0-10%). Serum TNF- $\alpha$  was markedly elevated (25.6 pg/mL, normal 0.6-2.8 pg/mL), while the concentration of infliximab was 3.95  $\mu$ g/mL. Liver and renal indices and coagulation tests were normal. Autoantibodies, including the rheumatoid factor, anti-nuclear antibody and anti-neutrophil cytoplasmic antibody, were all negative. Chest roentgenogram and electro- and echocardiogram were unremarkable. Computed tomography (CT) demonstrated thickened walls with enhancement effects in the aortic arch (Fig. 2A) and its main branches (Fig. 2B). These findings were absent in other parts of the aorta and large vessels. Ultrasonography in the bilateral carotid arteries showed homogeneous intimal thickening but no obvious increase in blood stream veloci-



**Figure 2.** Computed tomography demonstrates thickened walls with enhancement effects in the aortic arch (A, arrow) and left subclavian artery (B, arrow). These findings improved after corticosteroid treatment (C and D, arrows).

**Table 1.** Clinical Profiles of Reported Cases of Takayasu's Arteritis (TA) Associated with Crohn's Disease (CD)

Report	Sex	Development of TA	Age	At onset of TA			Treatment for TA
				Interval from onset of CD	Activity of CD	Treatment for CD	
Yassinger, 1976 [1]	F	Postdated	15	3 years	+	CS, SASP	Supportive treatment
Owyang, 1979 [2]	F	Postdated	15	2 years	+	SASP	Aneurysmectomy
Friedman, 1979 [3]	F	Postdated	24	3 years	+	CS, SASP	CS
Lenhoff, 1982 [4]	F	Postdated	24	0	+	CS	CS
Van Elburg, 1992 [5]	F	Antedated	14				CS
Hilario, 1998 [6]	M	Postdated	15	4 years	-	CS, SASP, NSAIDs	CS, AZT
Todini, 1999 [7]	F	Postdated	23	13 years	ND	-	CS*
	F	Postdated	24	2 years	-	CS, SASP	CS, CY
Biagi, 2001 [8]	F	Postdated	22	7 years	-	CS, 5-ASA	CS
	F	Antedated	35				CS
Levitsky, 2002 [9]	F	Postdated	21	8 years	-	CS, SASP	Surgical treatment
Reny, 2003 [10]	F	Postdated	36	4 years	ND	CS	CS
	F	Postdated	34	11 years	ND	CS	CS
	F	Antedated	30				CS
	F	Postdated	44	2 years	ND	CS	CS
Ohta, 2003 [11]	F	Antedated	16				CS
Kettaneh, 2003 [12]	F	ND	34	ND	ND	CS, AZT	CS, AZT
	F	Coincided	49	0	+	CS	CS
De Simone, 2006 [13]	F	Antedated	ND				Percutaneous angioplasty
Baqir, 2007 [14]	F	Postdated	20	1 year	+	ND	ND
Farrant, 2008 [15]	F	Antedated	24				-
Present patient	F	Postdated	20	4 years	-	Infliximab	CS

\*Immunosuppressive agents were also used, but details are unknown.

CS: corticosteroid, CY: cyclophosphamide, AZT: azathioprine, 5-ASA: 5-aminosalicylic acid, SASP: salicylazosulfapyridine  
NSAIDs: non-steroidal anti-inflammatory drugs, ND: not described

ties. The small intestine was slightly edematous on CT possibly because of CD involvement. There were no abnormal findings either in serological data, such as the anti-EB virus antibody, or on CT suggestive of infection.

Shortly after commencement of prednisolone at a dose of 40 mg/day (0.8 mg/kg), cervical tenderness and fever dramatically improved in parallel with a decrease in CRP and ESR. The difference in systolic blood pressure between the brachial arteries decreased from 18 to 8 mmHg, and CT demonstrated obvious improvement of thickening and enhancement effects (Fig. 2C and D). One month after admission, both infliximab and the human anti-chimeric antibody against it (HACA) were undetectable in serum with an elevated level of TNF- $\alpha$  (13.9 pg/mL). The patient was discharged from our hospital with prednisolone at a dose of 35 mg/day. Both TA and CD have remained in remission with a gradual decrease in the dose of prednisolone over the following 3 months.

## Discussion

The present patient showed anterior neck pain and fever with no evidence of infection while being treated with infliximab. On the basis of marked increases in inflammatory reactions, such as CRP and ESR, and CT findings demonstrating thickened walls with enhancement effects, she was diagnosed as having TA according to the classification criteria of the American College of Rheumatology (22). CT did not demonstrate either irreversible stenosis or aneurysmal formation in large vessels, and the difference in systolic blood pressure between the brachial arteries quickly decreased in response to prednisolone. These findings suggest that TA in the present patient occurred in a relatively short

period from onset of disease. Corticosteroid treatment was clearly effective for TA, and its dose has been successfully tapered in the outpatient clinic. We plan to restart the infliximab therapy for CD after reducing the dose of prednisolone to the minimum necessary to control the activity of TA in order to avoid infection.

The most notable point in the present patient is that TA developed during the infliximab therapy for CD. The precise pathogenesis of TA in the present patient remains unclear, but there are 2 possible causes worth consideration. One is an adverse effect of infliximab. A recent report has demonstrated that 132 patients developed vasculitis secondary to TNF-targeting agents, including infliximab (23). In that report, however, approximately 72% of the patients showed involvement of vasculatures localized to the skin, and there was no case of TA. Considering that granulomatous inflammation in TA is in part dependent on TNF as seen in CD (16, 18, 24), and suppression of this cytokine has been reported to show good therapeutic effects in both disorders (18-21), infliximab may be irrelevant to the pathogenesis of TA in the present patient.

The other possible cause of TA is an autoimmune inflammatory mechanism common with CD. With regard to the Th1/Th2 balance both TA and CD are Th1-predominant, and Th1 cytokines play an important role in the pathogenesis of these disorders (25, 26). Clinical details of 21 reported cases of TA associated with CD are summarized in Table 1 (1-15). CD preceded TA in 13 reported cases as seen in the present patient. In these cases TA developed while being treated with corticosteroid, azathioprine and/or disease modifying drugs, such as 5-ASA, irrespective of the activity of CD. To date, no report has described any CD patient showing development of TA during infliximab therapy. According to a re-

cent report the clinical outcome of CD patients treated with infliximab depends upon its serum concentration 1.5 to 2 months after administration (27). Disease activity of CD in the present patient was well controlled by infliximab, but this drug was undetectable in serum with a markedly elevated level of TNF- $\alpha$  2 months after administration. TA sometimes requires a higher dose of infliximab than CD in order to maintain remission (18). In the present patient, therefore, low serum levels of infliximab may have failed to sufficiently suppress an autoimmune inflammatory mechanism leading to the development of TA, such as Th1-skew status. As HACA was negative, low serum levels of this drug in the present patient are probably due to a rapid clearance of immunoglobulin, although the precise mechanisms remain unknown. Increasing the dose of infliximab was considered to be a possible therapeutic option, but this is not

yet allowed in Japan.

In summary, insufficient concentrations of infliximab may have allowed TA to develop in the present patient. Infliximab is clearly effective for CD, but other autoimmune disorders, such as TA, occasionally develop even under regular administration of this drug. To avoid overlooking these associated disorders, it is necessary to pay attention to signs and symptoms untypical of CD.

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