

[CASE REPORT]

Changes in Colonic Inflammation Related with Takayasu Arteritis during a 10-year Observation Period

Akinori Wada, Masaaki Higashiyama, Dai Hirata, Suguru Ito, Rina Tanemoto, Shin Nishii, Akinori Mizoguchi, Kenichi Inaba, Nao Sugihara, Yoshinori Hanawa, Kazuki Horiuchi, Yoshihiro Akita, Kazuyuki Narimatsu, Shunsuke Komoto, Kengo Tomita and Ryota Hokari

Abstract:

Takayasu arteritis (TA) sometimes presents with colitis, which may be diagnosed as inflammatory bowel disease unclassified (IBDU) because of atypical or mixed findings of ulcerative colitis (UC) and Crohn's disease. We herein report an 18-year-old girl presenting with colitis with an occasional high fever eventually diagnosed as TA with IBDU. Colonic inflammation was initially discontinuous and stronger in the proximal colon, atypical of UC. However, over 10-year observation, the distribution of colonic inflammation varied and became UC-like. Variations in TA-related colonic inflammations over time have been unclear. Our long-term observation might help clarify the details of TA-related colonic inflammation.

Key words: Takayasu arteritis (TA), inflammatory bowel disease unclassified (IBDU), ulcerative colitis (UC), colonic inflammation

(Intern Med 61: 475-480, 2022)

(DOI: 10.2169/internalmedicine.7287-21)

Introduction

Vasculitis is defined as inflammation directed at vessels that compromises or destroys the vessel wall, leading to hemorrhagic and/or ischemic events (1). Takayasu arteritis (TA) is a chronic vasculitis that mainly affects the aorta and its branches, and its etiology has not been uncertain (2). Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract with an unknown etiology. Although IBD and TA are rare diseases, there are some case reports of IBD complicated with TA (IBD-TA), and the frequency was estimated to be between 6.4% and 9.2% in Japan (3, 4) and almost the same in other countries (5.8-9.3%) (5). Therefore, there may be a pathophysiological link between these two diseases, although none has been clarified. While there have been several case reports and studies showing the co-existence of IBD and TA, few have described the changes in colonic findings over a long period of time in detail.

We herein report a case of IBD-TA that showed an altered

distribution of colonic inflammation over a 10-year period of treatment, which might be a distinct characteristic of colonic inflammation related to TA.

Case Report

An 18-year-old Japanese girl visited a general hospital with complaints of a continuous intermittent fever, diarrhea and bloody stool in 2011. She was diagnosed with ulcerative colitis (UC) (pancolitis type) in the hospital and treated with mesalazine for about one year (no precise information was obtained).

She was in remission but subsequently stopped visiting the hospital, and her abdominal symptoms reappeared half a year later. At that time, treatment was restarted with mesalazine (4 g/day), but her symptoms were resistant to mesalazine, and she was referred to our hospital in August 2012. Laboratory tests showed a slight increase in her white blood cells (WBCs; 9,500/ μ L), an elevated erythrocyte sedimentation rate (ESR; 97 mm/h), elevated C-reactive protein (CRP; 7.4 mg/dL) and increased platelet count (686,000/ μ L)

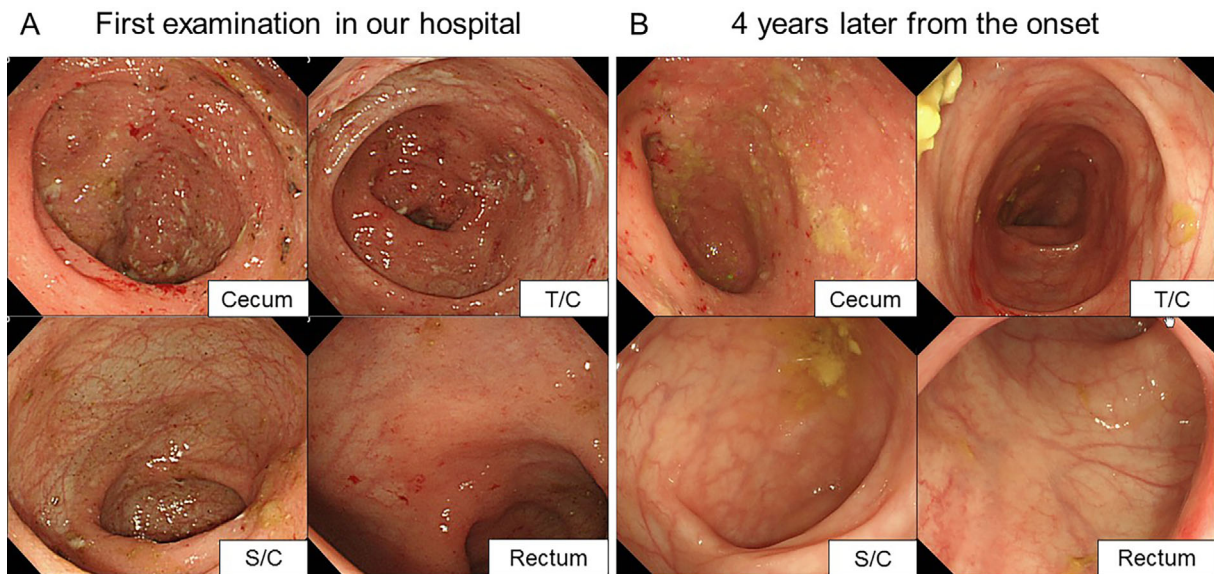


Figure 1. A: Colonoscopy images two years after the onset. Discontinuous distribution of mucosal inflammation was observed. Moderate inflammation from the cecum to the transverse colon and mild inflammation in the rectum along with normal mucosa from the descending colon to the sigmoid colon. B: Colonoscopy images four years after the onset. Moderate inflammation was observed only in the cecum and ascending colon. T/C: transverse colon, S/C: sigmoid colon

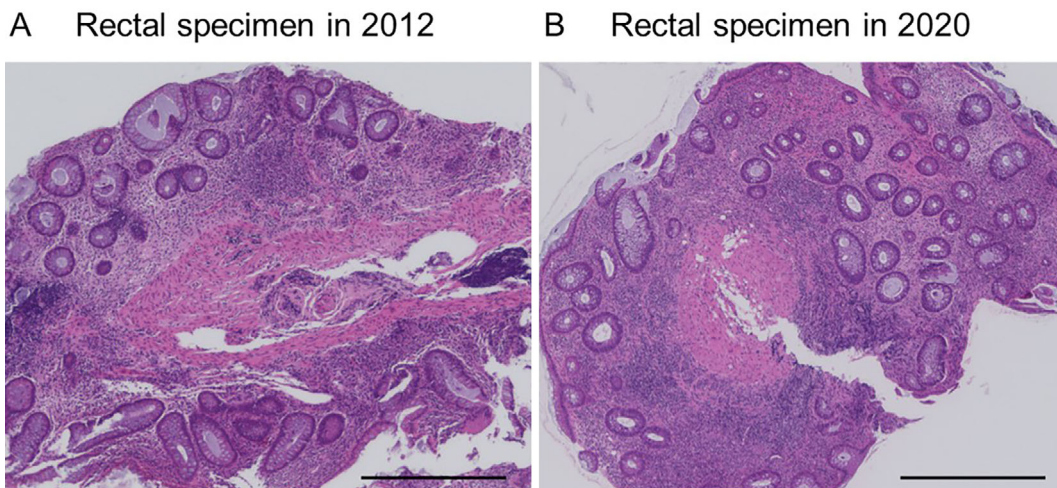


Figure 2. A: Histopathological images of a rectal biopsy specimen two years after the onset. Crypt distortions and proctocolitis with basal plasmacytosis were observed. There were no granuloma formations. B: Histopathological images of rectal biopsy specimen 10 years after the onset. Crypt distortions, Paneth cell metaplasia and proctocolitis with basal plasmacytosis were observed. There were no granuloma formations. Bar=500 μ m.

accompanied by a slightly anemic state (red blood cells: 3.4 million/ μ L, hemoglobin: 9.2 g/dL). Fecal culture showed no pathologic bacteria. The colonoscopy findings showed discontinuous distribution of mucosal inflammation, with moderate inflammation from the cecum to the transverse colon and mild inflammation in the rectum along with normal mucosa from the descending colon to the sigmoid colon (Fig. 1A). Histopathological findings showed proctocolitis with basal plasmacytosis (Fig. 2A). Colonoscopy showed inflammatory mucosa from the cecum to the transverse colon,

resembling a lesion in UC, not Crohn's disease (CD). However, the lesion was discontinuous, and the distribution was atypical of UC. Therefore, she was diagnosed with IBD unclassified (IBDU).

Prednisolone (PSL) 40 mg/day was administered, and the inflammation improved. PSL was then gradually reduced, but when the dose was reduced to 5 mg/day (three months later), a fever and bloody stool reappeared, and laboratory examinations revealed an elevated inflammatory response (CRP 3.0 mg/dL) and anemia (Hb 8.0 g/dL), even though

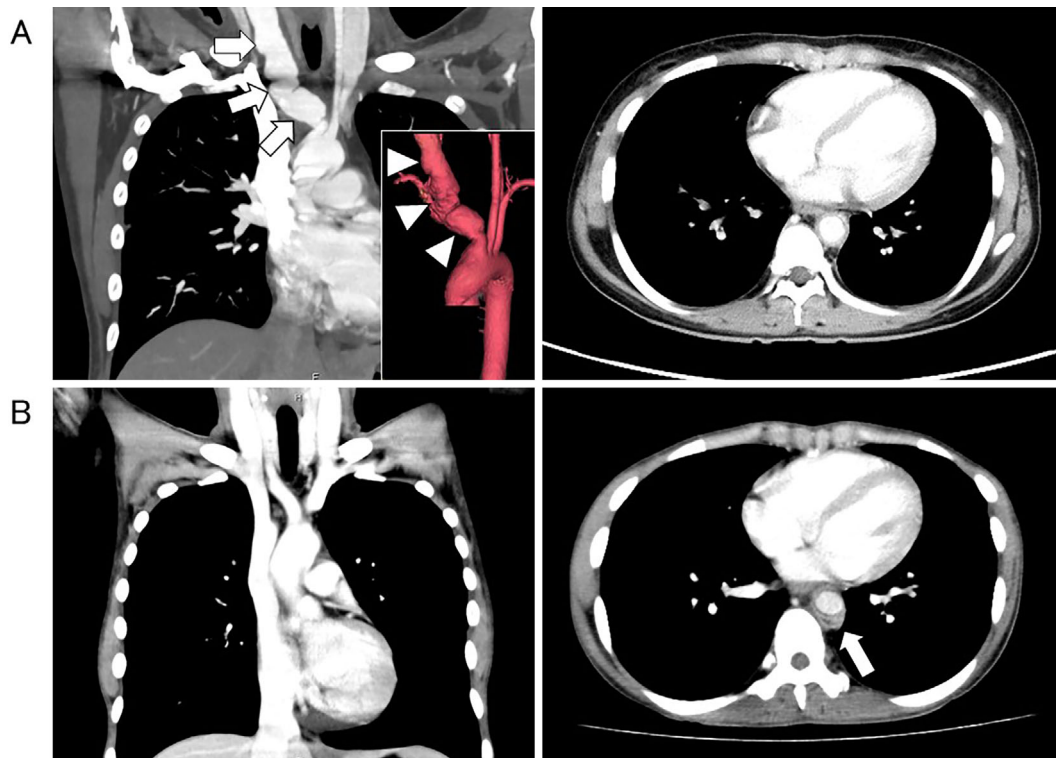


Figure 3. A: Computed tomography (CT) at the diagnosis of TA. Left: Dilated brachiocephalic artery (arrows, arrowheads in the inset) were observed. Three-dimensional reconstruction of the aorta and its branches is shown in the inset. Right: No obvious abnormal findings were observed around the aorta. B: CT taken for screening of a sustained fever one year before the diagnosis of TA. Left: No dilated brachiocephalic artery was observed. Right: Thickened soft tissue around the aorta was noticed retrospectively (an arrowhead).

azathioprine (50 mg/day) had been temporarily added. Thereafter, an increased PSL dose ameliorated the fever and inflammatory response. Infliximab (IFX) 5 mg/kg (200 mg per 8 weeks) was started for maintenance therapy, and PSL was gradually tapered off.

She achieved clinical remission temporarily. However, about half a year later, bloody stool reappeared along with a high fever. We shortened the infusion interval of IFX from 8 weeks to 5 to 6 weeks, and the high fever gradually improved, but the CRP level was not normalized. The dosage of IFX was increased to 300 mg from March 2014, and colonoscopy findings showed moderate inflammation in the proximal colon in July 2014 (Fig. 1B). However, she was suffering from mild bloody stool, and at the same time, upper respiratory symptoms (shortness of breath and cough) appeared.

Computed tomography (CT) showed marked dilatation of the brachiocephalic artery to the right common carotid artery (Fig. 3A), suggesting that the lesion was large-vessel vasculitis caused by TA. At that time, her blood pressure was within normal limits with no marked bilateral difference (90/58 mmHg). No arrhythmia or heart murmur was detected, nor were there any ocular or skin lesions. Laboratory data showed an increased inflammatory response (CRP 2.5 mg/dL), anemia (Hb 7.7 g/dL), and high level of IgG (1,938 mg/dL). IgM, IgA, IgG4, C3 and C4 were within the nor-

mal ranges. Antinuclear antibodies PR3-ANCA and MPO-ANCA were all negative. MR angiography performed at the same time showed no cerebrovascular inflammation. Positron emission tomography-CT (PET-CT) was not performed. Other vasculitides, congenital diseases, infections, Behçet's disease, and IgG4-related diseases were ruled out, and we diagnosed her with TA accompanied by IBDU according to "Guideline for Management of Vasculitis Syndrome (JCS 2008)" (6).

After the diagnosis, we checked her human lymphocyte antigen (HLA) type, and she had HLA-B52. On reviewing the previous findings from CT performed one year earlier for screening of a sustained fever (Fig. 3B), we noted thickened soft tissue around the aorta, suggesting that TA had already developed more than one year ago. She was then referred to a doctor in the department of collagen disease and administered PSL to treat TA. Her respiratory symptoms and CRP then gradually improved. As there have been reports of several patients suffering from an adverse effect of vasculitis induced by IFX (7) and her abdominal symptoms continued while receiving IFX, the dose and duration of IFX were decreased to 200 mg every 8 weeks. Furthermore, methotrexate was added while tapering the PSL.

For 1 year, remission was sustained, but bloody diarrhea appeared in March 2016. Her CRP level was slightly elevated (0.7 mg/dL), and colonoscopy showed diffuse inflam-

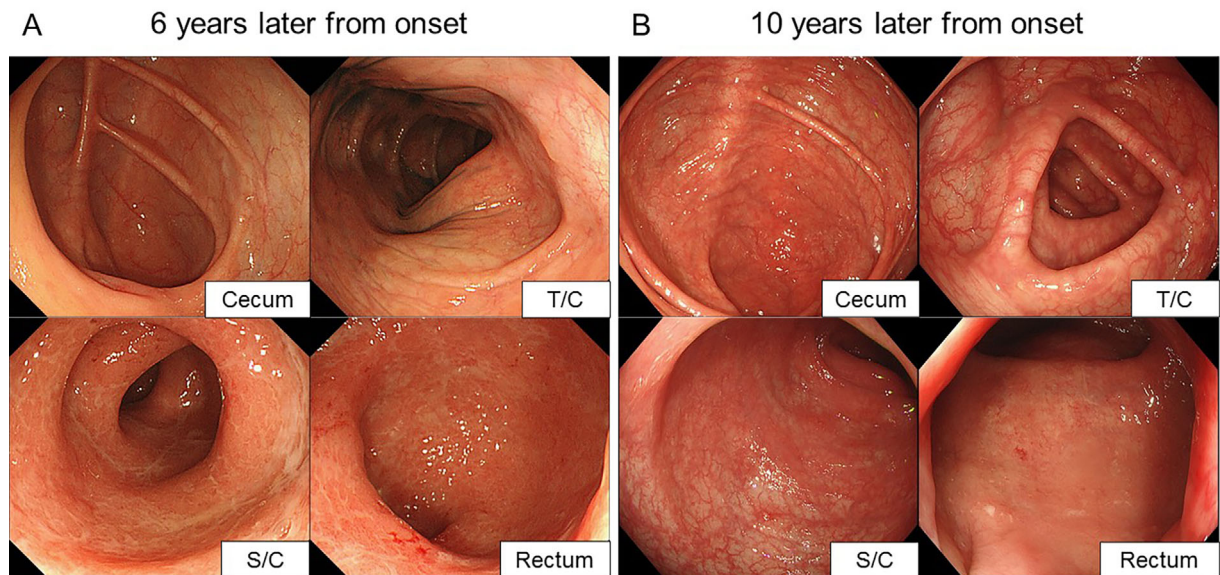


Figure 4. A: Colonoscopy images obtained six years after the onset. Mild inflammation from the sigmoid colon to the rectum was observed, resembling UC. Mucosal inflammation had mostly improved from the cecum to the descending colon. B: Colonoscopy images obtained 10 years after the onset. Inflammation in the sigmoid colon and rectum had mostly improved. T/C: transverse colon, S/C: sigmoid colon

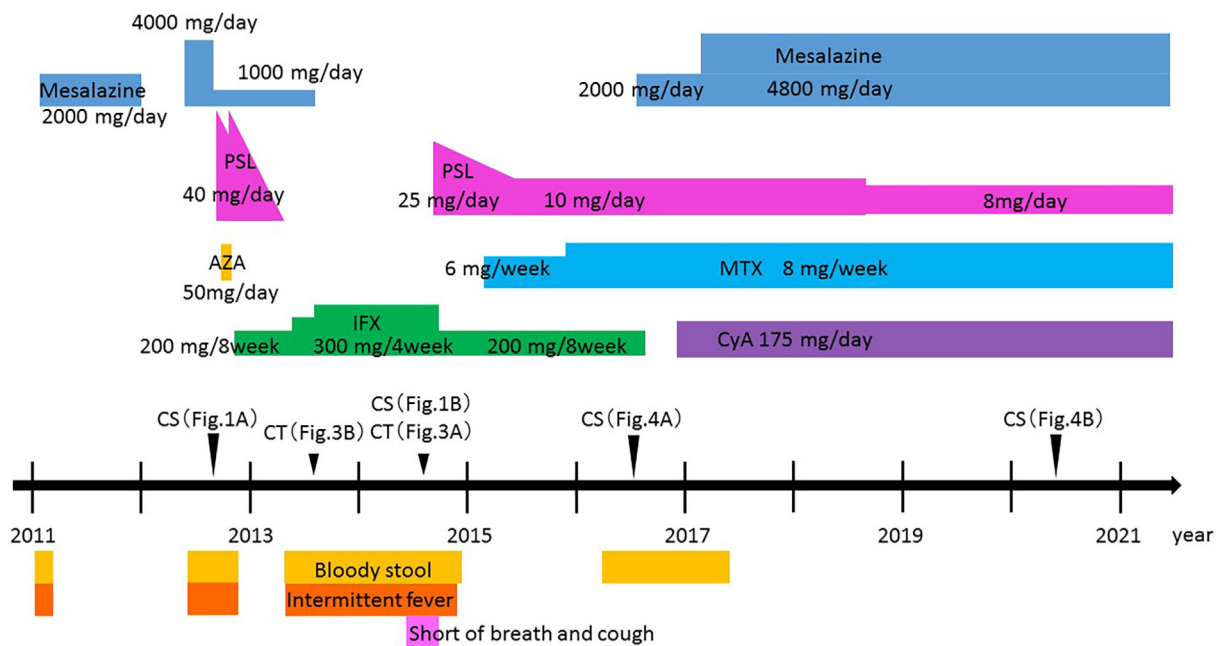


Figure 5. Summary of the medical history. PSL: prednisolone, IFX: infliximab, MTX: methotrexate, CyA: cyclosporine, AZA: azathioprine, CT: computed tomography, CS: colonoscopy

mation from the sigmoid colon to the rectum, as with UC (Fig. 4A). Since her abdominal symptoms did not improve sufficiently even while receiving IFX and adverse effects were concerned, IFX was eventually discontinued. As her abdominal symptoms did not improve sufficiently even after methotrexate (6 mg/week) was administered, cyclosporine was additionally administered to strengthen the treatment of TA. Her symptoms then improved, and CRP was negatively converted, with only mild inflammation in the sigmoid co-

lon and rectum remaining 10 years after the onset of the disease (Fig. 4B). A rectal specimen showed mild inflammation with crypt distortions, Paneth cell metaplasia and proctocolitis with basal plasmacytosis (Fig. 2B), showing no significant difference from the findings gathered previously.

The patient's 10-year treatment history is summarized in Fig. 5. The dilated lesions from the brachiocephalic artery to the right common carotid artery have not changed since the time of the diagnosis, and the patient continues to be under

observation.

Discussion

We herein described the 10-year clinical history of a young woman who developed TA while treating IBDU, during which atypical colonoscopy findings of IBD at the first examination gradually changed and eventually came to resemble typical UC. In cases of IBD presenting with an atypical distribution of colonic inflammation followed by an unexplained fever and increased inflammatory response, TA needs to be differentiated as an accompanying disease.

TA is defined as a granulomatous vasculitis involving the aorta and its major branches, leading to stenosis, occlusion or aneurysmal degeneration of the large arteries. TA is a rare disease, with about 6,000 cases registered in Japan in 2020 (8). The etiology of TA is still unknown; however, it is considered to be a T-cell-mediated autoimmune reaction against large vessels (9). TA and IBD are likely to merge, especially in UC. The frequency of IBD in TA patients was reported to be between 6.4% and 9.2% in Japan (3, 4), and TA and IBD are assumed to have a strong association. The mechanism underlying the merger of both diseases remains unclear.

HLA-B52 is known to be a common genetic background between TA and UC (3) but not between TA and CD. Akiyama et al. reported that the endoscopic features of IBD complicated with TA at the initial diagnosis showed discontinuous and focal mucosal inflammations (87.5%), leading to a typical distribution of UC subsequently in many cases (4), and it was reported that many patients developed IBD first, followed by TA subsequently (10, 11). These clinical characteristics and HLA type were all compatible with the present case. Given that TA and UC possess a common HLA haplotype, an altered distribution of colonic inflammation compared with typical UC might be a distinct characteristic of IBD-TA.

The guideline for the management of vasculitis syndrome was revised in 2017. In 2014, when the present patient was diagnosed with TA, she had systematic symptoms and marked dilatation of the aorta and its primary branches, findings compatible with the revised diagnostic criteria. In addition, other vasculitides, including arteriosclerosis, congenital vascular anomaly, inflammatory abdominal aortic aneurysm, infectious aneurysm, syphilitic mesoarteritis, giant-cell arteritis, vascular Behçet's disease and IgG4-related diseases, were ruled out. Therefore, the diagnosis of TA based on the 2008 guideline was valid, even based on the revised guideline of 2017 (12).

Glucocorticoids (GCs) are the first choice for the treatment of TA. However, TA often relapses during tapering, so in patients who are resistant to or dependent on GC, other immunosuppressive drugs or biologicals are recommended in the guideline concerning the management of vasculitis syndrome (12). Immunosuppressive drugs and anti-tumor necrosis factor (TNF) agents are also used for IBD patients

who are steroid-dependent or steroid-resistant, but there have been some cases in which those drugs were ineffective. While there are some case reports of IFX being effective for IBD with TA, there have been reports of patients with IBD treated with anti-TNF agents developing TA (13). Since TA manifested after the introduction of IFX, the possible involvement of IFX in the TA development in our patient could not be ruled out. However, according to a previous report demonstrating that 132 patients developed vasculitis secondary to TNF-targeting agents (7), vasculitis that occurs after anti-TNF antibody administration is typically small-vessel vasculitis, such as cutaneous vasculitis, peripheral neuropathy, glomerulonephritis and systemic vasculitis, with large-vessel vasculitides such as TA not observed. Therefore, the onset of TA was probably not related to IFX.

Interleukin-6 (IL-6) is a key cytokine playing an important role in the pathogenesis of TA, and tocilizumab (IL-6 receptor inhibitor) was reported to be effective for TA (14). However, since tocilizumab is associated with colonic perforation and perforated diverticular diseases during treatment for rheumatoid arthritis (15), careful attention might be necessary in patients with TA with IBD. It was also reported that IL12B was a susceptibility gene for TA (16), and IL-12/23p40, which is encoded in IL12B, might play a crucial role in TA pathogenesis and UC (3). There was also a report that the biological agent ustekinumab, an anti-IL-12/23p40 antibody, was effective in TA (17). Ustekinumab is also effective against both UC and CD (18, 19) and has already been used as a therapeutic agent. Therefore, ustekinumab might be a future treatment option of IBD with TA.

Not only suppression of vascular inflammation but also vascular intervention is important as a therapeutic strategy. The percentage of patients receiving intervention is reported to be increasing (12). However, the incidence of surgery-related late complication, including late detachment of the aortic prosthetic valve and coronary bypass graft insufficiency, is high (12). We need to pay careful attention to the timely application of vascular interventions. In the present patient, the dilated aortic lesions from the brachiocephalic artery to the right common carotid artery have not changed markedly following the diagnosis, and we have not yet applied vascular interventions.

Conclusion

We herein report a case of TA ascertained during treatment of IBDU observed for 10 years. Atypical colonic presentation might be a distinct characteristic of IBD-TA. Therefore, careful observation might be necessary for the atypical distribution of colonic inflammation.

The authors state that they have no Conflict of Interest (COI).

References

- Carlson JA. The histological assessment of cutaneous vasculitis. *Histopathology* **56**: 3-23, 2010.

2. Serra R, Butrico L, Fugetto F, et al. Updates in pathophysiology, diagnosis and management of Takayasu arteritis. *Ann Vasc Surg* **35**: 210-225, 2016.
3. Terao C, Matsumura T, Yoshifuji H, et al. Takayasu arteritis and ulcerative colitis: high rate of co-occurrence and genetic overlap. *Arthritis Rheumatol* **67**: 2226-2232, 2015.
4. Akiyama S, Fujii T, Matsuoka K, et al. Endoscopic features and genetic background of inflammatory bowel disease complicated with Takayasu arteritis. *J Gastroenterol Hepatol* **32**: 1011-1017, 2017.
5. Kilic L, Kalyoncu U, Karadag O, et al. Inflammatory bowel diseases and Takayasu's arteritis: coincidence or association? *Int J Rheum Dis* **19**: 814-818, 2016.
6. Group JCSJW. Guideline for management of vasculitis syndrome (JCS 2008). Japanese Circulation Society. *Circ J* **75**: 474-503, 2011.
7. Ramos-Casals M, Brito-Zerón P, Cuadrado MJ, Khamashta MA. Vasculitis induced by tumor necrosis factor-targeted therapies. *Curr Rheumatol Rep* **10**: 442-448, 2008.
8. Takayasu arteritis: Japan Intractable Disease information Center. 2020 [Internet]. Available from: <https://www.nanbyou.or.jp/entry/141>(in Japanese)
9. Seko Y, Minota S, Kawasaki A, et al. Perforin-secreting killer cell infiltration and expression of a 65-kD heat-shock protein in aortic tissue of patients with Takayasu's arteritis. *J Clin Invest* **93**: 750-758, 1994.
10. de Almeida MC, Caon AER, Facanali CBG, et al. Coexistence of Takayasu's arteritis in patients with inflammatory bowel diseases. *Gastroenterol Res Pract* **2021**: 8831867, 2021.
11. Sy A, Khalidi N, Dehghan N, et al. Vasculitis in patients with inflammatory bowel diseases: a study of 32 patients and systematic review of the literature. *Semin Arthritis Rheum* **45**: 475-482, 2016.
12. Isobe M, Amano K, Arimura Y, et al. JCS 2017 guideline on management of vasculitis syndrome - digest version. *Circ J* **84**: 299-359, 2020.
13. Minami N, Nakase H, Yoshino T, et al. Effect of infliximab on inflammatory bowel disease with Takayasu arteritis: case series and review of the literature. *Clin J Gastroenterol* **6**: 226-230, 2013.
14. Seyahi E. Takayasu arteritis: an update. *Curr Opin Rheumatol* **29**: 51-56, 2017.
15. Strangfeld A, Richter A, Siegmund B, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Ann Rheum Dis* **76**: 504-510, 2017.
16. Terao C, Yoshifuji H, Kimura A, et al. Two susceptibility loci to Takayasu arteritis reveal a synergistic role of the IL12B and HLA-B regions in a Japanese population. *Am J Hum Genet* **93**: 289-297, 2013.
17. Terao C, Yoshifuji H, Nakajima T, Yukawa N, Matsuda F, Mimori T. Ustekinumab as a therapeutic option for Takayasu arteritis: from genetic findings to clinical application. *Scand J Rheumatol* **45**: 80-82, 2016.
18. Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* **135**: 1130-1141, 2008.
19. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* **381**: 1201-1214, 2019.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).