

[CASE REPORT]

Aortic Arch Aneurysm in Behçet Disease Successfully Treated with Infliximab

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Abstract:

Aortic arch aneurysm (AAA) is a rare involvement in Behçet disease (BD). It is often life-threatening, yet few reports related to the treatment of AAA have been published. We herein report a 27-year-old woman with AAA caused by vascular BD. She was initially treated with prednisolone 1 mg/kg/d. However, the inflammation had not subsided after three weeks, so infliximab (IFX) was added for relief. After IFX administration, the C-reactive protein level normalized, and computed tomography at three months after therapeutic intervention revealed that the aneurysm had disappeared. This case suggests that early induction of IFX might be effective for aortic aneurysm in BD.

Key words: Behçet disease, vascular Behçet disease, aortic arch aneurysm, infliximab

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Introduction

Behçet disease (BD) is a chronic, relapsing multisystem disorder characterized by recurrent oral and genital ulcerations, cutaneous manifestations, and ocular, intestinal, neurologic, and vascular involvement. According to a previous study (1), vascular involvement occurs in 7% to 38% of BD patients. Arterial involvement, including aneurysm and arterial thrombosis, occurs in 3.6% to 31% of vascular BD patients (2, 3). The most common sites of aneurysms are the pulmonary and femoral arteries and the abdominal aorta (4, 5); reports of aortic arch aneurysm in BD are rare (6-8).

Aneurysm is often life-threatening, and the survival rate of BD patients with arterial involvement is lower than that of BD patients without it (9). The European League Against Rheumatism (EULAR) recommendations for the management of Behçet syndrome include surgical treatment for arterial aneurysm in addition to medical treatment with corticosteroids and cyclophosphamide (10). However, patients sometimes have new aneurysms, recurrences, or occlu-

sions (4). Although monoclonal anti-tumor necrosis factor (TNF) antibody is recommended for refractory pulmonary artery aneurysm in BD patients (10), to our knowledge, the use of monoclonal anti-TNF antibody for aortic aneurysm in the early phase of treatment has not been reported.

We herein report a case of aortic arch aneurysm in BD treated with prednisolone followed by the monoclonal anti-TNF antibody infliximab (IFX).

Case Report

A 27-year-old Japanese woman presented to our hospital 1 year ago with arthralgia, a fever, shoulder and back pain, and elevated levels of C-reactive protein (CRP; 10 mg/dL). Although computed tomography (CT) of the whole body showed peripheral pulmonary artery stenosis, the diagnosis was not confirmed. She was followed up because she had not presented with dyspnea, and the other symptoms spontaneously ameliorated, with the CRP decreasing to 1.0 mg/dL.

One year later, she presented with recurrent oral ulcers, folliculitis-like exanthema, and erythema nodosum on her legs, although she had no ocular lesions. CT of the chest

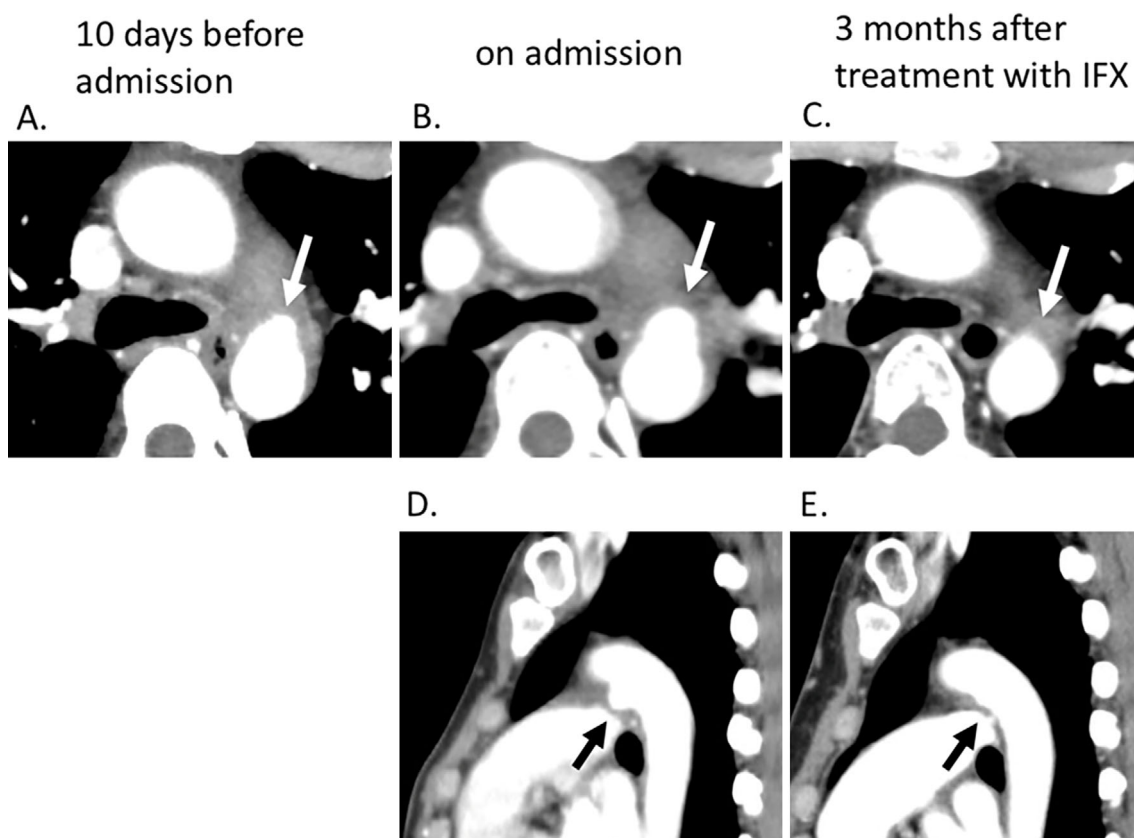


Figure 1. Chest computed tomography (CT) 10 days before admission, on admission, and 3 months after treatment with prednisolone and IFX. (A) Chest CT performed 10 days before admission. An aortic arch aneurysm was detected (arrow). (B and D) CT of the aorta on admission. The aneurysm had dilated over the course of 10 days (arrows) (B: axial image, D: coronal image). (C and E) CT of the aorta after three months of treatment with three IFX injections. The aortic arch aneurysm had almost disappeared (arrows) (C: axial image, E: coronal image). IFX: infliximab

and abdomen revealed an aortic arch aneurysm (Fig. 1A) and splenic and renal infarction, so she was admitted to our hospital. The laboratory data on admission showed an elevated white blood cell (WBC) count (13,500/ μ L), erythrocyte sedimentation rate (ESR; 56 mm/h), and CRP levels (12.3 mg/dL). Human leukocyte antigen (HLA) class I types were A2, B38, and B54, while neither HLA B51 nor A26 was detected. The tuberculosis-specific interferon gamma release assay, treponema palladium hemagglutininations assay (TPHA), rapid plasma reagin test (RPR), and immunology findings were all negative, including for antinuclear antibody titer, anti-DNA antibody, anti-SS-A antibody, anti-Sm antibody, anti-RNP antibody, lupus anticoagulant, proteinase-anti-neutrophil cytoplasmic antibody (PR3-ANCA), and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA).

Vascular BD was diagnosed according to the Japanese criteria (11) and International Criteria for BD (ICBD) (12) on the basis of the presence of oral aphthae, skin lesions, arthritis, and vascular lesions without any evidence of infection or other connective tissue diseases. Sarcoidosis, malignancy, pregnancy, and effects of new medications are included as differential diagnoses of erythema nodosum. However, sarcoidosis was considered unlikely because CT of the

chest didn't show enlarged mediastinal or hilar lymph nodes, and the serum soluble interleukin-2 receptor level was not elevated. Malignancy, pregnancy, and the effects of new medications were also excluded based on findings from esophagogastroduodenoscopy and colonoscopy, her menstrual history, and her medication history. While infections or arteriosclerosis are also differential diagnoses of aortic aneurysm, they were excluded because no infections, such as syphilis and tuberculosis, were detected, and she had no risk factors for arteriosclerosis, such as diabetes mellitus, dyslipidemia, hypertension, aging, and smoking. Takayasu arteritis was also excluded because CT of the chest and abdomen showed no wall thickening or stenosis of the aorta or its main branches.

Chest CT performed 10 days after the first scan showed dilation of the aortic arch aneurysm (Fig. 1B, D). Therefore, oral prednisolone (PSL) 40 mg/d (1 mg/kg/d) was administered immediately. PSL treatment for 3 weeks improved the skin lesion and the CRP level gradually decreased, but it remained positive at around 1 mg/dL. IFX (5 mg/kg) was added because remission of the vascular BD did not appear to have been achieved. We decided not to use cyclophosphamide in order to preserve her fertility. In addition to IFX, aspirin (100 mg/d) was administered for the splenic

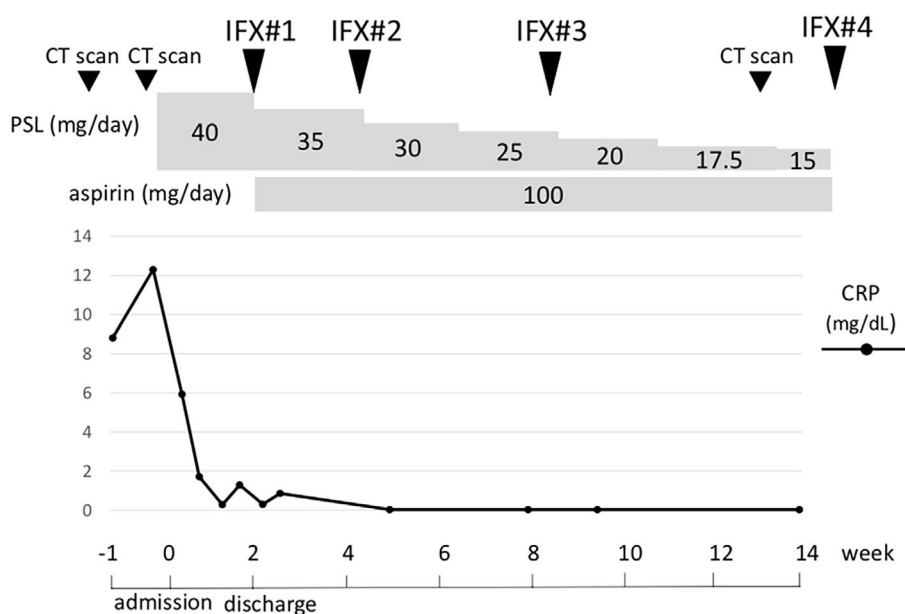


Figure 2. The patient's clinical course. PSL: prednisolone, IFX: infliximab, CRP: C-reactive protein, CT: computed tomography

and renal infarction. IFX was administered via intravenous infusion at weeks 0, 2, and 6 and every 8 weeks thereafter while the PSL was gradually tapered. After the second IFX injection, the CRP level remained below the detection limit. After three months of the treatment, chest CT showed that the aortic arch aneurysm had almost disappeared (Fig. 1C, E). The clinical course is summarized in Fig. 2. The aneurysm has not relapsed in the year since IFX was initiated.

Discussion

Arterial involvement in BD is rare, and little evidence is available on how to manage it. Although previous studies have shown the effectiveness of corticosteroids and immunosuppressants, such as cyclophosphamide and azathioprine, the mortality rate of BD patients with arterial involvement is still high because of rupture or occlusion as a result of the inflammation of the arterial wall (9, 13). Aortic aneurysms sometimes require emergency surgery or stenting because of the risk of rupture or occlusion. Medical treatment with corticosteroids and cyclophosphamide before surgical intervention improves the outcome; however, some BD patients with aneurysms suffer postoperative complications or recurrence (4, 14).

Recent studies have shown that monoclonal anti-TNF antibody was effective for severe and refractory BD, including BD with arterial involvement (15-18). Compared with the treatment using conventional immunosuppressants, anti-TNF α therapy decreased the relapse rate and the corticosteroid dose in both pulmonary and nonpulmonary aneurysm. Desbois et al. (17) reported four cases of BD with a nonpulmonary arterial aneurysm that was successfully treated with IFX. In three of those cases, the aneurysm was in the aorta,

and in the other, it was in an aortic branch. IFX was initiated 4 to 38 months after the diagnosis. Complete remission was achieved in three cases and partial remission in the other case within a few months. In the present case, the aortic aneurysm was almost completely eliminated by treatment with a glucocorticoid and the concomitant use of IFX for three months. Consequently, the results of those previous reports and our own case suggest that anti-TNF α therapy might induce the remission of aortic aneurysm without the need for surgery or stenting.

However, the ideal timing of the initiation of anti-TNF α therapy for vascular BD has not been established. Previous research showed that the median disease duration of BD before the initiation of monoclonal anti-TNF antibody for major vessel involvement was 21 months, and 1 patient failed to achieve complete regression of the aortic aneurysm (17). In previous studies on pulmonary artery aneurysm in BD, some patients who initiated anti-TNF antibody a few years after the diagnosis were unable to achieve the disappearance of their pulmonary artery aneurysm, although others were able to achieve complete regression (16, 18). Interestingly, in our case, IFX was initiated only three weeks after the diagnosis of vascular BD and achieved a good outcome. We therefore speculate that the early induction of anti-TNF α agent has a greater potential to achieve complete remission of arterial aneurysm than the late induction.

Although the pathogenic factors inducing arterial aneurysm in vascular BD remain unclear, previous studies have shown that levels of TNF α and matrix metalloproteinases (MMPs) in atherosclerotic disease are higher in human abdominal aortic aneurysm tissue than in aortic tissue without abdominal aortic aneurysm (19-21). These findings suggest that TNF α and MMPs are related to aneurysm formation. Furthermore, the serum levels of TNF α are higher in BD

patients than in healthy controls (22), and the serum levels of MMP-2 and MMP-9 were higher in vascular BD patients with aneurysm than in healthy controls or BD patients with mucocutaneous or ocular involvement (23). Regarding the murine model of abdominal aortic aneurysm induced by chemical inflammation in the arterial wall via the local injection of CaCl₂, the TNF α expression was reported to be upregulated one week after aneurysm induction (24). Moreover, TNF α elicits the activation and recruitment of immune cells to the inflammatory site and induces the secretion of proinflammatory cytokines and MMPs, of which MMP-2 and MMP-9 play an important role in inducing aortic aneurysm (25). Indeed, monoclonal anti-TNF antibody prevented several steps in the aneurysm formation process, such as elastic fiber disruption, macrophage infiltration, and the upregulation of the MMP-2 and MMP-9 expression in the aortic tissue of a murine model of abdominal aortic aneurysm (24). Consequently, TNF α is assumed to be a pivotal cytokine in the development of aortic aneurysm including the involvement of vascular BD. Therefore, monoclonal anti-TNF antibody may not only attenuate the formation of aortic aneurysm but also be more effective with early induction than after recurrence.

Several limitations associated with the present study warrant mention. First, the pure effect of IFX treatment could not be evaluated because both PSL and IFX were used during the remission induction phase. There is a possibility that aortic arch aneurysm was improved by only PSL. Second, biomarkers such as TNF α , MMP-2, and MMP-9 were not monitored. Measuring the blood levels of these biomarkers might be useful for evaluating the disease activity of vascular BD precisely and the effect of IFX treatment in detail. Finally, the observational period was only one year. Aortic aneurysm might recur in the long term.

In conclusion, our case of aortic arch aneurysm in BD was successfully treated by the addition of IFX in the early phase. This suggests that the early induction of IFX might be effective for aortic aneurysm in BD.

The patient presented in this report gave her informed consent for the publication of her case.

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

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