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Case Report

Successful Infliximab Therapy in a Patient with Refractory Takayasu's Arteritis

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Takayasu's arteritis (TA), a granulomatous vasculitis, affects the aorta and its major branches. Glucocorticoids are an effective treatment for patients with active TA, but some patients fail to achieve or maintain remission with the conventional therapy, and side effects resulting from long-term glucocorticoid therapy are potentially serious. Anti-tumor necrosis factor-α agents, such as infliximab, may be efficient in patients with refractory TA. We report on a 24-year-old female patient with refractory TA who was treated successfully with infliximab. Clinical remission was induced as determined by repeated ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography scans combined with assay of serological inflammatory markers. **(J Rheum Dis 2016;23:71-75)**

Key Words. Takayasu arteritis, Monoclonal antibodies, Positron-emission tomography

INTRODUCTION

Takayasu's arteritis (TA) is a chronic vasculitis of unknown etiology that features progressive development of stenosis, occlusion or aneurismal degeneration in large arteries. The mainstay in the treatment of active TA remains glucocorticosteroids for the induction and maintenance of remission, in spite of the unfavorable side effects. Combination immunosuppressant therapy is considered primarily in patients who have severe or persistent disease activity despite treatment with glucocorticoids or when remission cannot be maintained with acceptable doses of glucocorticoids. However, some patients fail to achieve remission with the combination treatment [1]. The use of anti-tumor necrosis factor-α (TNF-α) agents in the patients with refractory TA could be useful, since granulomatous inflammation is a typical feature of TA and because TNF-α is important in the formation of granulomas. Anti-TNF-α therapy is reportedly associated with remission in the majority of the patients, facilitating dose reduction or discontinuation of prednisone and other immunosuppressive therapy [2]. We present a case of refractory TA successfully treated with infliximab, in which clinical remission was observed.

CASE REPORT

A 24-year-old woman presented with pain and numbness in her right arm for the past two months, as well as recent-onset dizziness. The patient had no significant past medical or surgical history. She had never smoked and not been on any regular medication. There was no family history of early onset cerebral vascular accident. Significant clinical findings included a weak left radial pulse in comparison to the right and asymmetrical blood pressure measurements (left 90/60 mmHg and right 140/90 mmHg). Auscultation revealed bruits over the left subclavian arteries. The remaining systemic and general physical examinations were unremarkable. Laboratory findings showed an elevated erythrocyte sedimentation rate (ESR) of 120 mm/h (normal value $<$20 mm/h) and serum C-reactive protein (CRP) level of 12.88 mg/dL

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(normal value <0.5 mg/dL). At that time, computed tomography (CT) angiography showed diffuse wall thickening in the aortic arch, the right brachiocephalic trunk, left common carotid and subclavian arteries (Figure 1). She fulfilled the 1990 American College of Rheumatology classification criteria for TA and met the National Institutes of Health (NIH) criteria for active TA; the new onset of claudication, bruit and asymmetric blood pressures in the upper limbs, elevated ESR and the typical angiographic features [3,4]. She was prescribed 0.8 mg/kg oral prednisone with subsequent tapering. Additional antihypertensive therapy with losartan, atorvastatin and osteoporosis prophylaxis commenced. Although these therapies resulted in rapid clinical improvement, they failed to reduce steroid dose below 10 mg/d. Adjuvant treatments including methotrexate, azathioprine and tacrolimus were also tried but were ineffective in normalizing inflammatory indices (Figure 2). Furthermore, the patient developed Cushingoid symptoms of moon face, buffalo hump and truncal obesity, and constitutional symptoms despite ongoing treatment with prednisolone 15 mg/d. Although neither the arterial wall thickening nor stenosis showed significant difference in the follow-up CT angiography comparing with previous studies, she was considered to fulfill the NIH criteria for active TA based on clinical features and elevated ESR. Notably, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET) scan demonstrated intense ^{18}F-FDG uptake within the thickened, inflamed arterial walls (Figure 3A). Given the failure to achieve disease remission and undesirable outcome of glucocorticoids, the current literature was reviewed and discussed with the patient. Infliximab has been used as adjuvant therapy in the treatment of refractory TA [5]. Infliximab 3 mg/kg was administered at 0, 2, 6 and 14 weeks, along with methotrexate 10 mg per week. The patient's symptoms re-

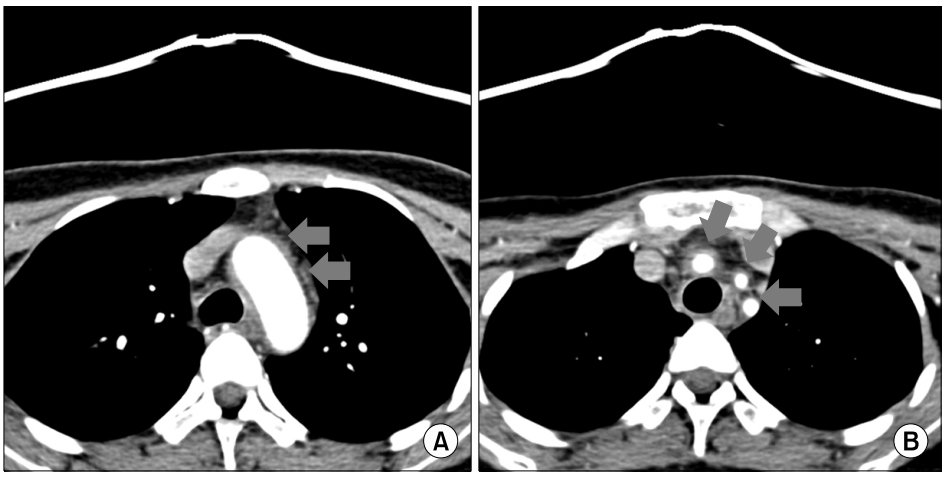

Figure 1. Contrast-enhanced computed tomography scan shows diffuse wall thickening (arrows) in (A) aortic arch, and (B) the right brachiocephalic trunk, left common carotid and subclavian arteries.

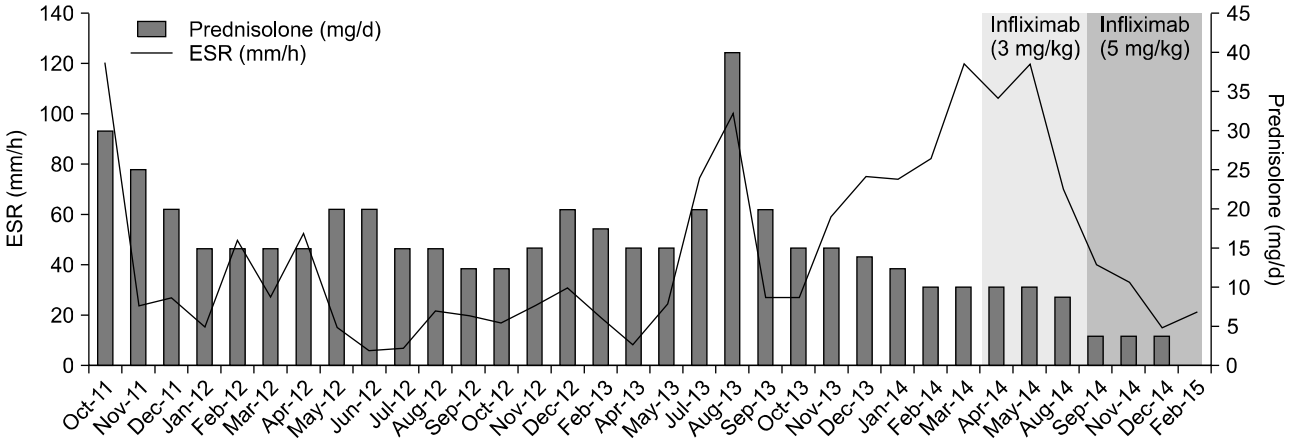

Figure 2. Treatment timeline showing the response of systemic inflammatory markers to glucocorticoid and infliximab during the course of treatment. Erythrocyte sedimentation rate (ESR) denotes erythrocyte sediment rate.

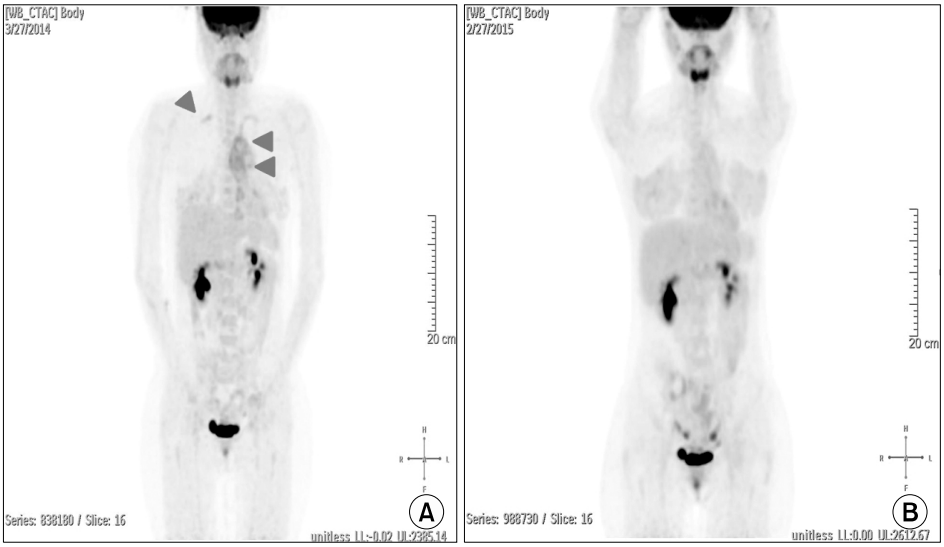

Figure 3. (A) Before infliximab treatment; ^{18}F-Fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography scan shows increased uptake of ^{18}F-FDG in the aortic arch and bilateral subclavian arteritis (arrowheads; visual grade = 3, the number of active vascular lesions = 5). (B) Twelve months after infliximab treatment: decreased uptake of ^{18}F-FDG is evident in the inflamed arterial walls (visual grade = 1, the number of active vascular lesions = 0).

solved 4 weeks after initiation of therapy but inflammatory indices remained elevated at 16 weeks (Figure 2). Infliximab dose was escalated to 5 mg/kg every 8 weeks after 22 weeks. Both ESR and serum CRP returned to normal after dose escalation of infliximab. Repeat ^{18}F-FDG PET scan 12 months after commencing infliximab confirmed decreased ^{18}F-FDG accumulation in the affected vessels (Figure 3B). Prednisolone was gradually tapered and eventually stopped. She has remained in clinical remission with a maintenance therapy (5 mg/kg every 8 weeks).

DISCUSSION

Glucocorticoids are still an effective treatment for patients with active TA. However, remission is reportedly achieved in only 60% of the patients treated with glucocorticoids alone and often requires additional cytotoxic agents [4]. Since almost half of the patients with remission have at least 1 relapse, they need repeated courses of therapy. Accordingly, adverse side-effects of these treatments may seriously impair health-related quality of life and some patients have continuous disease activity regardless of the conventional treatment. We hypothesized that our patient might benefit from the use of infliximab. In the pathogenesis of TA, T cells infiltrating the vessels walls might release strong pro-inflammatory cytokines including TNF-α and interleukin-6, which increase the recruitment of mononuclear cells within the vascular wall. Similar to rheumatoid arthritis and ankylosing spondylitis, biological agents targeting TNF-α have also been used for TA patients. While there are currently more than five anti-TNF-α agents, the majority of TA patients treated with the anti-TNF-α agents have received infliximab [6]. From a recent systematic review, 74.7% achieved remission and 32% discontinued glucocorticoid in 11 case series of refractory TA patients with infliximab [7]. However, since all of the evidence supporting the use of anti-TNF-α agents for refractory TA comes from the observational studies, this may reflect selection bias by study population and drug protocol. The patient in our case had been also treated for prolonged periods (29 months) with glucocorticoid and steroid-sparing agents prior to infliximab therapy, although it was effective for inducing clinical remission even without an increased dosage of glucocorticoid (Figure 2). Therefore, future randomized controlled studies are needed to determine whether anti-TNF-α agents in newly diagnosed TA patients or without glucocorticoid can be effective. Our case suggests that infliximab therapy might be a beneficial treatment option for TA patients who are unable to taper prednisone despite long-term conventional treatments.

The dosage or dosing interval of infliximab to ensure efficacy and safety in refractory TA has not been established. In a review of previous studies, infliximab was given at a dose of 3 to 5 mg/kg and approximately a third of the total patients required increased doses of anti-TNF-α agents over time to maintain remission [6]. The present case showed that dose escalation of infliximab may be necessary to achieve remission in TA patients with an inadequate response to initial dose. Although side effects have been reported in 20% of total cases including mainly infections [8], it is uncertain whether the dose escala-

tions affect the incidences of adverse events. However, screening for and treatment of active and latent tuberculosis should be initiated prior to treatment with infliximab in refractory TA, owing to the increased risk of active tuberculosis associated with the use of anti-TNF-α agents. Further studies are warranted to establish the optimal dosing regimen for the long term efficacy and safety of anti-TNF-α agents in refractory TA.

Inflammatory markers, such as ESR and CRP, are often useful for monitoring disease activity of TA. However, these inflammatory markers are reported to be unreliable surrogate markers for estimating the inflammatory activity of the disease during treatment with medication, since even patients considered clinically to be in remission may have a slow-acting inflammatory process in biopsy specimens [4]. ^{18}F-FDG PET scan is useful to detect inflammation of arteries and serve to detect active disease lesions before occlusion or narrowing of large branches of the aorta [9]. Since ^{18}F-FDG PET scan can distinguish vessel thickening due to fibrosis from active inflammation, it is useful for detection of active inflammation not only in patients with active TA before treatment but also in relapsing patients receiving immunosuppressive agents [10]. ^{18}F-FDG uptake correlates with clinical markers of inflammation and can be used to evaluate response to therapy [11]. In our case, concomitant CT angiography at times of ^{18}F-FDG PET scan did not show significant change in the involved arterial walls compared to the previous imaging studies despite elevated inflammatory markers. Furthermore, the disappearance of ^{18}F-FDG accumulations during the treatment with infliximab suggest that ^{18}F-FDG accumulation observed in TA directly indicates the inflammation in the vascular wall. Although prospective study would be helpful to investigate the usefulness of ^{18}F-FDG PET scan for the assessment of disease activity in TA patients, our case indicates that ^{18}F-FDG PET scan may have a role in the assessment for disease activity and response to treatment, especially in patients in whom disease activity is unclear based on other imaging modalities.

In conclusion, this case demonstrates that anti-TNF-α treatment may prove useful both for disease control and, especially, to avoid the risk of long-term corticosteroid-related toxicity. However, we have no answer concerning how long to maintain the treatment for long-term sustained remission. Whether anti-TNF-α agents should be considered earlier in the treatment algorithm of TA also remains an area of interest. Prospective randomized controlled trials are needed to answer these questions.

SUMMARY

The present case indicates that anti-TNF-α agents, such as infliximab, are efficient in patients with refractory TA, and that the dose escalations may be required to induce a remission for inadequate response to initial dose. Repeated ^{18}F-FDG PET scan can be useful for assessing the disease activity of TA along with serological inflammatory markers.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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