Successful treatment of tocilizumab-resistant large vessel pulmonary arteritis with infliximab

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ABSTRACT
Pulmonary hypertension associated with large vessel pulmonary arteritis (LVPA) has been reported in the course of Takayasu arteritis (TAK). Biologic therapies targeting inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin-6, have recently been successful to treat refractory TAK. Infliximab (IFX), an anti-TNF-α antibody and tocilizumab (TCZ), an anti-IL-6 receptor antibody may have similar efficacy and safety profile in the treatment of TAK. However, some cases are refractory to TNF inhibitors but respond to TCZ, and vice versa. Here, we report a severe case of LVPA, who was successfully treated with IFX but was refractory to TCZ and presented a discrepancy between serum C-reactive protein levels and fluorodeoxyglucose vascular positivity. This case would indicate heterogeneity of pathogenic mechanisms in LVPA and TAK.

1. Introduction
Large vessel pulmonary arteritis (LVPA) is an acute and chronic form of vasculitis resulting in inflammatory thickening, stenosis and occlusion of the large-sized pulmonary arteries. It is asymptomatic in most cases but sometimes fatal, leading to pulmonary hypertension (PH) and subsequent right heart failure. Takayasu arteritis (TAK), a systemic granulomatous large vessel vasculitis, is most commonly associated with LVPA [1], with any abnormalities of the pulmonary arteries detected by angiography or 18 F-fluorodeoxyglucose positron emission tomography (18 F-FDG PET) in 20–56% of TAK patients [2]. Biologic therapies targeting inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, have recently been successful to treat refractory TAK [3]. However, it remains unclear which cytokine is more dominant in the pathogenesis of LVPA complicated with TAK.

We herein present a severe case of LVPA who was successfully treated with infliximab (IFX), an anti-TNF-α antibody but was refractory to tocilizumab (TCZ), an anti-IL-6 receptor antibody. We also show a discrepancy between serum levels of C-reactive protein (CRP) and FDG uptake in the pulmonary arteries. This case would provide novel insights into the pathogenesis of LVPA as well as the assessment of disease activity in those patients.

2. Case report
A 50-year-old Japanese woman described polyarthritis, pyrexia (above 38°C), and dyspnea on exertion (WHO functional class III) for two months. Physical examination revealed systolic murmur (Levine IV) at the three to four left intercostal space as well as tenderness and swelling of six peripheral joints, including proximal interphalangeal joints, metacarpophalangeal joints, and wrists. Laboratory tests showed high erythrocyte sedimentation rate (89 mm/h), elevated serum CRP level (6.9 mg/dL), and elevated plasma brain natriuretic peptide level (288 pg/mL). Computed tomography (CT) of the chest showed edematous thickening of the brachiocephalic artery (Figure 1(A)) and stenosis of the right pulmonary artery (Figure 1(B)), without further abnormal findings such as pulmonary thromboembolism and interstitial pneumonia. 18 F-FDG PET demonstrated abnormal FDG uptake in the pulmonary arteries with standardized uptake value of up to 6.2 (Figure 1(C)). Angiography confirmed the severe stenosis of the right pulmonary artery (Figure 1(D)). PH had already developed with a mean pulmonary arterial pressure (mPAP) of 28 mmHg, a pulmonary arterial wedge pressure of 5 mmHg, and a pulmonary vascular resistance (PVR) of 4.99 W.U. evaluated by right heart catheterization. Magnetic resonance imaging detected erosion of carpal bones as well as...
synovitis in both wrists. She was found to carry the human leukocyte antigens B15 and B40.

Behçet’s disease and syphilis were excluded owing to the absence of aphthous stomatitis, rash, uveitis, and genital ulcer and the negative results of plasma reagin test and Treponema pallidum hemagglutination test. Although she was not classified into TAK due to the absence of age of <40 years at disease onset, claudication of extremities, decreased brachial artery pulse, and blood pressure difference, according to the ACR classification criteria in the 1990 [4], the presence of LVPA was definite. Given the chronic polyarthritis and bone erosions, rheumatoid arthritis was also compatible with her joint symptoms. Treatment with pulsed methylprednisolone and intravenous cyclophosphamide (500 mg/four weeks) followed by prednisolone of 40 mg/day was first effective with decreased pulmonary arterial systolic pressure estimated by echocardiography (ePASP) (63–36 mmHg) as well as decreased serum CRP levels (6.9–0.9 mg/dL). Pyrexia and joint swelling also disappeared. However, following glucocorticoid tapering, both ePASP (46 mmHg) and CRP (6.4 mg/dL) were elevated. By switching from intravenous cyclophosphamide to TCZ (162 mg/two weeks), serum CRP levels rapidly decreased (0.08 mg/dL) whereas ePASP continued increasing (61 mmHg) and dyspnea exacerbated. CT of the chest still showed edematous thickening of the brachiocephalic artery and stenosis of the right pulmonary artery and reexamination by 18 F-FDG PET again revealed abnormal FDG uptake in the pulmonary arteries with standardized uptake value of up to 6.2, indicating a discrepancy between CRP levels and the disease activity of LVPA. Following switch from TCZ to IFX (6 mg/kg/four weeks) [5] with methotrexate (8 mg/week), serum CRP levels slightly increased (around 1.0 mg/dL) whereas ePASP significantly decreased (30 mmHg). FDG uptake in the pulmonary arteries, stenosis of the right pulmonary artery and brachiocephalic artery were improved in parallel (Figure 2). Ten months after the first administration of IFX, PH had improved with a mPAP of 11 mmHg, and a PVR of 1.9 W.U. She remained remission with WHO functional class I on IFX, methotrexate, prednisolone of 10 mg/day, low-dose aspirin, and warfarin.

3. Discussion
To date, the main treatment of TAK still remains to be glucocorticoids. However, relapses occur in a number of patients during glucocorticoid tapering and other immunosuppressive agents therefore need
to be used concomitantly [6]. Recent studies have indicated an efficacy of biologics therapies targeting inflammatory cytokines, such as TNF-α [7] and IL-6 [8], to refractory TAK patients. TNF-α is a critical cytokine in granuloma formation as well as in the activation of endothelial cells, enhancing the adhesion of leukocytes and platelets to vascular endothelium. Elevated TNF-α expression in peripheral monocytes of TAK patients has been demonstrated [9]. Furthermore, TNF-α producing T cells were shown to be increased in TAK patients and to be correlated with disease activity of TAK [10]. IL-6 drives the differentiation of T cells toward Th17 phenotype, promoting the migration of inflammatory cells into various tissues including vessels. Enhanced expression of IL-6 was detected in aortic tissues from TAK patients and serum levels of IL-6 were correlated with TAK activity [11]. These two cytokine clusters have been associated with the immunopathogenesis, and interaction between Th1 cells and Th17 cells involved in these cytokine are involved in the development of TAK [12].

Tumor necrosis factor inhibitors and TCZ may have similar efficacy and safety profile in the treatment of TAK. However, some cases are refractory to TNF inhibitors but respond to TCZ, and vice versa. Recently, a French nationwide observational study including 49 TAK patients receiving TNF inhibitors, including IFX, etanercept and adalimumab, or TCZ showed the high efficacy of both treatments in refractory TAK patients [13]. In this study, however, at least 1 switch to another biologics treatment was necessary in 13 out of 49 patients, including 4 switches from TNF inhibitors to TCZ and 2 from TCZ to TNF inhibitors, during a median follow-up of 24 months, indicating a heterogeneity of pathogenic mechanisms in TAK patients. An anti-CD20 antibody, rituximab, and an anti-p40 antibody, ustekinumab, have also shown to be effective in some TAK patients [14,15].

Another challenging aspect of TAK is the assessment of disease activity. In a number of patients who appear to have silent disease, there is evidence of laboratory inflammation whereas in some others who disclose symptoms or signs of active disease, particularly those receiving TCZ, there is no elevation of inflammatory markers such as erythrocyte sedimentation rate and serum CRP levels. 18F-FDG PET is currently one of the most sensitive modalities to detect vessel inflammation [16]. In the present case, given the rapid decrease of serum CRP levels following TCZ therapy despite sustained

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Figure 2. Clinical course of the present case. ePASP: pulmonary arterial systolic pressure estimated by echocardiography; FC: functional class; IVCY: intravenous cyclophosphamide; TCZ: tocilizumab; IFX: infliximab; mPSL: methylprednisolone; PSL: prednisolone.
FDG uptake in the pulmonary arteries and worsening of PH, FDG uptake rather than CRP was more correlated with disease activity. A recent systematic review has demonstrated that serum CRP levels only moderately reflect the FDG vascular positivity in TAK [17]. However, it should be noted that not only laboratory inflammation but hot FDG PET scan may also be observed in patients in clinical remission. Therefore, disease activity of TAK should be assessed individually using comprehensive tools such as National Institutes of Health criteria, Birmingham Vasculitis Activity Score, Disease-Extent Index-Takayasu, and Indian Takayasu Clinical Activity Score 2010 [18–21].

In summary, the present case of severe LVPA, who was successfully treated with IFX but was refractory to TCZ and presented a discrepancy between serum CRP levels and FDG vascular positivity, would indicate heterogeneity of pathogenic mechanisms in LVPA and TAK. It would further be noted that TAK patients need individual and comprehensive assessment of disease activity in order to receive an optimal therapy.

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