Tocilizumab-induced leucocytoclastic vasculitis in a patient with rheumatoid arthritis

Sir, Biologic agents are widely used for the treatment of RA in today’s treat-to-target era [1]. Although their safety and efficacy are acceptable, autoimmune adverse events associated with biologics have increasingly been reported. According to the BIOGEAS Study Group [2], vasculitis and SLE are the most frequent autoimmune diseases induced by biologics, and most reports were associated with anti-TNF agents. Among 139 cases of vasculitis, 137 cases were related to anti-TNF agents, except for 1 case related to rituximab and 1 to abatacept. Cutaneous involvement is most frequent, and leucocytoclastic vasculitis has been reported only with anti-TNF agents [3]. We report the first case of tocilizumab-induced leucocytoclastic vasculitis in a patient with RA. Written informed consent for publication of this case was obtained from the patient.

A 62-year-old Japanese woman had been suffering from seropositive RA for 23 years. She had a history of treatment with infliximab for 5 years, but this was switched to etanercept because of secondary failure, and etanercept was switched to tocilizumab because of primary failure.

Subsequently she was treated with tocilizumab 8 mg/kg/month, MTX 4 mg/week and prednisolone 3 mg/day for 2.5 years, and low disease activity was achieved.

In April 2013 she presented with abdominal pain and arthralgia with a low-grade fever. Three weeks later she noticed the emergence of multiple palpable purpura on her forearms, buttocks, thighs and lower extremities (Fig. 1A). Most of her proximal interphalangeal joints were swollen and the 28-joint DAS (DAS28) increased to 5.98. ESR increased to 38 mm in the first hour (normal value <16 mm in women) and CRP was 5.35 mg/dl (normal value <0.3 mg/dl). Platelet count, renal function and urinalysis were normal. Serum IgG, IgA and IgM levels and complement factors (CH50, C3 and C4) were within normal limits. Serum anti-streptolysin O was negative. ANA and ANCA were negative. Circulating immunocomplex and cryoglobulin were absent. Upper gastrointestinal endoscopy showed normal gastric mucosa, and faecal occult blood testing was negative. Skin biopsy of the purpura of the lower legs revealed leucocytoclastic vasculitis with granulocyte invasion to small vessel walls in the dermis, nucleus disruption and extravasation of erythrocytes (Fig. 1B). Immunofluorescent staining did not show IgA deposition.

According to the 1990 ACR criteria, Henoch-Škönlein purpura can be diagnosed from clinical and pathological findings even when lacking IgA deposition. However, this case did not fulfil the definition of IgA vasculitis of the 2012 Revised International Chapel Hill Consensus Conference classification. We diagnosed this case as leucocytoclastic vasculitis.

The cause of the leucocytoclastic vasculitis was difficult to ascertain because no agents were newly administered before this episode. We considered the possibility of tocilizumab-induced leucocytoclastic vasculitis and discontinued the administration of tocilizumab. Subsequently palpable purpura rapidly disappeared, so we concluded that leucocytoclastic vasculitis was induced by tocilizumab. Because of sustained arthritis and abdominal pain,
prednisolone was temporarily increased to 20 mg/day and the symptoms resolved. As treatment for RA, abatacept 500 mg/month was started. Although prednisolone was rapidly tapered, relapse of vasculitis has not been observed so far and she has maintained low DAS28 scores.

The mechanisms that may contribute to the development of leucocytoclastic vasculitis in patients receiving biologics are not completely understood. The proposed mechanism by which anti-TNF agents induce vasculitis is a type III hypersensitivity caused by vascular deposition of an anti-TNF-α–TNF-α immunocomplex [4]. Tocilizumab is an antibody against the IL-6 receptor (IL-6 R) and it binds to cell-surface IL-6 R and the soluble form of IL-6 R. It has been reported that the soluble form of IL-6 R is saturated with tocilizumab as long as free tocilizumab is detectable, and this immunocomplex may be related to the development of tocilizumab-induced leucocytoclastic vasculitis [5]. However, it has not been elucidated whether this immunocomplex has a lower potential to induce vasculitis than the anti-TNF-α–TNF-α immunocomplex.

Recently two cases of tocilizumab-induced autoimmune disease have been reported [6, 7]. Interestingly, one case took 18 months to develop glomerulonephritis from the administration of tocilizumab [6] and the other took 28 months to develop sarcoidosis [7]. Our case took 30 months to develop leucocytoclastic vasculitis, and these periods of latency are obviously longer than vasculitis induced by anti-TNF agents. According to BIOGEAS Study Group, vasculitis induced by anti-TNF agents took 30 months to develop leucocytoclastic vasculitis, and these periods of latency are obviously longer than vasculitis induced by anti-TNF agents. According to BIOGEAS Study Group, vasculitis induced by anti-TNF agents took 32.95 weeks (S.D. 6.45) on average [2].

References
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Rheumatology 2014;53:1530–1532
doi:10.1093/rheumatology/keu028
Advance Access publication 7 March 2014

Successful multitarget therapy using mizoribine and tacrolimus for refractory Takayasu arteritis

Sir, Takayasu arteritis (TA) is a chronic, relapsing vasculitis affecting the aorta and/or its main branches. The presenting manifestations include fever, fatigue, weight loss, hypertension, headaches, strokes and elevated levels of acute-phase reactants, such as CRP, which correlate with disease activity. High-dose corticosteroid therapy is effective in TA, but such therapy alone cannot sustain long-term remission. Immunosuppressants such as MTX and CYC are used in corticosteroid-resistant patients [1]. Recently anti-TNF [1] and anti-IL-6 receptor [2] antibodies have been used for refractory TA. However, novel therapies for corticosteroid-resistant TA have not yet been standardized.