# A case of leukocytoclastic vasculitis associated with anti-tumor necrosis factor therapy

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Tumor necrosis factor-α (TNF-α) is one of the known cytokines, which is implicated in the pathogenesis of many chronic inflammatory diseases, including rheumatoid arthritis and ankylosing spondylitis [1]. Tumor necrosis factor-α inhibitors are increasingly used for the treatment of rheumatoid diseases. Anti-TNF-α therapy is generally well tolerated. However, there are a growing number of reports of the development of adverse events related to anti-TNF-α agents [2, 3]. A number of cutaneous side effects have been reported with anti-TNF-α therapy, including psoriatic eruption, lupus-like disorders and vasculitis [4]. However, only a few cases of leukocytoclastic vasculitis have been reported and they are rarely related to adalimumab [5–7].

Here we report a case of a patient with ankylosing spondylitis, who developed leukocytoclastic vasculitis after adalimumab treatment.

A 23-year-old male patient had a 13-year history of arthralgia, especially the knee joints and spine. In addition, he underwent surgical treatment of bilateral cleft lip and palate and surgical treatment of pyloric stenosis. In 2010, juvenile idiopathic arthritis was diagnosed. The patient received therapy with sulfasalazine (in 2010–2013), methotrexate (in 2010–2011) and periodically glucocorticoids and non-steroidal anti-inflammatory drugs, with no satisfactory treatment effects. In 2013, the patient was hospitalized in the Department of Rheumatology. The laboratory tests showed elevated inflammatory markers, with negative rheumatoid factor and positive HLA-B27 antigen. Radiological studies showed typical inflammation in the sacroiliac joints. The ankylosing spondylitis was diagnosed. The patient received adalimumab of 40 mg subcutaneously every 2 weeks and showed good response to therapy. After 35 months of treatment, the patient complained of pain and swollen ankles and appearance of skin lesions. Blotchy rash initially included the ankle and then spread to the entire lower limbs. Dermatological examination revealed purpura with erosions and blisters filled with the contents of seroblood (Figures 1, 2). There were no other systemic signs, however the patient was undergoing dental treatment. The laboratory tests showed no inflammatory markers, and results of all basic laboratory tests (complete blood count, renal, liver and thyroid function, urinalysis) were within the reference values. However, the laboratory tests showed an anti-nuclear antibody (ANA) 1/320 of a granular type of lighting. The anti-dsDNA, anti-extractable nuclear antigen (ENA) antibodies and anti-neutrophil cytoplasmic antibodies (ANCA: pANCA and cANCA) were negative. Moreover, HIV, HCV and HBV infections were excluded. Histopathological examination of the skin was performed. Based on the clinical and histopathological findings, the patient was diagnosed with leukocytoclastic vasculitis, probably due to therapy with adalimumab. Adalimumab was discontinued and methylprednisolone (8 mg/day) and cefuroxime (500 mg/day because of the patient's dental treatment) were prescribed. Also local treatment was prescribed (betamethasone and gentamycin). After 4 weeks the patient had complete resolution of symptoms.

The available safety data on autoimmune diseases induced by TNF-α inhibitors rely mainly on case reports, and information regarding their management and clinical significance is very limited. Ramos-Casals *et al.* have described the clinical characteristics of 113 patients who developed vasculitis (the most frequent type of vasculitis was leukocytoclastic vasculitis – in 79 cases) after receiving anti-TNF agents (etanercept in 59 cases, infliximab in 47, adalimumab in 5, and other agents in 2). However, the association of leukocytoclastic vasculitis and different anti-TNF inhibitors (human vs. humanized vs. chimeric) is unclear [8].

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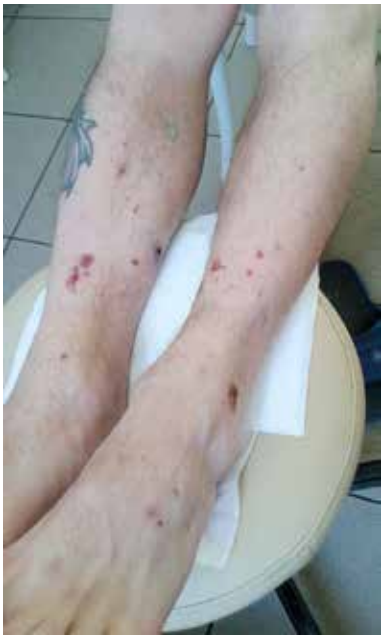

**Figure 1.** Leukocytoclastic vasculitis associated with anti-TNF-α inhibitor

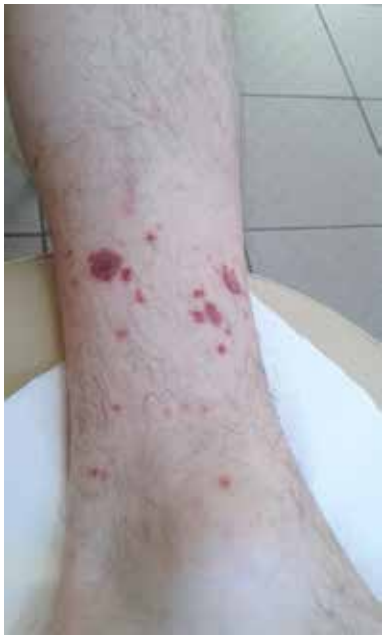

**Figure 2.** Leukocytoclastic vasculitis associated with anti-TNF-α inhibitor

The pathogenic mechanism for development of drug-induced leukocytoclastic vasculitis is not fully defined [9, 10]. Probably the auto-antibody against anti-TNF-α inhibitors (like adalimumab) may be related to the pathogenesis of this side effect [11, 12]. It has been suggested that immune complexes, such TNF-α/TNF-α-antibody are deposited in the small capillary, and can activate type III hypersensitivity reaction [13]. It has been also reported that the appearance of anti-drug antibody is closely related to the occurrence of ANA and paradoxical inflammations [13]. Usually after discontinuation of the TNF-α inhibitor, patients have complete resolution of symptoms [12].

In conclusion, drug-induced leukocytoclastic vasculitis is a rare complication, however early diagnosis is critical to successful patient outcome.

## Conflict of interest

The authors declare no conflict of interest.

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