Cutaneous vasculitis and granulomatous hepatitis as paradoxical adverse events of Infliximab

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To the editor,

Biological agents, namely TNFa inhibitors (iTNFa), revolutionised the treatment of inflammatory arthropathies. There are, however, possible side effects including paradoxical adverse events (PAEs), defined as immunological manifestations that may respond to treatment with biological agents and happen during treatment with this class of drugs. They are uncommon, may occur at any time during treatment and are classified as true or borderline PAEs, should the drug be approved for the treatment of the condition or have a theoretical therapeutic effect, respectively[1]. Vasculitis and granulomatous diseases are both classified as borderline PAEs of iTNFa[1]. We present a rare case of simultaneous presentation of infliximab-induced vasculitis and granulomatous hepatitis.

A 58-year-old man with psoriatic arthritis since 1998 was referred to our department in 2013. He had history of psoriasis, arterial hypertension, dyslipidemia and osteoporosis secondary to corticosteroid treatment. He was treated with methotrexate since disease onset but liver toxicity limited dose escalation beyond 10mg/week. Sulfasalazine association was tried but was suspended because of thrombocytopenia. In December 2017 he started infliximab therapy because of persistent peripheral activity, achieving rapid remission. Methotrexate dose was further reduced to 5mg/week due to liver toxicity (nevertheless maintained because of possible prevention of anti-infliximab antibodies).

In January 2019, he presented with a purpuric skin rash in his abdomen, trunk and lower limbs, accompanied by small necrotic lesions in his fingers (Figure 1). Routine blood tests showed increased transaminases (AST 87, ALT 125IU), gamma-glutamyl-transferase (gGT 512IU), alkaline phosphatase (AP 548IU) and inflammatory markers (C-reactive protein 26.3mg/L and erythrocyte sedimentation rate 53mm/h). The patient reported no fever, asthenia or anorexia, arthralgia/arthritis, respiratory or gastrointestinal symptoms. Infliximab infusion was postponed, methotrexate was suspended, and the patient was admitted for investigation. The main hypotheses placed were infection, paraneoplastic syndrome or adverse events of iTNFa.

Work-up included chest and abdomen computed tomography and an echocardiogram that were normal; serologies for HIV, HCV, HBV, HAV, CMV, EBV and blood cultures were negative. Immunological study showed positive (1:320) anti-nuclear antibodies but negative extractable nuclear antigens, anti-dsDNA, -histones, -mitochondrial, -liver-kidney, -smooth-muscle and -glycoprotein-210 antibodies. Bilirubin, immunoglobulin and albumin levels were normal and there were no coagulation defects. Cytolysis and cholestasis markers peaked at day 5 (AST 292, ALT 490, AP 367, gGT 955IU).

Skin and liver biopsies were performed and treatment with steroids (0.5mg/Kg/day) initiated with progressive resolution of skin rash, normalisation of liver changes and inflammatory biomarkers. Histology of skin and liver biopsies subsequently revealed leukocytoclastic vasculitis and granulomatous hepatitis with bile duct injury, respectively; Zeel-Nielsen stain revealed no alcohol-acid-resistant bacilli.

TNFa inhibitors are the main agents causing drug-induced vasculitis[2]. In Rheumatology, this PAE seems more common in patients with rheumatoid arthritis and receiving etanercept. Although vasculitis affecting medium size vessels and with peripheral nervous and kidney involvement are reported, the majority of reports concern exclusive cutaneous manifestations suggestive of small size vessel involvement like purpura lesions, as in this case. Reported timings between treatment initiation and the event vary substantially[2,3,4].

Regarding iTNFa-induced liver injury, reports vary from asymptomatic liver enzymes elevation to fulminant hepatitis requiring transplantation[5,6]. Infliximab seems to be the main culprit of liver injury induced by these agents, although granulomatous diseases (like in

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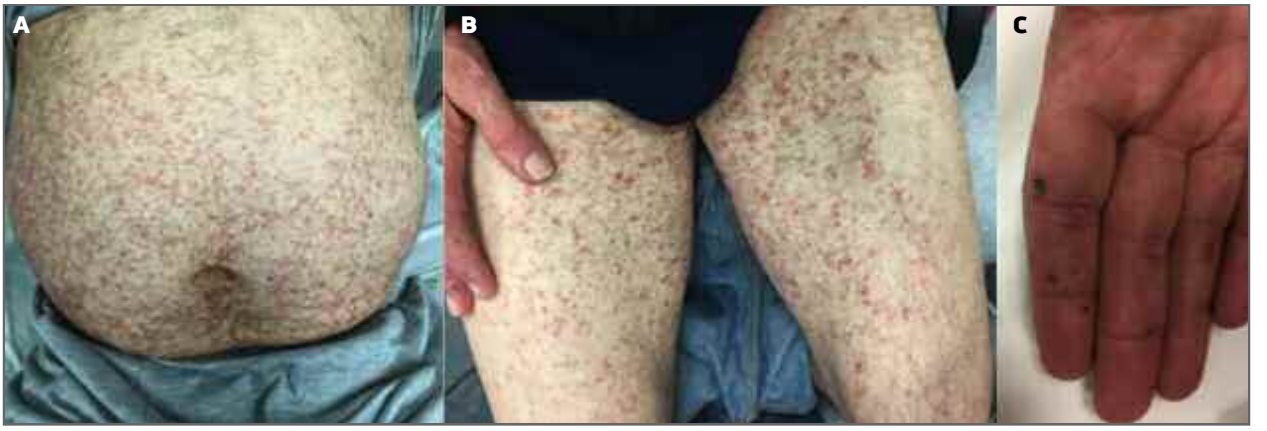

FIGURE 1. Panel A and B showing skin rash in the abdomen and lower limbs and panel C showing necrotic lesions in the patient's hand.

this particular case) are more associated with etanercept[1]. Mechanisms by which these drugs induce liver injury are elusive and may be related with direct toxicity or immune-mediated, with reports of iTNFa-induced autoimmune hepatitis[7].

Vasculitis and granulomatous diseases are considered "borderline" PAEs of treatment with iTNFa[1]. For both events, suspension of the offending agent and treatment with steroids have been suggested and the case seems to favor this approach. Exclusion of infection and neoplasia was crucial for the clinical picture to be attributed to infliximab.

The authors warn for the need to know less common adverse events of biological therapies and highlight the concurrent presentation of two uncommon events in the reported clinical case.

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