SHORT COMMUNICATION

Bullous Haemorrhagic Vasculitis Associated with Adalimumab in a Child with Juvenile Idiopathic Arthritis

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Cutaneous side effects related to treatment with anti-tumour necrosis factor-alpha (TNF-α) agents have been described in adults with inflammatory bowel diseases (IBD) or with rheumatic diseases, but in children reports are very rare. Reported skin manifestations are mainly local reactions at the injection site, psoriasis, cutaneous lupus and lupus-like syndromes, granuloma annulare, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis etc. (1). Herein we describe a girl treated with adalimumab (ADA) for juvenile idiopathic arthritis (JIA) who developed a bullous haemorrhagic vasculitic rash on the lower limbs that resolved after withdrawal of the drug.

CASE REPORT

A 13-year-old girl with oligoarticular JIA had started ADA at the age of 9 years because of incomplete disease control with methotrexate (MTX). Three years after the start of ADA the patient developed palpable and painless purpuric lesions on both ankles (**Fig. 1**A, B) that after few weeks spread to both legs (Fig. 1C, D) and subsequently evolved as bullous haemorrhagic, particularly on lateral aspect of left ankle and anterior-lateral aspect of right ankle (Fig. 1E, F). Her physical examination was otherwise normal, and she did not experience any systemic symptoms such as fever or myalgias and arthralgias. No history of infections or recent travel was reported, and no other drugs had been administered. Blood tests including acute phase reactants (ESR and CRP) were all normal, as well as complement levels, kidney and liver function tests, and autoimmune profile (anti-neutrophil cytoplasmic antibody ANCA, anti dsDNA, anticardiolipin, anti beta2 glycoprotein antibodies, and lupus anticoagulants); urine analysis was negative. Given the absence of other possible causes and the negative lab tests, a bullous Henoch–Schönlein purpura-like (HSP) rash related to ADA was suspected. Therefore, the drug was withdrawn, and a short course of prednisone was suggested. During the following weeks the rash gradually improved, with complete recovery of the larger lesions in a few weeks. Only isolated petechiae appeared in the following month and these gradually disappeared over time. Due to a relapse of arthritis of the left knee the anti-IL-6 inhibitor tocilizumab was started with good response; to date after 10 months no new vasculitic lesions have appeared.

DISCUSSION

ADA is a fully human monoclonal antibody anti-TNF-α approved for children with JIA, and with Crohn's disease and ulcerative colitis (UC). Cutaneous side effects related

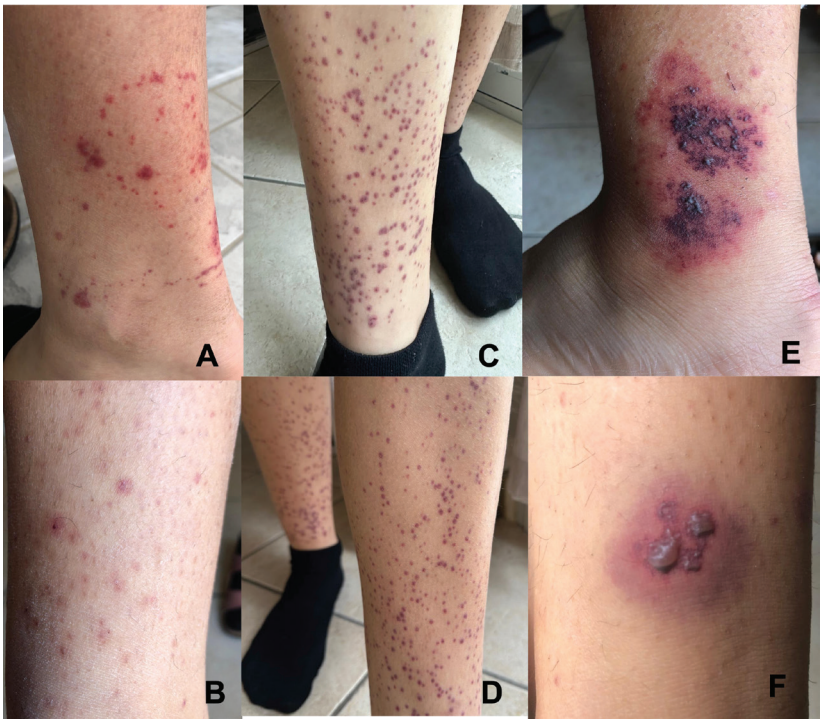

Fig. 1. Clinical evolution of vasculitic lesions. (A, B) Initial presentation of palpable purpura on the left and right ankles (C, D) After a few weeks the purpuric lesions spread to the whole surface of the right and left leg. (E, F) Subsequent evolution of the vasculitic lesions with necrotic and bullous haemorrhagic appearance on the lateral aspect of the left ankle and on the anterior-lateral aspect of the right ankle.

to treatment with TNFi have been described both in adults with rheumatic diseases and with IBD (2, 3).

The skin manifestations so far reported are quite heterogeneous, ranging from local reactions at the injection site to psoriasiform or eczematous eruptions, skin infections, and lupus-like rashes (2, 3). In a large Spanish database of 5,437 adult patients treated for chronic inflammatory rheumatic conditions with TNFi (etanercept, infliximab, or adalimumab) and representing 17,300 years of exposure, the most common reactions were psoriasiform changes, alopecia areata, cutaneous lupus, vitiligo, lichenoid eruption, morphea, granuloma annulare, and vasculitis (4). Similarly, in a study on 917 adults with IBD treated with TNFi during a median follow-up of 3.5 years, skin lesions developed in 29% of patients (psoriasiform eczema in 30.6%, eczema in 23.5%, xerosis cutis in 10.6%, palmoplantar pustulosis in 5.3%, psoriasis in 3.8%, and other skin lesions in 26.1%) (3).

The reports on paediatric patients are very limited and mainly related to the use of TNFi in IBD, for which the prevalence of cutaneous side effects is estimated to be greater than 11%, while data on children with rheumatic conditions are very scarce (4–9). Paradoxical psoriasiform eruptions have been reported in 5.8–8.1% of patients, skin infections in 2.9–5.6%, eczematous rash in 1.4–2.4%, and there are sporadic reports of morphea cases (5–8).

The pathogenesis of TNF-α-induced skin manifestations is still not entirely clear and different immune pathogenic mechanisms have been suggested, depending on the nature of the lesions.

In psoriatic-like lesions, the most frequent paradoxical skin reaction, a TNFi-induced cytokine imbalance between TNF-α and type 1-Interferons (IFN-α), has been reported as the key pathogenetic factor (10). Continuous therapeutic TNF-α blockade may cause a specific cytokine imbalance in the skin, triggering the development of inflammatory plasmacytoid dendritic cells (pDCs) and increased type-1 IFN production. Therefore, increased IFN-α activity induces abnormal trafficking and homing of pDCs and innate immune cells to the skin, in an inflammatory loop leading to paradoxical psoriatic-like lesions, mostly independent of adaptive immune responses, which is in contrast to the pathogenesis of "classical" psoriasis (11).

Furthermore, increased expression of the chemokine receptor CXCR3 on peripheral T-cells has been reported in RA patients treated with TNFi and this may lead to increased trafficking of activated T-cells to the skin. It has been suggested that this dysregulated immune response may then translate clinically to paradoxical psoriasis in genetically susceptible subjects (12).

Vasculitic lesions in patients treated with TNFi are rarely described, and in the paediatric population only a few cases have been reported (4, 7, 12–15). Data from pharmacovigilance show that, among possible causes of drug-induced IgA vasculitis, anti-TNF-α agents ADA and infliximab were suspected, in 13.2% and 7.3% of cases respectively, in adult patients treated for IBD or psoriasis while no paediatric case was associated with these drugs (14).

In a review of published reports of autoimmune diseases that developed in adults taking anti-TNF-α agents, among 379 diagnoses of a new autoimmune disease 118 cases of vasculitis were found; 102 of them had isolated cutaneous involvement, 44 were documented as leukocytoclastic vasculitis, and 2 were confirmed as HSP cases (12).

Sokumbi et al. performed a 13-year retrospective cohort with 345 adult patients using anti-TNF-α therapy, and they identified 8 cases of vasculitis induced by this treatment. The main indication for TNFi was RA (50%) and the most frequently involved organ was the skin (4 patients had palpable purpura, 2 ulcerated lesions, and 1 erythematous macules or blisters), the most used agent was infliximab, followed by etanercept and ADA (in 5, 2 and 1 patient, respectively) and only 1 patient had renal involvement with microscopic haematuria and proteinuria (15).

Complete remission of the skin lesions is described in 75% of cases after discontinuation of anti TNF-α, adopted as a strategy where the vasculitis becomes life-threatening or worsens drastically. In some cases, non-biologic disease-modifying antirheumatic drugs or corticosteroids are necessary depending on the individual case. After discontinuation of the drug patients continue to have vasculitic manifestations very rarely (12, 15).

The possible pathogenesis of vasculitis associated with TNFi is unknown. It has been hypothesized that the development of anti-drug antibodies may lead to an immune-complex-mediated hypersensitivity process leading to vasculitis (15).

The time interval between TNFi start and the onset of vasculitis in our patient was 3 years and this observation agrees with previous reports in which the time gap before skin adverse reactions is quite long, with median values of 13 to 21 months (range 7 to 72 months) (2, 3, 7, 8, 12, 13, 15).

In our patient the clinical distribution and appearance of the lesions were very similar to HSP, although with rare and unusual bullous haemorrhagic presentation but, without a biopsy, we cannot confirm this diagnosis.

To the best of our knowledge, this represents the first case of bullous haemorrhagic HSP-like vasculitic rash related to ADA in a child with JIA. Our patient had never presented previous clinical manifestations of vasculitis and no other possible infectious or immunological causes were found. Indeed, a causal link between the drug and the clinical picture might have been strengthened by a re-challenge with ADA while we observed only a favourable response to discontinuation of the drug (po-

sitive de-challenge), as in most reports in the literature, in which a re-challenge was performed in very few cases (2, 3, 12, 13, 15). Given the widespread use of TNFi this case highlights the importance for clinicians to be aware of any potential adverse reactions to reach the correct diagnosis and ensure appropriate treatment.

The authors have no conflicts of interest to declare.

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