Eosinophilic cellulitis (Wells' syndrome) as a cutaneous reaction to the administration of adalimumab

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A 72 year old female patient had a 30 year history of progressive rheumatoid arthritis treated ultimately with a combination of ciclosporin A plus corticosteroids and anti-inflammatory agents. Adalimumab was started as anti-tumour necrosis factor (TNF) monotherapy because the disease persisted. Ciclosporin A was discontinued 3 months before the initiation of adalimumab. At the site of the first adalimumab injection, a mild local reaction developed 6–8 hours later, not accompanied by general symptoms.

Three to 4 hours after the second adalimumab injection (15 days later), the patient presented at the emergency department with chest discomfort, epigastralgia, fever (38.4°C), rigor, fatigue, and malaise. At the same time, at the injection site (left thigh), a violaceous plaque (10×9 cm) had developed, emerging as an erythematous urticarial oedema (fig 1A). Laboratory investigation showed a raised erythrocyte sedimentation rate and increased C reactive protein and anaemia. An abdominal radiograph with the patient in an upright position showed air fluid levels, suggesting the presence of ileus.

Local and generalised manifestations were treated with intravenous fluid supplementation and antibiotics; steroids were given. Systemic manifestations gradually improved. The patient was discharged from hospital after 8 days, with the recommendation that treatment with corticosteroids by mouth should be gradually stopped and that the treatment of rheumatoid arthritis should be reconsidered by the consulting rheumatologist. The skin reaction progressively improved.

To investigate the nature of the reaction a skin biopsy was performed. It disclosed a prominent infiltrate of eosinophils, affecting the entire thickness of the dermis. Focal infiltration of lymphocytes was also noticed. Many blood vessels had considerable wall thickening. Prominent “flame figures” were found, consisting of eosinophilic necrotic collagen surrounded by granular debris (fig 1B). The histological features were consistent with the diagnosis of eosinophilic cellulitis (Wells' syndrome).

Eosinophilic cellulitis is a rare condition of unknown aetiology, often recurrent and autoremissive.¹ Its differential diagnosis includes different local and systemic skin reactions.² Although peripheral eosinophilia may occur, this is not sufficient for diagnosis of the syndrome.^{2–3} The pathophysiology of the lesions remains unknown. Excessive production has been described of interleukin 5, which is the main cytokine responsible for eosinophilic accumulation in a local Th2 immune response.² Many drugs have been causally related to Wells' syndrome (most commonly penicillin, tetracycline, anticholinergic agents, anaesthetics, and acetyl salicylic acid).³ No report has been published so far, involving the anti-TNF agents in the aetiopathogenesis of the syndrome.

In the present case, we suggest that initially a mild subcutaneous type I hypersensitivity reaction developed. After the second administration of the same biological agent a similar but augmented hypersensitivity reaction, resulted in eosinophilic cellulitis. Locally enhanced and specific systemic manifestations might be attributed to a type III complement dependent hypersensitivity reaction (mediated by immune complexes) due to resensitisation, leading to a generalised systemic immune complex (Arthus-like) reaction, and a severe, extended local eosinophilic response (Wells). The local type I reaction that followed the first antigen exposure might have caused a Th2 response (interleukin 5) and IgE and IgG isotype switching. After antigenic rechallenge, IgG-drug immunocomplexes might lead to an enhanced type III reaction with the typical clinical manifestations described here.

We conclude that Wells' syndrome with typical clinical and histopathological characteristics, may be a side effect of anti-TNF α treatment. Although other skin reactions to the administration of adalimumab have been recently described,⁴ as far as we know, this is the first report of Wells' syndrome developing after treatment with adalimumab (or any other anti-TNF α agent).⁵

This case report emphasises that a sufficient level of drug surveillance should be maintained, even for non-chimeric biological agents. Early identification and management of local reactions might prevent severe systemic manifestations.

Figure 1 Macroscopic (A) and microscopic (B) view of the local reaction at the injection site. Noted in the frame is the characteristic aggregation of necrotic collagen fibres (“flame figure”) with prominent eosinophilic invasion of the dermis.

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