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Delayed maculopapular, urticarial rash due to infliximab in two children with systemic onset juvenile idiopathic arthritis

Sir, The tumour necrosis factor-α (TNF-α) blockers (infliximab and etanercept) have been widely used for the treatment of uncontrolled rheumatoid arthritis in adults, but there is little experience with infliximab in children with juvenile idiopathic arthritis (JIA) [1, 2]. Here we describe adverse drug reactions in two children treated with infliximab for systemic onset JIA (s-JIA).

Patient A (girl, 10 yr) and patient B (boy, 16 yr) were diagnosed as having s-JIA at the ages of 3 and 7 yr respectively. Both received combined treatment with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (standard-dose oral prednisolone and intravenous pulse methyl prednisolone), methotrexate and cyclosporin A. Despite intensive treatment efforts, systemic features and destructive polyarthritis persisted in both patients. The patients also experienced growth retardation and osteoporosis. Because they did not respond to classical drug therapy, we planned to start infliximab infusion (doses of 5 mg/kg at weeks 0, 2 and 6, followed by doses given every 8 weeks). NSAIDs and oral corticosteroids were continued during the initial period of infliximab treatment. After two doses of infliximab infusion, the systemic illness was monitored by clinical and laboratory assessment in both patients; acute-phase reactants decreased remarkably and clinical parameters [visual analogue scale measurement (parental assessment) for global well-being and pain (scale 0–100 mm), Childhood Health Assessment Questionnaire] improved significantly.

The first and second infliximab infusions were tolerated well, except for a transient fever observed in both patients. On the 11th day of the first infusion of infliximab, bilateral severe conjunctival injection was noted in patient A. Two days later, an erythematous diffuse macular, papular and urticarial pruritic rash of the trunk and limbs, some of which showed a central clearing (Fig. 1), occurred and lasted 4 days. At the same time, she suffered from headache, high fever, sleeping disturbance, anorexia and vomiting. Laboratory assessment showed leucocytosis with a shift to the left, and an elevated serum C-reactive protein level. Light microscopic examination of a cutaneous punch biopsy revealed lymphocytic exocytosis in the epidermis, and oedema and perivascular inflammation (predominantly lymphocytes) in the dermis. These findings were considered to demonstrate an exanthematous cutaneous drug reaction. There was no immune deposition detectable by immunofluorescence microscopy.

After the first dose, bilateral conjunctivitis was also observed in patient B on the third day of therapy and resolved spontaneously at the end of the first week. An aphthous stomatitis, gingivitis, and oral herpes infection developed at the same time and continued until the second infliximab dose in patient B. A maculopapular rash similar to that observed in patient A was noted 18 days after the second infliximab infusion and persisted for about 1 week. Histological examination of these lesions showed necrotic keratinocytes and superficial perivascular mild lymphocytic and histiocytic infiltration in the dermis. We did not demonstrate any immune deposition by immunofluorescence microscopy. Both patients were negative for antinuclear antibody and double-stranded DNA antibody, and had normal complement levels. We did not stop infliximab treatment in either patient. Patient A has received seven and patient B has received six infliximab infusions so far, without significant complications. Treatment with corticosteroids was stopped in both patients after the third infusion of infliximab. They are now in remission, as shown by clinical and laboratory tests. Similar cutaneous eruption have not recurred.

Minor side-effects are commonly reported by most patients who receive infliximab. The most commonly reported side-effects are upper respiratory tract symptoms and mild rash and itching, beginning within 24 h of infusion and usually resolving in a few days without need for treatment [3, 4]. We believe that the delayed appearance of rash in our patients suggests the presence of an immunological preparation period. Although a similar rash may appear with an intercurrent viral infection, clinical and laboratory findings did not suggest a viral infection. The appearance of a rash



Fig. 1. Erythematous diffuse macular, papular and urticarial pruritic rash with central clearing on the right arm of the patient A.

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did also not resemble these children's previous s-JIA rash. A delayed onset of rash, as seen in our patients, has been reported in adult patients with rheumatoid arthritis as hypersensitivity and/or actual cutaneous vasculitis with infliximab and etanercept [3, 5, 6]. Cutaneous vasculitis has also been reported in a paediatric case with s-JIA due to etanercept [7]. Although we could not demonstrate evidence of vasculitis by light and immunfluorescence microscopy, the histological findings in cutaneous biopsy specimens suggest a hypersensitivity reaction [5]. Therefore, we conclude that a short-lived cutaneous rash may appear 2–3 weeks after the introduction of infliximab treatment as a delayed hypersensitivity reaction in children.

The authors have declared no conflicts of interest.

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The right place of ^{18}FDG PET for the diagnosis of giant cell arteritis—a response to the article of Brodmann *et al.*

Sir, I read with great interest the recent article of Brodmann *et al.* [1]. It is an interesting contribution that assesses the exact role of ^{18}FDG PET in the management of patients presenting with giant cell arteritis (GCA). The most important finding was the inability of ^{18}FDG PET to detect a metabolic signal at the level of temporal arteritis, while localizing 100% of extratemporal GCA involvement. Based on personal experience in evaluating GCA with ^{18}FDG PET, published recently [2], I would like to respond to the article of Brodmann *et al.*

The fact that ^{18}FDG PET is not suitable for the diagnosis of temporal arteritis is not really surprising. In the above-mentioned paper, we emphasized the limited spatial resolution of commercially available PET scanners. This is a technical limitation that prevents the detection of any metabolic signal within anatomical structures smaller than 4–5 mm in size. In addition, the physiological uptake of ^{18}FDG by the grey matter of the brain certainly obscures the slight uptake within the temporal arteries. As a consequence, ^{18}FDG PET should not be used for the diagnosis of temporal arteritis.

Although the authors rightly conclude that metabolic imaging cannot replace invasive biopsy, we note that only eight of out 22 patients had a temporal biopsy. Therefore, a definitive correlation with a pathological gold standard was provided in only 36% of cases.

Currently, the diagnosis of GCA and/or temporal arteritis is based on the ACR classification. Not only is biopsy-proven GCA just one among five of the ACR criteria (three out of five are needed for diagnosis), but also it is not unusual to have false-negative biopsies in GCA patients because their arterial disease is focal. Indeed, in the present series, 77% of patients (17/22) had GCA affecting the large vessels with concomitant involvement of the temporal arteries.

The interesting finding in this study was that 50% of patients presented with extratemporal GCA (11/22). In all of these cases, ^{18}FDG PET was positive and completely agreed with colour-coded duplex sonography. In particular, five of out 22 (23%) ^{18}FDG-avid patients had no evidence of temporal involvement.

In the study group, the diagnosis of GCA was initially made on clinical criteria, thereby, generating a bias with regard to the appropriate role of the imaging modalities. In a large population of patients who do not necessarily meet the ACR criteria (including the temporal biopsy), a positive whole-body ^{18}FDG PET may provide valuable metabolic arguments for the diagnosis of GCA.

In several series assessing the value of ^{18}FDG PET in large-vessel vasculitides, including a recent review co-authored with Daniël Blockmans, ^{18}FDG PET appears to be particularly useful in cases of GCA with atypical presentation (isolated inflammatory syndromes, fever of unknown origin or negative temporal biopsy). Such circumstances are often the cause of repeated, time-consuming and ultimately fruitless radiological studies. Thus, whole-body metabolic imaging may efficiently guide the diagnosis when extratemporal localizations are detected [3–5].

In this series, the sensitivity of colour-coded duplex sonography (CDD) in detecting temporal involvement based on the halo sign ($17/22 = 77\%$) is rather greater than that reported in the recent literature. Salvani *et al.* reported a sensitivity of only 40% in a large series of 86 patients [6], and Schmid *et al.* obtained a sensitivity of 50% in a series of 20 patients [7]. Besides the focal arterial involvement, the operator dependency and the learning curve characterizing the use of CDD probably explain the limited sensitivity of the technique.

In conclusion, until now there has been no perfect modality for the diagnosis of temporal GCA. Because of the particular pathological pattern of the arterial disease, neither CDD nor temporal biopsy has a sensitivity that is clinically suitable for detecting temporal GCA (i.e. >90%). ^{18}FDG PET may play a role in the management of atypical GCA, when the CDD and the temporal biopsy are non-contributive, by demonstrating extra-temporal localizations. Metabolic imaging may be also of interest for the assessment of the inflammatory process after corticoid therapy.

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