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Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a pre-existing anti-dsDNA antibody level

Sir, Drug-induced systemic lupus erythematosus (SLE) has been described for rheumatoid arthritis (RA) patients treated with the tumour necrosis factor-α (TNF-α)-blocking agents, infliximab and etanercept [1, 2]. This complication of clinically manifest SLE seems to be induced considerably less often, if not at all, in patients treated with the fully human anti-TNF-α antibody, termed adalimumab [3]. The present case report describes a patient who develops SLE upon conversion of infliximab to adalimumab and provides data that indicate the involvement of a Th1-driven inflammatory response in this patient.

A 56-yr-old Asiatic woman with a 26-yr-old history of severe disabling RA was previously unsuccessfully treated with hydroxychloroquine, α- penicillamine, azathioprine, prednisone and methotrexate. Rheumatoid factor was always strongly positive whereas anti-nuclear and anti-dsDNA antibody levels were not detectable.

In November 2001, TNF-α blocking treatment was started (infliximab: 3 mg/kg, once i.v. per 8 weeks) which induced a good clinical response. Gradually the clinical response waned; the effect of an infliximab-infusion lasted only 2–3 weeks. Therefore, after ≈2 yrs and a wash-out period of 8 weeks, this patient was switched to subcutaneous adalimumab 40 mg every other week (written consent of the patient was obtained according to the declaration of Helsinki and the design of the adalimumab study was approved by the UMC, Utrecht medical ethical committee).

At the start of adalimumab treatment, active polyarthritis was associated with a positive anti-nuclear antibodies (ANA) and an anti-dsDNA titre of 2451U/ml (Farr assay, normal range 0–101U/ml, Fig. 1A). These levels were raised during infliximab therapy since prior to infliximab therapy the level was 41U/ml. Despite this rise, apart, from arthritis, no clinical signs of SLE were present. The severe polyarthritis was rapidly reduced as indicated by the significant decreases in joint swelling and tenderness. After four bi-weekly injections she developed severe ulcerations of the buccal mucosa and the palatum. Five injections later, she was admitted to the hospital with fever, high erythrocyte sedimentation rate (ESR), leucopenia, anaemia and a photosensitive urticarial and papulosquamous rash on the exposed areas of her face and felt generally lethargic (Fig. 1A). Cultures of blood and urine were negative; a crista biopsy revealed no abnormalities. Skin biopsy at this time point (week 18) revealed vacuolization of basal keratinocytes with subepidermal blistering and a superficial and deep lymphocytic infiltrate consistent with lupus erythematosus (LE) (Fig. 1B). At this time point, strongly increased anti-dsDNA antibody levels were observed (Fig. 1A). A diagnosis of SLE was made and her adalimumab treatment was discontinued. She received three i.v. injections of 200 mg dexamethasone every other day. The patient generally felt better; the mucosal ulcerations and skin lesions disappeared. In contrast to this, anti-dsDNA levels were not reduced by dexamethasone pulse treatment.

The immunopathological mechanism for the development of SLE upon anti-TNF-α therapy is unclear. In animal models for SLE, the development of experimental SLE was suggested to involve two stages: increased Th1-driven [interferon-γ (IFNγ), interleukin (IL-2)] inflammatory responses including antibody formation, followed by ‘Th2’ cell responses (IL-4, IL-10) with persistent antibody levels [4]. Based on serum protein levels of patients with SLE, in particular, those who suffer from active disease, several studies have suggested the involvement of cytokines that induce Th1 responses [migration inhibitory factor (MIF), IL-12, IL-18] as well as Th1 activity itself (IFNγ, IL-2, IL-17) [5–7]. Along with the presence of this type of immune response, Th2 cell activity (IL-4) as well as IL-10 levels have been found to be increased and were found to correlate with markers of inflammation such as anti-dsDNA [6, 7].

To understand the anti-TNF-α-induced SLE immunopathology, serum cytokine levels were assessed in retrospective which could explain the development of this clinical finding. Interestingly, associated with a rise in ESR, adalimumab treatment strongly increased cytokines indicative of Th1 activity in contrast to ‘anti-inflammatory’ and Th2-associated cytokines, which were not significantly changed (Fig. 1C and D). In RA patients, the increase of systemic Th1 activity upon anti-TNF-α treatment can occur due to re-entry of inflammatory cells from the site of inflammation (joints) into the circulation or due to repression of TNF-α-inhibited Th1 activity [8, 9]. However, this is usually associated with decreased inflammation as indicated by decreased C-reactive protein (CRP) and ESR. In the presented patient, the development of skin inflammation and increased antibody levels could explain a rise in markers of inflammation such as ESR.

In contrast to the induction of antoantibodies, the clinical presentation of (biopsy-confirmed) active SLE upon adalimumab therapy is rarely, if at all, reported. As far as we know, this is the first article describing the biopsy-confirmed development of clinical SLE upon adalimumab treatment following infliximab therapy. Since infliximab treatment had already induced high anti-dsDNA levels, adalimumab treatment seems to have boosted the infliximab-induced mechanisms that were accompanied by pro-inflammatory activity. Finally, this may develop into the clinical presentation of SLE. Therefore caution may have to be taken when anti-dsDNA antibodies are present at the start of conversion therapy.

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<td>Increased cytokine and anti-dsDNA levels accompany SLE development upon infliximab-adalimumab conversion.</td>
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Letters to the Editor

Impaired endothelial function in patients with ankylosing spondylitis

Sir, With interest I read the article by Sari and associates [1] in which they describe impaired endothelial function in patients with ankylosing spondylitis (AS). The authors found reduced flow-mediated dilatation (FMD)—a marker of endothelial dysfunction—in AS-patients compared with healthy controls. Sonographically evaluated intima-media thickness of the common carotid artery was comparable in both groups. The authors excluded patients from the study who had traditional cardiovascular risk factors, such as a history of myocardial infarction, diabetes mellitus, hypertension, renal failure, family history of premature coronary heart disease and subjects on lipid-lowering drugs. Even an oral-glucose tolerance test was performed to recognize patients with undiagnosed diabetes. However, patients (and controls) who were smokers were not excluded. Thus, about one-third of the subjects in each group had a history of smoking. I do not understand why those subjects were included in this study, because smoking is clearly known to impair endothelial function [2–4]. Would there be any difference if smokers are excluded from the analysis? In addition, it is not clear why the authors could not find any correlation between smoking and endothelial function, as it seems very likely that smoking has more impact on endothelial function than AS. What is the authors’ explanation for this finding? Comparing all smokers with all non-smokers (regardless of AS) would there be the same FMD in both groups?

There is growing evidence that inflammation plays a major role in the initiation and progression of atherosclerosis [5]. Furthermore, it is now well-known that inflammatory rheumatic diseases such as rheumatoid arthritis, primary systemic vasculitis and systemic lupus erythematosus go along with profound changes in function and structure of the cardiovascular system [6–9]. Whether this is also true for AS remains open to debate. I strongly appreciate the work of Sari and co-workers [1] on this topic, but definitely more data are necessary to clarify the impact of AS on endothelial function and its possible role in the development of premature atherosclerosis.

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