Safety of the use of anti-IL17A treatment in a patient with certolizumab-induced sarcoidosis

Sirs,

Different granulomatous-induced diseases have been described as paradoxical reactions under TNFα inhibitors (TNFi) , especially etanercept (1, 2). In this clinical setting, the cessation of the therapy is generally required. We report here a case of sarcoidosis occurring under certolizumab in a patient with non-radiographic axial spondyloarthritis (nRxAxSpA) with a favourable outcome under secukinumab.

A 45-year-old French Caucasian woman was diagnosed with HLA-B27-positive nRxAxSpA three years ago. Due to poor response to NSAIDs, she started certolizumab with a favourable response. Prior to starting the treatment, she had normal chest x-ray and PPD test. In January 2016, after 6 months of certolizumab, the patient developed severe renal insufficiency (glomerular filtration rate [GFR]: 18 mL/min). Both NSAIDs and certolizumab were suspended. A renal biopsy showed granulomatous interstitial nephritis with giant cells but without caseation (Fig. 1). An ^{18}F-fluorodeoxyglucose (FDG)-PET CT was performed, showing multiple foci of uptake in the mediastinum corresponding to mediastinal, supraclavicular and hilar lymphadenopathies. Inflammatory lesions with non-caseating granuloma were observed on histopathological examination of bronchial biopsies. All stains and cultures of bronchial tissue specimens were negative for fungi and mycobacteria. The patient was then treated by prednisone 60 mg/day, leading to mild improvement of renal function after two months (GFR:44 mL/min). A repeat FDG-PET CT was performed in January 2017, showing new foci of FDG uptake corresponding to abdominal lymphadenopathies and spleen involvement, while thoracic inflammatory lesions were resolved. Methotrexate (MTX) 15 mg weekly was then introduced in February 2017. There was no effect on SpA symptoms after 6 months, but the treatment was associated with total normalisation of PET CT. Secukinumab was then started in June 2017 in association with MTX (Fig. 2). This combination led to a minor improvement in axial symptoms (ASDAS score: 3.9) after 6 months, but renal disease remained stable (GFR: 42 mL/min) and there was no recurrence of inflammatory lesions on PET CT follow-up.

Since TNF-α is involved in the mechanisms leading to granuloma formation, TNFi have been tested in sarcoidosis, but randomised controlled trials failed to demonstrate a clinical benefit (3, 4). Conversely, TNFi may be associated with various granulomatous-induced lesions, a phenomenon considered as a paradoxical adverse event (1, 2). The mechanisms that might explain such granulomatous diseases remain only partially understood and involve IFNγ production, partial TNF-α neutralisation as well as lack of apoptosis, which may be associated with etanercept (1). However, etanercept is not the only TNFi that has been associated with granulomatous reactions, with other TNFi also involved. The management of such granulomatous diseases remains challenging, and depends on the severity of disease and the existence of alternative drugs (2, 5). In our case, the renal insufficiency was severe and GFR remained impaired despite cessation of certolizumab, and required corticosteroid therapy.

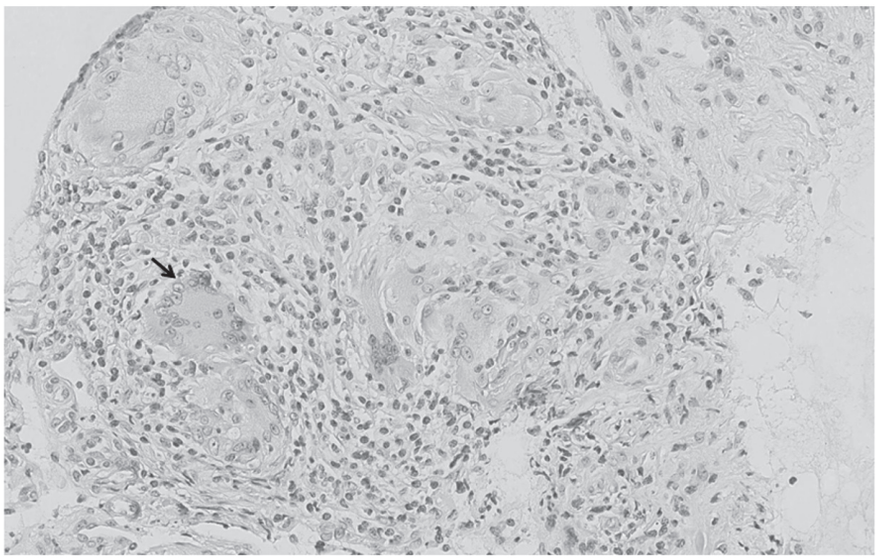

Fig. 1. Histopathological findings on renal biopsy (HES x 27) showing interstitial agglomerate of epithelioid cells and multinucleated giant cells (arrow) without caseous necrosis. The granulomatous infiltrate is concentrated near the arteries. There is no interstitial fibrosis and no noticeable glomerular lesions. Specific staining by PAS, Graham and Ziehl are negative for fungus and mycobacteria (Dr Sophie Felix, department of pathology, University Hospital of Besancon, 25000 Besancon, France).

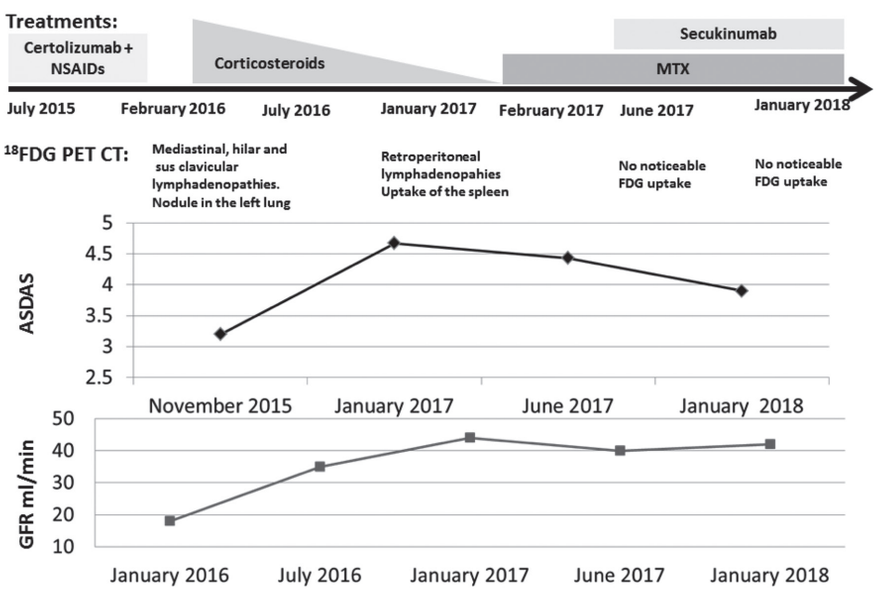

Fig. 2. Clinical course of the present case (GFR: glomerular filtration rate; ASDAS: ankylosing spondylitis disease activity score; ^{18}FDG -PET CT: ^{18}fluorodeoxyglucose positron emission tomography / computed tomography; MTX: methotrexate) (secukinumab was given 150 mg weekly the first month and then monthly).

IL-17A has been shown to be essential for granuloma formation in response to mycobacteria infections in mice (6). Increased IL-17A expression has been described in patients with sarcoidosis (7). IL-17A$^+$CD4$^+$ T cells were found to infiltrate sarcoid lung tissue from patients with different stage of sarcoidosis (8, 9). However, the exact contribution of IL-17A to sarcoidosis remains currently unknown. To date, no trial has evaluated the clinical efficacy and safety of IL-17A blocking agents in sarcoidosis. Secukinumab is not currently approved for the treatment of nRxAxSpA, but a clinical trial is in progress (10). Our patient received

secukinumab for 6 months with a very mild improvement in axial symptoms. However, she had no side effects and there was no recurrence or flare of sarcoidosis during the treatment period. This case suggests that in a patient developing granulomatous-induced disease during TNFi treatment, IL-17A blockade may be a safe alternative.

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The patient gave written informed consent for the publication of this case and the imaging material.

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