

## Retroperitoneal Fibrosis During Etanercept Therapy for Rheumatoid Arthritis

To the Editor:

Retroperitoneal fibrosis (RPF) is a rare disease characterized by fibro-inflammatory tissue surrounding the abdominal aorta and frequently encasing the ureter<sup>1</sup>. Empirical therapy includes high doses of corticosteroids as first-line treatment, and in some refractory cases immunosuppressive agents such as azathioprine, mycophenolate mofetil, or tamoxifen<sup>1</sup>. However, some patients fail to respond to immunosuppressive treatment. New drugs are needed for this patient subset. Catanoso, *et al* reported the case of a woman with idiopathic RPF whose condition improved after receiving infliximab, a monoclonal antibody directed against tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )<sup>2</sup>. In contrast, we describe the cases of 2 patients who developed RPF while receiving etanercept, a soluble receptor, another TNF- $\alpha$  blocker for RA. In the Rheumatology Department of Clermont-Ferrand Teaching Hospital, 2 patients with rheumatoid arthritis (RA) developed RPF while receiving TNF- $\alpha$  blockers for RA.

**Case 1.** A 57-year-old man was effectively treated with etanercept 50 mg/week for seronegative RA for 4 years. He was also treated with perindopril for arterial hypertension and rosuvastatin and aspirin for lower limb arterial disease. He presented with acute lower back pain with fever in 2004. Inflammatory markers were slightly elevated: erythrocyte sedimentation rate (ESR) 31 mm/h, upper limit of normal (ULN) 30 mm; C-reactive protein (CRP) 36 mg/l, ULN 3 mg/l, without renal impairment (creatinine 54  $\mu$ mol/l, ULN 84  $\mu$ mol/l; Modification of Diet in Renal Disease formula (MDRD) clearance 72 ml/min). Computed tomography (CT) scan revealed hydronephrosis of the left kidney with periiliac vessel cuff encasing the left ureter. A surgical biopsy was taken and a double-J stent inserted. The retroperitoneal tissue retrieval showed nonspecific inflammatory changes with reactive lymph nodes. The anti-TNF- $\alpha$  treatment was discontinued and high-dose corticosteroid therapy (methylprednisolone 1 mg/kg/day) was initiated. Three months later, the control CT scan revealed no worsening of the lesions. Adalimumab, a TNF- $\alpha$  monoclonal antibody, was started 1 year later because of reactivation of the rheumatic disease, with no side effects or worsening of RPF observed.

**Case 2.** A 52-year-old woman with seropositive and erosive RA was treated with methotrexate 15 mg/week and etanercept 50 mg/week for 7 years. She did not receive treatment known to induce RPF. In 2010, she presented with right lower back pain. Inflammatory markers were high (ESR 37 mm/h, CRP 38 mg/l). There was no renal dysfunction (creatinine 78  $\mu$ mol/l, MDRD clearance 82 ml/min) but slight proteinuria (0.35 g/24 h). The CT scan revealed hydronephrosis of the right kidney with a periaortic and periiliac vessel cuff suggestive of RPF. Etanercept was discontinued and a double-J stent inserted in the right ureter. An 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan showed high metabolism of the perivascular cuff (standardized uptake value = 3.6) and abnormal FDG uptake of the left breast, which led after microbiopsy to the diagnosis of localized breast adenocarcinoma. A surgical biopsy of the perivascular retroperitoneal tissue was taken and revealed nonspecific inflammatory tissue without granuloma or neoplastic cells. The breast cancer was treated by surgery, radiochemotherapy (5-fluorouracil, epirubicin, and cyclophosphamide), and hormone therapy (letrozole). One year later, the repeat CT scan of the abdomen showed marked improvement in the RPF (Figure 1). Methotrexate has been continued alone with no flares.

We describe 2 patients who developed RPF while receiving anti-TNF therapy (etanercept for RA).

Nearly one-third of RPF are secondary to a variety of causes<sup>1</sup>. Medications, radiotherapy, and infections, particularly tuberculosis, can induce RPF. Another frequent cause of secondary RPF is malignant disease. It results from an exuberant desmoplastic response to retroperitoneal metastases (prostate, breast, colon) or to the retroperitoneal primary tumor<sup>3</sup>. In our second patient, breast cancer was found on further exami-

nation, after undergoing FDG-PET/CT. It could not be excluded that RPF could be secondary to the breast cancer, even though no neoplastic cells were found on surgical biopsy, and the area of adenocarcinoma was contained.

Pathogenesis of idiopathic RPF remains unclear, its pathological appearance shows the coexistence of fibrous and inflammatory components<sup>1</sup>. Atherosclerosis has been advanced as a causative factor in susceptible hosts<sup>1</sup>, and could have played a role in our first patient. Nearly half of idiopathic RPF cases could be associated with IgG4-related disease<sup>4</sup>. Finally, RPF is frequently associated with autoimmune diseases, and notably with chronic rheumatic diseases such as RA, as in both our patients<sup>3</sup>. For some authors, RPF is considered part of the spectrum of chronic periaortitis, a large vessel vasculitis<sup>1</sup>. Although the role of TNF- $\alpha$  in its pathogenesis is still obscure, it led to successful TNF- $\alpha$  antagonist therapy (infliximab) in the treatment of 1 patient with RPF, as in large vessel vasculitis<sup>2</sup>. Nonetheless, in both our cases, RPF appeared despite several years using etanercept, a soluble receptor directed against TNF- $\alpha$ . Despite sharing a common therapeutic target, there are differences between the 2 classes of TNF- $\alpha$  antagonists in terms of mechanisms of action<sup>5</sup>. This could explain the differences observed between classes of TNF blockers in Crohn disease, in which only monoclonal antibodies (adalimumab or infliximab) are effective. Moreover, occurrence of a disease for which a treatment is known to be effective, called a paradoxical effect, has been reported for TNF blockers in psoriasis, inflammatory bowel diseases, sarcoidosis, episcleritis or uveitis, and vasculitis<sup>6,7,8,9,10,11,12</sup>.

Verhoeven, *et al*, reported a case of aortitis, which may favor the occurrence of subsequent RPF, occurring also during etanercept therapy for ankylosing spondylitis, but to our knowledge, this is the first case of RPF during anti-TNF treatment<sup>13</sup>. RPF is a rare disease (prevalence 1/100,000), so finding RPF in 2 patients with RA is surprising. This raises the question of an activating role of etanercept in the development of RPF.

Our report should prompt caution when considering the safety of TNF- $\alpha$  blockade, particularly etanercept, in the treatment of RPF.

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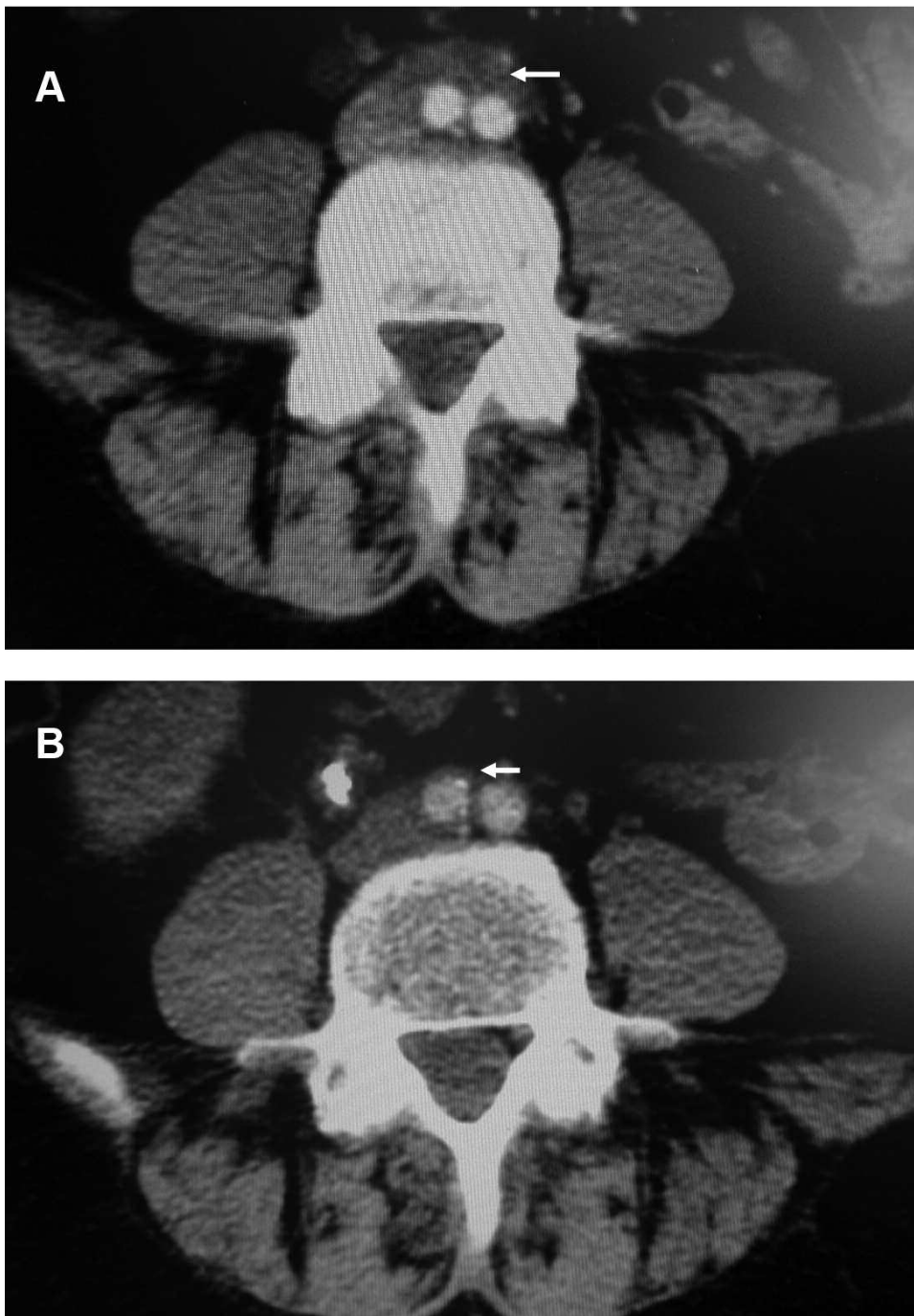


Figure 1. Abdominal computed tomographic scan, coronal image. (A) Initial and (B) followup scan 1 year later: A. Periiliac vessel cuff (arrow); B. Improvement in periiliac vessel cuff.

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