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Efficacy of infliximab in a patient with refractory idiopathic retroperitoneal fibrosis

M.G. Catanoso[1], L. Spaggiari[2], L. Magnani[1], N. Pipitone[1], A. Versari[3], L. Boiardi[1], G. Pazzola[1], P. Pattacini[2], C. Salvarani[1]

[1]Rheumatology Unit, [2]Department of Radiology, and [3]Department of Nuclear Medicine, Azienda Ospedaliera ASMN, IRCCS, Reggio Emilia, Italy.

Maria Grazia Catanoso, MD
Luca Magnani, MD
Nicolò Pipitone, MD, PhD
Luigi Boiardi, MD, PhD
Giulia Pazzola, MD
Carlo Salvarani, MD
Lucia Spaggiari, MD
Pierpaolo Pattacini, MD
Annibale Versari, MD

Please address correspondence and reprint requests to:
Dr Carlo Salvarani,
Servizio di Reumatologia,
Azienda Ospedaliera ASMN, IRCCS,
Viale Risorgimento 80,
42123 Reggio Emilia, Italy.
E-mail: salvarani.carlo@asmn.re.it

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ABSTRACT

Glucocorticoids are the mainstay of treatment of idiopathic retroperitoneal fibrosis (IRF). However, relapses are frequent upon tapering of the glucocorticoid dose. A variety of traditional immunosuppressants have been proposed as steroid-sparing agents, but some patients fail to adequately respond to combined glucocorticoid and immunosuppressive therapy.

We report a patient with IRF refractory to combined glucocorticoid and methotrexate therapy treated with the anti-TNF-α monoclonal antibody infliximab. Infliximab was administered at 5 mg/kg/bodyweight at week 0, 2, 6 and 8-weekly thereafter for 3 consecutive years. Drug efficacy and safety were assessed clinically and by laboratory tests at treatment onset and subsequently before each infusion. In addition, ^{18}F-Fluorodeoxyglucose (FDG) positron emission computerised tomography (PET/CT) and abdominal CT scans were used to monitor disease activity and response to treatment. Infliximab therapy resulted in a satisfactory clinical and laboratory response paralleled by an improvement in imaging findings. No serious adverse events were noted. Infliximab may be an effective and safe treatment for refractory IRF. A controlled study is required to confirm our findings.

Introduction

Idiopathic retroperitoneal fibrosis (IRF) is a rare disorder characterised by a fibro-inflammatory tissue that spreads from the inflamed adventitia of the abdominal aorta and iliac arteries into the retroperitoneum, often leading to ureters' encasement and hydronephrosis. Other common clinical features of IRF include constitutional manifestations and abdominal or back pain (1). In some patients, vascular inflammation may also involve other vessels, especially the thoracic aorta and its branches (2). These findings led us to propose that IRF be included among the large-vessel vasculitides (3).

Glucocorticoids are the cornerstone of therapy of IRF. However, some patients have a chronic-relapsing course and may need long-term glucocorticoid therapy (4-6). Adjunctive immunosuppressants may reduce relapse rates and glucocorticoid requirements (6-10), but some patients fail to adequately respond to combined treatment. Therefore, in this subset of patients there is a need for new drugs.

We report herein a case of IRF resistant to combined glucocorticoid and methotrexate therapy that responded to infliximab.

Case report

A 60-year-old woman presented in June 2006 with fatigue, abdominal pain, anorexia, and weight loss. She was receiving anti-hypertensive drugs for arterial hypertension, The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were raised at 85 mm/1st h and 4.60 mg/dl (normal value <0.50 mg/dl), respectively. Autoimmune serology and tests for common infectious diseases including tuberculosis were negative. A chest radiograph was unremarkable, while tumour markers and fecal occult blood were within limits. Further imaging was requested to investigate the cause of the patient's complaints.

Computerised tomography (CT) of the chest and abdomen showed concentric vessel wall thickening of the ascending thoracic aorta consistent with vasculitis, as well as a homogeneous perivascular cuff (maximum periaortic thickness: 59 mm) isodense to muscle surrounding the abdominal aorta and iliac arteries. The perivascular tissue had also encased the right ureter leading to right-sided hydronephrosis.

IRF was diagnosed. Secondary causes of retroperitoneal fibrosis including radiotherapy, surgery, intake of sclerosing drugs, infections, and tumours were excluded by the clinical history, laboratory tests, and by the imaging findings that showed no atypical features of the retroperitoneal mass such as tissue heterogeneity. Erdheim-Chester disease was excluded by the lack of perirenal retroperitoneal fibrosis and of typical manifestations such as bone pain. Prednisone (1 mg/kg/day) was commenced with marked clinical improvement and normalisation of inflammatory markers within a few weeks. A stent was also

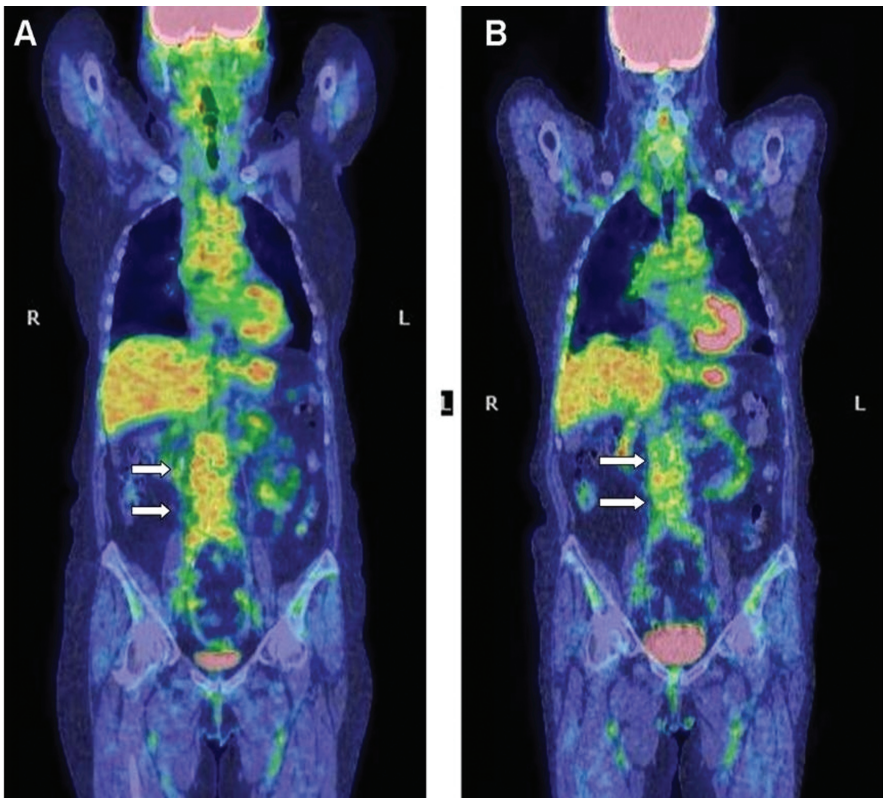

Fig. 1. FDG PET: Coronal image before (**A**) and after (**B**) infliximab.
A. Abnormal FDG uptake in the infrarenal abdominal aorta and surrounding peritoneal tissue (vascular/liver SUV ratio: 1.2) (arrows).
B. In the same areas (arrows) the FDG uptake significantly decreased (vascular/liver SUV ratio: 0.9).

inserted into the right ureter with rapid resolution of the right-sided hydronephrosis. However, attempts to taper the prednisone dose below 7.5 mg/day resulted in three clinical flares that required an increase in the prednisone dosage. Methotrexate (15 mg/weekly) was thus added as steroid-sparing agent. Despite the addition of methotrexate, in July 2007 while on prednisone 7.5 mg/day and methotrexate 15 mg/weekly, the patient had a new flare characterised by fatigue, abdominal pain, and diffuse aches and pains. ESR was 72 mm/1st h, and CRP 7 mg/dl.

Fluorodeoxyglucose (FDG) positron emission/computerised tomography (PET/CT) was performed to assess disease activity and extent. PET/CT vascular FDG uptake was expressed as standardised uptake value (SUV) relative to liver uptake (vascular SUV/liver SUV ratio).

Vascular uptake was also graded on a 0–3 scale (0=no uptake, 1=low-grade uptake, 2=intermediate-grade uptake, and 3=high-grade uptake) as detailed elsewhere (11). We considered the disease active if the vessels involved and/or the retroperitoneal mass showed ≥grade 2 FDG uptake (12). PET/CT revealed grade 2 FDG uptake around the abdominal aorta spreading from the origin of the renal arteries to the aortic bifurcation (Fig. 1A). SUV ratio (abdominal aorta and surrounding retroperitoneal mass/liver) was 1.20. A repeat CT scan showed only a slight reduction in the size of the abdominal periaortic cuff (maximum periaortic thickness: 57 mm).

Because of persistently active disease despite conventional treatment, adjunctive therapy with infliximab 5 mg/kg at week 0, 2, 6 and 8-weekly thereafter was commenced. The patient gave informed consent before infliximab treatment, which was approved by the local ethics committee.

Four months later, the patient was asymptomatic, while the ESR and CRP decreased to 25 mm/1st h and 0.41 mg/dl, respectively. Prednisone was successfully tapered off by March 2009**.** Two months later, the right ureteral stent was successfully removed. At the last follow-up (October 2011) the patient was in clinical and laboratory remission on methotrexate and infliximab therapy.

PET/CT was repeated and revealed a decrease in vascular FDG uptake with SUV ratio (infrarenal abdominal aorta and surrounding retroperitoneal tissue/liver) of 0.9 (Fig. 1 B).

CT scan of the abdomen showed a decrease in the retroperitoneal mass (maximum periaortic thickness: 52 mm).

Discussion

Patients with IRF are usually managed with glucocorticoids, often combined with immunosuppressants, but some patients are refractory to conventional treatment. There is evidence that TNF-· inhibitors may be efficacious in patients with resistant large-vessel vasculitis (13). In this regard, a recent report also confirmed the efficacy of the anti-TNF-alpha monoclonal antibody- adalimumab in a patient with large vessel vasculitis associated to sarcodosis refractory to corticosteroids and methotrexate (14).

Therefore, although there is no data on the efficacy of TNF-α inhibitors in IRF, we decided to treat our patient with the TNF-α blocker infliximab. Our results showed a full clinical and laboratory response to therapy paralleled by an improvement in imaging findings. More specifically, the retroperitoneal mass as assessed by CT shrank, albeit only modestly, after the onset of infliximab therapy. On the other hand, PET/CT demonstrated reduction in FDG uptake by the retroperitoneal mass.

Such a residual retroperitoneal mass characterised by slight FDG uptake following therapy is consistent with metabolically inactive tissue. (15-17). In addition, infliximab therapy allowed discontinuation of glucocorticoids and removal of the right ureter stent. These findings convergently point to efficacy of infliximab in this case of refractory IRF. In conclusion, this case suggests that infliximab may be a useful and safe therapeutic option for patients with IRF refractory to the traditional immunosuppressive treatment. Controlled studies are warranted to confirms our results.

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