Clinical and Experimental Rheumatology 2005; 23: 231-234.

Post-treatment residual tissue in idiopathic retroperitoneal fibrosis: active residual disease or silent "scar" ? A study using ^{18}F-fluorodeoxyglucose positron emission tomography

A. Vaglio, P. Greco, A. Versari[1], A. Filice[1], R. Cobelli[2], L. Manenti[3], C. Salvarani[4], C. Buzio

Department of Clinical Medicine, Nephrology and Health Sciences, University of Parma, Parma; [1]Division of Nuclear Medicine, Arcispedale S. Maria Nuova, Reggio Emilia; [2]Department of Radiology, University of Parma, Parma; [3]Division of Nephrology and Dialysis, Hospital Desenzano sul Garda; [4]Rheumatology Service, Arcispedale S. Maria Nuova, Reggio Emilia, Italy.

Augusto Vaglio, MD; Paolo Greco, MD; Annibale Versari, MD; Angelina Filice, MD; Rocco Cobelli, MD; Lucio Manenti, MD; Carlo Salvarani, MD; Carlo Buzio, MD.

Please address correspondence to: Prof. Carlo Buzio, Dipartimento di Clinica Medica, Nefrologia e Scienze della Prevenzione, Università degli Studi di Parma, Via Gramsci no. 14, 43100 Parma, Italy.
E-mail: carlo.buzio@unipr.it

Received on September 13, 2004; accepted in revised form on November 30, 2004.

Key words: Idiopathic retroperitoneal fibrosis, fluorodeoxyglucose, positron emission tomography, residual disease, corticosteroids, tamoxifen.

ABSTRACT

Objective. *Medical treatment is often effective in idiopathic retroperitoneal fibrosis (IRF) but frequently leads to residual retroperitoneal masses that may represent active disease or simply consist of inactive fibrotic tissue. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is a functional imaging modality that reliably assesses disease activity in a number of inflammatory diseases including IRF. We used ^{18}F-FDG PET to evaluate the metabolic activity of residual masses in a series of IRF patients.*

Methods. *We studied 7 consecutive IRF patients, all of whom presented constitutional symptoms and/or pain, and had high acute-phase reactant levels; 6 had ureteral involvement. IRF was diagnosed by means of computed tomography (CT), which revealed a peri-aortoiliac mass in all cases. Three patients underwent surgical ureterolysis and 2 received ureteral stents. Subsequently, 5 patients received prednisone, one sequential treatment with prednisone and tamoxifen, and one prednisolone plus methotrexate. All of the patients underwent ^{18}F-FDG PET at varying times after the end of treatment.*

Results. *The presenting signs/symptoms improved in all patients and the levels of acute-phase reactants significantly decreased or normalised. Ureteral obstructive disease resolved in all cases. Post-treatment CT revealed a considerable reduction in the amount of IRF, but all of the patients had a residual retroperitoneal mass. PET revealed slight aorto-iliac ^{18}F-FDG uptake in only one patient; all of the others were negative. No patient relapsed during the follow-up.*

Conclusions. *Post-treatment residual masses are frequent in IRF patients but, in most cases, probably represent metabolically inactive tissue.*

Introduction

Idiopathic retroperitoneal fibrosis (IRF) is characterised by the presence of a fibro-inflammatory retroperitoneal mass that often entraps the ureters or other abdominal organs (1). Histology shows a mixture of lymphocytes, plasma cells and macrophages within a framework of fibroblasts and collagen bundles (1, 2). IRF is diagnosed by means of computed tomography (CT) or magnetic resonance imaging (MRI), which are also useful in the follow-up (1). The treatment can be surgical and/or medical: the former is required when severe obstructive complications are present; the latter, usually based on corticosteroids, often leads to a substantial reduction in the size of the retroperitoneal mass (3, 4). However, despite effective medical treatment, the presence of residual periaortic and peri-iliac tissue is often observed, and it is not known whether the residual mass is still metabolically active or simply represents a fibrous "scar" (3-5).

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a functional imaging modality widely used in oncology, but increasing evidence suggests that it can be useful in the evaluation of various inflammatory diseases, including IRF (6, 7). In a previous report, we have shown that it is highly reliable in assessing disease activity in IRF (8).

In this study, we used ^{18}F-FDG PET to evaluate the metabolic activity of residual retroperitoneal masses in a series of IRF patients whose disease considerably regressed after prolonged medical treatment.

Patients and methods

We studied 7 consecutive IRF patients referred to our Department between June 2001 and January 2003. IRF was diagnosed by means of abdominal CT in all cases. The patients' characteristics at disease onset are shown in Table I.

Treatment

Three patients (patients 1, 2 and 3) underwent laparotomy for ureterolysis, and two (patients 5 and 6) received ureteral stents. The remaining patient with ureteral involvement (patient 7) was neither treated surgically nor received stents.

All of the patients underwent medical treatment: 5 (patients 2, 3, 4, 6 and 7) received a 9-month course of steroids (oral prednisone 1 mg/kg/day for one month and then gradually tapered off); one (patient 5) started on the same

Table I. Characteristics of the 7 patients with idiopathic retroperitoneal fibrosis at the time of disease onset.

Patient no.	Sex	Age (yrs.)	Clinical symptoms	Ureteral involvement	ESR* (mm/1h)	CRP** (mg/l)	Distribution of IRF$
1	M	43	Low back pain	Bilateral	130	200	Periaortic and pericaval
2	M	50	Back, flank and perineal pain, constitutional symptoms	Bilateral	48	41	Periaortic and periiliac
3	M	55	Back pain, claudication, constitutional symptoms	Bilateral	71	41	Periaortic, periiliac and pericaval
4	M	39	Abdominal and back pain, claudication and constitutional symptoms	Absent	25	8	Periaortic and periiliac
5	F	70	Abdominal pain, claudication, constitutional symptoms and inferior vena cava syndrome	Unilateral	47	37	Periaortic, periiliac and pericaval
6	M	37	Constitutional symptoms	Bilateral	90	15	Periaortic, periiliac and pericaval
7	M	62	Back pain, constitutional symptoms	Bilateral	50	16	Periaortic and periiliac

*ESR: Erythrocyte sedimentation rate; ** CRP: C-reactive protein (normal value < 5 mg/l); $IRF: Idiopathic retroperitoneal fibrosis.

prednisone schedule, but was switched to tamoxifen (a fixed oral dose of 30 mg/day) 2 months later because of steroid-induced diabetes mellitus, with tamoxifen being stopped after 10 months; and one (patient 1) was treated with prednisolone (8 mg/day p.o.) and methotrexate (10 mg/week i.m.) for 16 months.

CT and ^{18}F-FDG PET evaluation

The localisation of IRF on CT at the time of disease onset is reported in Table I. All of the patients were followed up by means of repeat CT scans performed approximately every 4-6 months during the course of treatment, and then every year. CT was also performed at the time of the ^{18}F-FDG PET. We started using ^{18}F-FDG PET to evaluate IRF patients in April 2003. The median time between the end of treatment and ^{18}F-FDG PET was 15 months (range 3-24).

^{18}F-FDG PET was performed using a dedicated system (C-PET ADAC): a whole-body scan was acquired using a C-PET ADAC scanner 90 minutes after the intravenous administration of ^{18}F-FDG (2 MBq/kg body weight). The images, which were processed by iteratively reconstructing both the raw and attenuation-corrected data, were reviewed by two independent nuclear medicine physicians who were blinded to the patients' clinical conditions and the CT data. The images were visually evaluated, and ^{18}F-FDG-uptake in the abdominal periaortic region was graded using a semiquantitative scale (0 = no abnormal uptake; 1 = moderate uptake; 2 = marked uptake).

Table II. Characteristics of the 7 patients with idiopathic retroperitoneal fibrosis at the time of ^{18}F-fluorodeoxyglucose positron emission tomography evaluation. The type and duration of medical treatments are also shown.

Pt. no.	Medical treatment (duration)	Residual mass thickness (cm)*	Reduction in IRF**	ESR¶ (mm/lh)	CRP¥ (mg/l)	^{18}F-FDG§ uptake (score)$
1	Prednisolone plus methotrexate (16 months)	0.8	80%	20	1.9	0
2	Prednisone (9 months)	1.5	40%	10	7.9	0
3	Prednisone (9 months)	2	50%	33	8.4	0
4	Prednisone (9 months)	1.5	60%	15	2.3	1
5	Prednisone (2 months) followed by tamoxifen (10 months)	1	70%	11	1.4	0
6	Prednisone (9 months)	1	60%	24	1.6	0
7	Prednisone (9 months)	1.6	50%	9	5.8	0

*As assessed by computed tomography; **IRF: idiopathic retroperitoneal fibrosis; ¶ESR: erythrocyte sedimentation rate; ¥CRP: C-reactive protein (normal value < 5 mg/l); §FDG: fluorodeoxyglucose. $According to a semiquantitative scale: score 0 = no abnormal uptake; score 1 = moderate uptake; score 2 = marked uptake.

Results

The presenting signs and symptoms rapidly improved in all cases. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels significantly decreased or normalised in all patients.

The ureteral stents were removed in patients 5 and 6 after respectively four and six months of medical therapy; in patient 7, who did not undergo surgery or receive a stent, the prompt resolution of bilateral hydronephrosis was sonographically observed one month after the start of treatment. Further sonographies were regularly repeated in all of the patients, only one of whom (patient 6) was found to have moderate and stable unilateral hydronephrosis.

CT showed that the size of the retroperitoneal masses decreased 40-80% (median 60%) (Table II); at the end of treatment, all of the patients had residual retroperitoneal peri-aortic and periiliac tissue (Table II).

Figures 1 and 2 contain CT scans showing the change in IRF before and after treatment in patients 4 and 6.

^{18}F-FDG PET

During the post-treatment follow-up, none of the patients showed any symptoms or signs attributable to disease relapse. None of them had persistently high ESR and CRP levels. The values at the time of ^{18}F-FDG PET are shown in Table II.

The CT scans performed between the end of treatment and the time of ^{18}F-FDG PET also showed stable disease in all of the patients.

The ^{18}F-FDG PET studies revealed no abnormal uptake in the aorto-iliac region in six cases (patients 1, 2, 3, 5, 6 and 7); the seventh (patient 4) showed moderate focal uptake in the aorto-iliac region (Table II). Figures 1C and 1D show the PET images of the patient with residual moderate uptake (patient 4), and Figures 2C and 2D those of a patient with no abnormal uptake (patient 6).

After the ^{18}F-FDG PET, the patients were followed up for a median of 10 months (range 3-12); none of them showed any clinical, laboratory or radiological signs suggesting a disease relapse.

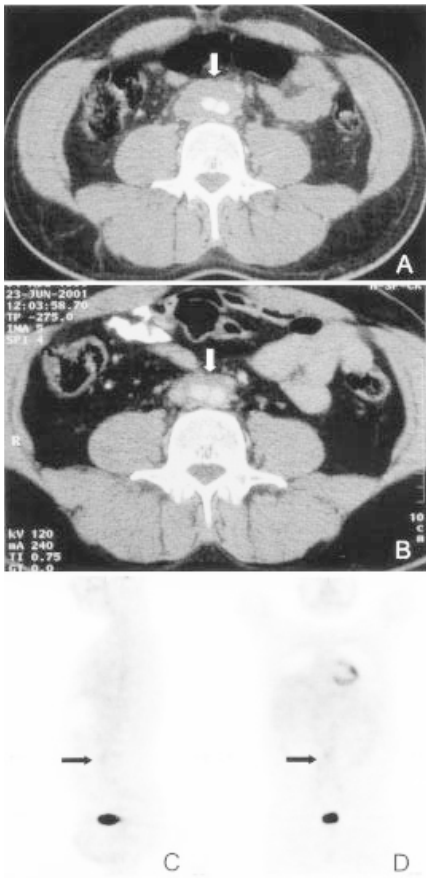

Fig. 1. (**A**) Pre-treatment computed tomographic appearance of idiopathic retroperitoneal fibrosis in patient 4: the scan (taken at the level of the common iliac arteries) shows a peri-iliac retroperitoneal mass (**arrow**).
(**B**) Post-treatment computed tomography scan showing a marked reduction in the size of the mass with residual retroperitoneal peri-iliac tissue (**arrow**).
(**C, D**) Positron emission tomography scans (**C**, sagittal and **D**, coronal views) after treatment showing slight and focal ^{18}F-fluorodeoxyglucose uptake in the aorto-iliac region (**arrow**).

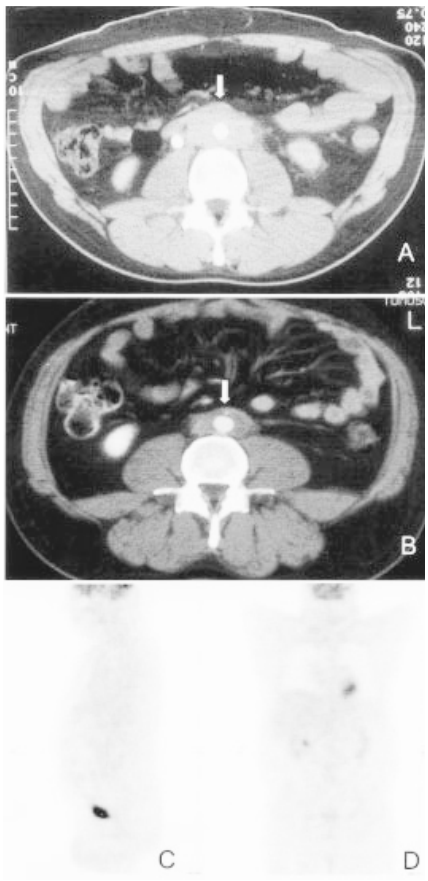

Fig. 2. (**A**) Pre-treatment computed tomographic appearance of idiopathic retroperitoneal fibrosis in patient 6: the scan (taken at the level of the lower abdominal aorta) shows a peri-aortic retroperitoneal mass (**arrow**).
(**B**) Post-treatment computed tomography scan showing a considerable reduction in the size of the mass with residual retroperitoneal peri-aortic tissue (**arrow**).
(**C, D**) Positron emission tomography scans after treatment (**C**, sagittal and **D**, coronal views) showing no abnormal ^{18}F-fluorodeoxyglucose uptake.

Discussion

IRF is a chronic inflammatory disease of unknown origin; its prognosis is usually good but, if left untreated, it may cause severe obstructive complications and a persistent systemic inflammatory response (1). There are no guidelines concerning the medical treatment of IRF; however, corticosteroids seem to represent the mainstay of therapy because, in most cases, their administration alone or in combination with other immunosuppressive drugs reduces the bulk of the fibro-inflammatory mass and improves the patients' general condition (3-5, 9); recent reports have shown that tamoxifen can also be effective (10).

However, the medical treatment of IRF frequently leads to residual retroperitoneal masses revealed by CT or MRI. The management of these masses is a dilemma for clinicians because there is no reliable and non-invasive means of assessing the presence of active disease inside the residual tissue.

^{18}F-FDG PET is based on the differential uptake of ^{18}F-FDG by actively metabolising cells. ^{18}F-FDG is transported into cells on the basis of their rate of glycolysis and so, given the high glycolytic rate of malignant cells, PET scans can visualise active neoplastic lesions as areas of focal hypermetabolism (11). Inflammatory cells such as lymphocytes, plasma cells, neutrophils and fibroblasts also avidly take up ^{18}F-FDG (12), which is why ^{18}F-FDG PET is being used to image an increasing number of inflammatory diseases (6, 13).

The evaluation of post-treatment residual disease is a major indication for ^{18}F-FDG PET in oncology because this modality seems to be highly reliable in discriminating persistent viable tumour and fibrotic changes (14).

Our IRF patients underwent prolonged medical treatment, which led to the regression of the retroperitoneal mass, improvement of the clinical condition and, in most cases, normalisation of acute-phase reactant levels. However, post-treatment CT revealed that all of the patients had residual masses of varying thicknesses, and so we decided to use ^{18}F-FDG PET to evaluate the possible presence of metabolic/inflammatory activity within the residual tissue. Six of the seven patients had no abnormal ^{18}F-FDG uptake, and the seventh showed only moderate focal aor-

to-iliac ^{18}F-FDG accumulation. During the follow-up, none of the patients showed clinical, laboratory or radiological signs of disease relapse. These findings suggest that the post-treatment residual tissue observed in our patients had very low or absent metabolic activity, as it can be observed in fibrotic tissue.

Our results may have potential implications for the clinical management of IRF patients. First, they show that, despite effective medical therapy, a residual mass is frequent and, in most cases, probably represents a silent "scar". Secondly, although not proved by our study, it is likely that metabolically inactive residual tissue will not to respond to further medical therapy. Finally, the results of ^{18}F-FDG PET may also play a role in predicting the post-treatment prognosis.

Some limitations of our study must be acknowledged: our patients underwent ^{18}F-FDG PET only after medical treatment and so it is not known whether they had a pathological ^{18}F-FDG uptake at disease onset. However, all previous reports-including ours- concerning ^{18}F-FDG PET in IRF have shown that ^{18}F-FDG uptake is always strikingly higher in the early active stages of the disease (7, 8, 15); in addition, the technical procedure and the PET scanner used in this study are the same as those used in our previous work (8). The relatively short follow-up of our patients may be a further limitation, and so longer prospective studies are required to assess the long-term prognostic impact of PET results.

In conclusion, medical therapy can be effective in IRF patients although it often leaves residual retroperitoneal masses; on the basis of our ^{18}F-FDG PET findings, these masses seem to be metabolically inactive and may therefore be simply fibrotic tissue.

Acknowledgement

We are indebted to Dr. Pietro Schianchi for his help in preparing the photographs.

References

1. GILKESON GS, ALLEN NB: Retroperitoneal fibrosis. A true connective tissue disease. *Rheum Dis Clin North Am* 1996; 22: 23-38.
2. VAGLIO A, CORRADI D, MANENTI L, FERRETTI S, GARINI G, BUZIO C: Evidence of autoimmunity in chronic periaortitis. A prospective study. *Am J Med* 2003; 114: 454-462.
3. BAKER LR, MALLINSON WJ, GREGORY MC *et al*.: Idiopathic retroperitoneal fibrosis. A retrospective analysis of 60 cases. *Br J Urol* 1987; 60: 497-503.
4. KARDAR AH, KATTAN S, LINDSTEDT E, HANASH K: Steroid therapy for idiopathic retroperitoneal fibrosis: dose and duration. *J Urol* 2002; 168: 550-5.
5. SCAVALLI AS, SPADARO A, RICCIERI V *et al*.: Long-term follow-up of low-dose methotrexate therapy in one case of idiopathic retroperitoneal fibrosis. *Clin Rheumatol* 1995; 14: 481-4.
6. SCHIRMER M, CALAMIA KT, WENGER M, KLAUSER A, SALVARANI C, MONCAYO R: 18-fluorodeoxyglucose positron emission tomography: a new explorative perspective. *Exp Gerontol* 2003; 38: 463-70.
7. DRIESKENS O, BLOCKMANS D, VAN DEN BRUEL A, MORTELMANS L: Riedel's thyroiditis and retroperitoneal fibrosis in multifocal fibrosclerosis: positron emission tomographic findings. *Clin Nucl Med* 2002; 27: 413-5.
8. VAGLIO A, VERSARI A, FRATERNALI A, FERROZZI F, SALVARANI C, BUZIO C: ^{18}F-fluorodeoxyglucose positron emission tomography in the diagnosis and follow-up of idiopathic retroperitoneal fibrosis. *Arthritis Rheum* 2005; 53:122-5.
9. MARCOLONGO R, TAVOLINI IM, LAVEDER F *et al*.: Immunosuppressive therapy for idiopathic retroperitoneal fibrosis: a retrospective analysis of 26 cases. *Am J Med* 2004; 116: 194-7.
10. BOUROUMA R, CHEVET D, MICHEL F, CERCUEIL JP, ARNOULD L, RIFLE G: Treatment of idiopathic retroperitoneal fibrosis with tamoxifen. *Nephrol Dial Transplant* 1997; 12: 2407-10.
11. NABI HA, ZUBELDIA JM: Clinical applications of ^{18}F-FDG in oncology. *J Nucl Med Technol* 2002; 30: 3-9.
12. ISHIMORI T, SAGA T, MAMEDE M *et al*.: Increased ^{18}F-FDG uptake in a model of inflammation: Concanavalin A-mediated lymphocyte activation. *J Nucl Med* 2002; 43: 658-63.
13. BLOCKMANS D, STROOBANTS S, MAES A, MORTELMANS L: Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. *Am J Med* 2000; 108: 246-9.
14. WEIHRAUCH MR, RE D, SCHEIDHAUER K *et al*.: Thoracic positron emission tomography using ^{18}F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood* 2001; 98: 2930-4.
15. BLOCKMANS D, VAN MOER E, DEHEM J, FEYS C, MORTELMANS L: Positron emission tomography can reveal abdominal periaortitis. *Clin Nucl Med* 2002; 27: 211-2.