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-aorto-iliac 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 peri-aortic 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...
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 18F-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 18F-FDG PET. We started using 18F-FDG PET to evaluate IRF patients in April 2003. The median time between the end of treatment and 18F-FDG PET was 15 months (range 3-24).

18F-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 18F-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 18F-FDG-uptake in the abdominal periaortic region was graded using a semiquantitative scale (0 = no abnormal uptake; 1 = moderate uptake; 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 peri-iliac tissue (Table II).

Figures 1 and 2 contain CT scans showing the change in IRF before and after treatment in patients 4 and 6.
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 18F-FDG PET are shown in Table II.

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

The 18F-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 18F-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.

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.

18F-FDG PET is based on the differential uptake of 18F-FDG by actively metabolising cells. 18F-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 18F-FDG (12), which is why 18F-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 18F-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 18F-FDG PET to evaluate the possible presence of metabolic/inflammatory activity within the residual tissue. Six of the seven patients had no abnormal 18F-FDG uptake, and the seventh showed only moderate focal nor-
to-dieci 18F-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 respond to further medical therapy. Finally, the results of 18F-FDG PET may also play a role in predicting the post-treatment prognosis.

Some limitations of our study must be acknowledged: our patients underwent 18F-FDG PET only after medical treatment and so it is not known whether they had a pathological 18F-FDG uptake at disease onset. However, all previous reports—including ours—concerning 18F-FDG PET in IRF have shown that 18F-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 18F-FDG PET findings, these masses seem to be metabolically inactive and may therefore be simply fibrotic tissue.

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References