ABSTRACT

Retroperitoneal fibrosis is a syndrome characterised by the presence of fibrosclerotic tissue in the retroperitoneum, often encasing the ureters. In most cases, retroperitoneal fibrosis is idiopathic, but may also be associated with large-vessel vasculitis at distant sites, with the so-called IgG4-related sclerosing disease, as well as with exposure to some medications, infections, malignancies, surgery, or radiation. 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a nuclear medicine technique which is able to accurately identify in vivo areas characterised by elevated glucose metabolism, such as inflammatory, infective, and neoplastic lesions. There is mounting evidence suggesting that FDG-PET may have a role in assessing disease activity in idiopathic retroperitoneal fibrosis, but the role of FDG-PET in secondary retroperitoneal fibrosis is less established. Herein, we present four patients with retroperitoneal fibrosis of different etiology (isolated idiopathic, associated with large-vessel involvement, associated with carcinoid tumour, and secondary to pergolide) who underwent FDG-PET as part of their workup. The implications of FGD-PET results in the diagnosis and treatment of retroperitoneal fibrosis of different etiology are discussed.

Introduction

Retroperitoneal fibrosis is a syndrome whose hallmark lesion is retroperitoneal fibrosclerotic tissue, often encasing the ureters and blood vessels (1). In the majority of cases, retroperitoneal fibrosis is idiopathic, but may also be associated with exposure to certain medications, infections, malignancies, surgery, or radiation (1, 2). Idiopathic retroperitoneal fibrosis is typically characterised by a mixed inflammatory and fibrotic tissue spreading from the adventitia of the aorta (3) with or without overrepresentation of IgG4 plasma cells (4), and may coexist with large-vessel vasculitis of the thoracic aorta and/or of the main aortic branches, with autoimmune disorders, or both (1, 5). Less frequently, retroperitoneal fibrosis may arise in the context of a generalised sclerosing disorder called multifocal fibrosclerosis characterised by the same histopathological features as IgG4-related sclerosing disease (3). Idiopathic retroperitoneal fibrosis is currently included in the spectrum of chronic periaortitis together with inflammatory abdominal aorta aneurysms and periaeurysmal retroperitoneal fibrosis (5). More specifically, idiopathic retroperitoneal fibrosis is characterised by a retroperitoneal fibro-inflammatory tissue in the absence of a dilated aorta, while in inflammatory abdominal aorta aneurysms the fibro-inflammatory tissue develops around a dilated aorta, and in periaeurysmal retroperitoneal fibrosis the fibro-inflammatory tissue spreads from a dilated aorta into the retroperitoneum (5).

A careful workup is crucial in establishing whether retroperitoneal fibrosis is idiopathic or associated with infection, malignancy, or other causes. Inflammatory indices are usually raised in the context of inflammation, although they may not reflect accurately disease activity (6). Enhanced CT and MR of the abdomen are considered the investigations of choice to diagnose CP (1). However, both abdominal CT and MR are unable to detect vascular inflammatory lesions at other sites, which have been reported in 43% of patients with chronic periaortitis (5).

Recently, evidence has been accruing supporting the role of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in diagnosing
and monitoring large-vessel vasculitis and chronic periaortitis, including idiopathic retroperitoneal fibrosis (7-9).

FDG-PET is able to identify in vivo areas characterised by elevated glucose metabolism, such as inflammatory, infective, and neoplastic lesions (10, 11). FDG-PET has the advantage over other imaging techniques of visualising near-ly the entire body, thus revealing the full extent and distribution of metabolically active disorders, and may be more sensitive than inflammatory markers (6) and MR (12) in assessing disease activity in chronic periaortitis. In addition, FDG-PET may also detect infections or neoplasms which may be associated with retroperitoneal fibrosis.

In this paper, we aimed to highlight the role of FDG-PET in the workup of four cases of retroperitoneal fibrosis of different etiology (isolated idiopathic, associated with large-vessel involvement, associated with carcinoid tumour, and secondary to pergolide). The implications for diagnosis and treatment are discussed.

Case 1

A 58-year-old woman developed at age 48 lower limb claudication. Past medical history revealed appendectomy, hypertension, and vestibular migraine. She had been found to be positive for lupus anticoagulant on repeated testing. Her medications included estrogen replacement therapy, chlorthalidone, baby aspirin, as well as dihydroergotamine mesylate and levosulpiride on an “as required” basis. She was otherwise well and had no clinical features consistent with connective tissue disease and no history of venous thrombosis. Colour-Doppler ultrasonography of the lower limbs was unremarkable, whereas CT angiography showed a hypointense cuff surrounding the abdominal aorta and the iliac arteries with enhancement at the aortic bifurcation. Both the abdominal aorta and the common iliac arteries were stenotic. The periaortic mass spread to, and encased the left ureter, leading to hydronephrosis of the left kidney. The patient was referred to the Rheumatology Department for a second opinion.

Laboratory investigations on admission showed a raised ESR at 75mm/1st hour and C-reactive protein (CRP) 23.7g/dl (normal values <6), creatinine 1.4mg/dl and otherwise overall normal biochemistry. ANA was positive at 1:160 with a coarse speckled pattern, but anti-ENA and anti-DNA-double stranded antibodies (anti-DNA-ds) were negative. LAC was positive, whereas anticardiolipin antibodies were negative. Colour-Doppler ultrasonography confirmed the presence of a periaortic cuff and also revealed stenosis of the left renal artery with decreased intraparenchymal blood flow. Renal scintigraphy with technetium-99m mercaptoacetyltriglycine (Tc-99m MAG3) showed no alterations of the right kidney, while the left kidney could not be visualised.

Whole-body FDG-PET scan (Fig. 1a) demonstrated increased tracer uptake of grade 3 on a 0–3 scale (13) around the vena cava and the aorta spreading from the origin of the renal arteries to the aortic bifurcation.


Fig. 1a. FDG-PET (coronal view) of a 58-year-old woman with idiopathic retroperitoneal fibrosis. The exam shows increased tracer uptake of grade 3 (on a 0–3 scale) around the vena cava and the aorta spreading from the origin of the renal arteries to the aortic bifurcation. Case no. 1.

Fig. 1b. FDG-PET (coronal view) of the same patient shown in Figure 1a after the onset of glucocorticoid therapy showing absence of increased tracer uptake.
Occasionally. Her prednisone could be tapered off at the end of 2009, while the left pigtail stent was removed one year later. So far, she is still asymptomatic and her ESR remains within the normal range.

**Case 2**

A 63-year-old woman presented in 2006 with a four-year history of inflammatory low back pain which had subsequently spread to the abdomen. ESR was 85mm/1st hour and CRP 46g/dl, while autoimmune serology was negative. X-rays of the lumbar spine and CT of the sacro-iliac joints revealed no signs of spondylitis. Combined CT scan of the chest and abdomen showed a periaortic cuff around the thoracic and abdominal aorta extending to the proximal supra-aortic vessels and iliac arteries. Right ureter encasement causing ipsilateral kidney hydronephrosis was also observed. PET-CT showed grade 2 tracer uptake (equal to the physiological liver uptake) in the thoracic and abdominal aorta as well as in the iliac arteries, proximal femoral, subclavian, axillary, and carotid arteries. A periaortic mass extending to the kidneys with grade 2 positivity and increased volume of the left kidney due to pelvis dilation were also noted (Fig. 2a). Colour-Doppler ultrasonography of the temporal arteries showed no inflammatory halo. A diagnosis of CP associated with involvement of the thoracic aorta and of the supra-aortic arteries was made. The patient was treated with prednisone 1mg/kg/day with a tapering scheme and with the placement of a double-J ureteral stent. Her symptoms gradually abated, while Colour-Doppler ultrasonography performed two months later demonstrated resolution of the right hydronephrosis. The ESR and CRP returned to normal within one month after treatment onset (7mm/1st hour and 0.16g/dl, respectively). CT of the abdomen showed no change in the abdominal mass from the prior study. A repeat PET-CT revealed grade 2 tracer uptake in the thoracic and abdominal aorta and grade 1 uptake in the iliac arteries, proximal femoral, subclavian, axillary and carotid arteries. To avoid further exposure to glucocorticoid treatment, infliximab (5mg/kg every 2 months after a loading course) was started. Again, the patient responded well to treatment, and the stent could be successfully removed. The ESR and CRP decreased to 27mm/1st hour and 5g/dl, respectively. CT of the abdomen disclosed an abdominal mass basically unchanged from prior studies, while a third PET-CT performed in May 2010 showed only mild (grade 1) periaortitis and vasculitis (Fig. 2b).

**Case 3**

A 43-year-old Moroccan man with an uneventful past medical history started complaining in April 2008 of lumbar pain. Laboratory investigations showed mild normocytic anemia with hemoglobin 12.8g/dl, ESR 39mm/1st hour and C-reactive protein 5.6g/dl. Biochemistry including creatinine was normal except for mild hypercholesterolemia.
CT scan showed no major alterations in the lumbar spine, while it visualised a retroperitoneal mass encasing the right ureter, inferior vena cava, abdominal aorta, and right iliac artery. Colour-Doppler ultrasonography of the renal arteries demonstrated normal blood flow in the right artery and markedly decreased flow in the left artery in the absence of hydronephrosis or of reduced intraparenchimal flow. Bipolar kidney diameter was 11.8cm bilaterally. Renal scintigraphy revealed decreased renal function on the right (41% compared to the left kidney function). Whole-body FDG-PET (Fig. 3a) revealed elevated (grade 3) tracer uptake in the retroperitoneal mass. Surgery was organised for diagnostic purposes and to remove as much as possible of the retroperitoneal mass as well as to place an intraluminal pigtail stent in the right ureter. Histology of the retroperitoneal mass showed dense fibrosis with interspersed myofibroblasts and mixed lymphocyte and plasma cell infiltration in the absence of neoplastic cells, consistent with retroperitoneal fibrosis. However, a sample from the terminal ileum demonstrated neoplastic cells that subsequent staining showed to be positive for keratin AE1/AE3, chromogranin, and synaptophysin with a proliferative index <1%. These findings were found to be consistent with a well-differentiated endocrine carcinoid tumour. Further investigations showed normal levels of urinary 5-hydroxyindoloacetic acid and of serum cortisol, ACTH, LH, FSH, prolactin, testosterone, insulin, gastrin, parathyroid hormone, growth hormone, insulin growth factor-1, neuro-specific enolase, and chromogranin A. Histology with intestinal anastomosis was performed with resolution of the patient's complaints. A final diagnosis of retroperitoneal fibrosis associated with carcinoid tumour of the terminal ileum was made and prednisone prescribed at 1mg/kg/day for one month with a tapering scheme over seven months. The patient's symptoms resolved, and the glucocorticoid dose was slowly tapered. PET with the somatostatin-analog 68Gallium-DOTATOC performed six months later revealed increased tracer uptake in the mesogastrium and to the left of L2 which was thought to be suspicious for lymph node metastases. Excision of the lymph nodes visualised by 68Gallium-DOTATOC was performed, but histology revealed only reactive alterations in the absence of malignant cells. Eight months after the onset of the clinical manifestations the prednisone dose was down to 35mg/day, the patient had no complaints attributable to his condition, while the ESR and CRP values had normalised (8 mm/1st hour and 1.3g/dl, respectively). Creatinine was also within limits (0.95mg/dl). Abdominal CT performed three months later showed a persistent retroperitoneal mass and slight dilation of the right calyx which was thought to be suspicious for lymph node metastases. The patient remained asymptomatic, but in view of the persistent retroperitoneal mass the prednisone dose was tapered very slowly to 25mg/day over one year. Abdominal CT and whole-body FDG-PET were repeated one year later. Abdominal CT demonstrated a smaller residual mass in the aortocaval area, between the common iliac arteries, and the internal and external iliac arteries bilaterally. The right pigtail stent appeared to be well positioned. The patient remained asymptomatic, but in view of the persistent retroperitoneal mass the prednisone dose was tapered very slowly to 25mg/day over one year. Abdominal CT and whole-body FDG-PET were repeated one year later. Abdominal CT demonstrated a smaller residual mass in the aortocaval area, between the common iliac arteries, and the internal and external iliac arteries bilaterally. The right pigtail stent appeared to be well positioned.
were performed with clinical benefit. Retroperitoneal fibrosis secondary to pergolide was suspected and the putative offending drug withdrawn. The patient was referred to the Rheumatology Department for a second opinion. Complete blood count, ESR, CRP, and biochemistry on admission were within limits except for mildly raised creatinine at 1.21mg/dl. Autoimmune serology including ANA, anti-ENA, anti-ds-DNA, and anti-neutrophil cytoplasmic antibodies was entirely negative. Colour-Doppler ultrasonography of the renal arteries revealed severe stenosis of the left renal artery. Bipolar kidney diameter was 13cm on the right and 8cm on the left. Whole-body FDG-PET (Fig. 4) showed no increased tracer uptake, consistent with metabolically inactive retroperitoneal fibrosis. On the basis of the patient’s history and of the results of the investigations, a diagnosis of retroperitoneal fibrosis probably induced by pergolide was made. A CT angiography and follow-up in Nephrology were organised, but no specific treatment was prescribed.

**Discussion**

Herein, we have presented four cases of retroperitoneal fibrosis of different etiology (isolated idiopathic, associated with large-vessel involvement, paraneoplastic, and secondary to pergolide treatment) in which FDG-PET had a major role in the diagnostic workup and in guiding treatment choice. The first patient of this series was diagnosed with idiopathic retroperitoneal fibrosis. Since this patient used to take occasionally dihydroergotamine mesylate to treat migraine attacks, we also considered the possibility that she might have drug-induced retroperitoneal fibrosis. However, while a few cases of retroperitoneal fibrosis triggered by dihydroergotamine have been published, they have usually been reported in patients abusing or taking regularly this medication (14, 15). Therefore, we thought that dihydroergotamine-induced retroperitoneal fibrosis was unlikely. FDG-PET confirmed the active inflammatory nature of the retroperitoneal mass, thus prompting us to start glucocorticoid therapy. Idiopathic retroperitoneal fibrosis is characterised by a fibro-inflammatory retroperitoneal mass in the early stages, while in the late stages fibrous scarring only may residuate (16). Clearly, glucocorticoid treatment is indicated only in the presence of active inflammation. FDG-PET is probably the most reliable investigation to detect ongoing inflammation (6, 12). Therefore, the evidence of increased tracer uptake on FDG-PET scan in our patient strongly supported our decision to start prednisone therapy.

The second patient described herein had CP associated with large-vessel involvement elsewhere. We have previously reported that 43% of a series of CP patients had evidence of vasculitis of the thoracic aorta, of the supra-aortic arteries, or of both (5). Of all imaging techniques, FDG-PET has the unique ability to visualise not only the abdominal aorta and the periaortic tissue, but also the other large vessels, with the exception of the renal and temporal arteries. As a case in point, in this patient FDG-PET proved essential to diagnose large-vessel vasculitis.

FDG-PET also has a pivotal role in monitoring the disease course including response to treatment. Treatment of retroperitoneal fibrosis usually results in shrinking of the retroperitoneal mass. Residual mass probably represents in most cases metabolically inactive tissue, but may also be an expression of ongoing inflammation. FDG-PET has been shown to discriminate between metabolically active tissue, which is thought to be an expression of smoldering disease activity, and metabolically inactive tissue, which is probably just residual scarring (17), and thus drive further therapeutic management. In this case, FDG-PET demonstrated active disease after the prednisone course, prompting us to initiate infiximab therapy. In contrast, a subsequent FDG-PET performed under infliximab showed only minimal (grade 1) uptake in the periaortic mass, consistent with a good response to treatment. It is unclear whether the slight residual uptake observed under infliximab therapy represented smoldering disease activity or simply tissue remodelling.
The third case described in this paper is of retroperitoneal fibrosis associated with a carcinoid tumour of the gut. Carcinoid tumours are slow-growing neoplasms, originating from enterochromaffin cells (18), which take up and concentrate amines and their precursors, and can thereby be detected by nuclear medicine techniques (19). Since they are not metabolically very active, FDG-PET has a somehow limited sensitivity in visualising these tumours (20), although detection of carcinoid metastases by FDG-PET has occasionally been reported (21, 22). PET with radiolabeled amine analogs is probably more sensitive and specific than FDG-PET in identifying primary carcinoids and their metastases (19).

Carcinoid-associated fibrosis is a rare complication which may affect the heart, lung, or the retroperitoneum (23), even before the triggering carcinoid becomes clinically manifest (24). Release of serotonin by carcinoids has originally been invoked to explain the pathogenesis of this complication (25). However, the lack of correlation between circulating levels of serotonin and the development of fibrosing heart disease (26), on the one hand, and the detection of elevated expression of profibrotic molecules such as transforming growth factor-β (27) and epidermal growth factor (28) in carcinoid specimens, on the other, suggest that other mediators may be involved in driving fibrosis, most likely via the activation of myofibroblasts (29). Finally, lymphocyte aggregates have been found in some histological samples of carcinoid-associated retroperitoneal fibrosis (30), raising the possibility that, at least in some cases, the process leading to carcinoid fibrosis may be fibro-inflammatory rather than simply fibrosing. The presence of activated myofibroblasts, lymphocytes, or both within areas of fibrosis may explain the high FGD accumulation reported in retroperitoneal fibrosis associated with carcinoid tumours (23), since both myofibroblasts and lymphocytes increase their glucose uptake upon stimulation (31). From the point of view of treatment, glucocorticoids have been demonstrated to be able to inhibit not only inflammatory cells, but also myofibroblasts (32, 33), and may thus be effective in treating retroperitoneal fibrosis regardless of whether the pathogenic process is primarily fibro-inflammatory or fibrosing in nature.

In our patient, FDG-PET was unable to visualise the carcinoid tumour, in keeping with the limited ability of FDG-PET to detect slow-growing tumours (20). In contrast, it proved valuable in demonstrating the retroperitoneal fibrosis. FDG-PET was also useful in monitoring response to treatment. In this case, inflammatory markers were only mildly raised during active, untreated disease, and thus of very limited value to gauge the response to glucocorticoids. Abdomen CT was useful to determine the size of the retroperitoneal mass as well as to rule out renal complications, but an abdomen CT performed two years after the onset of the clinical manifestations and of glucocorticoid therapy still showed the presence of a retroperitoneal mass, although smaller in size. The patient had a good clinical response to therapy and no flare upon slowly tapering the glucocorticoid dose, but clinical manifestations are known not to be reliable indicators of disease activity in retroperitoneal fibrosis (6). Therefore, FDG-PET was repeated at the same time as the last CT scan of the abdomen to define disease activity. Since FDG-PET was negative, we judged the residual retroperitoneal mass visualised by the CT scan to represent inactive retroperitoneal tissue. Again, this case exemplifies, like case 2, the role of FDG-PET in discriminating between metabolically active and inactive retroperitoneal tissue, with obvious therapeutic implications.

The fourth case of retroperitoneal fibrosis we have presented was judged to be likely to be secondary to pergolide treatment, although an idiopathic form could not be confidently ruled out. A variety of medications have been mapped to the development of retroperitoneal fibrosis, mainly methysergide and the ergot-derived dopamine agonists (bromocriptine, cabergoline, pergolide), but not the nonergot-derived drugs (apomorphine, pramipexole, ropinirole, rotigotine) (1, 34). The pathogenic mechanisms of drug-associated retroperitoneal fibrosis are not fully elucidated, but agonism of 5-HT_3 serotonin receptors has been invoked (35, 36). However, numerous reports of pergolide-induced fibrosis have also documented raised inflammatory markers (37–40), suggesting that pergolide may also act as a hapten triggering an inflammatory response (37). Consistent with this concept, an inflammatory infiltrate has been documented in some (41), although not all cases (37, 39). To our knowledge, there are no published reports of FDG-PET in patients with pergolide-related fibrosis, but theoretically FDG-PET could be useful in determining the organs affected and disease activity. In our patient, FDG-PET was negative, suggesting inactive disease or possibly low-grade fibrosing disease. Because inflammatory markers were normal and FDG-PET was negative, we decided not to prescribe glucocorticoids. However, even if the role of pergolide in inducing fibrosis in our patient remained debatable, to be on the safe side we stopped pergolide, since drug-induced retroperitoneal fibrosis has been shown to regress following the withdrawal of the offending medication (42).

In conclusion, this report highlights the potential applications and pitfalls of FDG-PET in four cases of retroperitoneal fibrosis of different etiology. We believe that FDG-PET should be part of the investigations used to determine disease extent, activity, and response to therapy in CP.

References

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