RadioGraphics

Retroperitoneal Fibrosis: Role of Imaging in Diagnosis and Follow-up[1]

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SA-CME

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LEARNING OBJECTIVES FOR TEST 5

After completing this journal-based SA-CME activity, participants will be able to:

- List the epidemiologic features, pathogenetic mechanisms, and clinical features of RPF.
- Discuss the diagnostic approach to RPF and the value of imaging techniques.
- Describe the role of laboratory tests and imaging techniques in follow-up of idiopathic RPF.

TEACHING POINTS

See last page

Retroperitoneal fibrosis (RPF) encompasses a range of diseases characterized by proliferation of aberrant fibroinflammatory tissue, which usually surrounds the infrarenal portion of the abdominal aorta, inferior vena cava, and iliac vessels. This process may extend to neighboring structures, frequently entrapping and obstructing the ureters and eventually leading to renal failure. The idiopathic form of RPF accounts for more than two-thirds of cases; the rest are secondary to factors such as drug use, malignancies, or infections. If promptly diagnosed and treated, idiopathic and most other benign forms of RPF have a good prognosis. In contrast, malignant RPF, which accounts for up to 10% of cases, has a poor prognosis. Therefore, the most important diagnostic challenge is differentiation of benign from malignant RPF. Imaging plays a key role in diagnosis of RPF. Cross-sectional imaging studies, particularly multidetector computed tomography (CT) and magnetic resonance (MR) imaging, are considered the imaging modalities of choice. Imaging features may help distinguish between benign and malignant RPF, but in some cases histopathologic examination of the retroperitoneal tissue is needed for definitive diagnosis. CT and MR imaging, along with positron emission tomography with fluorine 18 fluorodeoxyglucose, also play an important role in management and follow-up of idiopathic RPF.

Abbreviations: ANCA = antineutrophil cytoplasmic antibody, FDG = fluorine 18 fluorodeoxyglucose, IgG4 = immunoglobulin G4, IVC = inferior vena cava, RPF = retroperitoneal fibrosis

RadioGraphics 2013; 33:535–552 • **Published online** 10.1148/rg.332125085 • **Content Codes:** CT GU MR NM

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Introduction

Retroperitoneal fibrosis (RPF) encompasses a range of diseases characterized by proliferation of aberrant fibroinflammatory tissue, which usually surrounds the infrarenal portion of the abdominal aorta, inferior vena cava (IVC), and iliac vessels. This process may extend to neighboring structures, frequently entrapping and obstructing the ureters and eventually leading to renal failure (1–3).

The idiopathic form of RPF accounts for more than two-thirds of cases. The rest are secondary to other factors, mostly use of certain drugs (derivatives of ergot alkaloids) and neoplasms (lymphoma, retroperitoneal sarcoma, carcinoid tumor, and metastatic disease from primary cancers of the stomach, colon, breast, lung, genitourinary tract, or thyroid gland), which account for 12% and 10% of all cases, respectively (3,4). Other causes of secondary RPF include infections (histoplasmosis, tuberculosis, actinomycosis), radiation therapy (RPF limited to the radiation field), major trauma, major abdominal surgery, retroperitoneal hemorrhage or hematoma, and proliferative diseases (Erdheim-Chester disease and other histiocytoses) (1,3,5). Among environmental and occupational agents, asbestos exposure has been demonstrated to increase the risk of developing idiopathic RPF (6–10).

Idiopathic RPF may be included under the umbrella of chronic periaortitis, along with inflammatory abdominal aortic aneurysms and perianeurysmal RPF (1,11,12). Although these conditions share some histopathologic characteristics (1,7,12,13), they probably represent separate and distinct conditions because they exhibit several distinct clinical, epidemiologic, and pathogenetic features (9).

Diagnosis and management of RPF represent a challenge for clinicians. Because of the nonspecific nature of the symptoms and the lack of sensitive and specific laboratory tests, RPF is frequently detected only after severe renal failure has been established. Furthermore, if promptly diagnosed and treated, most benign forms of RPF have a good prognosis, whereas malignant RPF carries a very poor prognosis, with a mean survival of less than 6 months (5).

In this article, we review current concepts about RPF, with emphasis on the key role of multidetector computed tomography (CT) and magnetic resonance (MR) imaging in diagnosis and management of benign and malignant RPF. We also discuss the role of fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) positron emission tomography (PET) in management and follow-up of idiopathic RPF.

Basic Concepts of RPF

Epidemiology

Idiopathic RPF is a rare condition, with a prevalence of about 1.3 per 100,000 population (8). There is no evidence of familial clustering and no clear ethnic predisposition (6). Although it can occur at any age, the onset of signs and symptoms is typically seen in people aged 40–65 years (4,9,14–16).

Chronic periaortitis is two to three times more common in men than in women (4,5,14–17). When idiopathic RPF is considered separately from other types of chronic periaortitis, it occurs with similar frequency in men and women (9).

Pathogenesis

Atherosclerotic aortic disease is a common condition among patients with idiopathic RPF. Idiopathic RPF has traditionally been considered an excessive local inflammatory response to antigens, such as oxidized low-density lipoproteins and ceroid, that are present in atherosclerotic plaques of the aorta (11,12).

However, several findings suggest that atherosclerotic aortic disease could be only a predisposing condition in susceptible hosts and that idiopathic RPF may be a manifestation of systemic autoimmune or inflammatory disease rather than the result of a local reaction (1,2,7,10,18,19). These findings include constitutional symptoms, high concentrations of acute-phase reactants, positive autoantibodies, and frequent associations with a wide variety of systemic inflammatory and autoimmune diseases, such as systemic lupus erythematosus, ankylosing spondylitis, Wegener granulomatosis, antineutrophil cytoplasmic antibody (ANCA)–positive rapidly progressive glomerulonephritis, and primary biliary cirrhosis (1).

Idiopathic RPF may also manifest as part of a rare and newly recognized fibroinflammatory systemic condition known as immunoglobulin G4 (IgG4)–related disease. This condition encompasses a large number of previously recognized medical disorders, such as Riedel thyroiditis and mediastinal fibrosis. A condition previously identified as multifocal fibrosclerosis—an immune-mediated systemic syndrome characterized by fibroinflammatory involvement of multiple organ systems that may include idiopathic RPF, autoimmune pancreatitis, sclerosing cholangitis (20,21), and pericardial fibrosis (22)—is now more appropriately regarded as IgG4-related disease (23).

Among secondary forms of RPF, the malignant form is the most relevant due to its poor prognosis. Most cases of secondary malignant RPF result from a severe desmoplastic response to retroperitoneal metastases—mainly from carcinoma of the breast, colon, stomach, lung, thyroid gland, or genitourinary tract—or to retroperitoneal primary tumors such as Hodgkin or non-Hodgkin lymphoma and various types of sarcoma (1,18). Carcinoid tumors may induce RPF without metastasizing to the retroperitoneum, probably by means of a serotonin-mediated mechanism or release of profibrogenic growth factors (1,24).

Pathologic Features

Macroscopically, idiopathic RPF typically appears as a gray-white, hard retroperitoneal plaque with ill-defined margins that surrounds the abdominal aorta, iliac vessels, and—in most instances—IVC and ureters. It is usually centered at the level of the fourth and fifth lumbar vertebrae, following the course of the aorta beyond the common iliac bifurcation. In rare cases, it extends anteriorly to the mesenteric root (2,18). Idiopathic RPF can have atypical locations without periaortic involvement, such periduodenal, peripancreatic, pelvic, or periureteral locations or close to the renal hilum, although occurrence in such locations is rare (1,25).

Histologically, the disease has two stages: an early active cellular stage and a late inactive fibrotic stage. The early stage is characterized by an immature fibrotic process, typically paraaortic, with capillary proliferation and a diffuse and perivascular infiltrate of abundant inflammatory cells—predominantly T and B lymphocytes, plasma cells, and fibroblasts—in a loose matrix of collagen fibers. In this stage, the tissue is often edematous and highly vascular.

As the disease progresses, the collagen tends to become hyalinized with reduction of cellular activity. The mature plaque is composed of relatively acellular and avascular dense hyalinized collagen and scattered calcifications (1–3,18,26–29). Immunohistochemical analysis reveals that most of the inflammatory cells are positive for the IgG4 isotype (27) and the DR subregion of human leukocyte antigen (HLA-DR) (30).

The macroscopic and microscopic appearances of most secondary forms of RPF are almost identical to those of the idiopathic form. Nevertheless, RPF secondary to malignancy is usually more irregularly shaped and atypically located than idiopathic disease (1). Histologic features are similar to those of the early phase of idiopathic fibrosis, with the exception of small foci of neoplastic cells among the inflammatory cells in the collagen mesh (3).

Invasion and disruption of muscle and bone structures suggest malignant RPF or an infectious cause. Demonstration of monoclonality of the lymphoplasmacytic component at immunohistologic studies is very suggestive of lymphoma. The presence of hemosiderin indicates hemorrhage. In RPF secondary to infections such as tuberculosis, histologic analysis may show granulomas (1).

Clinical Features

Idiopathic RPF commonly manifests as an insidious process. The initial signs and symptoms are often nonspecific, such as malaise, anorexia, weight loss, low-grade fever, and poorly localized pain over the flank, lower back, or abdomen (2,14,17,19,27). As the degree of fibrosis progresses, the symptoms are mainly related to entrapment and compression of retroperitoneal structures.

Teaching Point

In about 56%–100% of patients with idiopathic RPF, the fibroinflammatory tissue entraps the ureters and causes obstructive uropathy and subsequent renal failure. Ureteral involvement is bilateral in most cases. Some patients present with nonfunctioning kidneys as a result of long-lasting obstructive uropathy (1,2,5,8,15,17,19,27,31). Oliguria that progresses to anuria and signs and symptoms related to azotemia such as nausea, vomiting, and altered consciousness may result (2). Renal vessel involvement may contribute to renal insufficiency or cause renovascular hypertension (8–10).

Extrinsic compression of retroperitoneal lymphatic vessels and veins causes lower extremity edema. Deep vein thrombosis can also arise. Involvement of the gonadal vessels may result in scrotal swelling, varicocele, or hydrocele (1,18). Involvement of the mesentery, small intestine, duodenum, and colon has been described, which leads to constipation and rarely to intestinal ischemia (32). Claudication due to compression of the great vessels is a less frequent clinical manifestation (1).

It is important to emphasize that the clinical manifestations of idiopathic and secondary RPF often overlap; thus, they are not useful in differential diagnosis between both forms of RPF.

Laboratory Findings

Laboratory findings in idiopathic RPF often reflect an acute-phase reaction, with high erythrocyte

sedimentation rate and C-reactive protein levels in 80%–100% of patients (2,14,19,31,33). Mild to moderate anemia is also frequent (2). Development of azotemia usually depends on whether the ureteral obstruction is partial or complete and unilateral or bilateral. These laboratory test results are nonspecific and can also be found in secondary forms of RPF (1).

Tests for antinuclear antibodies, rheumatoid factor, and antibodies against smooth muscle, double-stranded DNA, extractable nuclear antigen, and neutrophil cytoplasm are sometimes positive. Among these findings, antinuclear antibodies are the most frequent in idiopathic RPF (19,34). These autoantibodies are useful in screening for the autoimmune disorders associated with idiopathic RPF, although in most instances titers of these antibodies are low and their positivity is nonspecific (1).

There are no laboratory tests that allow differentiation between idiopathic and secondary forms of RPF. However, there are particular abnormalities, such as positive tumor markers and a positive fecal blood test, that should raise suspicion of a secondary form of RPF related to malignancy.

Imaging Features

Ultrasonography.—Ultrasonography (US) has poor overall sensitivity in detection of RPF (1,17,35). Subtle or early changes of RPF can be missed at US because of overlying gas- or fluid-filled bowel loops (3).

Typically, RPF is seen as a hypoechoic or isoechoic, well-demarcated but irregularly contoured retroperitoneal mass anterior to the lower lumbar spine or sacral promontory (35,36).

US features such as caudal extension beyond the sacral promontory and absence of lobulation suggest a benign cause; however, these signs are nonspecific and do not allow exclusion of malignancy, given that malignant RPF and most cases of malignant lymphadenopathy can have similar US features (3,37,38).

Abdominal US may reveal varying degrees of unilateral or bilateral hydronephrosis or hydroureter due to entrapment of the ureters. US may also be useful for detection of conditions frequently associated with RPF, such as primary biliary cirrhosis, bile duct dilatation due to sclerosing cholangitis, and focal or diffuse pancreatic distortion due to sclerosing pancreatitis (37).

Conventional Radiography.—Abdominal radiographs usually do not show remarkable findings.

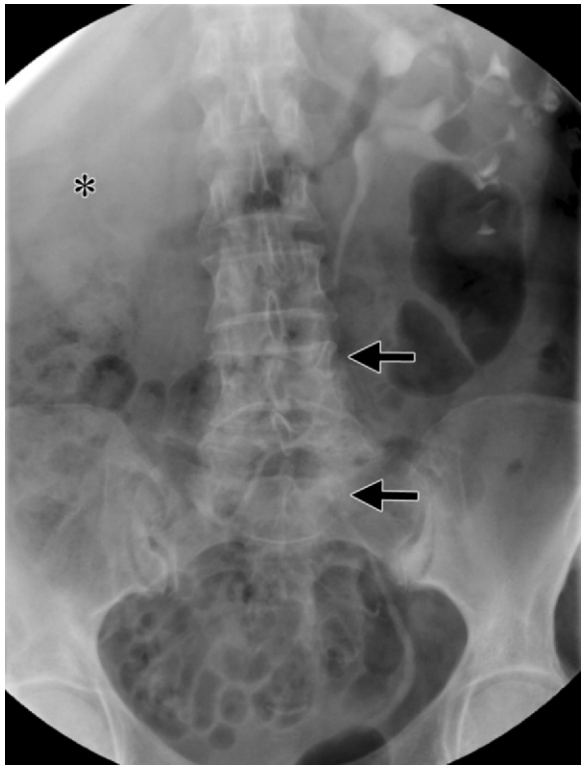


Figure 1. Urography of RPF. Excretory urogram shows medial deviation of the middle third of the left ureter and tapering of the ureteral lumen at the L4–S1 vertebral level (arrows). Note also the delay in excretion of contrast material in the right kidney (*).

A central soft-tissue mass and loss of the normal psoas shadow can be seen in late stages of RPF, but these are inaccurate and variable findings (37,39).

Intravenous Urography and Retrograde Pyelography.—Intravenous urography and retrograde pyelography, once considered the techniques of choice for evaluation of RPF, have been obviated in many instances because of improvements in cross-sectional imaging.

Intravenous urography usually demonstrates the classic triad of medial deviation of the middle third of the ureters, tapering of the lumen of one or both ureters in the lower lumbar spine or upper sacral region, and proximal unilateral or bilateral hydroureteronephrosis with delayed excretion of contrast material (5,25) (Fig 1).

Nevertheless, this approach has limited sensitivity and specificity. Primary ureteral tumors, periureteral lymph nodes, or inflammatory strictures of the ureter can result in similar radiologic findings (3). In addition, medial deviation of the ureters is identified in 20% of unaffected subjects (40). Furthermore, in some patients with idiopathic RPF, ureters can be entrapped in their normal anatomic position (3,40).

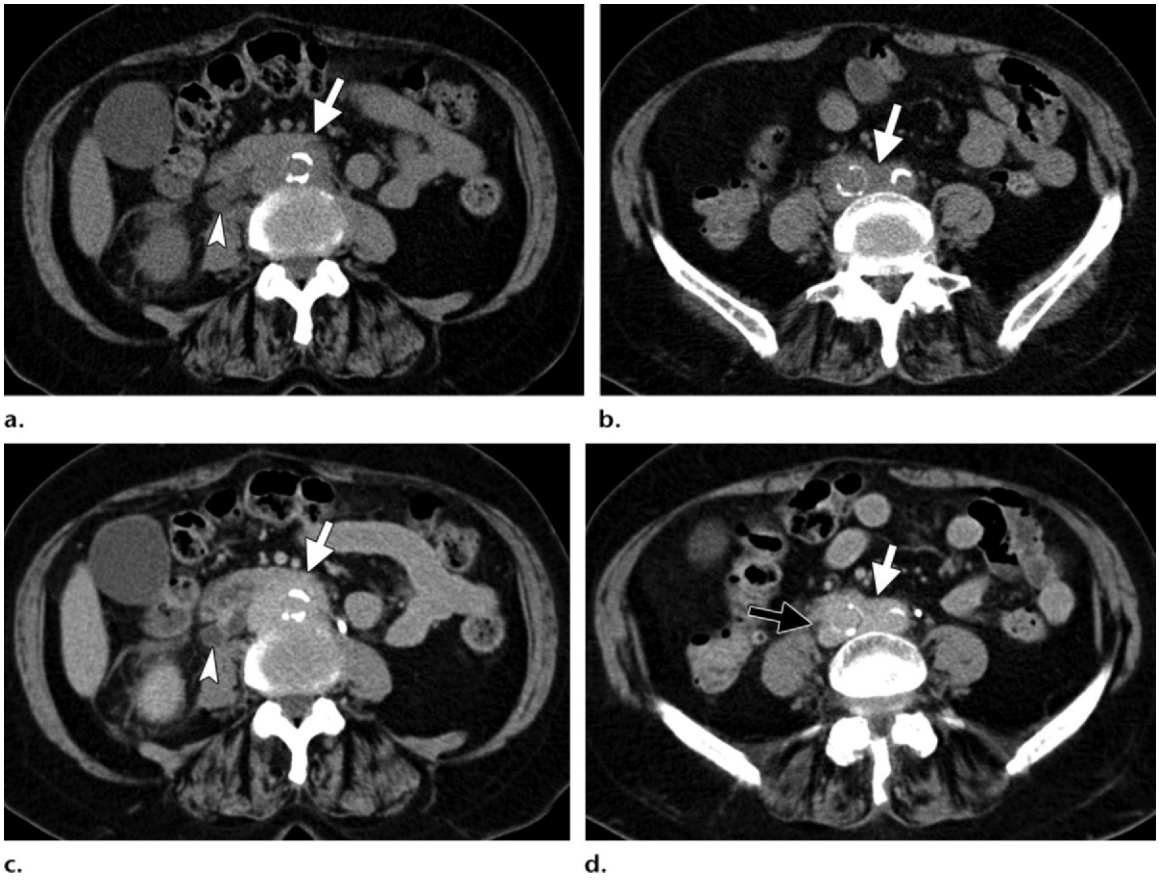


Figure 2. CT of RPF. **(a, b)** Axial nonenhanced CT images show an irregular retroperitoneal mass (arrow) that is isoattenuating to muscle. The mass is located anterior and lateral to the lower abdominal aorta and iliac arteries; it spares the posterior aspect of the aorta and does not cause anterior aortic displacement. Arrowhead in **a** = right proximal hydroureter. **(c, d)** Contrast-enhanced CT images obtained 180 seconds after contrast material administration show avid enhancement of the mass (white arrow), a finding suggestive of early-stage RPF. The right proximal hydroureter (arrowhead in **c**) is secondary to distal encasement of the ureter by the mass (black arrow in **d**). Note the delayed renal excretion of contrast material.

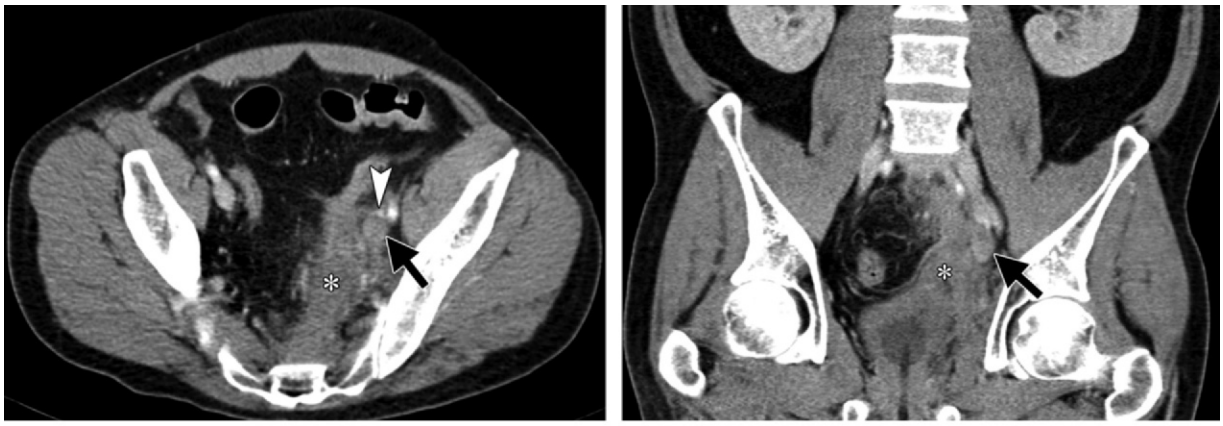
Retrograde pyelography can be an alternative diagnostic procedure when impaired renal function precludes administration of intravascular contrast material or results in failure to opacify the renal collecting system (7,39,41). A catheter can be passed easily through the narrowed area, thus suggesting that the cause of obstruction is disturbance of normal ureteral peristalsis due to entrapment of the ureter in the fibroinflammatory tissue rather than mechanical compression (42).

Teaching Point

Multidetector CT.—Multidetector CT (3,8–10,43,44), along with MR imaging (45–47), has become the mainstay of noninvasive diagnosis of RPF. Multidetector CT allows comprehensive evaluation of the morphology, location, and extent of RPF and involvement of adjacent organs and vascular structures (37,44,48). Moreover, abdominal multidetector CT may allow detection of diseases often associated with idiopathic RPF (eg, autoimmune pancreatitis) or demonstrate an underlying cause in cases of secondary RPF (eg, malignancy). However, a considerable number of patients may have renal impairment secondary to obstructive uropathy, which precludes administration of intravenous contrast agents.

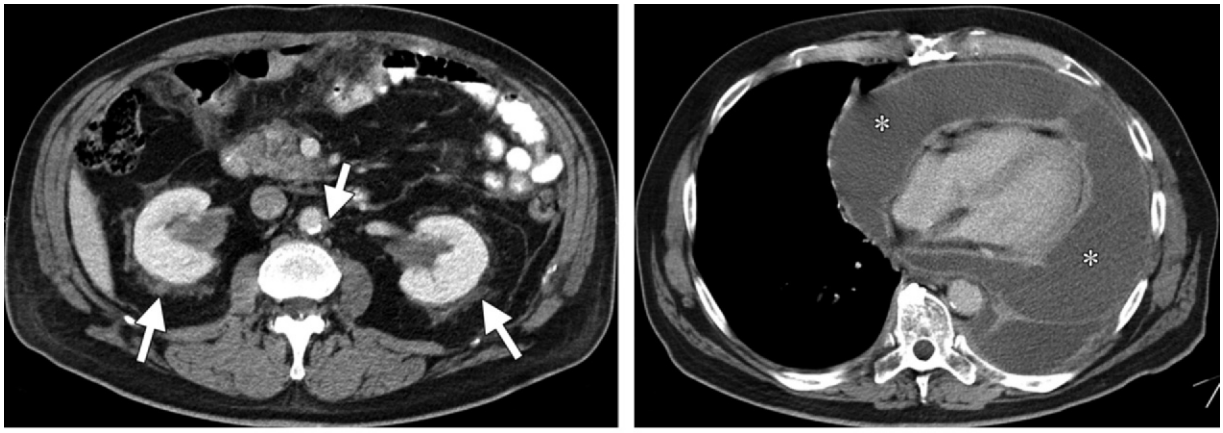
The typical morphologic findings of idiopathic and most benign secondary forms of RPF consist of a well-delimited but irregular soft-tissue periaortic mass, which extends from the level of the renal arteries to the iliac vessels and often progresses through the retroperitoneum to envelop the ureters and IVC (8–10,18,25). The mass usually lies anterior and lateral to the aorta, sparing the posterior aspect and not causing aortic displacement (3,8,10) (Fig 2).

However, the appearance and extension of the periaortic mass at multidetector CT vary considerably. The fibroinflammatory tissue can spread inferiorly to the pelvis (8) or may extend cranially



a. b.

Figure 3. Wegener granulomatosis in a 42-year-old man. Axial **(a)** and coronal reformatted **(b)** CT images, obtained 60 seconds after intravenous contrast material administration, show an ill-defined mass (*) in the left hemipelvis adjacent to the left iliac vessels. Note the presence of a localized lymphadenopathy (arrow), which compresses the left iliac vein (arrowhead in **a**). Histologic analysis was required to make the diagnosis of idiopathic RPF.

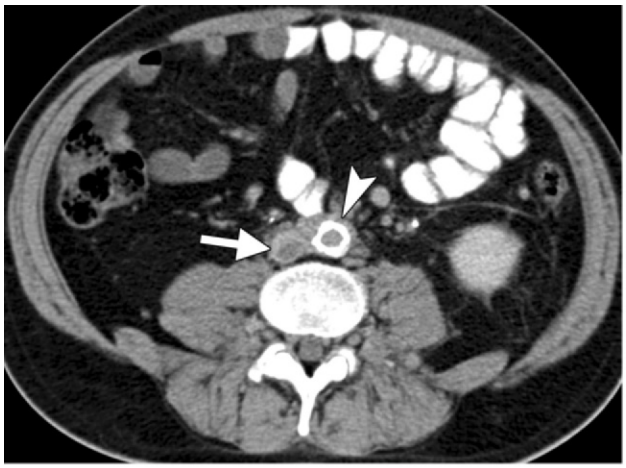


a. b.

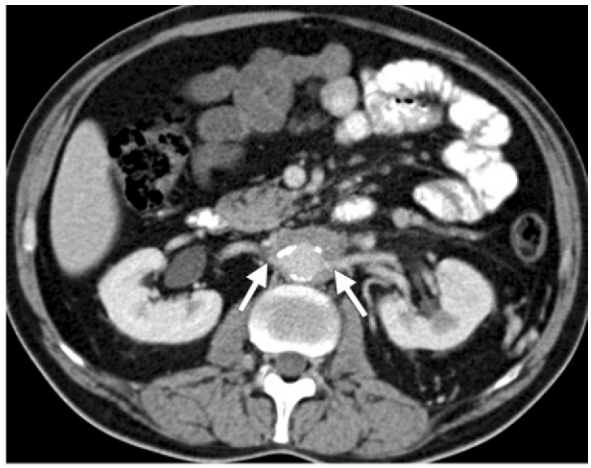
Figure 4. Multifocal fibrosclerosis (histologically confirmed idiopathic RPF and chronic pericarditis with pericardial fibrosis) in a 48-year-old man who was cytoplasmic ANCA (c-ANCA) positive. **(a)** Axial CT image obtained 60 seconds after intravenous contrast material administration shows minimal soft-tissue stranding (arrows) around the abdominal aorta and both kidneys. **(b)** Thoracic CT image shows massive pericardial effusion (*).

to the level of the renal hila, where on rare occasions it may involve retroperitoneal structures such as the duodenum (49) or the renal pelvis and kidney (20,21). Idiopathic RPF atypically located without involvement of the paraaortic area is remarkably uncommon and may represent a diagnostic challenge (18,25,27) (Fig 3). In these atypical forms, the fibroinflammatory tissue often appears as a poorly circumscribed retroperitoneal mass (1). Rarely, the fibrotic process is seen at multidetector CT as only minimal soft-tissue stranding around the abdominal aorta and other retroperitoneal structures (3) (Fig 4a).

At nonenhanced multidetector CT (Fig 2a, 2b), the attenuation of the fibroinflammatory tissue is similar to that of psoas muscle (25,48). After administration of intravenous contrast material, the enhancement depends on the stage



5a.



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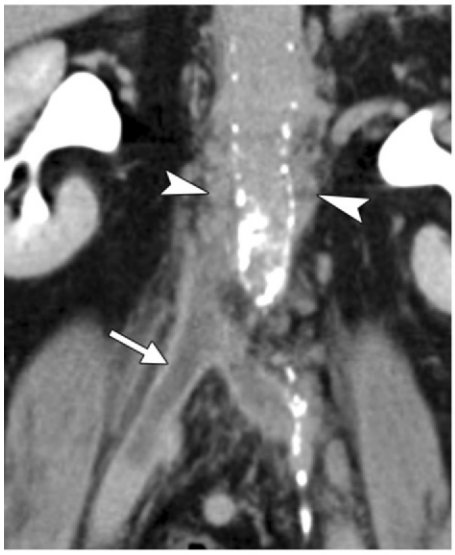


5b.

Figures 5, 6. **(5)** Idiopathic RPF in a 68-year-old man. Axial **(a)** and coronal reformatted **(b)** CT images, obtained 180 seconds after intravenous contrast material administration, show a filling defect in the IVC (arrow in **a**) that extends to both common iliac veins (arrow in **b**), a finding compatible with deep vein thrombosis. Note the subtle plaque-like soft-tissue attenuation (arrowheads) anterior and lateral to the aorta, a finding that corresponds to idiopathic RPF. **(6)** RPF in a 56-year-old woman. Axial CT image obtained 60 seconds after intravenous contrast material administration shows a soft-tissue mass that surrounds the abdominal aorta and the origins of the renal arteries (arrows).

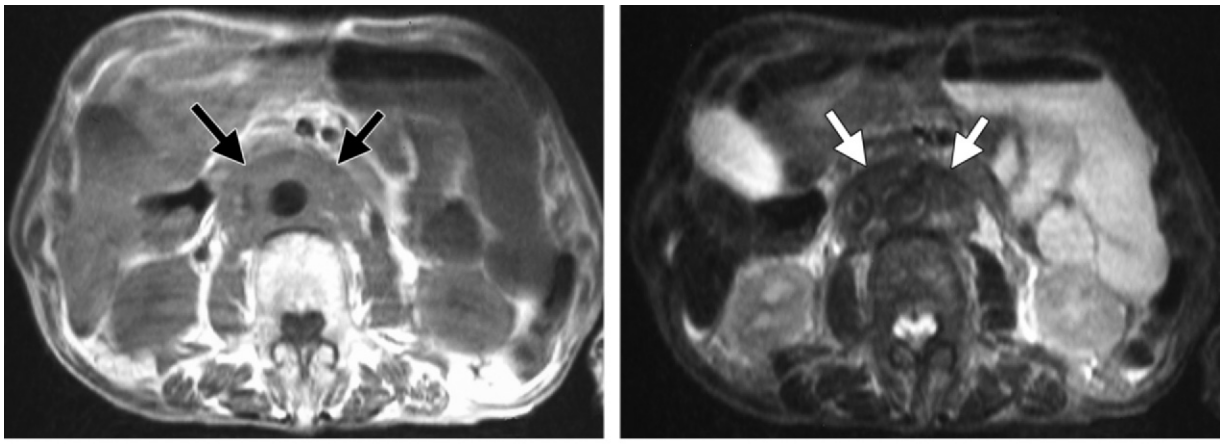
of the disease. Avid enhancement may be seen in the early stages of the disease (Fig 2c, 2d), whereas in the late, inactive stages, little or absent enhancement may be seen (25,38).

This behavior could be useful in assessing the patient's response to therapy. A decrease in contrast enhancement may reflect a favorable response to treatment. However, the degree of contrast enhancement is difficult to quantify and thus cannot be used confidently to assess the metabolic activity of idiopathic RPF (1). The main utility of CT in follow-up is its high sensitivity for detection of changes in the size of the retroperitoneal fibroinflammatory mass (50,51).

Multidetector CT is useful for detection of other findings, such as hydronephrosis, which is seen in 56%–100% of cases (5,8,15,31); deep vein thrombosis, which is seen in approximately 6% of cases (8,15) (Fig 5); and renal vessel involvement, which is seen in 2%–35% of cases (8,9,15) (Fig 6) and may be an overlooked feature of idiopathic RPF.

In idiopathic RPF, localized lymphadenopathy adjacent to the fibroinflammatory mass is seen in 25% of cases. It is characterized by multiple infracentimetric lymph nodes, which are probably related to the retroperitoneal reaction and should not heighten suspicion of malignancy (8).

Thoracic CT may also be useful in detection of extraabdominal imaging features related to conditions that may be associated with idiopathic RPF, such as multifocal fibrosclerosis (eg, chronic pericarditis with massive pericardial effusion) (22) (Fig 4b) and asbestos exposure (unilateral or bilateral pleural plaques or pleural thickening) (8).



a. b.

Figure 7. Histologically confirmed idiopathic RPF. Axial T1-weighted **(a)** and T2-weighted **(b)** MR images show a retroperitoneal mass (arrows) surrounding the abdominal aorta and IVC. The mass has low signal intensity on both images, a finding suggestive of late-stage disease.

MR Imaging.—MR imaging is equivalent to CT in allowing comprehensive assessment of the characteristics of RPF and its effect on adjacent retroperitoneal structures and also in demonstrating diseases often associated with idiopathic RPF or an underlying cause in cases of secondary RPF. The major advantage of MR imaging over CT is its far superior contrast resolution (46). In patients with severe impairment of renal function, care must be taken before administration of gadolinium-based contrast agents because of the risk of nephrogenic systemic fibrosis (52). However, even precluding administration of intravenous gadolinium contrast material, MR imaging has higher contrast resolution than CT.

MR imaging also allows assessment of the urinary tract in patients with RPF by using high-speed, heavily T2-weighted sequences such as half-Fourier acquisition single-shot turbo spin echo (HASTE) (Siemens Healthcare, Erlangen, Germany) or rapid acquisition with relaxation enhancement (RARE), precluding the need for administration of intravenous contrast material and without the risk of radiation. Thus, HASTE and RARE MR urography are alternatives to intravenous urography or CT urography in patients with severe renal failure (39,53).

Idiopathic RPF typically has low signal intensity on T1-weighted images. The signal intensity on T2-weighted images is variable and reflects the degree of associated active inflammation (hypercellularity and edema). After administration of intravenous gadolinium contrast material, early soft-tissue enhancement mirrors the degree of inflammatory activity observed at T2-weighted imaging.

Active inflammation, which is predominant in early idiopathic RPF, may be recognized as high T2 signal intensity and early contrast enhancement. Conversely, the late inactive stage is relatively acellular and hypovascular, with predominant fibrosis; thus, it usually demonstrates low T2 signal intensity and little or absent contrast enhancement (3,18,25,29,37,54) (Fig 7). These features may help in assessment of the response to treatment. A decrease in T2 signal intensity and in gadolinium contrast enhancement usually reflects a favorable response to treatment (47), although in some cases there may be occult residual inflammation in the retroperitoneal fibrous mass (50,51).

Positron Emission Tomography.—PET with ^{18}F-FDG is a functional imaging modality well established in oncology and infectious diseases. Recently, several studies have highlighted the potential role of ^{18}F-FDG PET in assessment of various inflammatory diseases, including idiopathic RPF (13,50,51,55–63).

The sensitivity of ^{18}F-FDG PET is very high, which allows detection and quantification of the

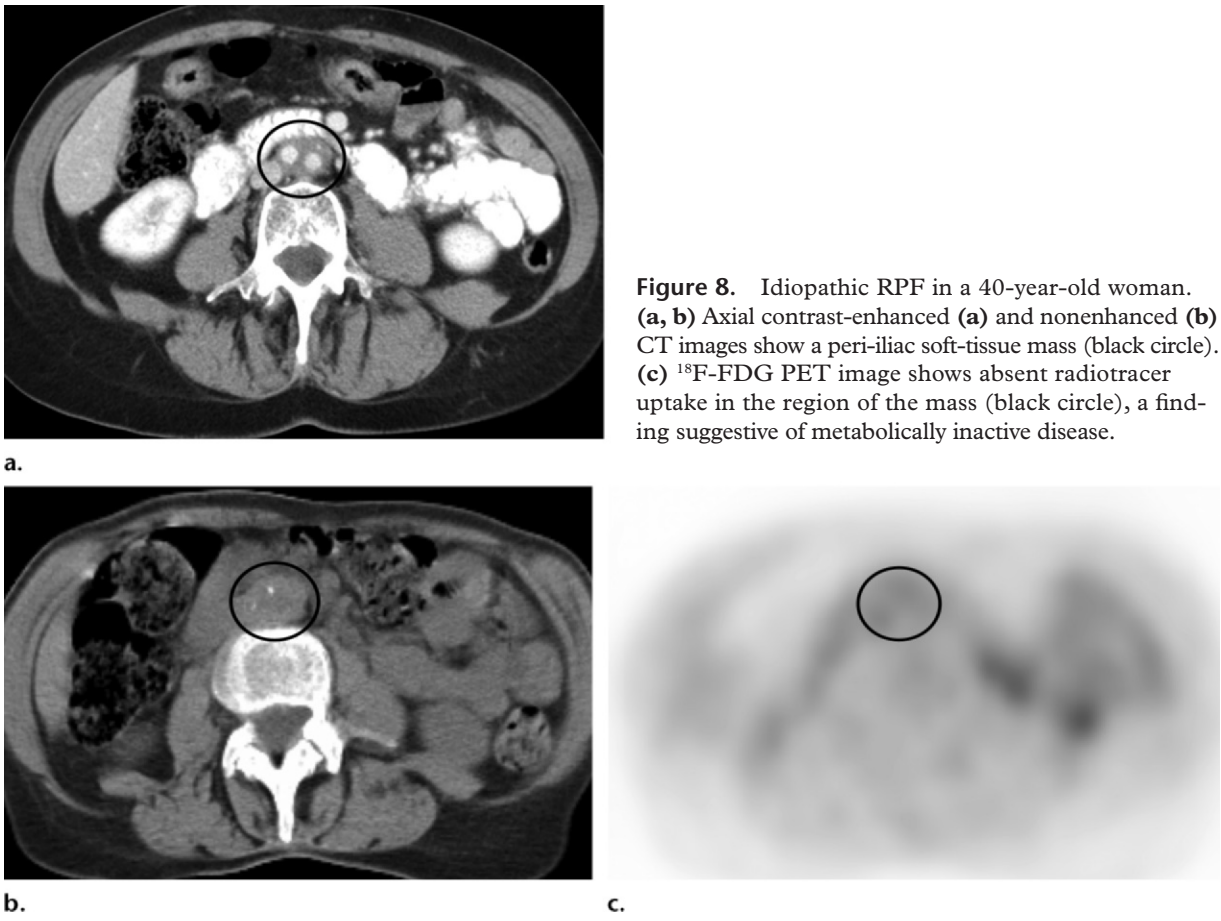


Figure 8. Idiopathic RPF in a 40-year-old woman. **(a, b)** Axial contrast-enhanced **(a)** and nonenhanced **(b)** CT images show a peri-iliac soft-tissue mass (black circle). **(c)** ^{18}F-FDG PET image shows absent radiotracer uptake in the region of the mass (black circle), a finding suggestive of metabolically inactive disease.

metabolic activity of retroperitoneal lesions (Fig 8) irrespective of a benign or malignant underlying cause. Nevertheless, because of its low specificity, ^{18}F-FDG PET is not useful for diagnosis of idiopathic and other benign forms of RPF (37,50,51,61,64). Furthermore, FDG uptake in the aortic wall can occur in elderly patients, especially those with hyperlipidemia and a history of cardiovascular disease (65).

^{18}F-FDG PET allows whole-body examination. Thus, it allows assessment of the full extent and distribution of vascular and perivascular inflammatory involvement in idiopathic RPF (13,59). It can also reveal remote diseases such as multifocal fibrosclerosis or may demonstrate infectious, neoplastic, or other autoimmune processes with which RPF may be associated (7,24,56–58,60). ^{18}F-FDG PET may also be useful in identifying more appropriate sites for biopsy (31).

Immunosuppressive therapy is believed to be most useful during the inflammatory phase of the disease. ^{18}F-FDG PET may be superior to anatomic CT and MR imaging and to use of serum inflammatory markers in revealing active inflammation and thus allow prediction of posttreatment prognosis (28,58,61).^{18}F-FDG PET may also be used during follow-up to assess response to treatment and disease relapse (58,61).

Despite the potential added role of ^{18}F-FDG PET as a guide for management of idiopathic RPF, to date only anecdotal case reports, small retrospective case series, and one small prospective study (63) have been published, to our knowledge. Therefore, the results of these studies must be regarded as preliminary, and further investigation of the utility of ^{18}F-FDG PET for this application is warranted.

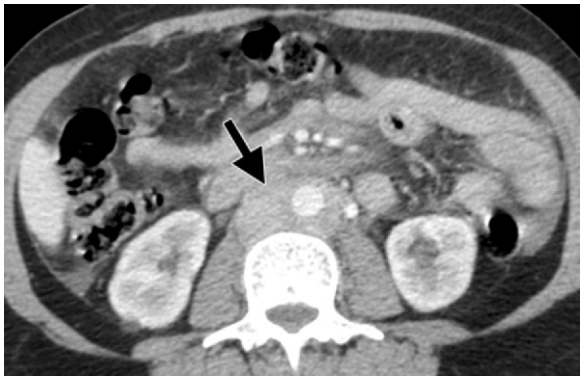


Figure 9. Histologically confirmed non-Hodgkin lymphoma in a 34-year-old man with human immunodeficiency virus (HIV) infection. Axial CT image obtained 60 seconds after contrast material administration shows a well-delimited soft-tissue mass (arrow) surrounding the aorta and IVC. Note the slight anterior displacement of the aorta from the spine, a finding suggestive of malignancy.

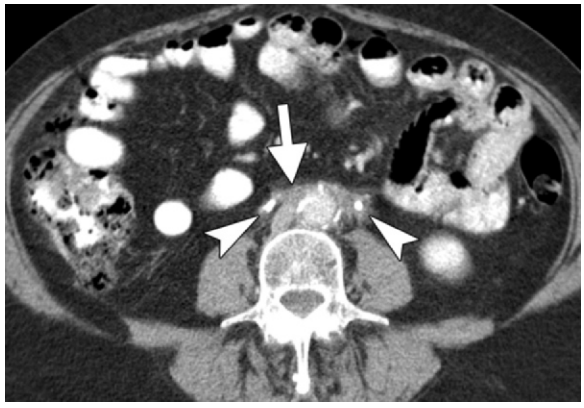


Figure 10. RPF in a 56-year-old man. Axial CT image obtained 60 seconds after contrast material administration shows a plaque-like area of attenuation (arrow) surrounding the aorta and IVC. Peripheral infiltration encases both ureters (arrowheads) and does not separate the aorta from the spine, findings indicative of benign RPF. Note the bilateral ureteral stents.

Management of RPF

Cross-sectional Imaging in the Differential Diagnosis

Most benign secondary forms of RPF (eg, RPF related to the ingestion of drugs) are radiologically indistinguishable from the idiopathic form of the disease.

Teaching Point

If appropriately diagnosed and treated, idiopathic and most other benign forms of RPF have a good outcome, whereas RPF secondary to malignancy has a poor prognosis (5). Therefore, at imaging, the most important challenge is to differentiate benign from malignant RPF. Several features that may help differentiate between these conditions have been described.

Anterior displacement of the aorta and IVC is usually seen in malignant RPF (Fig 9). Enlargement of the lymph nodes located posterior to the great vessels could explain this finding. Conversely, in benign RPF, the soft-tissue mass usually spares the posterior aspect of the great vessels and does not cause vascular displacement (Figs 2, 10) (3,8,10,37,43). Nonetheless, this distinguishing feature lacks sensitivity and specificity and this generalization is not always correct (3,8) (Figs 11, 12).

Lymphomas are often found in a more cephalic location in the retroperitoneum, whereas benign RPF is mainly located distal to the renal hilum (44). Nevertheless, extension of benign RPF cranially to the renal hilum is not uncommon. Therefore, the extent of the mass is of limited clinical utility (37).

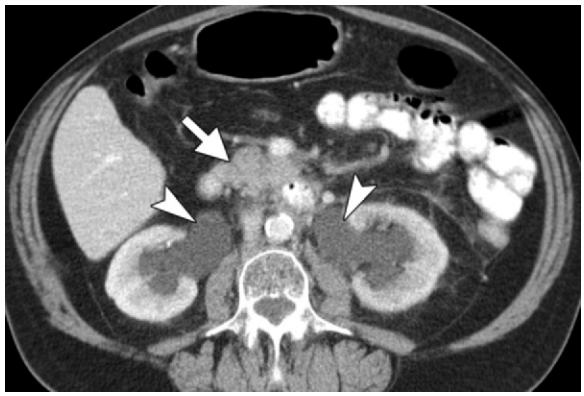


Figure 11. Breast cancer in a 73-year-old woman. Axial CT image obtained 60 seconds after contrast material administration shows a retroperitoneal soft-tissue mass (arrow) but no anterior displacement of the aorta. However, the mass has a lobulated anterior margin. Its malignant nature was confirmed with biopsy. Note the bilateral hydronephrosis (arrowheads) due to ureteral encasement.

In malignant RPF, the retroperitoneal mass usually has a nodular aspect, often exerting mass effect on neighboring structures (3,66) (Fig 11), whereas in benign RPF the retroperitoneal mass often has an infiltrative aspect, enveloping rather than displacing adjacent structures (48) (Fig 10). However, the morphologic features of both benign and ma-

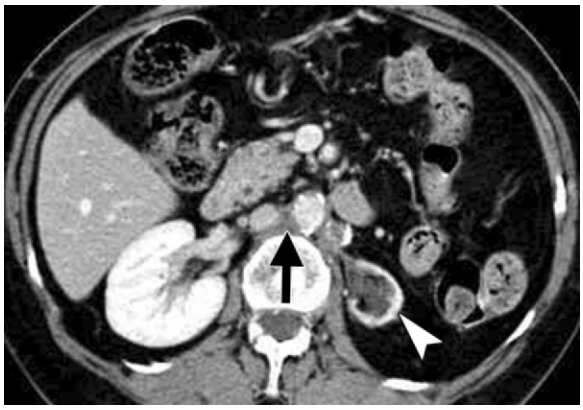


Figure 12. Metastatic melanoma in a 45-year-old woman. Axial CT image obtained 60 seconds after contrast material administration shows a hypoattenuating periaortic soft-tissue mass (arrow) with smooth margins. The aorta is not separated from the underlying spine. Although these features are suggestive of benign disease, the mass was proved to be malignant RPF. Note the atrophy of the left kidney (arrowhead), which was probably secondary to chronic obstruction. (Courtesy of Aleksandar Radosevic, MD, Hospital del Mar, Barcelona, Spain.)

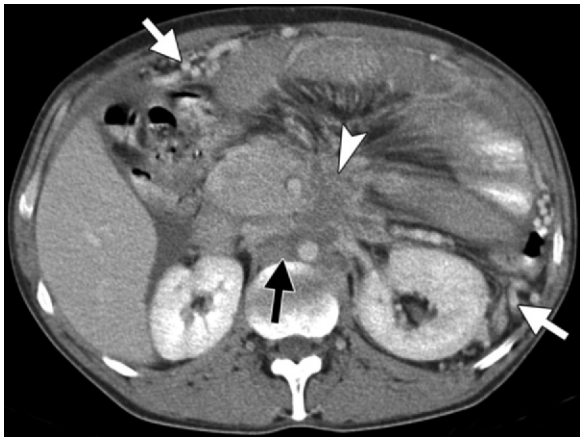


Figure 13. RPF secondary to tuberculosis in a 42-year-old man with human immunodeficiency virus (HIV) infection and a history of tuberculous lymphadenitis who presented with abdominal pain and fever. Axial CT image obtained 60 seconds after contrast material administration shows a markedly hypoattenuating paraaortic mass (black arrow) that infiltrates the pancreatic body (arrowhead) and the superior mesenteric and splenic veins. Note the presence of collateral venous circulation (white arrows) secondary to venous obstruction. A presumptive diagnosis of RPF secondary to tuberculosis was made. Antibiotic treatment was instituted, with improvement in the patient's clinical condition.

lignant RPF can be variable, and this distinction may not hold true in many cases (37) (Fig 12).

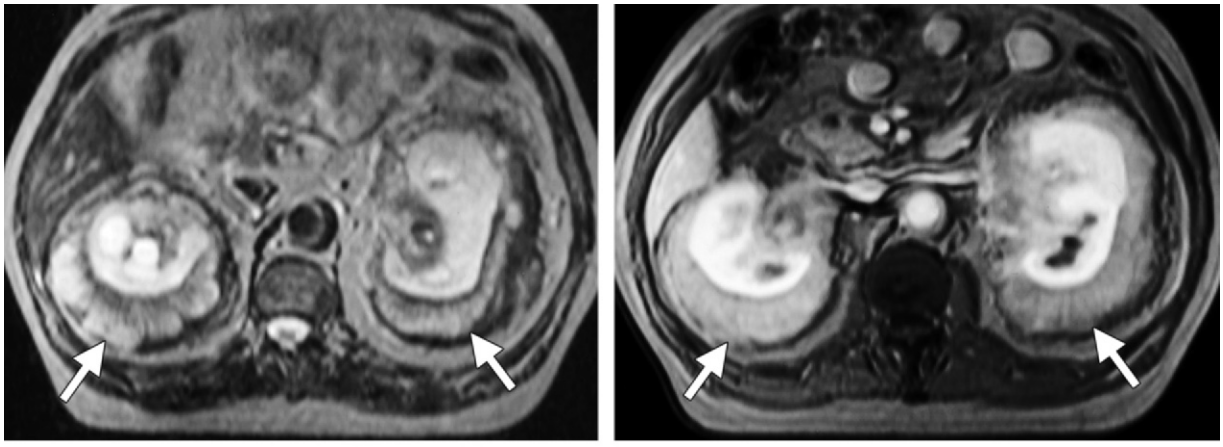
In early stages, both malignant and benign RPF may show enhancement after intravenous administration of contrast material (25,38). Therefore, enhancement is not helpful in the differential diagnosis between benign and malignant disease.

Whether benign or malignant, RPF typically has low signal intensity on T1-weighted MR images. Malignant RPF is typically associated with hypercellularity and inflammatory edema of the retroperitoneal soft tissue, which appear as high signal intensity on T2-weighted images (46). High signal intensity on T2-weighted images also appears in idiopathic RPF in the active inflammatory stage, whereas low T2 signal intensity reflects poor or absent inflammatory activity (3,18,25,29,37,54). Therefore, a retroperitoneal mass that has low signal intensity on T2-weighted images is highly suggestive of benign RPF in the late inactive stage (Fig 7). On the other hand, high T2 signal intensity cannot be used to differentiate between malignant and early-stage idiopathic RPF (18,25,46).

Hence, although all of these features may be useful for diagnosis of RPF, differentiation between the idiopathic and malignant forms of the disease cannot be made only on the basis of cross-sectional imaging findings (38,46).

The differential diagnosis should include entities with a similar appearance. Perianeurysmal fibrosis may have morphologic features and an enhancement pattern similar to those of idiopathic RPF, with the exception of the encased aorta, which is pathologically dilated (7,9). Primary amyloidosis involving the retroperitoneum is a rare disease and can cause diffuse retroperitoneal involvement (67) or may be localized (68), mimicking idiopathic RPF.

Acute retroperitoneal hematomas may have high attenuation on nonenhanced CT images and high signal intensity on nonenhanced T1-weighted images, with absence of enhancement on contrast-enhanced images. In infectious processes such as tuberculosis affecting the retroperitoneum, there may be areas of necrosis within the mass, which appear as high-signal-intensity areas on T2-weighted images and markedly hypoattenuating areas on multidetector CT images (37) (Fig 13). Retroperitoneal sarcoma should also be



a. b.

Figure 14. Histologically confirmed idiopathic RPF with exclusively perirenal involvement. T2-weighted **(a)** and gadolinium-enhanced T1-weighted **(b)** MR images show bilateral perirenal soft-tissue masses with high T2 signal intensity (arrows in **a**) and enhancement (arrows in **b**), findings suggestive of active inflammatory disease.

included in the differential diagnosis, especially if the mass has a tumefactive appearance (3).

When RPF is found in an atypical retroperitoneal location, such as perirenally (Fig 14), the differential diagnosis is expanded and should include rare conditions such as Castleman disease, Erdheim-Chester disease, and extramedullary hematopoiesis (20,21,35,54,66,69).

Diagnosis

There are no standardized diagnostic criteria for idiopathic RPF. Diagnosis is difficult and is often delayed because of the insidious and nonspecific nature of the symptoms. Results of routine laboratory tests are also nonspecific. Hence, diagnosis depends on a high degree of suspicion.

The presumptive diagnosis is based on radiologic findings, with multidetector CT and MR imaging considered the imaging modalities of choice (1,18,25,70). Recognition of the typical imaging findings, interpreted in light of the clinical, biochemical, and immunologic data, is suggestive of benign RPF (1,70).

Teaching Point

However, histopathologic examination of the retroperitoneal tissue obtained with biopsy is mandatory to establish the definitive diagnosis in the presence of *(a)* clinical, laboratory, or radiologic findings suggestive of underlying malignant disease or infection; *(b)* atypical location of the mass (eg, pelvic, peripancreatic, perirenal); *(c)* progression of the mass or absence of response to immunosuppressive therapy; or *(d)* lack of experience with diagnosis and clinical management of RPF (1,7,8,15,17,26,27,31,51,71).

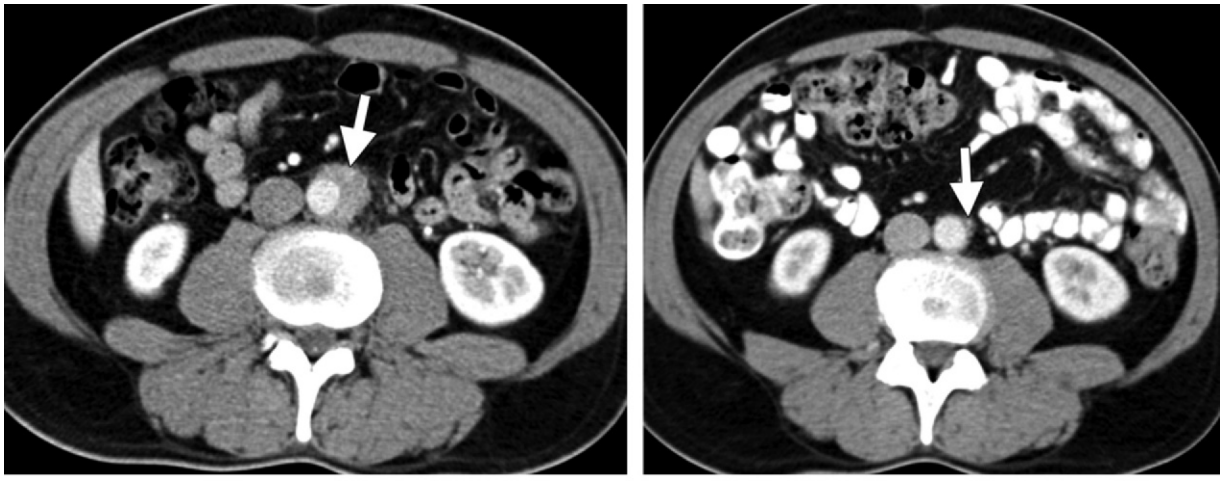
Although an open surgical approach with multiple deep biopsies is traditionally preferred, laparoscopic biopsy may be appropriate in selected cases (3,14,72). In malignant RPF, there may be small amounts of malignant cells diffusely dispersed in the surrounding desmoplastic reaction; thus, CT-guided fine-needle aspiration or core biopsy is considered far less effective and less reliable than deep surgical or laparoscopic biopsy (3,72). PET scans may be useful in identifying the most appropriate sites for biopsy (31).

Treatment

The aims of treatment of idiopathic RPF are multiple: to inhibit or relieve the obstruction of the ureters or other retroperitoneal structures, to switch off the acute-phase reaction and its systemic manifestations, and to prevent disease recurrence or relapse (1).

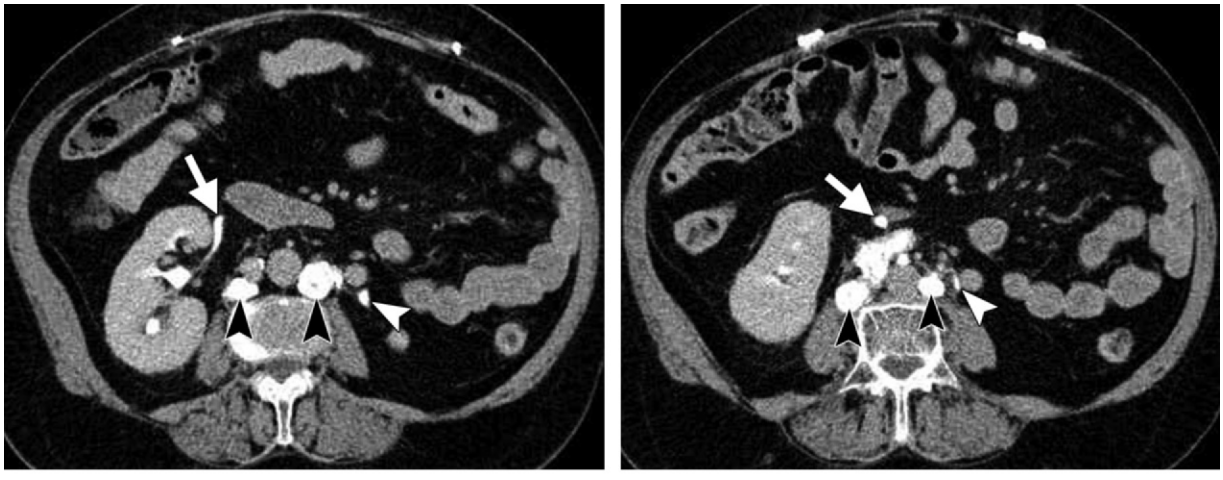
Traditionally, the approach has been surgical, but at present, after the initial relief of urinary tract obstruction, medical strategies are used in most cases (15). To our knowledge, there are no guidelines for the medical treatment of idiopathic RPF, given the lack of randomized trials (73). Corticosteroids are normally considered the first-line treatment for patients with newly diagnosed idiopathic RPF (33,74).

In most patients, corticosteroid treatment results in prompt improvement of symptoms and a decrease in or normalization of acute-phase reactants and often leads to a reduction in size of the retroperitoneal mass (Fig 15) and resolution of obstructive complications (1,7,33,37). Other immunosuppressive drugs (eg, methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, chlorambucil) or tamoxi-



a. b.

Figure 15. Idiopathic RPF in a 53-year-old man with constitutional symptoms. **(a)** Axial CT image obtained 60 seconds after contrast material administration shows a retroperitoneal paraaortic mass (arrow) without ureteral entrapment. The presumptive diagnosis was idiopathic RPF. Steroid treatment was instituted. **(b)** Follow-up CT image 6 months later shows almost complete resolution of the mass (arrow).



a. b.

Figure 16. Surgical treatment for obstructive uropathy secondary to idiopathic RPF. Axial CT images (**a** at a higher level than **b**) obtained 180 seconds after contrast material administration show intraperitonealization of the right ureter (arrow). Note the periaortic mass with calcifications (black arrowheads), which contacts but does not encase the left ureter (white arrowhead) on its way through the retroperitoneum. (Case courtesy of Aleksandar Radosevic, MD, Hospital del Mar, Barcelona, Spain.)

fen, either alone or in combination with corticosteroids, can be used as steroid-sparing agents or in steroid-refractory cases (9).

Acute renal failure secondary to periureteral involvement requires prompt intervention to prevent permanent renal damage. In addition to corticosteroid therapy, drainage of the upper urinary tract—by temporary placement of nephrostomy tubes or ureteral stents—may be necessary (1,26,33,39). In patients who respond to medical therapy, the nephrostomy tubes or ureteral stents may be removed. Descending ureterography through the nephrostomy tube or subsequent clamping of the tube can be performed to ensure ureteral patency before removal.

Surgery is reserved for refractory cases. The standard surgical approach involves open biopsy, ureterolysis, and ureteral transposition with omental wrapping of the involved ureter (1,18,26,37,75). Laparoscopic ureterolysis and intraperitonealization of the ureter is an effective and less invasive alternative to conventional open surgery (Fig 16). However, both laparoscopic and

open surgical techniques are not without complications, such as ureteral devascularization, tears, or strictures with ureteral leakage or urinary fistula. In the presence of vascular involvement, such as renal artery stenosis secondary to extrinsic compression, endovascular stent placement may be necessary (9,10).

^{18}F-FDG PET could play a useful role in predicting the success of immunosuppressive therapy. Patients with high baseline ^{18}F-FDG uptake are more likely to respond to immunosuppressive therapy. On the other hand, patients with metabolically inactive residual disease, which is characterized by attenuated or absent ^{18}F-FDG accumulation, probably will not respond to immunosuppressive therapy and might be referred for surgical management earlier in the course of the disease (58,61).

Long-term low-dose therapy with corticosteroids and immunosuppressants is usually required to prevent relapse of idiopathic RPF (17). Effective management of secondary forms of RPF requires an approach based on the cause, when identified.

Follow-up

The prognosis of idiopathic RPF is usually good if it is appropriately diagnosed and treated. In most cases, it does not lead to long-term morbidity or affect patient survival (2). However, idiopathic RPF demonstrates a chronic relapsing course that requires frequent and long-term follow-up (16).

The major difficulty in follow-up of idiopathic RPF is assessment of the presence and degree of inflammatory activity, as therapeutic decisions depend on this information. After the initiation of therapy, assessment of disease activity is usually based on clinical symptoms, serial measurements of serum inflammatory markers, and imaging findings. Constitutional symptoms and high erythrocyte sedimentation rate and C-reactive protein levels are often found in active disease (28,33,51,63). However, these features are nonspecific and lack sensitivity and thus do not always reflect inflammatory activity (51,57).

Among imaging techniques, US is a satisfactory and cost-effective noninvasive modality that is useful in follow-up of ureterohydronephrosis (1). However, it is not reliable for assessing changes in size of the retroperitoneal fibroinflammatory tissue.

Teaching Point

Multidetector CT and MR imaging allow accurate assessment of variations in size of the retroperitoneal tissue (2,28,51,63). However, despite effective medical treatment with a clinical response and reduction of acute-phase reactants, residual retroperitoneal tissue is frequently observed (50,51,58). Management of this condition represents a challenge because these masses may represent clinically occult residual inflammation or may simply be inactive fibrotic tissue (50,51).

In comparison with the erythrocyte sedimentation rate and C-reactive protein levels, ^{18}F-FDG PET emerges as a more sensitive modality for assessing the metabolic activity of these residual masses and demonstrating disease relapse (50,51,57,63). In addition, despite decreasing enhancement at multidetector CT or MR imaging, active disease may still be apparent at ^{18}F-FDG PET (57).

In most patients with clinically stable disease and significantly decreased concentrations of acute-phase reactants, posttreatment residual masses may show subtle or absent ^{18}F-FDG uptake and thus probably represent sclerotic, metabolically inactive residual disease. On the other hand, increased ^{18}F-FDG accumulation within the mass is suggestive of recurrent disease (50,51,57,63) (Fig 17). Timely diagnosis allows early modulation of medical therapy before complications such as obstructive uropathy occur, thus avoiding nephrostomy tube placement (51).

^{18}F-FDG PET could also be used as a guide for the tapering or withdrawal of immunosuppressant therapy and for stent removal, as well as for planning other surgical interventions (51). For example, in a patient treated for obstructive uropathy with upper urinary tract drainage, absence of ^{18}F-FDG uptake suggests that stents or nephrostomy tubes could be safely removed. Note that these management decisions are based on a single preliminary study with a small number of patients (51); further analysis in regard to the utility of ^{18}F-FDG PET for these applications is warranted. Moreover, the overall duration of therapy, the regimen of follow-up tests, and the length and modality of drug tapering have yet to be determined (51), and large prospective studies are needed to address these issues.

Conclusion

In recent years, there have been great advances in our knowledge of RPF, and multidetector CT, along with MR imaging, has become the mainstay of noninvasive diagnosis of RPF. These imaging

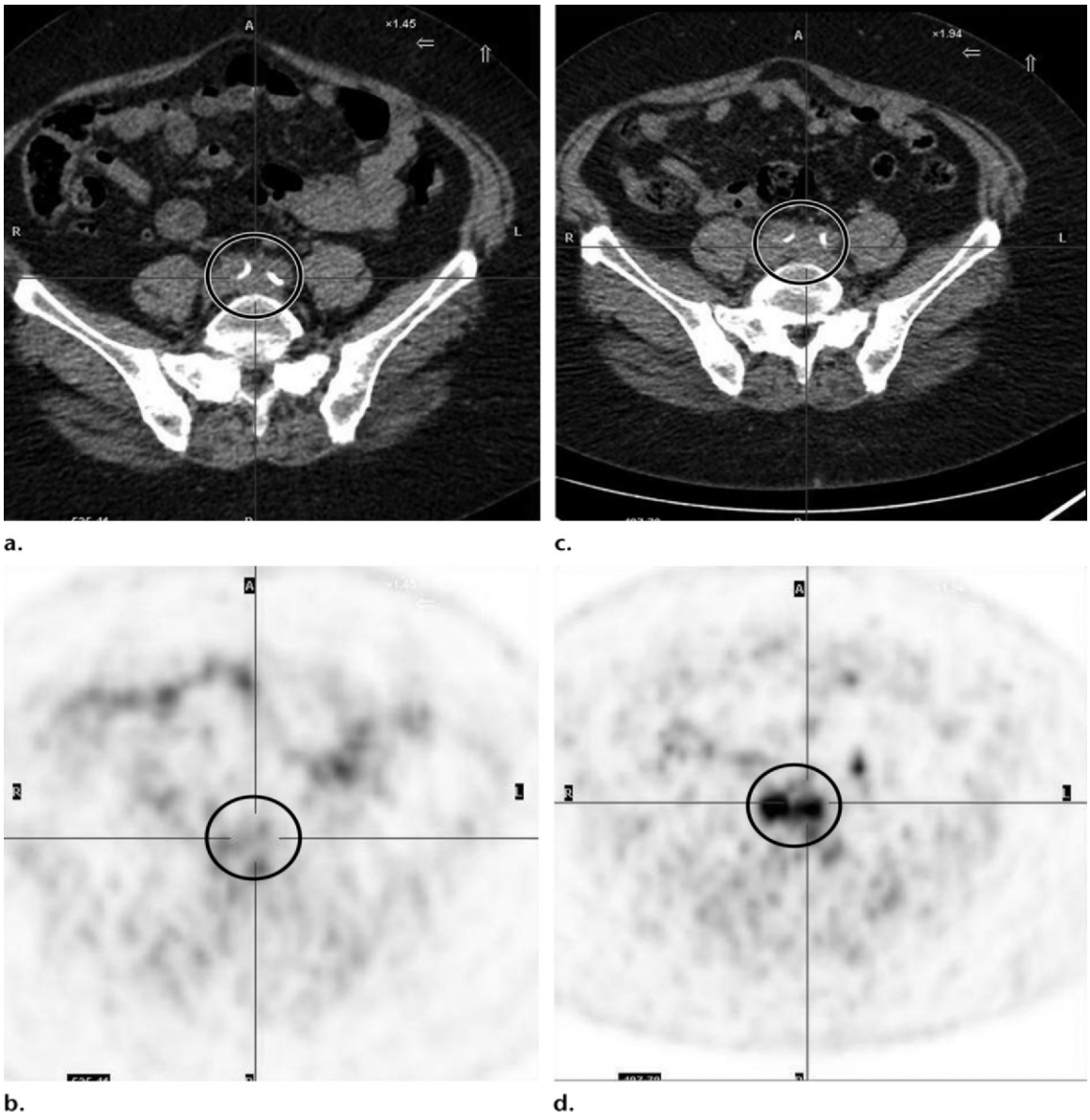


Figure 17. Follow-up of idiopathic RPF with ^{18}F-FDG PET/CT in a 45-year-old man who was receiving steroid treatment. **(a)** Axial CT image shows a retroperitoneal mass surrounding the iliac vessels (black circle). **(b)** Axial PET image shows no pathologic FDG uptake in the region of the mass (black circle), a finding suggestive of metabolically inactive residual disease. **(c)** Axial CT image 3 months after withdrawal of steroid treatment shows persistence of the retroperitoneal mass (black circle). **(d)** Axial PET image 3 months after withdrawal of steroid treatment shows intense FDG uptake in the region of the mass (black circle), a finding suggestive of relapse of inflammatory disease. (Case courtesy of Alejandro Fernandez Leon, MD, PhD, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.)

modalities allow comprehensive evaluation of the morphology, location, and extent of RPF and involvement of adjacent organs. The most important challenge is differentiation of benign RPF from malignant forms. Several multidetector CT and MR imaging features that may help distinguish these conditions have been described. Biopsy allows histologic confirmation of RPF and should be performed if differentiation between benign and malignant forms cannot be achieved on the basis of clinical, laboratory, and radiologic findings.

^{18}F-FDG PET has emerged as a promising tool in the management of idiopathic RPF and may play a useful role in predicting the success of

immunosuppressive therapy. ^{18}F-FDG PET may also be helpful during follow-up to assess treatment response and demonstrate inflammatory relapse. It is hoped that future evidence-based recommendations will lead to appropriate management of this challenging condition.

Acknowledgment.—The authors thank Esther Moreno for English language assistance.

Disclosures of Conflicts of Interest.—**R.S.I.:** *Related financial activities: none. Other financial activities:* speaker for MSD Norway.

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Retroperitoneal Fibrosis: Role of Imaging in Diagnosis and Follow-up

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RadioGraphics 2013; 33:535–552 • **Published online** 10.1148/rg.332125085 • **Content Codes:** CT GU MR NM

Page 537
In about 56%–100% of patients with idiopathic RPF, the fibroinflammatory tissue entraps the ureters and causes obstructive uropathy and subsequent renal failure. Ureteral involvement is bilateral in most cases. Some patients present with nonfunctioning kidneys as a result of long-lasting obstructive uropathy.

Page 539
Multidetector CT, along with MR imaging, has become the mainstay of noninvasive diagnosis of RPF. Multidetector CT allows comprehensive evaluation of the morphology, location, and extent of RPF and involvement of adjacent organs and vascular structures. Moreover, abdominal multidetector CT may allow detection of diseases often associated with idiopathic RPF (eg, autoimmune pancreatitis) or demonstrate an underlying cause in cases of secondary RPF (eg, malignancy).

Page 544
If appropriately diagnosed and treated, idiopathic and most other benign forms of RPF have a good outcome, whereas RPF secondary to malignancy has a poor prognosis. Therefore, at imaging, the most important challenge is to differentiate benign from malignant RPF. Several features that may help differentiate between these conditions have been described.

Page 546
However, histopathologic examination of the retroperitoneal tissue obtained with biopsy is mandatory to establish the definitive diagnosis in the presence of *(a)* clinical, laboratory, or radiologic findings suggestive of underlying malignant disease or infection; *(b)* atypical location of the mass (eg, pelvic, peripancreatic, perirenal); *(c)* progression of the mass or absence of response to immunosuppressive therapy; or *(d)* lack of experience with diagnosis and clinical management of RPF.

Page 548
Multidetector CT and MR imaging allow accurate assessment of variations in size of the retroperitoneal tissue. However, despite effective medical treatment with a clinical response and reduction of acute-phase reactants, residual retroperitoneal tissue is frequently observed. Management of this condition represents a challenge because these masses may represent clinically occult residual inflammation or may simply be inactive fibrotic tissue. In comparison with the erythrocyte sedimentation rate and C-reactive protein levels, ^{18}F-FDG PET emerges as a more sensitive modality for assessing the metabolic activity of these residual masses and demonstrating disease relapse. In addition, despite decreasing enhancement at multidetector CT or MR imaging, active disease may still be apparent at ^{18}F-FDG PET.