Retroperitoneal fibrosis

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Retroperitoneal fibrosis encompasses a range of diseases characterised by the presence of a fibro-inflammatory tissue, which usually surrounds the abdominal aorta and the iliac arteries and extends into the retroperitoneum to envelop neighbouring structures—eg, ureters. Retroperitoneal fibrosis is generally idiopathic, but can also be secondary to the use of certain drugs, malignant diseases, infections, and surgery. Idiopathic disease was thought to result from a local inflammatory reaction to antigens in the atherosclerotic plaques of the abdominal aorta, but clinicolaboratory findings—namely, the presence of constitutional symptoms and the high concentrations of acute-phase reactants—and the frequent association of the disease with autoimmune diseases that involve other organs suggest that it might be a manifestation of a systemic autoimmune or inflammatory disease. Steroids are normally used to treat idiopathic retroperitoneal fibrosis, although other options—eg, immunosuppressants, tamoxifen—are available. The outlook is usually good, but, if not appropriately diagnosed or treated, the disease can cause severe complications, such as end-stage renal failure. Here, we review the different aspects of retroperitoneal fibrosis, focusing on idiopathic retroperitoneal fibrosis and on the differential diagnosis associated with the secondary forms.

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Retroperitoneal fibrosis is a rare disease characterised by the presence of a retroperitoneal tissue, consisting of chronic inflammation and marked fibrosis, which often entraps the ureters or other abdominal organs.[1] The idiopathic form of the disease accounts for more than two thirds of cases, with the rest being secondary to other factors—eg, neoplasms, infections, trauma, radiotherapy, surgery, and use of certain drugs.[2] The first description of idiopathic retroperitoneal fibrosis is credited to the French urologist Albarran[3] who, in 1905, reported the surgical treatment of an extensive fibrotic retroperitoneal process causing ureteral obstruction. The abnormality did not become an acknowledged disease process until 1948, however, when Ormond[4] published his account of two cases in English. Since then, major advances have been made in the understanding and management of idiopathic retroperitoneal fibrosis. The introduction of medical therapy, mainly based on corticosteroids, has greatly improved patients' outcome,[5,6] and the availability of imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), has provided non-invasive and reliable methods of diagnosis and follow-up.[7]

In the past two decades, results of a series of studies that had focussed on the pathogenesis of the disease have suggested that idiopathic retroperitoneal fibrosis could be included under the umbrella term chronic periaortitis, along with inflammatory abdominal aortic aneurysms and perianeurysmal retroperitoneal fibrosis.[8,9] The three entities have similar histo-pathological characteristics, including adventitial and periadventitial inflammation, medial thinning, and advanced atherosclerosis: in idiopathic retroperitoneal fibrosis, the aorta is not dilated and the surrounding fibro-inflammatory tissue might or might not encase adjacent structures; in inflammatory abdominal aortic aneurysms the tissue develops around a dilated aorta, but does not cause obstructions; and perianeurysmal retroperitoneal fibrosis involves an inflammatory aneurysm, the surrounding tissue of which entraps the adjacent organs (figure 1).[9]

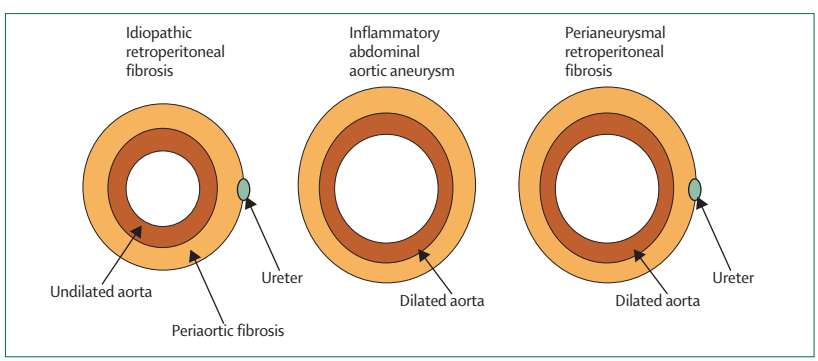

Figure 1: **Schematic representation of idiopathic retroperitoneal fibrosis, inflammatory abdominal aneurysm, and perianeurysmal retroperitoneal fibrosis**

The confusion engendered by these definitions can be overcome by simply distinguishing non-aneurysmal from aneurysmal forms of chronic periaortitis. Chronic periaortitis was thought to result from a local inflammatory reaction to antigens in the atherosclerotic plaques of the abdominal aorta;[8–10] however, findings of studies done during the past 10 years, mainly of the protean systemic manifestations of the disease and its association with other autoimmune disorders, have challenged this theory and lend support instead to the notion of an underlying systemic autoimmune process.[11,12]

Epidemiology and diagnosis

The epidemiological characteristics of retroperitoneal fibrosis are not well established, and only data on the

Search strategy and selection criteria

We searched PubMed without any date limits and EMBASE between 1980 and 2005, mainly using the search terms "retroperitoneal fibrosis" and "periaortitis"; we largely selected articles published in English during the past 10 years without excluding older papers that we considered to be highly relevant to the topics discussed in this Seminar. We also included some review papers and a book chapter, providing insightful overviews on retroperitoneal fibrosis and related diseases.

idiopathic form are available: a report of a study done in Finland[13] noted that idiopathic retroperitoneal fibrosis has an incidence of 0·1 per 100 000 person-years and a prevalence of 1·38 per 100 000 inhabitants in the study area. No clear ethnic predisposition has emerged.

Men are affected twice to three times as often as women; the mean age at presentation is 50–60 years, but reports of the condition in children and older adults are not uncommon.[14] There is no evidence of familial clustering, and only in anecdotal cases has the disease been reported in twins and siblings.[15]

There are no standardised diagnostic criteria for retroperitoneal fibrosis. However, CT or MRI scans, or both, are the modalities of choice for the diagnosis and follow-up of the disease. The finding of a soft-tissue mass, surrounding the abdominal aorta and the iliac arteries and with the possible encasement of neighbouring structures such as ureters and inferior vena cava, usually suggests a diagnosis of retroperitoneal fibrosis. The presence of raised concentrations of acute-phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), can help to substantiate the diagnosis. A histological examination of the retroperitoneal tissue is usually needed when the mass shows atypical localisations—eg, pelvic, peripancreatic—or when other clinical or laboratory findings suggest the presence of underlying malignant disease or infections.[12]

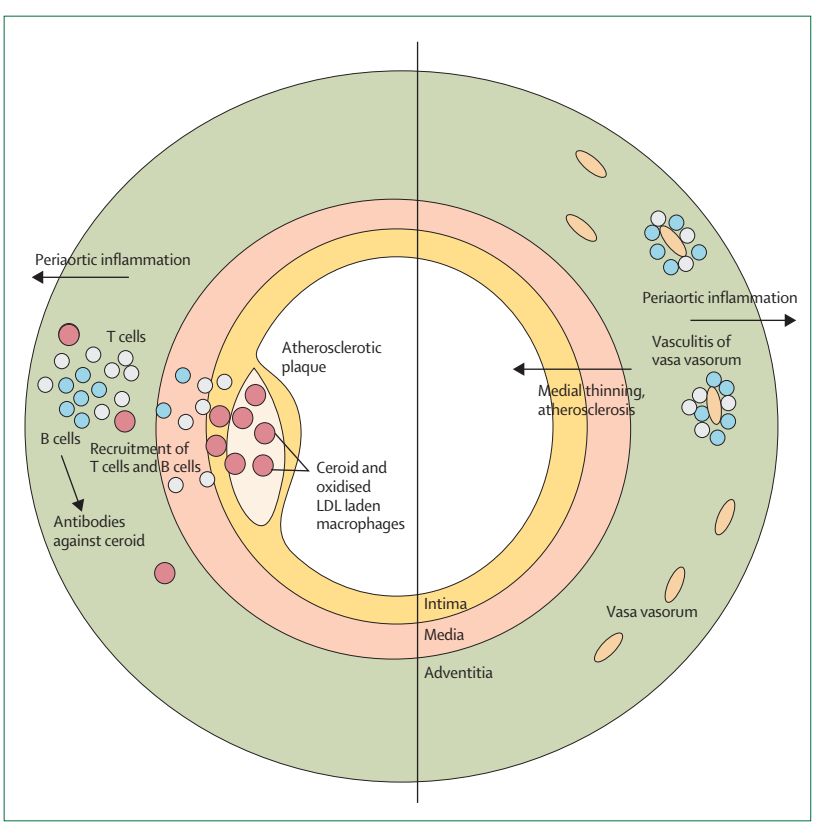

Figure 2: **Two potential pathogenetic mechanisms of chronic periaortitis**
Left of vertical line: hypothesis of autoallergic aortitis presented—atherosclerotic plaque macrophages elaborate antigens, such as oxidised LDL and ceroid, and present them to immunocompetent cells, such as B lymphocytes and T lymphocytes. These are recruited and activated in medial and adventitial aortic layers. B cells produce antibodies to ceroid, which are found in close apposition to extracellular ceroid. The inflammatory reaction then extends into the periaortic retroperitoneum. Right of vertical line: chronic periaortitis is initiated in adventitia, with an inflammatory involvement of vasa vasorum; a vasa vasorum vasculitis is often seen in chronic periaortitis. This inflammatory process can cause weakening of aortic wall with medial thinning and promote atherosclerosis, and also extend into surrounding retroperitoneum.

Pathogenesis

Idiopathic retroperitoneal fibrosis

The pathogenesis of idiopathic retroperitoneal fibrosis is unclear. The leading theory was proposed by Mitchinson and Parums,[8–10] who first defined chronic periaortitis as a range of diseases—including idiopathic retroperitoneal fibrosis—characterised by advanced aortic atherosclerosis, medial thinning, and pronounced adventitial and periaortic inflammation and fibrosis. These investigators suggested that chronic periaortitis could be a consequence of a local inflammatory reaction to oxidised low-density lipoproteins (LDL) and ceroid (a lipoproteic polymer that results from LDL oxidation within plaque macrophages, which can also be artificially obtained by oxidation of LDL), which are often found in the atherosclerotic plaques of the abdominal aorta (figure 2). Mitchinson and Parums proposed that, when the aortic media is thinned or breached, these oxidised lipids are presented by plaque macrophages to immunocompetent cells such as T lymphocytes and B lymphocytes; this action initiates a self-perpetuating inflammatory response that eventually leads to an aortic wall inflammation mainly concentrated in the media and adventitia. This hypothesis is supported by various findings: in patients with chronic periaortitis, IgG are detectable in close apposition to extracellular ceroid;[16] ceroid-laden macrophages are seen in adventitia and in nearby lymph nodes;[17] T lymphocytes and B lymphocytes in the media and adventitia show markers of activation and proliferation,[18] and high levels of gene transcripts for interferon γ, interleukin 1α, interleukin 2 and its receptor, and interleukin 4 are seen in aortic wall sections;[19] and, finally, serum antibodies to oxidised LDL and ceroid are more common in patients with chronic periaortitis than in controls.[10] However, patients with idiopathic retroperitoneal fibrosis often have constitutional symptoms, raised concentrations of acute-phase reactants, positive autoantibodies, and associated autoimmune diseases, involving other organs. These findings suggest that idiopathic retroperitoneal fibrosis is a manifestation of a systemic autoimmune disease rather than an exaggerated local reaction to atherosclerosis.[1,7,11,12,14]

The pathogenesis of idiopathic retroperitoneal fibrosis is probably multifactorial. The genetic component to the disease was thought to be small.[1] However, the results of a case-control study[20] of 35 patients indicate that the disease is significantly associated with HLA-DRB1*03, an allele linked to various autoimmune diseases—namely, type 1

diabetes mellitus, myasthenia gravis, and systemic lupus erythematosus.[21]

The idea of a systemic disease is also supported by similarities to systemic large-vessel vasculitides: in some patients with idiopathic retroperitoneal fibrosis, the vascular inflammatory process is not only localised to the abdominal aorta and the common iliac arteries, but also involves the thoracic aorta and its branches,[22,23] as noted in giant-cell arteritis and Takayasu's arteritis.[24] There is also histological evidence of pronounced aortic adventitial inflammation, which is seen in other large-vessel vasculitis. A frequent finding in idiopathic retroperitoneal fibrosis is represented by a vasculitis of the adventitial aortic vasa vasorum and periaortic retroperitoneal small vessels,[1,11,25,26] which could promote medial thinning and aneurysm formation. Concurrently, its extension into the adjacent retroperitoneum could give rise to the fibro-inflammatory reaction typical of chronic periaortitis (figure 2).[11] Indeed, the autoimmune reaction to plaque antigens could be an epiphenomenon of this immune-mediated process. Thus, that chronic periaortitis arises as a primary aortitis with its inflammatory trigger localised in the adventitia cannot be discounted.

A further potential pathogenetic mechanism might be mediated by antibodies against fibroblasts, which activate fibroblasts from patients with systemic sclerosis in vitro.[27,28] Preliminary evidence shows that they are detectable in about one third of patients with idiopathic retroperitoneal fibrosis and that they are internalised by fibroblasts isolated from the retroperitoneal tissue.[29] Further studies are needed to investigate the functional effects of these antibodies.

Over the past 5 years, the analysis of retroperitoneal biopsies from patients with idiopathic retroperitoneal fibrosis has indicated the presence of IgG4-bearing plasma cells, which are involved in the pathogenesis of sclerosing pancreatitis, a disorder sometimes associated with idiopathic retroperitoneal fibrosis.[30] Furthermore, several infiltrating B cells show clonal or oligoclonal immunoglobulin heavy chain rearrangement.[26] These findings raise the question of whether a primary B-cell disorder might contribute to the pathogenesis of the disease.

Finally, environmental factors might play a part. Occupational exposure to asbestos, for example, significantly increases the risk of developing idiopathic retroperitoneal fibrosis.[13]

Secondary retroperitoneal fibrosis

Secondary retroperitoneal fibrosis is caused by a broad range of factors (table)[1,2,7,31–48] and has many potential pathogenetic mechanisms. The most common cause is use of particular drugs, which mainly include derivatives of ergot alkaloids—eg, methysergide, ergotamine[2]—and dopamine agonists—eg, pergolide, methyldopa;[31,49] β blockers,[50] hydralazine,[32] and analgesics—eg, aspirin, phenacetin[33]—are also associated with retroperitoneal fibrosis, but their causative role is controversial. Methysergide and the other ergot derivatives can cause fibrotic reactions that affect not only the retroperitoneum, but also the pericardium, the pleura, and the lungs.[34] Their mechanisms of action are unknown, though they are probably mediated by serotonin.[7]

In most cases secondary to malignant disease, retroperitoneal fibrosis results from an exuberant desmoplastic response to retroperitoneal metastases—eg, carcinoma of the prostate, breast, colon—or to the retroperitoneal primary tumour—eg, Hodgkin's and non-Hodgkin lymphomas, various types of sarcomas.[7,36] Carcinoids may induce retroperitoneal fibrosis without metastasising to the retroperitoneum, probably through a serotonin-mediated mechanism[35] or by the release of profibrogenic growth factors such as platelet-derived growth factor, insulin-like growth factors, epidermal growth factor, and the family of transforming growth factors α and β.[51]

When secondary to infections, retroperitoneal fibrosis is usually caused by the local spread of a contiguous infectious focus—eg, spinal or paraspinal abscesses in patients with tuberculosis.[38] Radiotherapy can also cause retroperitoneal fibrosis because of the sclerosing effects of radiation; in such instances, retroperitoneal fibrosis is usually limited to the radiation field.[40] Other, uncommon, causes of secondary retroperitoneal fibrosis include trauma, major abdominal surgery, and proliferative disorders, such as Erdheim-Chester disease—a rare form of non-Langerhans cell histiocytosis—and other histiocytoses.[37,42–46]

Pathology

The typical macroscopic appearance of idiopathic retroperitoneal fibrosis is that of a white, hard retroperitoneal plaque of varying thickness, which surrounds the abdominal aorta, the iliac vessels, and, in most instances, the inferior vena cava and the ureters. The plaque usually develops between the origin of the renal arteries and the pelvic brim, although presacral extension is not uncommon; only in rare cases does it extend anteriorly to the mesenteric root or posteriorly to the spinal cord.[1,7,52]

	Examples
Drugs[2,7,31–34]	Methysergide, pergolide, bromocriptine, ergotamine, methyldopa, hydralazine, analgesics, β blockers
Malignant diseases[1,2,7,35–37]	Carcinoid, Hodgkin's and non-Hodgkin's lymphomas, sarcomas, carcinomas of the colon, prostate, breast, stomach
Infections[38,39]	Tuberculosis, histoplasmosis, actinomycosis
Radiotherapy[37,40,41]	Testicular seminoma, colon carcinoma, pancreatic carcinoma
Surgery[42–44]	Lymphadenectomy, colectomy, hysterectomy, aortic aneurysmectomy
Others[45–48]	Histiocytoses, Erdheim-Chester disease, amyloidosis, trauma, barium enema

Table: **Major causes of secondary retroperitoneal fibrosis**

In some instances, idiopathic retroperitoneal fibrosis shows atypical localisations, which might be periduodenal, peripancreatic, pelvic, periureteral, or close to the renal hilum, and thus not characterised by aortic involvement. In these atypical forms, the plaque appears as a poorly circumscribed retroperitoneal mass; this appearance makes the differential diagnosis more challenging and requires histological assessment.[7,53]

The microscopic appearance of idiopathic retroperitoneal fibrosis is commonly described as a sclerotic tissue infiltrated by a mixture of mononuclear cells, but the proportion of these two components varies with disease stage. In the early stage, the tissue is often oedematous and highly vascular, and there is active chronic inflammation with large numbers of mononuclear cells within fibroblasts and collagen bundles.[1,7,52] In the late stages, histology shows pronounced sclerosis and scattered calcifications.

The inflammatory infiltrate consists of lymphocytes (CD 20+ B cells usually outnumber T cells, which are mainly CD4+),[11] macrophages, plasma cells, and eosinophils; neutrophils are absent. The infiltrate can be both diffuse and arranged in a nodular, perivascular pattern (figure 3); in some instances, transmural infiltration and fibrinoid necrosis of small and medium-sized retroperitoneal vessels is seen.[1,11,52] The fibrous tissue often has a perivascular or perineural disposition. Granulomas are uncommon. Several spindle-shaped, fibroblast-like cells are present (figure 3), and some of them have immunohistochemical characteristics of tissue macrophages.[54]

The aortic wall also undergoes changes, which include atherosclerotic degeneration of the intima, medial thinning, and pronounced adventitial inflammation. The inflammatory infiltrate is similar to the retroperitoneal one, its pattern diffuse or arranged in nodular aggregates; these are often centred on adventitial vasa vasorum, which can show necrotising vasculitis.[11,23] Aortic wall inflammation has been shown in the thoracic aorta, even in the absence of periaortic fibrosis; this finding lends support to the notion that an aortitis can precede idiopathic retroperitoneal fibrosis.[23]

The macroscopic and the microscopic appearance of most secondary forms of disease is identical to that of idiopathic disease.[7] However, when secondary to malignant disease, retroperitoneal fibrosis is usually more irregularly shaped and atypically localised than in idiopathic disease. Furthermore, a careful microscopic examination generally reveals neoplastic cells interspersed within the abundant fibrous tissue; invasion and disruption of neighbouring muscle and

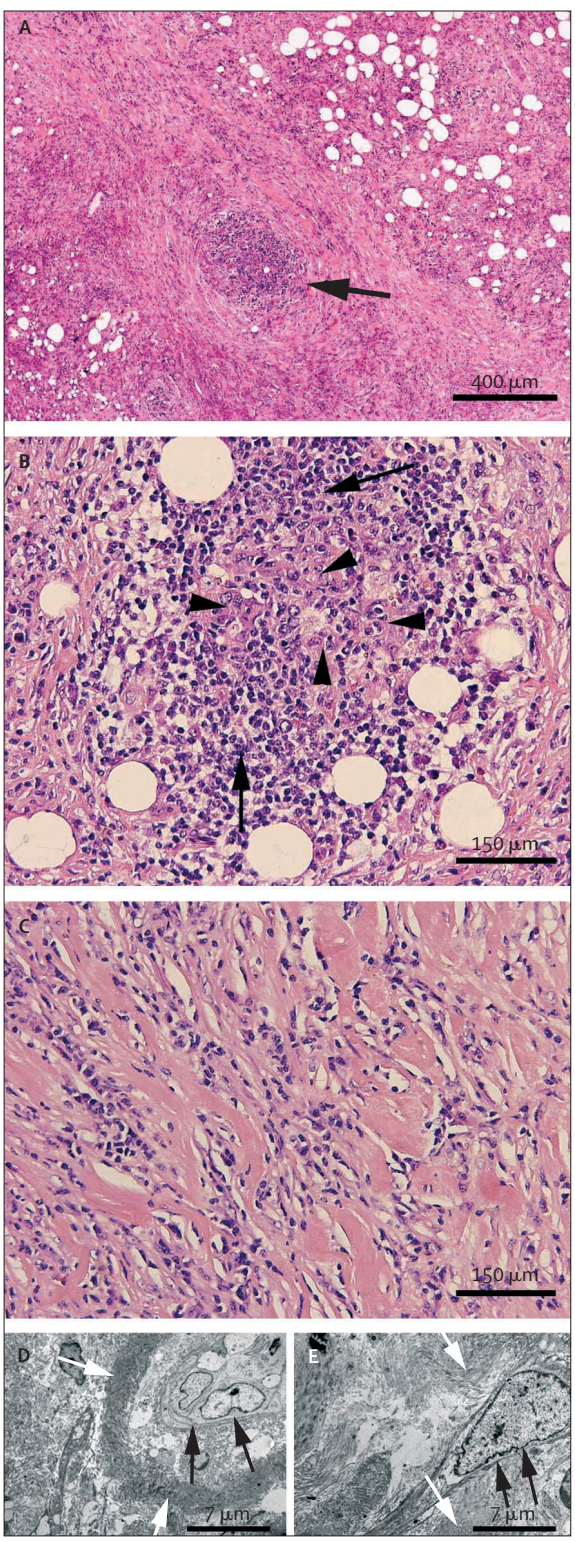

Figure 3: **Microscopic appearance of idiopathic retroperitoneal fibrosis**
Tissues A–C stained with haematoxylin an eosin. A=sclerotic tissue with chronic inflammatory infiltrate; pattern is both diffuse and nodular (arrow). B=perivascular inflammatory aggregate mainly consisting of mononuclear cells and scattered eosinophils (arrowheads=small retroperitoneal vessels; arrows=mononuclear cells). C=diffuse mononuclear cell inflammatory infiltrate interspersed within thick and abundant collagen bundles. D and E=electron micrograph of idiopathic retroperitoneal fibrosis: in D collagen fibres (white arrows) form a band around small retroperitoneal vessel (black arrows); in E spindle-shaped fibroblast (black arrows) surrounded by dense collagen fibres (white arrows).

Panel 1: Main presenting clinical signs and symptoms of idiopathic retroperitoneal fibrosis

- Pain—eg, abdominal, flank, back
- Constitutional symptoms—eg, fatigue, anorexia, weight loss, fever
- Hydrocoele, varicocoele, or testicular pain
- Deep vein thrombosis
- Polyuria or frequency, or both
- Claudication
- Leg oedema
- Constipation
- Oliguria
- Dysuria

bone structures is not uncommon in such secondary disease.[7]

In lymphomas, the inflammatory infiltrate can be monoclonal.[37] The presence of granulomas can suggest an underlying infection—eg, tuberculosis. Haemosiderin deposits usually indicate haemorrhage, which can in turn be the result of trauma. In radiotherapy-induced retroperitoneal fibrosis, the tissue is mainly sclerotic, with only small amounts of inflammatory cells.[40]

Clinical manifestations

The clinical manifestations of idiopathic and secondary retroperitoneal fibrosis often overlap, thus they are not useful in the differential diagnosis between the two disease groups. The clinical signs and symptoms that herald the onset of retroperitoneal fibrosis are non-specific; however, patients usually report two types of manifestations: localised (likely due to the presence of the retroperitoneal mass and its mechanic or compressive effects) and systemic (possible expression of the inflammatory nature of the disease).

Localised symptoms include side, back, or abdominal pain, which is the commonest clinical manifestation (panel 1).[6,11,12,55,56] The pain is often described as dull, constant, and not exacerbated by movement or palpation. However, if the ureter is involved, the pain can be more colic-like. Lower extremity oedema—probably related to extrinsic compression of retroperitoneal lymphatics and veins—and deep vein thrombosis can also arise.[7] Deep vein thrombosis is sometimes a late complication of retroperitoneal fibrosis, arising as a consequence of chronic venous compression or obstruction. Scrotal swelling, varicocoele, or hydrocoele are frequent, and probably result from involvement of the gonadal vessels. Constipation is not uncommon, whereas small bowel obstruction due to direct involvement of the duodenum is rare.[57] Haematuria, polyuria, and urinary infections are sometimes reported, and patients with advanced bilateral ureteral obstruction can develop oligoanuria and symptoms related to uraemia.[1,6] Claudication and intestinal ischaemia are less common clinical manifestations.[50]

In most patients, the localised symptoms are preceded by or coexist with systemic or constitutional symptoms, which include fatigue, low-grade fever, nausea, anorexia, weight loss, and myalgias.[11] These manifestations can be insidious and of varying duration.

Physical examination is usually inconclusive: abdominal or lumbar tenderness and, in some instances, a palpable and tender abdominal mass might be present. A periumbilical bruit might be heard, particularly when the aorta is dilated.

Because of the non-specific nature of the presenting clinical manifestations and the paucity of physical findings, there is often a considerable delay between onset of symptoms and diagnosis, which leads to the late complications of advanced retroperitoneal fibrosis; among these, ureteral obstruction with secondary acute or chronic renal failure is the most common and severe. Ureteral involvement is reported in 80–100% of cases.[6,11] At presentation, such involvement is often bilateral, but in patients with an apparently unilateral obstruction contralateral disease can develop even within a short period. Some patients also present with non-functioning kidneys, probably caused by long-lasting hydronephrosis.[6]

Laboratory findings

The results of routine laboratory tests are consistent with inflammatory disease: concentrations of acute-phase reactants, such as ESR and CRP, are high in 80–100% of patients.[11,56,58] These laboratory tests are often used to monitor the clinical course of the disease,[56] though they do not always reliably mirror disease activity.[59] Azotemia usually depends on the extent of ureteral obstruction. Mild-to-moderate anaemia is usually noted, to which both chronic inflammation and—when present—renal insufficiency can contribute. Leucocytosis, eosinophilia, proteinuria, and microscopic haematuria are less common.[1] The above laboratory test results can arise in idiopathic and secondary forms of retroperitoneal fibrosis.

Of the tests for autoimmune disease, positive anti-nuclear antibodies are the most frequent, and are detected in as many as 60% of patients with idiopathic retroperitoneal fibrosis.[11] Rheumatoid factor, and antibodies against smooth muscle, double stranded DNA, extractable nuclear antigen, and neutrophil cytoplasm are also sometimes positive. In most instances, titres of these antibodies are low and their positivity can be non-specific, but in some patients they suggest the presence of an associated connective tissue disease or vasculitic syndrome.[11,50,60] The presence of antibodies against thyroid microsome and thyroglobulin usually indicates autoimmune thyroiditis, probably the most frequent autoimmune disease associated with retroperitoneal fibrosis.[11] Although the real incidence of autoantibodies has not been well established and their

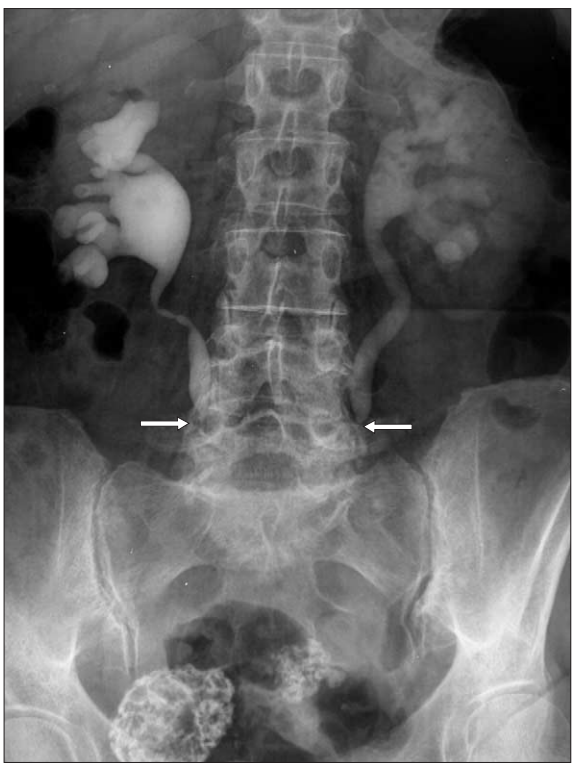

Figure 4: **Intravenous urography in patient with idiopathic retroperitoneal fibrosis**
Scan shows classic triad of medial deviation and extrinsic compression (arrows) of ureters and hydroureteronephrosis.

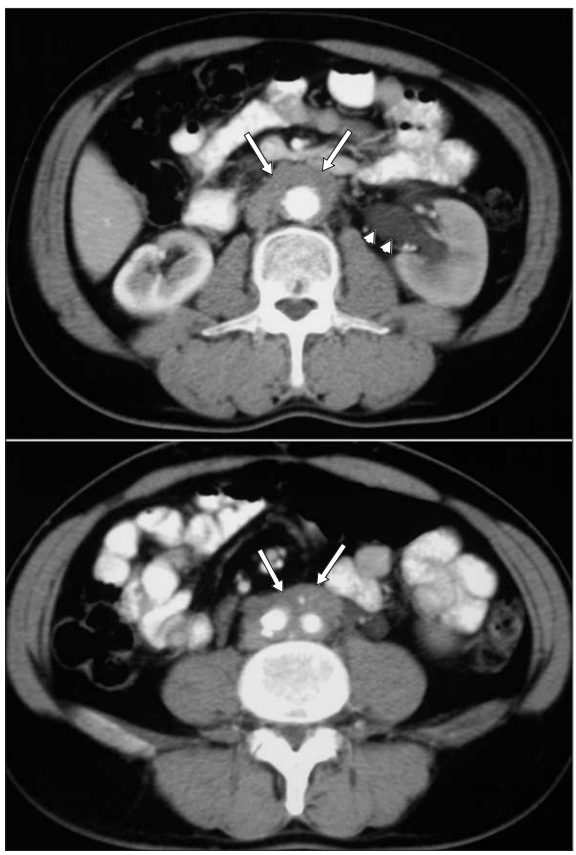

Figure 5: **Abdominal CT scan in patient with idiopathic retroperitoneal fibrosis**
Scans show soft tissue mass, surrounding abdominal aorta (arrows, upper panel) and common iliac arteries (arrows, lower panel) with associated left ureterohydronephrosis (arrowheads, upper panel).

clinical significance is still uncertain, they are useful in screening for the autoimmune disorders associated with retroperitoneal fibrosis.

There are no laboratory tests that can identify the secondary forms of retroperitoneal fibrosis only; however, in cases secondary to certain malignant diseases, particular abnormalities—eg, high concentrations of neoplastic markers, hypercalcaemia, positive faecal blood test—are present.

Imaging

Imaging studies are essential in the diagnosis and management of retroperitoneal fibrosis, and can sometimes help to differentiate between idiopathic and secondary disease.

Sonography should be done as a first-line study, especially when an azotemic patient is being assessed; on ultrasound, idiopathic retroperitoneal fibrosis appears as a hypoechoic or isoechoic mass, which can involve the ureters and, thus, cause unilateral or bilateral hydronephrosis.

Intravenous urography usually reveals the triad of medial deviation, extrinsic compression of the ureters, and hydronephrosis (figure 4).[53] However, these aspects can be caused by ureteral tumours, inflammatory processes, and adenopathy, as well as by retroperitoneal fibrosis. Furthermore, medial ureteral placement is seen in up to 20% of healthy individuals.[61] CT and MRI are the most reliable imaging modalities for the diagnosis of idiopathic retroperitoneal fibrosis. On unenhanced CT, idiopathic retroperitoneal fibrosis usually appears as a homogeneous plaque, isodense with muscle, surrounding the lower abdominal aorta and the iliac arteries, and often enveloping the ureters and the inferior vena cava (figure 5).[7,53] Unlike the idiopathic form, most retroperitoneal fibrosis secondary to malignant diseases tend to displace the aorta anteriorly and the ureters laterally. Administration of contrast medium improves visibility in the early, inflammatory stages of idiopathic retroperitoneal fibrosis, but not in later stages. However, the extent to which contrast is enhanced cannot be used reliably to assess the metabolic activity of idiopathic retroperitoneal fibrosis.

MRI allows the avoidance of nephrotoxic contrast medium and provides a better definition against the surrounding tissues, mainly when fat-saturation images are used. Idiopathic retroperitoneal fibrosis is hypointense in T1-weighted images; in T2-weighted

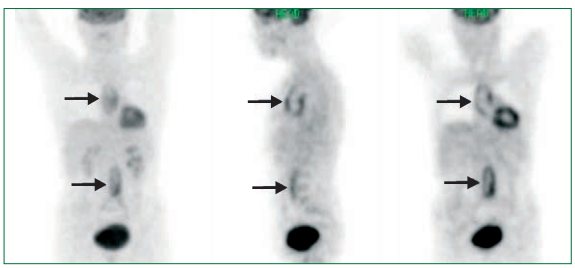

Figure 6: **Whole-body ^{18}FDG-PET in patient with idiopathic retroperitoneal and mediastinal fibrosis**
Scans show pronounced uptake of ^{18}F-fluorodeoxyglucose in thoracic and abdominal aorta (arrows; left panel=tridimensional view, central panel=sagittal view, right panel=coronal view).

images its intensity is high in the early or active stages of disease because of tissue oedema and hypercellularity, and low in the late stages.[7,53] The presence of an inhomogeneous signal on T2-weighted images suggests malignant retroperitoneal fibrosis.[62]

Fluorodeoxyglucose-positron emission tomography (FDG-PET), a functional imaging modality well established in oncology, is increasingly used in the assessment of various inflammatory diseases—namely, large vessel vasculitis.[63] Although FDG-PET is not useful for the diagnosis of retroperitoneal fibrosis, because of its low specificity, it can be considered a reliable means of assessing the metabolic activity of the retroperitoneal mass.[59] FDG-PET also allows whole-body imaging. As such, it can reveal other diseased sites, such as those seen in multifocal fibrosclerosis, and detect occult neoplastic or infectious processes to which retroperitoneal fibrosis can be secondary or associated.[35,64] Finally, in idiopathic retroperitoneal fibrosis, FDG-PET can be used to assess the full extent of vascular inflammatory involvement (figure 6).[22]

Associated autoimmune diseases

Patients with idiopathic retroperitoneal fibrosis often have mild manifestations of an autoimmune disease—eg, presence of autoantibodies and raised concentrations of acute-phase reactants. In others, their disease actually develops in the setting of well defined systemic autoimmune disorders—eg, systemic lupus erythematosus, vasculitic syndromes[60,65]—or associates with the so-called organ-specific autoimmune diseases—eg, Hashimoto's thyroiditis, sclerosing cholangitis.[11] The most important associations between retroperitoneal fibrosis and autoimmune diseases are listed in panel 2.[11,12,14,30,44,50,52,60,64–79] Although the onset of the associated diseases usually coincides with that of retroperitoneal fibrosis, in several instances onset can be metachronous.[68,70]

Mutlifocal fibrosclerosis is a complex syndrome characterised by a fibro-inflammatory involvement of different organs and structures. Retroperitoneal fibrosis, mediastinal fibrosis, Riedel's thyroiditis, sclerosing cholangitis, and orbital pseudotumour are part of this disease range,[64,74,75] and most have an autoimmune origin; their histopathological characteristics overlap, but the pathogenetic mechanisms that link these conditions are unknown.

***Panel 2*: Main associations between retroperitoneal fibrosis and autoimmune or inflammatory diseases**

Autoimmune thyroid disease
Hashimoto's thyroiditis[11,12]
Riedel's thyroiditis[52,64–66]
Graves' disease[66]

Small and medium-sized vessel vasculitis
Wegener's granumolatosis[67,68]
Polyarteritis nodosa[44]
Microscopic polyangiitis[60]
Hepatitis C virus-related cryoglobulinaemia[69]

Ankylosing spondylitis[70,71]

Systemic lupus erythematosus[14,50,65]

Rheumatoid arthritis[11,14,72]

Glomerulonephritis
ANCA-positive rapidly progressive glomerulonephritis[11,60]
Membranous nephropathy[73]

Sclerosing cholangitis[74,75]

Primary biliary cirrhosis[76,77]

Sclerosing pancreatitis[30,78]

Uveitis[79]

ANCA: anti-neutrophil cytoplasmic antibodies.

The frequency of the association between retroperitoneal fibrosis and other autoimmune diseases is unknown, mainly because the published reports are limited to single cases or small case series.[11,68–70] However, we think that these associations are probably underestimated and that doctors should always approach retroperitoneal fibrosis in the setting of a potentially systemic disease.

Differential diagnoses

In addition to the above discussed idiopathic and secondary forms of retroperitoneal fibrosis, the retroperitoneum can also be affected by another group of fibrosing disorders, which, unlike retroperitoneal fibrosis, are primarily characterised by a prominent fibroblast proliferation that may or may not be associated with an inflammatory component.[80]

Retroperitoneal fibromatosis is histologically characterised by a uniform proliferation of fibroblasts, arranged in interlacing bundles. It probably originates from the connective tissue of the muscles and their overlying fascia; it has an infiltrative growth, often recurs after surgical excision, but does not metastasise.[81] In

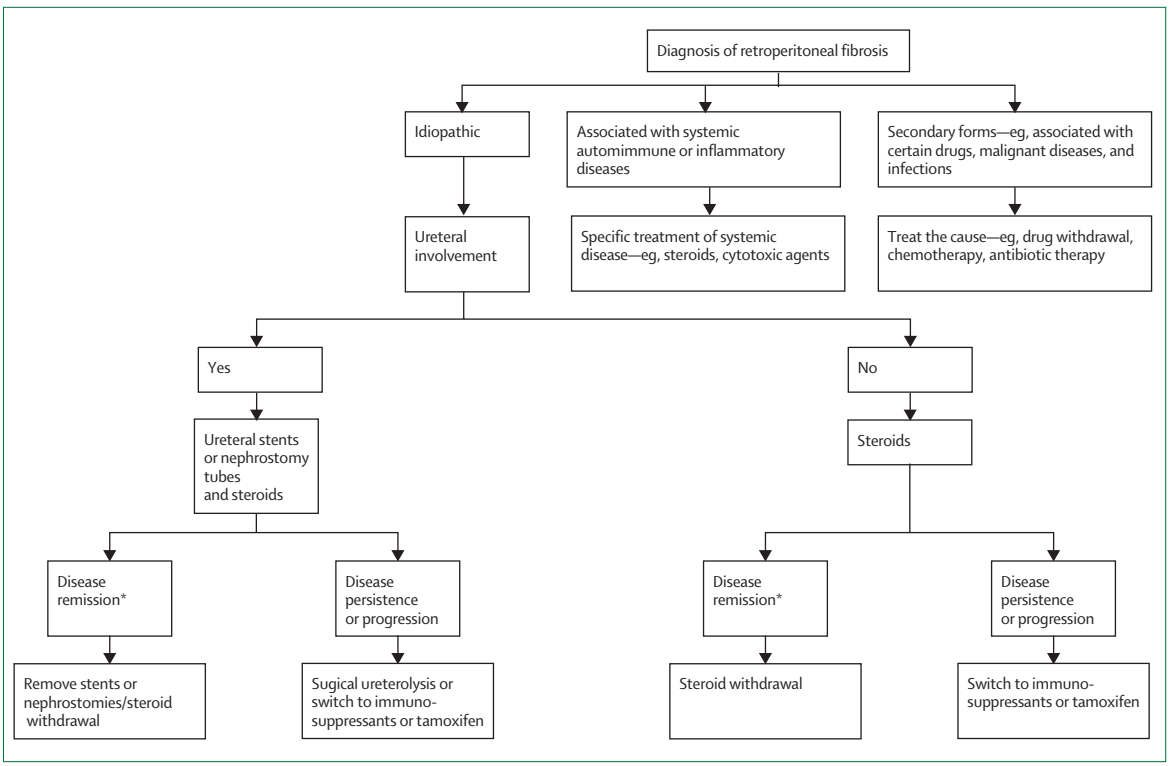

***Figure 7*: Proposed algorithm for the management of retroperitoneal fibrosis**
*Defined on basis of clinical findings (remission of symptoms), normalisation of concentrations of acute-phase reactant, CT or MRI evidence of regression of retroperitoneal mass, or resolution of obstructive complications.

most cases, retroperitoneal fibromatosis is associated with Gardner's syndrome, a variant of familial adenomatous polyposis.

Inflammatory myofibroblastic tumour (inflammatory pseudotumour) mainly affects children; when localised to the retroperitoneum, its appearance is that of a huge mass with infiltrative borders. It is histologically characterised by myofibroblast proliferation often associated with myxoid and inflammatory areas. It also has potential for local recurrence, but distant metastases are rare.[82]

Inflammatory malignant fibrous histiocytoma and inflammatory fibrosarcoma show increased cellularity and vascularity, nuclear atypism, and mitoses. In the case of inflammatory malignant fibrous histiocytoma, the atypical cells can be rare and require careful inspection of the inflammatory milieu.[80]

Treatment and course

The aims of treatment of idiopathic retroperitoneal fibrosis are multiple: to stop the progression of the fibro-inflammatory reaction, 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.

Corticosteroids are the most used drugs. They suppress the synthesis of most of the cytokines involved in the acute-phase reaction, reduce the inflammatory component, and inhibit collagen synthesis and maturation.[83] Corticosteroids achieve prompt improvement of symptoms, and often lead to a reduction in size of the retroperitoneal mass and resolution of obstructive complications.[1,6,12,56] Unfortunately, however, some patients are resistant to steroids. Furthermore, the optimum dose and duration of steroid therapy are not well established, because most published studies involve only small case series and are retrospective and uncontrolled. An initial daily dose of prednisone 40–60 mg is usually administered and, to prevent relapses, treatment courses of up to 2 years are sometimes recommended.[56,84] Immunosuppressants are also frequently used. Among these, cyclophosphamide and azathioprine can induce stable disease remissions and regression of the mass, although they can be very toxic.[58,84,85] The successful use of methotrexate,[86] cyclosporin,[87] and mycophenolate mofetil[88] has also been anecdotically reported. No randomised studies have so far compared the effectiveness and toxicity of immunosuppressive drugs with steroids. Finally, tamoxifen has been used successfully in several cases,[89–91] but its real effectiveness is uncertain because of the lack of larger studies. Therefore, we believe that, in clinical practice, immunosuppressants and tamoxifen should be used as second-line therapy in steroid-refractory patients.

Surgery is usually done to relieve ureteral obstruction; open ureterolysis with intraperitoneal transposition and omental wrapping of the ureters is judged the best surgical approach.[1,6,7] In small case series, laparoscopic ureterolysis was also successful.[92] Surgery allows multiple retroperitoneal biopsies to be done. However, surgical treatment addresses only the issue of ureteral obstruction;[6,56] it does not prevent disease progression and recurrence, and has no effect on systemic manifestations.[6] As such, medical therapy is usually recommended in idiopathic retroperitoneal fibrosis.

Surgery can be preceded or followed by steroid treatment. However, when the imaging, clinical, and laboratory findings are consistent with a diagnosis of idiopathic retroperitoneal fibrosis, a conservative approach with temporary placement of ureteral stents or nephrostomy tubes followed by medical therapy is recommended,[2,56] with surgery reserved for refractory cases (figure 7).

When retroperitoneal fibrosis develops around an aneurysmal aorta—ie, inflammatory abdominal aortic aneurysm, perianeurysmal retroperitoneal fibrosis—different treatment options are available. Surgery is usually done when the aortic diameter exceeds 4·5–5 cm;[55,93] open repair is the traditional method,[94] although endovascular prosthesis placement also works.[95] No clear differences between inflammatory and non-inflammatory abdominal aortic aneurysms are apparent in terms of risk of rupture, post-operative complications, and long-term outcome.[96–98] Resolution of periaortic fibrosis after surgery still represents a controversial issue: although almost complete regression of the perianeurysmal mantle has been described in many cases,[97] findings of several studies indicate that it frequently persists or even progresses after surgery or endovascular treatment.[94,99] This uncertainty raises the question of whether a post-operative course of steroids would be beneficial in these patients.[55] Steroids alone might be the treatment of choice when there are no surgical indications for aneurysm repair, to improve the symptoms and to reduce the bulk of the periaortic mass and its associated obstructive complications.[12,55]

After the initiation of therapy, patients with retroperitoneal fibrosis are usually monitored by subjective symptoms and regular assessment of ESR and CRP concentrations. Sonography is a non-invasive modality useful in the follow-up of ureteral obstruction. CT and MRI are reliable in the assessment of the changes in size of the retroperitoneal tissue.[1]

The outlook for patients is usually considered to be good,[1] but severe complications such as chronic renal failure, requiring renal replacement therapy, can arise. No predictors of response to therapy, corticosteroid requirement, or disease relapse have been identified. The relapse rate after discontinuation of therapy is difficult to establish, mainly because most of the published studies do not have an adequate follow-up. However, ureteral obstruction is estimated to recur in up to half of patients who undergo surgery alone and in about 10% of those also treated with steroids.[6,58]

In some instances, despite effective medical treatment, a residual retroperitoneal tissue is identified. However, a study[100] with FDG-PET has shown that, in most patients with stable clinical condition and significantly decreased concentrations of acute-phase reactants, these residual masses have very little or absent FDG accumulation, thus suggesting the presence of a sclerotic, inactive, residual disease, probably unresponsive to further treatment.

Treatment of the secondary forms of retroperitoneal fibrosis requires, when possible, an approach based on cause. In drug-induced retroperitoneal fibrosis, drug withdrawal generally results in resolution of the disease.[31,101,102] However, steroid treatment is sometimes also needed.[31] In retroperitoneal fibrosis secondary to infections, steroids are usually contraindicated whereas specific antimicrobial therapy is recommended. When retroperitoneal fibrosis is secondary to malignant disease or other proliferative disorders, such as histiocytosis, the therapeutic approach varies from patient to patient. Thus, chemotherapy or radiotherapy, or both, might be indicated, according to the type of underlying neoplasm.[103] Anecdotal cases of retroperitoneal fibrosis related to carcinoids have also shown great response to corticosteroids.[35]

Unfortunately, various types of secondary retroperitoneal fibrosis, such as those caused by untreatable cancer, trauma, major surgery, and radiotherapy, have no clear indications for systemic medical treatment and might only draw benefit from palliative surgical approaches, aimed at relieving the obstructive complications, or from the placement of ureteral stents and nephrostomies.

Future perspectives

Retroperitoneal fibrosis is a largely obscure and multifaceted disease. Diagnostic criteria are needed, as are new methods for the differential diagnosis between the idiopathic and secondary forms of the disease. Studies on the complex pathogenesis of the idiopathic disease could elucidate the role of immune-mediated mechanisms and provide new clues for treatment. Finally, the optimum dose and duration of steroid therapy and the role of other potentially useful agents, such as immunosuppressants and tamoxifen, need to be investigated.

Conflict of interest statement

We declare that we have no conflict of interest.

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