

Idiopathic Retroperitoneal Fibrosis

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ABSTRACT

Idiopathic retroperitoneal fibrosis (RPF), reviewed herein, is a rare fibro-inflammatory disease that develops around the abdominal aorta and the iliac arteries, and spreads into the adjacent retroperitoneum, where it frequently causes ureteral obstruction and renal failure. The clinical phenotype of RPF is complex, because it can be associated with fibro-inflammatory disorders involving other organs, is considered part of the spectrum of IgG4-related disease, and often arises in patients with other autoimmune conditions. Obstructive uropathy is the most common complication, although other types of renal involvement may occur, including stenosis of the renal arteries and veins, renal atrophy, and different types of associated GN. Environmental and genetic factors contribute to disease susceptibility, whereas the immunopathogenesis of RPF is mediated by different immune cell types that eventually promote fibroblast activation. The diagnosis is made on the basis of computed tomography or magnetic resonance imaging, and positron emission tomography is a useful tool in disease staging and follow-up. Treatment of idiopathic RPF aims at relieving ureteral obstruction and inducing disease regression, and includes the use of glucocorticoids, combined or not with other traditional immunosuppressants. However, biologic therapies such as the B cell-depleting agent rituximab are emerging as potentially efficacious agents in difficult-to-treat cases.

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The term retroperitoneal fibrosis (RPF) is used to describe a condition of variable etiology characterized by a highly fibrotic retroperitoneal mass that frequently causes ureteral obstruction. RPF encompasses the idiopathic form (>75% of the cases) and secondary forms, which include cases secondary to malignancies, infections, drugs, radiotherapy, or other conditions.^{1,2}

Idiopathic RPF is a rare disease, with an estimated incidence of 0.1–1.3 cases/100,000 persons per year, and a prevalence of 1.4 cases/100,000 inhabitants.^{2,3} The male-to-female ratio is 2:1–3:1, and the mean age at onset ranges between 55 and 60 years.^{4,5} Although RPF has become the most used name for this disease, it does not adequately reflect its pathology or its exact

topography. The disease usually involves the adventitia of the abdominal aorta and the iliac arteries and the surrounding retroperitoneum, and histologically shows a mixture of fibrous tissue and chronic inflammation.⁶ In addition, it also frequently affects the thoracic aorta.⁷ For these reasons, the term “chronic periaortitis,” coined in the 1980s, seems to be more appropriate. Chronic periaortitis also includes inflammatory abdominal aortic aneurysms (without ureteral involvement) and perianeurysmal fibrosis (with ureteral involvement); the two latter conditions are clinically and histologically similar to idiopathic RPF except for aortic aneurysmal dilatation.^{8–10}

During the last decade, the concept of IgG4-related disease (IgG4-RD) has

emerged: IgG4-RD embraces fibro-inflammatory disorders affecting different structures (e.g., pancreas, biliary tract, lymph nodes) and is characterized by lympho-plasmacytic inflammation, irregular and pronounced fibrosis, and infiltration by IgG4⁺ plasma cells. Idiopathic RPF belongs to this disease spectrum.^{11,12} Finally, idiopathic RPF may be associated with systemic (e.g., small-vessel vasculitis, rheumatoid arthritis) and organ-specific (e.g., Hashimoto thyroiditis) autoimmune diseases, which makes the puzzle of its nosology even more complex.¹

PATHOLOGY

Idiopathic RPF is a fibro-inflammatory disease, histologically hallmarked by fibrous tissue and chronic inflammation. The fibrous tissue comprises an extracellular matrix composed of type I collagen fibers organized in thick irregular bundles and often encircling small retroperitoneal vessels (Figure 1). Fibroblasts show signs of activation and transition into myofibroblasts (α -smooth muscle actin expression), and are probably the major source of collagen production.⁶ They rarely show mitoses, although they have been shown to undergo clonal proliferation.¹³

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The inflammatory infiltrate consists of numerous lymphocytes, plasma cells, and macrophages. Neutrophil infiltration is rare, and so are granulomas. The inflammatory cells are interspersed within the collagen bundles (“diffuse” pattern), but are also organized in nodular aggregates, usually around small vessels. Such aggregates have a B cell core surrounded by T cells, which are predominantly CD4⁺. In some cases, these lymphoid follicles have the structure of germinal centers (Figure 1), which reveals ectopic lymphoneogenesis, a process typical of chronic autoimmune diseases.^{6,14} Plasma cells account for a significant proportion of the inflammatory cells, and when the IgG4⁺/total IgG⁺ plasma cell ratio is >40%, RPF is classified as “IgG4-related” if other features such as storiform fibrosis, eosinophil infiltration, and obliterative phlebitis are also present.^{11,15} Mast cells

are also found. They are identified using tryptase immunostaining, which also demonstrates their degranulating state, a finding consistent with their active participation in the fibro-inflammatory reaction.¹⁶

The aforementioned lesions involve not only the periaortic retroperitoneum, but also the aortic wall. In typical cases with periaortic RPF distribution, the fibro-inflammatory reaction mainly involves the aortic adventitia, whereas the other aortic layers may show atherosclerotic changes; this is the basic notion behind the concept of chronic periaortitis, which was initially described as an exaggerated fibro-inflammatory, adventitial, and peri-adventitial reaction to atherosclerotic plaque components.^{9,17,18} Such aortic wall lesions may also occur in the thoracic aorta and its major branches in patients whose periaortitis extends to involve these

vascular territories; thoracic aorta involvement can be seen in both IgG4⁺ and IgG4[−] cases.⁷

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Clinical Signs and Symptoms

Systemic symptoms (*e.g.*, fatigue, anorexia, weight loss), possible expression of an inflammatory status, often herald the disease onset (Table 1). They usually coexist with back, flank, or abdominal pain. Pain is usually dull, does not modify with position, and transiently responds to nonsteroidal anti-inflammatory drugs; in cases of ureteral involvement, it may mimic a ureteral colic. Constipation may be another disease-related manifestation, although it is rarely severe. Other urologic manifestations are frequent: they range from testicular pain, often accompanied by hydrocele and/or varicocele—due to spermatic vein encasement by RPF—to retrograde ejaculation and erectile dysfunction. Other less common manifestations include frequency, hematuria, and dysuria.^{2,4,5,19}

Ureteral and Renal Complications

Ureteral involvement is the most common disease-related complication; the disease usually causes medial ureteral deviation, and frequently obstruction of the pelvic ureteral tract.²⁰ This is why RPF limited to the periaortic space rarely causes ureteral obstruction, whereas RPF with peri-iliac extension frequently does. Ureteral encasement can be unilateral or bilateral, and in the latter case ARF is frequent; in cases with unilateral involvement, contralateral progression can occur weeks to years after the initial presentation.^{4,5} An interesting finding at diagnosis is renal hypoplasia/atrophy (diameter <8.5 cm), at a frequency of 8%–30% (Table 1). Whether this is due to previous ureteral obstruction, renal artery stenosis by RPF, or other causes, is still unclear. Indeed, idiopathic RPF can extend to the renal vascular peduncle;¹⁰ this may cause compression of renal veins (which is often slowly

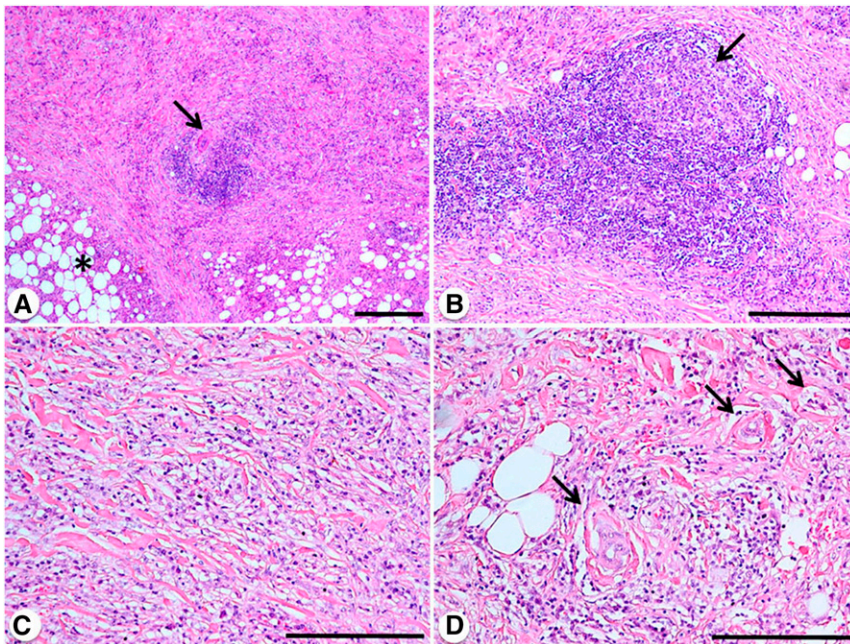


Figure 1. Histopathology of idiopathic RPF. (A) Low-power magnification view of a retroperitoneal biopsy showing abundant and irregular fibrosis replacing normal retroperitoneal soft tissues (asterisk), and an inflammatory infiltrate organized in a lymphoid aggregate that is centered around a small retroperitoneal artery (arrow). (B) A lymphoid nodular aggregate with a clear (germinal) center (arrow) is visible. (C) Diffuse pattern of the inflammatory infiltrate, mainly consisting of lymphocytes and plasma cells that are diffusely interspersed within collagen bundles. (D) These collagen bundles form rinds around small retroperitoneal vessels (arrows). Hematoxylin and eosin (A–D). Original magnification, ×4 in A (bar is 0.5 mm); ×10 in B (bar is 300 μm); ×20 in C and D (bar is 300 μm).

Table 1. Main demographic, clinical and laboratory findings of patients with idiopathic RPF in four different clinical series

	Mayo Clinic, Rochester (n=185) ⁴	Johns Hopkins University, Baltimore (n=48) ¹⁹	A. Schweitzer Hospital, Dordrecht (n=53) ²	University Hospital, Parma (n=210)
Mean age at diagnosis, years	58	54	64	58
Male gender, %	61	54	77	70
Systemic symptoms, % ^a	27	60	92	66
Pain (flank, abdominal), %	38	94	92	81
Testicular manifestations (pain, varicocele, hydrocele), %	13	27	46	51
Constipation, %	12	NA	30	28
Lower extremity edema, %	13	23	8	15
Lower extremity claudication, %	2	NA	11	12
Hydronephrosis, %	57	67	55	72
Unilateral, %	25	21	40	29
Bilateral, %	32	46	15	43
Renal atrophy, %	8	NA	21	30
Impaired renal function, % ^b	42	NA	66	57
Mean ESR, mm/h	32	40	45	63
Mean CRP, mg/L	20.7	NA	23	32
Mean serum creatinine, mg/dL	1.3	NA	1.4	3.9 ^c
Mean Hb, g/dL	12.6	11.6	12.4	12.5
Increased ESR, %	53	NA	74	85
Increased CRP, %	47	NA	62	78

NA, not available; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin. Normal CRP values are <5 mg/L.

The series included in this table were selected essentially on the basis of their sample size and the accuracy of data reporting.

In the first series (Mayo Clinic) data were collected retrospectively, whereas in the remaining series they were collected prospectively. Data included in the Parma series are unpublished.

For testicular manifestations, the percentage was calculated on male patients only.

^aSystemic symptoms include: fatigue, anorexia, weight loss and low-grade fever.

^bImpaired renal function indicates a serum creatinine level >1.2 mg/dL.

^cIn this series, the distribution of serum creatinine was not normal, therefore we also report median (range) serum creatinine levels, which are 1.4 (0.5–23) mg/dL.

progressive and allows the formation of collateral circles),²¹ and renal arteries with resulting reno-vascular hypertension. New-onset hypertension or worsening of preexisting hypertension is found in up to one-third of patients at diagnosis.¹⁹

Vascular Complications

Aneurysmal forms of RPF must be carefully followed for timely repair of the aortic aneurysm; interestingly, both surgical and endovascular repair have been associated with regression of perianeurysmal RPF, although RPF may also develop following endovascular treatment of atherosclerotic aortic aneurysms.²² Idiopathic RPF typically arises around the aorta and iliac arteries, but stenosis of these vessels is quite rare.^{2,4} Conversely, venous compression (mainly of the inferior vena cava) is common, and can cause lower limb edema, to whose pathogenesis lymphatic compression

may contribute. Again, probably due to the slow progression of venous encasement, collateral circles develop, therefore inferior vena cava syndrome, deep vein thrombosis, and pulmonary embolism are uncommon.^{4,19,23}

Other vascular districts may also be involved. The periaortic tissue can extend to the mesenteric and celiac arteries, causing stenosis and ischemic complications resembling mesenteric vasculitis.²⁴ Up to one-third of patients with abdominal RPF also have thoracic aorta involvement, most of them presenting with thoracic aorta aneurysm, the progression of which must also be carefully monitored.⁷

Laboratory Findings

Acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein levels are increased in the majority of patients at presentation and are routinely used to monitor disease

activity. Although high baseline acute-phase reactants are associated with a more symptomatic disease, these parameters poorly predict response to therapy and do not correlate with mass regression.^{25,26} Additionally, relapses commonly occur when acute-phase reactants are still normal.²⁷ Serum IL-6 is also high, reflecting an acute-phase response; its correlation with disease activity or prognosis is unexplored.²⁸ High IgG4 levels have been linked to IgG4-related RPF, but a systematic assessment of IgG4 in idiopathic RPF is lacking. However, the exact proportion of patients with high serum IgG4, as well as the prognostic significance of this biomarker are still unknown. Experimental studies on small cohorts showed that serum chemokines such as chemokine (C-C motif) ligand 11 (CCL11)/eotaxin-1¹⁶ and CCL18²⁹ are increased during active disease; CCL18 correlates with RPF thickness variations after therapy.²⁹

ASSOCIATION WITH AUTOIMMUNE OR FIBRO-INFLAMMATORY DISEASES

One intriguing aspect of idiopathic RPF is its association with autoimmune disorders, which highlights the pathogenic relevance of autoimmune mechanisms. Autoimmune thyroiditis is the most frequently associated autoimmune condition: in a recent case-control study, idiopathic RPF patients had a prevalence of anti-thyroperoxidase antibodies of 24.7% (versus 10.6% in healthy controls) and ultrasound evidence of thyroiditis; after a median follow-up of 45 months, 25% of RPF patients developed hypothyroidism requiring L-thyroxine. Where available, histology

showed typical Hashimoto thyroiditis or its fibrous variant.³⁰ However, cases of Riedel thyroiditis were also described.³¹

Other associations include rheumatoid arthritis,³² ankylosing spondylitis,³³ ANCA-associated vasculitis,^{34–36} systemic lupus erythematosus,³⁷ and psoriasis.³⁸ Idiopathic RPF has also been linked to different types of GN, particularly membranous nephropathy (MN).^{39,40} This association is interesting, because MN is an IgG4-mediated disease;⁴¹ however, target antigens in MN associated with RPF or IgG4-RD probably differ from those (e.g., phospholipase A2 receptor) detected in classic MN.^{39,42–45}

Idiopathic RPF can also be associated with fibro-inflammatory conditions

involving other structures, especially sclerosing pancreato-cholangitis, fibrosing mediastinitis, orbital pseudotumor, and sclerosing sialoadenitis; this multiorgan disorder was once referred to as multifocal fibrosclerosis.⁴⁶ The recognition of a shared histopathologic background between these lesions— with main features being irregular (“storiform”) fibrosis, lymphoplasmacytic infiltrates and abundance of IgG4⁺ plasma cells— provided the rationale for their inclusion in the spectrum of IgG4-RD.⁴⁷ Recent studies have demonstrated that, based on histologic findings (e.g., IgG4⁺ plasma cell infiltration), ≤50% of idiopathic RPF can be histologically classified as “IgG4-related” even when the disease is

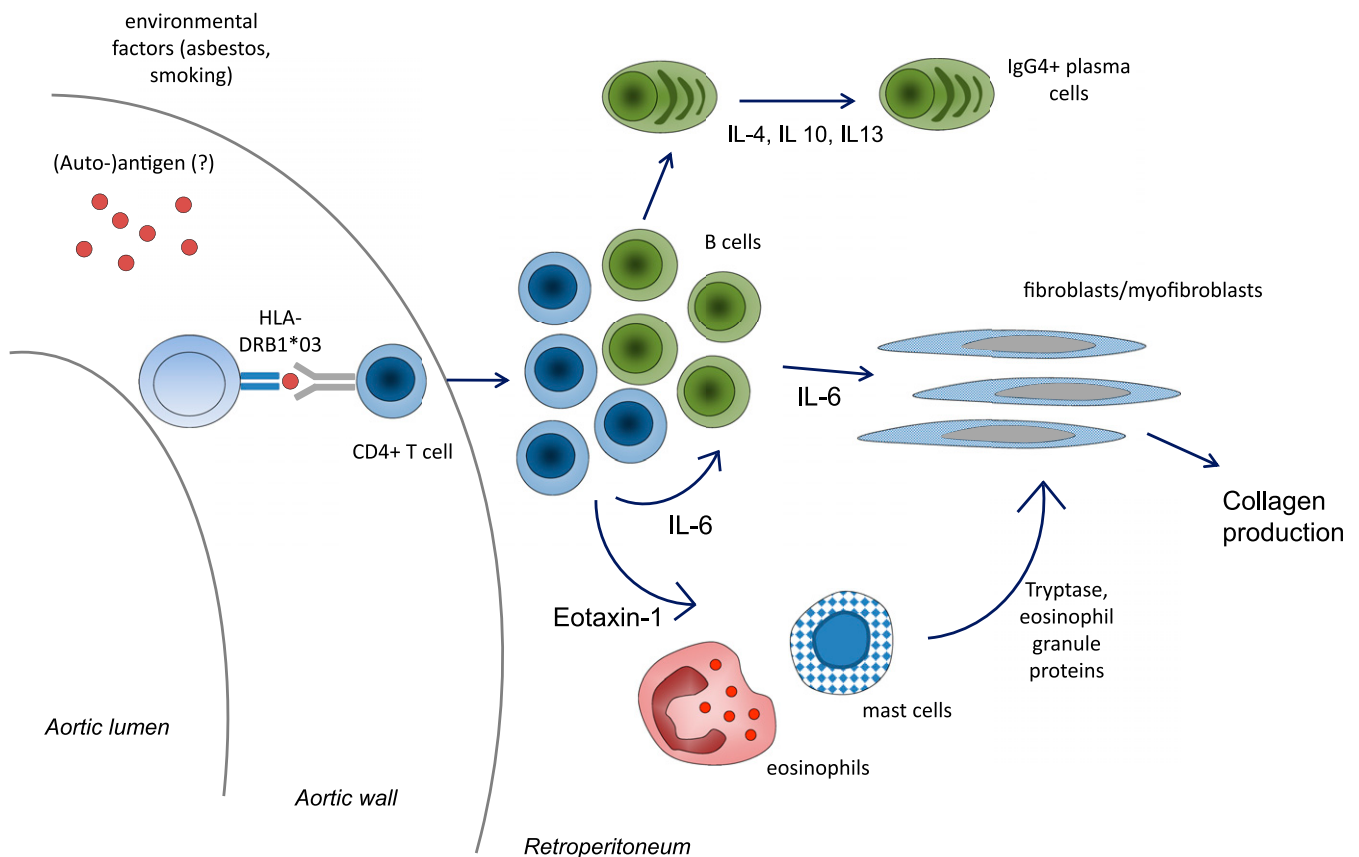


Figure 2. Immunopathogenetic mechanisms of idiopathic RPF. Susceptibility to idiopathic RPF is conferred by exposure to environmental agents (asbestos, smoking) and by genetic factors such as HLA class II alleles (HLA-DRB1*03). The presence of a restricted HLA class II repertoire makes it likely that the disease is antigen-driven, although the triggering antigens are as yet unknown. Antigen-presenting cells present such hypothetical antigens to CD4⁺ cells within the aortic wall or the surrounding retroperitoneum. CD4⁺ T cells expand, secrete IL-6, which is able to activate B cells and fibroblasts. CD4⁺ T cells also secrete Th2 cytokines such as IL-4, IL-10 and IL-13, which drive B-cell expansion and maturation into plasma cells, and may lead to preferential expansion of IgG4-producing plasma cells. Lymphoid cells also secrete eotaxin-1, which drives recruitment of eosinophils and mast cells, whose products are also able to activate fibroblasts. Once activated, fibroblasts mature into myofibroblasts and secrete collagen. This pathogenetic hypothesis and the resulting cartoon have been generated on the basis of the available evidence on the immunopathogenetic mechanisms of the disease. See text for further details.

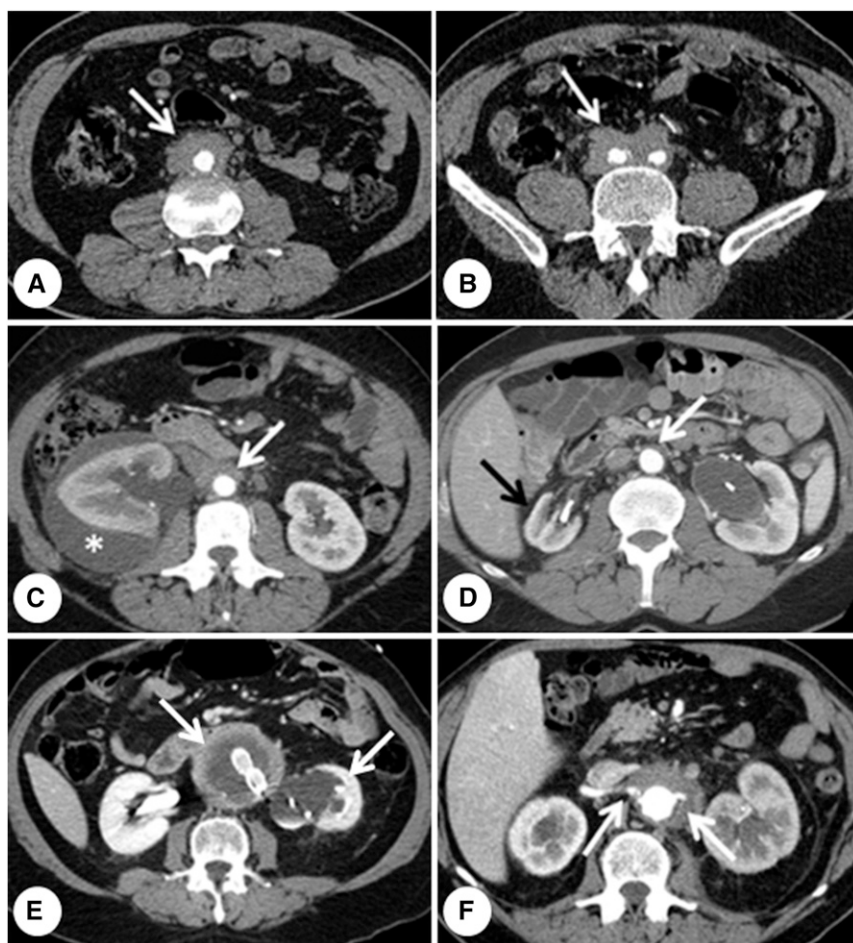


Figure 3. Computed tomography findings in idiopathic RPF. (A, B) Typical idiopathic RPF that develops around the anterior and lateral sides of the abdominal aorta (A, arrow) and both common iliac arteries (B, arrow). (C) A rare complication of idiopathic RPF, that is a perirenal urinoma (asterisk) due to severe right-hand ureteral obstruction; the arrow indicates the periaortic tissue. (D) In a patient with periaortic (white arrow) and peri-iliac (not shown) RPF, marked hypoplasia of the right kidney (black arrow) as well as severe left-hand hydronephrosis. Indwelling ureteral stents can be seen bilaterally in the renal pelvis. (E) Typical case of perianeurysmal RPF, where the periaortic tissue surrounds an aneurysmal aorta (left-hand arrow) and causes hydronephrosis of the left kidney (arrow), which appears atrophic. Endovascular aorto-iliac prosthesis can be seen in the aortic lumen. (F) Periaortic idiopathic RPF encasing the origin of both renal arteries (arrows).

not associated with other IgG4RD lesions;^{11,15} however, systematic analyses of large cohorts are lacking. IgG4-related and -unrelated RPF do not appear to differ clinically, except for a higher frequency of extra-retroperitoneal manifestations in the former group; in particular, they have similar demographic and laboratory characteristics, comparable mass location and thickness, and almost identical rates of ureteral involvement.¹¹ Therefore, it is likely that they represent different ends of the same

disease spectrum. Additionally, how often RPF overlaps with other IgG4-RD manifestations is still unclear.

PATHOGENESIS

Idiopathic RPF, as part of the spectrum of chronic periaortitis, was initially viewed as a localized reaction to antigens contained in the atherosclerotic plaques of the abdominal aorta such as oxidized low-density lipoproteins.⁴⁸ Such

antigens would be presented by plaque macrophages to lymphoid cells residing in the adventitia, where they would elicit a fibro-inflammatory response.^{8,9,17,18} This theory, however, cannot explain the complex clinical spectrum of idiopathic RPF, particularly the associations with autoimmune or fibro-inflammatory diseases involving other organs. Additionally, the disease can develop in patients without atherosclerotic lesions or involve vascular territories spared by atherosclerosis.^{7,10} These findings raised the question whether idiopathic RPF is a manifestation of a systemic condition rather than a localized reaction to atherosclerosis.

The pathogenesis of the disease is multifactorial. Environmental agents play a definite role: an association with asbestos exposure has been postulated, and anecdotal cases of pleural asbestosis in RPF patients have been described.^{3,49} A recent case-control study confirmed the predisposing role of asbestos exposure and also identified smoking as a risk factor. Interestingly, smoking and asbestos had a multiplicative effect on disease risk, with an odds ratio of 12.04 (95% confidence interval, 4.32 to 38.28) in co-exposed subjects.²³ The role of other environmental or infectious agents remains elusive. Genetic determinants also contribute to disease susceptibility. Idiopathic RPF is associated with HLA-DRB1*03, a risk factor for other autoimmune diseases such as lupus erythematosus and type 1 diabetes.⁵⁰ Other genetic associations include the $\Delta 32$ polymorphism of the gene encoding CCR5, a chemokine receptor,⁵¹ and the TTCCAT haplotype of the gene encoding CCL11/eotaxin-1.¹⁶

CD4⁺ T cells are abundant in idiopathic RPF biopsies;⁶ in IgG4-RD lesions they show a T-helper 2 (Th2)-polarization and produce IL-4, IL-5, and IL-13, although regulatory T cells are also found.⁵² In idiopathic RPF, it has been shown that T cells also locally produce IL-6, which can activate B cells and fibroblasts. B lymphocytes account for a high proportion of infiltrating cells and may be precursors of plasma cells; Th2 cytokines may induce the enrichment of

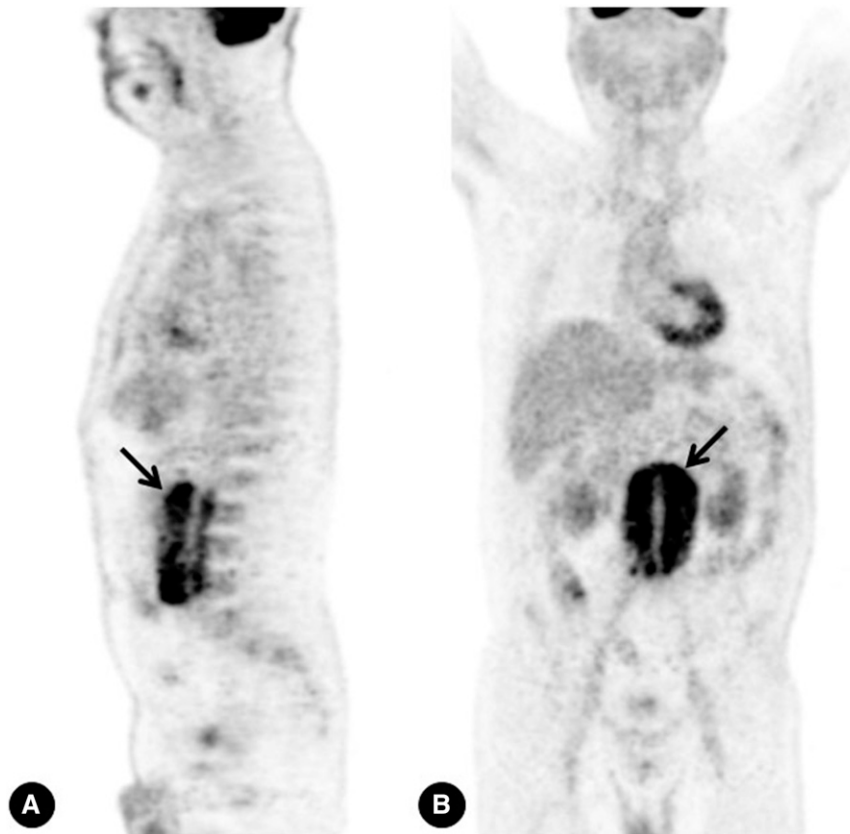


Figure 4. PET findings in idiopathic RPF. ^{18}F -FDG PET scans in a patient with idiopathic RPF show intense accumulation of ^{18}F -FDG around the abdominal aorta (arrows) (A, sagittal view, B, coronal view).

the IgG4⁺ plasma cell subset, although this has not yet been proven in RPF.⁴⁷ The pathogenic importance of the IL-6-mediated axis and of B cells was confirmed *in vivo* by the efficacy of therapies targeting the IL-6 receptor (tocilizumab)²⁸ and the B cell marker CD20 (rituximab),⁵³ but it must be acknowledged that these data are limited to small case series. Th2 responses are often characterized by tissue eosinophilia, which is also observed in idiopathic RPF and IgG4-RD. Tissue recruitment of eosinophils can be driven by chemokines such as CCL11/eotaxin-1, whose tissue expression and serum levels are high in idiopathic RPF. Eotaxin-1 also induces recruitment of mast cells, which have been found in idiopathic RPF lesions. Notably, in idiopathic RPF biopsies, eosinophils and mast cells strongly express CCR3, the receptor for CCL11/eotaxin-1.¹⁶ Eosinophil and mast cell products (*e.g.*, eosinophil granule

proteins, tryptase) stimulate fibroblast proliferation and collagen production.¹⁶ Fibroblasts can also be activated by CCL18, a chemokine whose serum levels are increased in idiopathic RPF.²⁹ The immunopathogenesis of idiopathic RPF is summarized in Figure 2.

DIAGNOSIS

Imaging Studies and Role of Biopsy

Idiopathic RPF is usually diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). On CT, it appears as a homogeneous plaque surrounding the anterolateral sides of the abdominal aorta and encircling the common iliac arteries (Figure 3); medial ureteral deviation and/or obstruction and inferior vena cava encasement are common. The tissue is muscle-isodense and has varying degrees of contrast enhancement.^{54,55} On MRI, its intensity is

low in T1-weighted images and variable (high in active stages) in T2-weighted images. Contrast enhancement and diffusion coefficient values are useful in differentiating active and inactive lesions.⁵⁶ When RPF has a bulky appearance, inhomogeneous intensity on MRI, extends above the origin of the renal arteries, or tends to displace the aorta anteriorly, it is more likely to be malignant. Also, malignant RPF causes medial ureteral deviation less frequently than idiopathic RPF.⁵⁷

^{18}F -Fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) has emerged as a useful tool for the assessment of RPF activity (Figure 4);^{27,58,59} this technique also detects the metabolic activity of post-treatment residual disease and thus guides subsequent therapy.⁶⁰ Notably, ^{18}F -FDG PET allows whole-body imaging and can help identify extra-retroperitoneal lesions to which RPF may be associated (*e.g.*, thoracic periaortitis, IgG4-RD) or secondary lesions (*e.g.*, malignancies).^{7,61} However, ^{18}F -FDG PET has little diagnostic utility because many infectious, inflammatory, or neoplastic lesions also accumulate ^{18}F -FDG.

Although no guidelines exist, retroperitoneal biopsy is usually performed (via open, laparoscopic, or CT-guided approaches) in cases with atypical localization (*e.g.*, periureteral, perirenal),^{54,62,63} or with clinical or imaging findings consistent with neoplastic RPF.⁵⁷ The percentage of biopsy-proven cases varies widely among series, with a range of 24%–77%.^{4,5,64}

Differential Diagnosis

Malignancies and infections are the major challenges for the diagnosis of RPF. Malignancies that can mimic RPF on CT/MRI include retroperitoneal lymphomas and sarcomas, and retroperitoneal metastases from various types of carcinomas.^{54,55} Carcinoids can cause RPF—through as yet unclear mechanisms—even without metastasizing to the retroperitoneum.⁶⁵ Among infections, tuberculosis should always be considered: it can spread into the retroperitoneum from neighboring foci or be disease-triggering when located

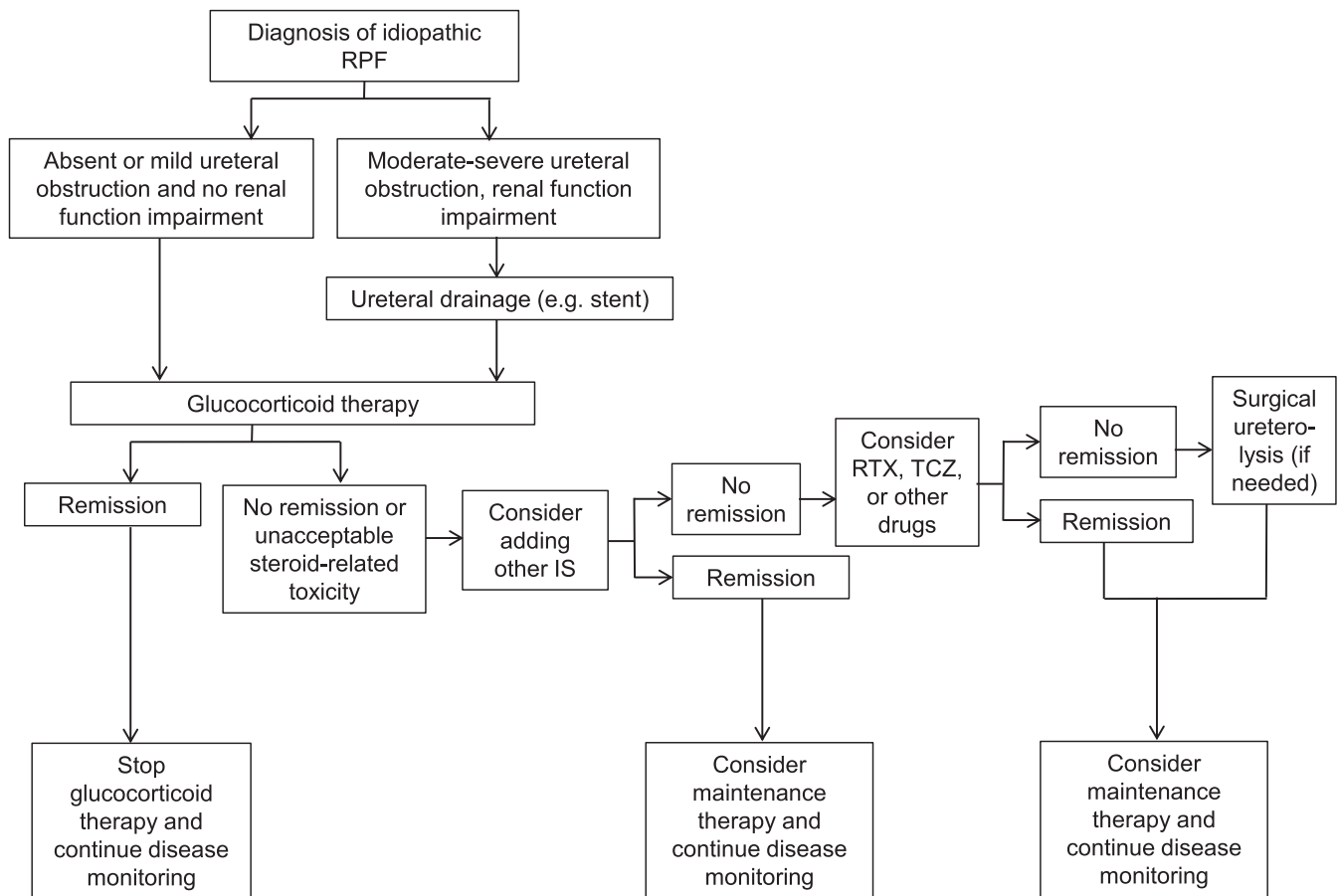


Figure 5. Proposed therapeutic algorithm for idiopathic RPF. IS, immunosuppressants (particularly mycophenolate mofetil, methotrexate, azathioprine, cyclophosphamide); RTX, rituximab; TCZ, tocilizumab.

distantly.⁶⁶ Pelvic actinomycosis may mimic pelvic RPF and should be suspected particularly in women with a history of intrauterine device use.⁶⁷

RPF has traditionally been linked to the use of drugs, particularly ergot alkaloids (e.g., methysergide, ergotamine) and dopamine agonists (e.g., pergolide); intriguingly, recent reports described RPF developing during anti-TNF α therapy for rheumatoid arthritis.⁶⁸ Radiotherapy, major abdominal surgery, and trauma are uncommon causes of RPF. RPF also develops in Erdheim–Chester disease, a non-Langerhans histiocytosis that – unlike idiopathic RPF – tends to infiltrate the perirenal space.⁶⁹ Finally, Takayasu and giant-cell arteritis can cause diffuse aortic thickening and thus mimic RPF, but they lack retroperitoneal diffusion and ureteral involvement.⁷

TREATMENT AND OUTCOME

The first goal of treatment is the relief of ureteral obstruction. Surgical ureterolysis with intraperitonealization and omental wrapping of the ureters is no longer the first-line approach, and conservative procedures (e.g., double-J stent or nephrostomy placement) followed by medical therapy are preferred.⁷⁰ Ureteral stenting allows better quality of life than does nephrostomy and is usually successful; however, stents and nephrostomies have comparable complication rates (e.g., infection, obstruction).⁷¹ Although no guidelines exist, when ureteral obstruction is mild and there is no kidney function impairment, it seems advisable to start medical therapy without urinary drainage.

Glucocorticoids are the first-line therapy, with initial doses of 0.75–1 mg/kg

per day of prednisone gradually tapered to 5–7.5 mg/day within 6–9 months.^{5,72} Remission generally indicates symptom and hydronephrosis resolution, together with acute-phase reactant normalization and radiographic regression. Remission rates after steroid therapy range between 75% and 95%;^{5,72} mean mass thickness reduction is around 50%.⁵ Glucocorticoids are rapidly effective, and most of the radiographic response is seen in the first weeks of treatment. However, they can also fail to induce mass regression, and chronic residual hydronephrosis may require surgical ureterolysis.

Tamoxifen, an anti-estrogen agent with potential antifibrotic activity, has been proposed as an alternative to glucocorticoids⁷³ particularly in patients experiencing steroid-related toxicity or when there are contraindications to glucocorticoids.^{64,74} However, in a recent

randomized controlled trial, an 8-month treatment with tamoxifen was significantly less effective than a treatment with prednisone of equal duration in maintaining remission in patients treated with prednisone induction (1 mg/kg per day for 1 month).⁵ Therefore, to date, the efficacy of tamoxifen is not supported by controlled trials and its superiority to other agents is unproven.

Immunosuppressants have been used in combination with glucocorticoids; however, it is still debated whether they actually potentiate glucocorticoid efficacy or function as steroid-sparing agents. Mycophenolate mofetil is widely used, also given its good tolerability and lack of contraindications in patients with renal insufficiency.^{75,76} Cyclophosphamide has also been effectively used as initial therapy followed by maintenance with other immunosuppressants, but is currently not recommended as first-line therapy.^{77,78}

The patients who achieve remission must be carefully followed using laboratory examinations, periodic ultrasound (to monitor hydronephrosis and aneurysmal dilatation) and CT/MRI studies (able to accurately define size and morphologic changes of RPF) to allow early detection of relapses. Long-term maintenance therapy must be considered, particularly in patients with aggressive disease. Idiopathic RPF is indeed a chronic-relapsing disorder, with relapse rates of up to 72%.⁷² Importantly, relapsing patients often experience multiple relapses and are thus exposed to high cumulative glucocorticoid doses. In such cases, methotrexate has been successfully used as a steroid-sparing agent.⁷⁹ Figure 5 shows a proposed therapeutic algorithm for idiopathic RPF.

Although rare, refractory cases also occur. In such patients, anecdotal reports demonstrated the efficacy of biologic agents, namely the anti-IL-6 receptor tocilizumab,²⁸ and rituximab,⁵³ a B cell-depleting agent also effective in IgG4-RD.⁸⁰ Notably, rituximab was reported as efficacious in both IgG4⁺ and IgG4⁻ cases, although studies comparing the response to treatment in these two subgroups are lacking.^{53,80}

Despite its chronic-relapsing course, idiopathic RPF shows good patient and

renal outcomes. Studies with long-term follow-up (median, 48–61 months) provide mortality rates of 3.3%–7.3%.^{4,5} Varying degrees of chronic renal insufficiency occur in up to 32% of the patients,⁴ but end-stage renal disease is exceedingly rare.

CONCLUSIONS

Idiopathic RPF is an idiopathic disease that sits in the spectrum of fibro-inflammatory disorders and should be viewed as a potentially systemic condition. Genetic and environmental agents confer disease susceptibility and represent active areas of research. Immune-mediated and autoimmune mechanisms play relevant pathogenic roles; new therapies targeting specific pathways will complement traditional immunosuppressive approaches.

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DISCLOSURES

None.

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