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Retroperitoneal Fibrosis Is Still an Underdiagnosed Entity with Poor Prognosis

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Keywords
Idiopathic and secondary retroperitoneal fibrosis · Inflammation · Computed tomography · Magnetic resonance imaging · F-Fluorodeoxyglucose positron emission tomography

Abstract

Background: Retroperitoneal fibrosis (RPF) is a rare disease characterized by the presence of inflammatory and fibrous retroperitoneal tissue that often encircles abdominal organs including the aorta and ureters. Data on the incidence of this disease are limited. Summary: The disease may be idiopathic or secondary to infections, malignancies, drugs, or radiotherapy. The idiopathic form is an immune-mediated entity and a part of the broader spectrum of idiopathic diseases termed chronic periaortitis, characterized by a morphologically similar fibroinflammatory changes in the aorta and surrounding tissues. Taking into account the dominant symptoms and clinical characteristics of patients with periaortitis, 2 subtypes of disease could be distinguished. The vascular subtype includes patients with nondilated aorta or with inflammatory abdominal aortic aneurysm, both with and without involvement of adjacent structures and with numerous risk factors for atherosclerosis. In the renoureteral subtype, obstructive uropathy manifesting with hydronephrosis and acute kidney injury is the predominant finding. Due to the variety of symptoms, diagnosis of RPF remains challenging, difficult, and often delayed. A series of diagnostic tests should be performed, in order to confirm the diagnosis idiopathic RPF. Laboratory workup includes evaluation of inflammatory indices and immunological studies. A biopsy and histopathological evaluation may be necessary to confirm diagnosis and differentiate the disease. Computed tomography, magnetic resonance imaging, and positron emission tomography are the modalities of choice for the diagnosis and follow-up of this disease. Management of ureteral obstruction, hydronephrosis, and aortic aneurysms often requires surgical evaluation and treatment. The pharmacological treatment of RPF has been evaluated in a few randomized trials and is mainly based on observational studies. Steroid therapy remains the gold standard of treatment. Key Messages: Nowadays, multidisciplinary team approach with clinical and diagnostic experience in both primary and secondary RPF as well as 2 major subtypes should be offered. Centers specialized in rare diseases with collaboration with other units and referral system yield the best possible outcomes.

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Retrospective Study

Retroperitoneal Fibrosis Is Still an Underdiagnosed Entity with Poor Prognosis

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Introduction

Retroperitoneal fibrosis (RPF) is a rare disease with unknown etiology that is marked by inflammation and progressive development of a fibrotic mass around the aorta and other large vessels in retroperitoneal space. Sterile sclerosing infiltration expands and covers the abdominal aorta, usually below renal arteries, and could involve adjacent structures like ureters, iliac arteries and veins, vena cava inferior, pelvic plexuses, and other regional organs.

The disease has been reported for the first time in 1905 by Albarran [1]. An author of a more detailed description of 2 cases of RPF was Ormond [2]. Since that time –1948, the eponym of Ormond’s disease is used as the name of RPF. It was initially recognized as an extensive fibrosis which could cause ureteral obstruction necessitating surgery. In 1960, the same author collected and described another 82 cases of RPF [3]. Currently, reports of a greater number of patients with RPF are rarely published. Nowadays, along with the progress of medicine and development of imaging techniques, the disease is often diagnosed at earlier stages. Due to its clinical diversity and the involvement of various organs, the disease is a challenge for specialists in various fields.

The etiopathogenesis of RPF still remains an enigma. Local inflammatory response to atherosclerotic plaque antigen, as a starting mechanism of chronic inflammatory process, is one of the postulated causes. The second one is the local autoimmune process, understood as a part of systemic immune-related process. Some pieces of evidence suggest that a significant proportion of idiopathic RPF can be classified as part of the immune disorder described as IgG4-related disease. It affects multiple organs including the pancreas, lacrimal glands, retroperitoneum, and aorta and is characterized by presence of IgG4 lymphoplasmatic infiltration, fibrosis, and obliterative phlebitis.

Epidemiology

There are limited data regarding prevalence of RPF. In some studies, the annual incidence of idiopathic RPF is estimated at 0.1/100,000 persons per year, while other data indicate that disease prevalence is approximately 1.3–1.4 cases per 100,000 inhabitants per year [4–6].

The increasing recognition of the disease probably results from the development of imaging techniques, their greater availability, and more frequent immunological testing. The disease is most often diagnosed at the age of 40–60 years and is more common in men than in women (male-to-female ratio 2:1–3:1). In population observed in our practice (unpublished data), it occurs usually in the 5th to 6th decades of life (mean age at diagnosis was 60 ± 9 years), although in a prospective evaluation of van Bommel et al. [6], the mean age at onset was 64 years. The male-to-female ratio was in that study more than 3:1, but in observations from other studies reaches up to 5.8:1 [6, 7].

The main risk factors for RPF occurrence are exposure to asbestos or tobacco which almost quadruples the risk of developing the disease. The combination of both of these risk factors is associated with an 8- to 12-fold increased risk of RPF [8–10]. On the other side, HLA may play a role in susceptibility to RPF, and it was found that HLA-DRB*03 may have a potential pathogenetic involvement. Depending on the width of the aorta and the presence of its wall’s inflammation, several forms of RPF are distinguished. In idiopathic retroperitoneal inflammation (IRPF), the aorta is not dilated and the inflammation spreads to the surrounding tissues. In the case of aneurysmal aortic dilatation with an inflammation involving the aortic wall, an inflammatory abdominal aortic aneurysm (IAAA) is diagnosed. When, in addition to aortic inflammation, the fibrosis affects also the surrounding tissues, usually the diagnosis of perianeurysmal retroperitoneal fibrosis is made. Estimated frequency of IAAA is 2.3% to even 10% of all abdominal aneurysms of the aorta [11, 12].

Another type of division, taking into account the cause of infiltration, apart from idiopathic retroperitoneal fibrosis (IRPF), distinguishes secondary forms of the disease with identified causes. These forms of RPF are usually associated with identifiable factors such as malignancy following radiotherapy, infections, medicinal treatments, and multiple drugs. The idiopathic form of RPF is most common, while data on incidence of secondary disease as well as its prevalence in males and females are virtually unknown.

Primary RPF-IgG4 and Non-IgG4 Related

In recent years, numerous autoimmune diseases involving various organs and associated with the presence of IgG4 have been distinguished. Currently, they are referred to as IgG4-related diseases. There is a growing body of evidence that approximately half of the patients with idiopathic RPF should be also diagnosed and classified as patients with IgG4-related disease (IgG4-RD) (Table 1). IgG4-related disease can be described as a systemic fibro-
inflammatory sclerosing process with multiorgan infiltration of IgG4-positive plasma cells in the affected tissues. The clinical manifestation of diseases may vary significantly, and the disease may run as sclerosing pancreatitis and cholangitis, sialadenitis, and dacryoadenitis (previously named Mikulicz’s disease) or involve different localizations such as the lacrimal gland, salivary gland, pharynx, lymph nodes, thyroid gland, skin, lung, liver, pancreas kidneys, large vessels, and mediastinum [13, 14]. Studies on IgG4-RD revealed that abundant infiltration of IgG4-positive plasma cells was found in biopsies from some patients with RPF. The division into idiopathic RPF and RPF belonging to IgG4-related diseases is debatable and requires differentiation in immunohistochemical and histopathological tests. Additionally, the significance of the division for therapeutic management remains unclear.

To distinguish between idiopathic and IgG4-related RPF, a biopsy result is required, with a typical histological and immunohistochemical picture. In IgG4-related RPF biopsies, a prominence of storiform fibrosis, obliterative phlebitis, and eosinophilia was demonstrated, while in idiopathic RPF, nonspecific hyalinized fibrosis sheets were found [14]. The currently recognized criteria for the diagnosis of the IgG4-RD are presented in Table 1 [15]. Serological studies in IgG4-RD patients are nonspecific. High serum IgG4 levels are found in more than 60% of patients, usually those with multiple organ involvement, but elevated serum IgG4 levels are often associated with conditions that mimic IgG4-RD, such as connective tissue diseases [16]. Other immunoglobulins, including IgM, IgA, and other IgG subclasses, are often elevated in IgG4-RD, although generally not in the IgG4 range [16]. Based on various criteria, the prevalence of RPF classified as IgG4 related ranges from 29 to 60% [14–17]. In some reports, IgG4-related RPF cases showed significant male predominance, higher relapse rate, and more frequent multifocal involvement [12–14, 18–20].

Secondary RPF

The incidence of secondary fibrosis is much less frequent than idiopathic and affects no more than one-third of patients with RPF. The main secondary factors (Table 2) are malignancies (carcinoid, sarcomas, colorectal, breast, prostate, bladder cancers, and Hodgkin and non-Hodgkin lymphomas) [21, 22]. RPF is often the consequence of the cancer metastases in the peritoneum or a primary retroperitoneum tumor (prostate, colon, bladder, breast, and lymphomas, respectively). Drugs, which may traditionally be a contributing factor of RPF, belong to ergot alkaloids (methysergide and ergotamine), dopamine agonists (pergolide and methyldopa), β-blockers, hydralazine, and phenacetin. As medicine advances, new drugs suspected of having an effect on fibrosis appear on the horizon. Some reported biological agents – infliximab and etanercept – may trigger fibrotic reaction in the peritoneum, but the relationship is still unclear [23–26]. Infection such as tuberculosis, histoplasmosis – especially in HIV-positive patients, and actinomycosis may also be responsible for RPF [27]. Secondary cause of RPF may be radiation therapy in the past, with the shortest period between the moment of radiotherapy to the fibrosis appearance less than 2 years [28]. Other factors include retroperitoneal hemorrhage, prior surgery – colectomy, aortic aneurysmectomy, and lymphadenectomy, as well as ureteral catheters and vascular stents – catheters implanted for therapeutic purpose promote inflammation and stimulate and support the fibrous inflammation process [29]. Secondary amyloidosis, mesenteric panniculitis, and histiocytosis (e.g., Erdheim-Chester disease) were described in case reports as risk factors for RPF [29, 30].

A completely different disease, although it has a similar name in it, is nephrogenic systemic fibrosis. The disease was reported for the first time in 1997 and has only been described in patients with advanced chronic kidney disease (CKD) stage 4 or 5. Most of them were undergo-
ing dialysis. The disease can lead to tissue fibrosis related to the stimulation of fibroblasts after intravenous administration of gadolinium [31]. However, a disease that is similar in name could cause fibrosis in different areas of the body, especially in skin and subcutaneous tissue. The different locations are the lung, pleura, heart, sclera, skeletal muscles, dura mater, and esophagus and diaphragm.

Today, we use more modern contrast media on magnetic resonance imaging (MRI), e.g., gadobenate, gadoteridol, gadobutrol, and gadoterate (second group of contrast media), and nephrogenic systemic fibrosis, using the contrasts of this group, occurs with frequency <0.07% in patients with stage 4 and 5 CKD [32, 33]. Other predisposing factors include acute thrombosis, myocardial infarction, rheumatologic diseases, recent major surgery, administration of epoetin during dialysis, acidosis, and hyperphosphatemia. The disease is characterized by pain, redness, skin thickening, and hardening, which we can try to cure using painkiller and massages. There is no causal treatment so far, and the only remedy is prophylaxis and use, if necessary, of the contrast media for MRI from the second group if the glomerular filtration rate is less than 30 mL/min. RPF has not been reported after administration of gadolinium contrast medium for MRI.

Unfortunately, there are no radiological, microbiological, and biochemical methods that would uniquely differentiate between primary and secondary fibrosis. Therefore, patients at first diagnosis must have undergone a series of diagnostic tests, both biochemical and imaging (computed tomography [CT] and MRI) or endoscopic, in order to exclude secondary causes of fibrosis, especially malignancies [31].

**Clinical Presentation**

The clinical presentation of RPF often includes constitutional symptoms, like joint pain, fatigue syndrome, low-grade fever, weight loss, and dull pain in the lower abdomen, the flank, or the back area (Table 3). Sometimes symptoms depending on ureteral obstruction with subsequent kidney failure predominate. In males, urogenital symptoms such as testicular pain, hydrocele, varicocele, or erectile dysfunction may also be present [6, 32].

| Table 2. Major causes of secondary retroperitoneal fibrosis |
|------------------------------------------------------------|
| Drugs | β-Blockers, methysergide, pergolide, bromocriptine, ergotamine, methyldopa, hydralazine, phenacetin, etanercept, infliximab |
| Malignant tumors | Carcinoid, Hodgkin and non-Hodgkin lymphomas, sarcomas, carcinomas of the colon, stomach, prostate, breast |
| Radiotherapy | Testicular seminoma, cervix, pancreatic carcinoma, colon carcinoma |
| Infections | Tuberculosis, actinomycosis, histoplasmosis |
| Surgery | Colectomy, hysterectomy, aortic aneurysmectomy, lymphadenectomy |
| Others | Erdheim-Chester disease, amyloidosis, histiocytosis, trauma, barium enema, retroperitoneal hemorrhage, vascular prostheses |

| Table 3. Clinical and laboratory findings of patients with idiopathic retroperitoneal fibrosis |
|----------------------------------------------|
| Clinical presentation | Incidence, % |
| Pain (flank, back, lower abdomen, scrotum) | Up to 90 |
| Hydronephrosis | 60–75 |
| Systemic symptoms (malaise, anorexia, nausea, weight loss, low-grade fever) | Up to 60 |
| Impaired kidney function | 40–65 |
| Testicular manifestations (pain, varicocele, hydrocele) | >50% of men |
| Raised inflammatory markers | 60–70 |
| Anemia | 60 |
| Hypertension | 30–50 |
| Lower extremity edema | 20–25 |
| Renal atrophy | 20 |

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The triad of chronic abdominal pain, weight loss, and elevated inflammatory markers in patients with an abdominal aortic aneurysm is highly suggestive of an IAAA and may be important in the preoperative preparation of the patients for aneurysm repair [33]. Less frequently, RPF may manifest itself in vascular complications, such as venous thrombosis or ischemic claudication [16]. Patients with IgG4-related RPF complained of symptoms related to associated autoimmune illnesses rather than the more classic abdominal and/or back pain associated with IRPF [34, 35].

Due to the main symptoms and clinical characteristics of patients with RPF at our center, 2 subtypes of patients may be distinguished. In the vascular subtype, patients with an inflammation of nondilated aorta or IAAA can be found, both with and without the fibrous tissue mass surrounding the aorta as described at the beginning of the manuscript with images shown in Figure 1a–d. These patients used to be obese or overweighted males, in the 5th or 6th decade of life, heavy smokers, with lipid disorders, hypertension, and prediabetic states. A significant proportion of patients have concomitant chronic coronary

Fig. 1. A patient with vascular subtype of retroperitoneal fibrosis. a CT of abdominal aortic aneurysm with fibrous tissue mass surrounding the aorta. b CT of the aorta and left femoral artery with surrounding fibrous mass. c MRI of abdominal aortic aneurysm with fibrous mass surrounding the aorta. d CT of abdominal aortic aneurysm after pharmacological treatment and after endovascular stent graft placement.
artery syndrome, peripheral atherosclerosis, and a history of cardiovascular events. In this subpopulation of patients, other autoimmune diseases rarely can be found. Uibu et al. [36] as well as Goldoni et al. [37] revealed that a history of cigarette smoking and/or exposure to asbestos increases the risk of RPF 3- to 4-fold, and a multiplicative effect was found between both occupational factors with 8–12 increased risk.

In patients with the renoureteral subtype, clinical features, especially early signs, are nonspecific, making diagnosis difficult and often delayed. The most common clinical symptom is body position unrelated pain in the lower back, sometimes radiating to the inguinal region and suggesting renal colic. A pain is persistent, reacts poorly to opiates, and often radiates to the testicles [38, 39]. Frequent complication of the disease is obstructive ureopathy manifesting with hydronephrosis. Involvement of the ureter is uni- or bilateral, often initially asymptomatic, and consists of ureter’s compression usually in the middle of its part (Fig. 2). Significant bilateral ureter obstruction causes hydronephrosis, and with complete closure of the ureters, it may result in anuria. In one-third of cases, in the moment of diagnosis, hypoplasia of one of the kidneys is also found, which indirectly indicates a long-term process. In many patients, compression of the renal vein and artery is also observed with subsequent hypertension de novo or its control deterioration [6]. The fact of the appearance of hydronephrosis, even bilateral, is not an absolute indication for the ureteral catheter implantation. The indications for the catheters implantation or nephrostomy are only anuria, progressive/not drug corresponding AKI, or urinary tract infection. Most patients with renoureteral complications at the onset of the disease do not show signs of the metabolic syndrome which, however, occurs after steroid therapy.

**Diagnostic Approach**

Diagnostics of RPF include biochemical tests, immunological assessment, histopathological evaluation of biopsies, and a series of tests using visualization techniques. It should be noted that inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated in more than half of the patients with RPF. In our cohort of 39 patients, ESR was elevated in all patients, and median CRP was 13.8 (minimum 3 mg/L, maximum 130 mg/L). It seems that despite the use of inflammatory markers as measures of disease activity and treatment outcomes, they poorly correlate with the advancement of the disease in imaging tests. Many patients are diagnosed with leukocytosis, eosinophilia, and more than half with anemia secondary to renal failure and chronic inflammation. In our material, 22 patients had elevated creatinine levels (median 1.4 mg/dL, minimum 0.82 mg/dL and maximum 17.4 mg/dL), proteinuria, and hematuria. Some patients may have positive antinuclear antibodies, but anti-cytoplasmic antibodies (ANCA), antibodies to smooth muscle (ASMA), rheumatoid factor (RF), and anti-thyroid autoantibodies (anti-TPO, anti-TG) are much less frequently observed. Presence of the A antigen against Sjögren’s syndrome (Ro/SSA), B antigen against La/Sjögren syndrome (SSB), and anti-cytoplasmic neutrophil antibodies (ANCA) may implicate co-existent immune-mediated conditions. Among the most commonly used visualization techniques are ultrasonography, CT, MRI, and recently PET. Abdominal ultrasound is the most common screening test for initial diagnosis. Unfortunately, the sensitivity of this study is low, especially in the initial period of the disease, and often not sufficient to distinguish between retroperitoneal fibroinflammatory mass and the neoplastic condition. Conventional radiography is not useful for RPF diagnosis, and intravenous urography has been discontinued due to improvements in cross-sectional imaging [40, 41]. CT, MRI, and PET are the mainstay of noninvasive diagnosis of the disease. CT allows for an evaluation of the RPF localiza-

![Fig. 2. A patient with renoureteral subtype of retroperitoneal fibrosis. A 74-year-old male with obstructive uropathy due to ureter involvement manifesting with hydronephrosis.](image-url)
Retroperitoneal Fibrosis: Vascular and Renoureteral Subtypes

It is not entirely clear whether all RPF patients should undergo a biopsy. A biopsy of retroperitoneal mass is mandatory in any case when the diagnosis of the disease cannot be based on tests performed so far. Thus, this modality should be performed if differentiation from malignancy, infection-related inflammation, or an IgG4-related form of the disease is required. Sometimes a biopsy is performed additionally during the surgical procedures as removal of ureteral obstruction. Histopathological material is rarely obtained during aortic aneurysms surgery, since recently mainly endovascular procedures are performed. Most often, the biopsy is performed under CT guidance; however, PET scans may also be useful in identifying more appropriate sites for biopsy. In our center, we did not perform a single biopsy due to the localization of the mass inaccessible for the CT or too close to the aorta. Histopathologic images of surgical specimens or biopsies may slightly differ depending on the duration of the disease. In the initial stages of the diseases, microscopic evaluation reveals fibroblastic proliferation with a pleomorphic inflammatory cell infiltrate consisting predominantly of lymphocytes T and B, plasma cells, and macrophages in a loose matrix of collagen fibers [51–53]. As the disease progresses, the infiltration of inflammatory cells diminishes and hyalinized collagen and minor calcifications form the main mass of the tumor.

Treatment

There are some main goals of treatment of RPF:
1. Obtaining an analgesic effect and disappearance of clinical symptoms of the disease
2. To relieve the obstruction of the aorta and organs in retroperitoneal space, caused by fibrosis
3. To stop the progression of the fibrotic process and to obtain the regression of the infiltrate with the release of the pulled-in structures
4. To prevent recurrence of disease

For analgesic treatment, nonsteroidal anti-inflammatory drugs are usually used before diagnosis, i.e., before radiological or biopsy results (if any) are obtained. Considering the inflammatory etiology of pain, drugs with a high anti-inflammatory component are preferred in the initial period of hospitalization. Once the diagnosis is confirmed, the treatment strategy depends on the cause of the disease, i.e., whether it is primary or secondary RPF, and on the involvement and advancement of ureteral obstruction or concomitant renal failure. In the case of secondary drug-induced RPF, the obvious starting point for therapy is discontinuation of the causative drug. After elimination of the etiological factor, the further regimen of immunosuppressive therapy in the form of secondary and primary RPF are similar.

Due to the fact that RPF is an uncommon disease, treatment of the disease is mainly empirical, based on case studies, small groups, or usually retrospective studies [54–67]. In recent years, there have been reports on the prospective evaluation of treatment in large groups and few randomized studies. In patients requiring urological supplies or surgical treatment procedures, immunosuppressive therapy is initiated after the decompression of the ureters.

In case of presentation with bilateral hydronephrosis and acute kidney injury, urinary tract decompression is mandatory in most cases especially with anuria and urinary tract infection. The most common method of restoring the patency of the ureters is the use of JJ-type ureteral

Retropertioneal Fibrosis: Vascular and Renoureteral Subtypes

Kidney Blood Press Res 2022;47:151–162
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157
catheters. In the case of inability to insert ureteral catheters, it is necessary to decompress hydronephrosis by inserting a nephrostomy. The 2 techniques have shown comparable complication rates, but stenting allows a better quality of life [67].

In rare cases, surgical access with ureterolysis is required to release the fibrous infiltrate around the ureter. Open ureterolysis remains the gold standard for surgical treatment, but its purpose is only to resolve the ureteric obstruction, not to treat the RPF. Laparoscopic and robotic approaches have been reported to be feasible, but no prospective, comparative trials have been performed due to the rarity of the disease [68]. In case of unilateral obstruction, urological intervention is suggested when severe hydronephrosis is present, to protect the kidney from chronic damage. In milder cases, urinary diversion can be avoided if prompt medical therapy is started, even if close ultrasound monitoring is needed to exclude obstruction worsening [69]. In pharmacological treatment, the drugs of first choice are steroids. Depending on authors, there are some strategies for using glucocorticoid therapy in RPF. The most frequently used treatment regimen was proposed by Vaglio et al. [17]. Prednisone is started at a dose of 1 mg/kg body weight per day, no more than 80 mg, for the first month, and the dose is gradually reduced over the following months to the maintenance dose 5 mg/day (0.5 mg/kg in the second month, 0.25 mg/kg the third and fourth, and then tapered off during the following 5 months) [39]. The efficacy of this schema has been proven in various studies and in 1 randomized clinical trial [17, 54, 55]. Patients with good radiological response can be tapered off more quickly within this range, whereas patients with extensive and slowly regressive RPF require longer treatment, even for more than 1–3 years [66]. Neither the level of inflammatory markers nor the activity of FDG is a predictor of a good response to steroid therapy [47, 56, 57]. In case of glucocorticoid resistant-disease or in these patients with glucocorticoid contraindications, other immunosuppressive drug options are available and examined. There are many single case reports or prospective series and retrospective studies describing the effective use of drugs such as mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate, and cyclosporin [48, 58–65]. There is also documented successful use of colchicine, as a typical antifibrotic drug [66]. In recent years, biological therapies based on the use of monoclonal antibodies have also been developed in the case of RPF. The effectiveness of tocilizumab and rituximab has been shown in a small series of studies [70, 71]. Hormonal antiestrogen tamoxifen, with antifibrotic activity, previously active in desmoid tumor, was widely used in the empirical treatment of RPF and effective in retrospective studies. Unfortunately, a randomized controlled trial definitely showed the inferiority of tamoxifen versus prednisone in maintaining remission [39]. Tamoxifen can therefore be considered only as an alternative option in patients who have contraindications to steroids.

In the forms of RPF associated with aortic aneurysm, surgical follow-up is recommended, and indication to intervention, surgical or endovascular, does not differ from that considered for common atherosclerotic aortic aneurysms [72]. Although the treatment modalities of IgG4-related RPF do not differ much from idiopathic RPF, differentiation between the 2 diseases is essential. The availability of serum IgG4 levels for monitoring treatment response and follow-up can curtail the repeated radiological imaging and associated contrast exposure. Second, the diagnosis of IgG4-related RPF shall alert the clinician to look out for extraretroperitoneal diseases on follow-up of this multiorgan disease [73]. It seems also that in IgG4-related RPF, lower doses of steroids can be considered than in idiopathic forms of RPF.

Outcomes

Untreated disease, especially in cases related to unrecognized cancer, may lead to death, but the mortality rate has not been fully established, and it most certainly differs from tumor to tumor. Lee et al. [74] concluded that in patients within a 1-year pause between RPF and cancer diagnosis, the mortality rate was higher than in those with a 5-year interval between diagnoses and cancer and were more advanced at the time of diagnosis.

In primary cases, the mortality rate should be lower, but we do not have such comparisons. It can most certainly depend on the number and type of organs whose function has been impaired and the disease’s response to treatment. Moroni et al. [75] compared RPF treatment in 3 patient groups. All patients received steroids – the first group associated with ureterolysis, the second with azathioprine, and the third one received stenting or nephrostomy. The results in short-term (reduced the fibrotic mass) and long-term (stable serum creatinine) observation were similar regardless of the group.

Idiopathic RPF is a chronic and relapsing disease with long periods of remission and a chance of complete recovery. The duration of remissions and relapses may vary depending on existing risk factors, type of management, or accompanying complications [17]. Long-term follow-up of patients and the evaluation of RPF regression may be difficult due to imprecise indices of the dis-
ease severity. Usually, such an assessment is based on regression of clinical symptoms and biochemical indices of inflammation and the size of the retroperitoneal mass reduction in visualization studies. In one study after 1 year of follow-up in 46 patients (79.31%), an improvement in symptoms was observed [76]. Additionally, among them, 21 patients showed reduction in acute-phase reactants, and 4 patients showed a regression in the retroperitoneal mass within 6 months. In another study, among 151 patients with idiopathic RPF, relapses defined as worsening of imaging findings 1 year after treatment were observed in 18 patients (12%) and death in 11 (7%) patients [32].

Unmet Needs
There are many needs for the diagnosis and treatment of patients with RPF:
1. Standards of care need to be developed.
2. Rare Disease Centers for these patients need to be organized in order to provide better, more specialist, and comprehensive treatment – at present, the clinics treating patients with RPF are dispersed, have various diagnostic and therapeutic possibilities, and have a little opportunity for extensive studies. Also, cooperation with many specialists is often difficult. An algorithm of diagnosis and management of RPF is proposed (Fig. 3). Algorithm on diagnosis and management of retroperitoneal fibrosis.
3. PET should be performed as standard, although it will not help in recognizing the forms of fibrosis, but it will indicate a metabolically active tissue which may be a focus of active fibrosis or an active cancer. So, it will also indicate an area that requires more detailed research and show residual active tissue after the treatment [73].
4. New double-blind studies for RPF treatment warrant consideration due to the availability of new biological drugs, e.g., rituximab, which has been shown to be effective in treating IgG4-related RPF [70].
Conclusions: What We Can Offer to Patients with RPF in the 21st Century

RPF is a rare condition with inflammatory and fibrous tissue present in the retroperitoneum. As RPF may be idiopathic or secondary to other causes, at first, secondary causes should be excluded, mainly malignancy. Most patients with RPF present with pain in the lower back, abdomen, or flank and therefore could be diagnosed by various specialties. As kidney function is often decreased at the time of presentation, due to the urinary tract obstruction, patients may be denied imaging studies with contrast which may lead to delayed diagnosis and treatment. Based on the clinical experience, caution needs to be exercised when administering iodinated contrast media, but it is not advisable to postpone the diagnosis because of fear of renal complications as it seems that post-contrast AKI is not a great risk for patients, even those with CKD [77]. Consequently, the fear of using contrast agents is not justified. In addition, despite many clinicians do not perform a biopsy in patients who have an imaging diagnosis of idiopathic RPF, in certain cases, this diagnostic approach should be taken into account, i.e., patient scheduled for vascular surgery for abdominal aortic aneurysm repair (in the case of inflammatory aneurysms or perianeurysmal fibrosis) or for surgical ureterolysis to treat urinary tract obstruction. Biopsy is to be taken into account also in the following settings such as atypical location of the mass (e.g., not peri-aortoiliac but instead in a pelvic, isolated peri-ureteral, or peri-bladder location), suspicion of an underlying malignancy or infection on the basis of clinical and laboratory findings, bulky appearance of the retroperitoneal tissue, extension above the origin of the renal arteries, or anterior displacement of the aorta by CT or MRI (suggestive of possible malignancy), and if local expertise with radiologic diagnosis of RPF is limited (tissue confirmation is needed for diagnosis).

As diagnosis of RPF becomes a challenge for specialists in internal medicine, nephrology, cardiology, angiology, urology, etc., in the 21st century, we can offer multidisciplinary team approach with clinical and diagnostic experience with expertise in both primary and secondary RPF as well as the 2 major subtypes. Centers specialized in rare diseases with collaboration with other units and referral system yield the best possible outcomes.

Statement of Ethics

This study protocol was reviewed and approved by the Bioethics Committee at the Medical University of Warsaw, Approval No. AKBE/116/2021. The need for written informed consent was waived by the Bioethics Committee at the Medical University of Warsaw due to the retrospective design and analysis of medical records.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

I.L., M.W., J.L., and J.M. conceived the manuscript, collected the literature, and drafted the manuscript. All authors edited and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Albarran J. Retention renale par peri-ureterite: liberation externe de l’uretere. Assoc Fr Urol. 1905;9:511–7.
2 Ormond JK. Bilateral ureteral obstruction due to envelopment and compression by an inflammatory retroperitoneal process. J Urol. 1948;59:1072–9.
3 Ormond JK. Idiopathic retroperitoneal fibrosis: an established clinical entity. JAMA. 1960;174:1561–8.
4 Urban ML, Palmisano A, Nicastro M, Corradi D, Buzio C, Vaglio A. Idiopathic and secondary forms of retroperitoneal fibrosis: a diagnostic approach. Rev Med Interne. 2015;36:15–21.
5 Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. Lancet. 2006;367:241–51.
6 van Bommel EFH, Jansen I, Hendriksz TR, Aarmoudse AL. Idiopathic retroperitoneal fibrosis: prospective evaluation of incidence and clinic-radiologic presentation. Medicine. 2009;88:193–201.
7 Peng L, Zhang P, Li J, Liu Z, Lu H, Zhu L, et al. IgG4-related aortitis/periaortitis and periarteritis: a distinct spectrum of IgG4-related disease. Arthritis Res Ther. 2020 May 4;22(1):103.
8 Scheel PJ Jr, Feeley N. Retroperitoneal fibrosis: the clinical, laboratory, and radiographic presentation. Medicine. 2009;88:202–7.
Retroperitoneal Fibrosis: Vascular and Renoureteral Subtypes

Palmsino A, Urban ML, Corradi D, Cobelli R, Alberici F, Maritati F, et al. Chronic peri-
arteritis with thoracic aorta and epiaortic ar-
tery involvement: a systemic large vessel vas-
culitis? Rheumatology. 2015;54:2004–9. 

Goldoni M, Bonini S, Urban ML, Palmsino A, De Palma G, Gallietti E, et al. Asbestos and smoking as risk factors for idiopathic retro-
peritoneal fibrosis: a case-control study. Ann Intern Med. 2014;161:181–8. 

Dalainas I, Nano G, Ranucci M, Bianchi P, Stegher S, Casana R, et al. Inflammatory ab-
dominal aortic aneurysms. A 20-year experi-
ence. J Cardiovasc Surg (Torino). 2007 Jun; 48(3):305–8. 

Rasmussen TE, Hallett JW Jr. Inflammatory aortic aneurysms. a clinical review with new perspectives in pathogenesis. Ann Surg. 1997; 225:155. 

Rossi GM, Rocco R, Accorsi Buttini E, Mar-
visi C, Vaglio A. Idiopathic retroperitoneal fi-
brosis and its overlap with IgG4-related di-
brosis. Intern Emerg Med. 2017;12:287–99. 

Khosroshahi A, Carruthers MN, Stone JH, Vaglio A, Corradi D, Cobelli R, Zompatori M, Buzio C. Tuberculosis as a trig-
ger of retroperitoneal fibrosis. Clin Infect Dis. 2005;41:72–5. 

De Melio J, Crevits I. Retroperitoneal fibrosis: a rare mimicker of perirenal hematoma Ra-
diol Case Rep. 2020;15:2530–4. 

Cervera-Bonilla S, Garcia Mora M, Rodriguez-Osa P, Messa O, Mendoza Díaz S. Medical challenge posed by retroperitoneal fibrosis: case reports and literature review. Cureus. 2020;12(1):e6624. 

Pegoraro F, Papo M, Maniscalco V, Charlotte F, Haroche J, Vaglio A. Erdheim-Chester dis-
ease: a rapidly evolving disease model. Leuke-
nia. 2020;34:2840–57. 

Peisen F, Thaiss WM, Ekert K, Horger M, Amend B, Bedle J, et al. Retroperitoneal fi-
brosis and its differential diagnoses: the role of radiological imaging. Rofo. 2020;192:929–36. 

Kermanni TA, Crowson CS, Achenbach SJ, Lu-
ington N, Versari A, Boiardi L, et al. Identifying clinical subgroups in IgG4-
related pleural and lung fibrosis in patients with idiopathic retroperitoneal fibrosis: a tool for the ‘tailored’ management of retroperitoneal fibrosis: a nephro-urological experience. Nephrol Dial Transpl. 2010;25(8):2603–10. 

Nakajo M, Jinouchi S, Tanabe H, Tateno R, Nakajo M. 18F-fluorodeoxyglucose positron emission tomography features of idiopathic retroperitoneal fibrosis. J Comput Assist Tomogr. 2007;31(4):539–43. 

Wang Y, Guan Z, Gao D, Luo G, Li K, Zhao Y, et al. The value of 18F-FDG PET/CT in the distinction between retroperitoneal fibrosis and its malignant mimics. Semin Arthritis Rheum. 2018 Feb;47(4):593–600. 

Fernando A, Pattison J, Horsfield C, D’Cruz D, Cook G, O’Brien T. [(18)F]-Fluorode-
oxyglucose positron emission tomography in the diagnosis, treatment stratification, and moni-
toring of patients with retroperitoneal fibrosis: a prospective clinical study. Eur Urol. Jun 2017;71:926–33. 

Marcologno R, Tavolini IM, Laveder F, Busa M, Noventa F, Bassi P, et al. Immunosuppres-
sive therapy for idiopathic retroperitoneal fi-
brosis: a retrospective analysis of 26 cases. Am J Med. 2004;116(3):194–7. 

Peisen F, Thaiss WM, Ekert K, Horger M, Amend B, Bedle J, et al. Retroperitoneal fi-
brosis: a retrospective analysis of 26 cases. Am J Med. 2004;116(3):194–7. 

Confidential communication. 

Kidney Blood Press Res 2022;47:151–162
DOI: 10.1159/000521423
53 Gilkeson GS, Allen NB. Retroperitoneal fibrosis: a true connective tissue disease. 
Rheum Dis Clin North Am. 1996;22:23–38.

54 van Bommel EF, Siemens C, Hak LE, van der Veer SJ, Hendrikz TR. Long-term renal and patient outcome in idiopathic retroperitoneal fibrosis treated with prednisone. Am J Kidney Dis. 2007;49:615–25.

55 Kardar AH, Kattan S, Lindstedt E, Hanash K. Steroid therapy for idiopathic retroperitoneal fibrosis: dose and duration. J Urol. 2002;168:550–5.

56 Magrey MN, Husni ME, Kushner I, Calabrese LH. Do acute-phase reactants predict response to glucocorticoid therapy in retroperitoneal fibrosis? Arthritis Rheum. 2009;61:674–9.

57 Raffiotta F, da Silva Escoli R, Quaglini S, Rognoni C, Sacchi L, Binda V, et al. Idiopathic retroperitoneal fibrosis: long-term risk and predictors of relapse. Am J Kidney Dis Dec. 2019;74:742–50.

58 Grotz W, von Zedtwitz I, Andre M, Schollmeyer P. Treatment of retroperitoneal fibrosis by mycophenolate mofetil and corticosteroids. Lancet. 1998;352:1195.

59 Jois RN, Kerrigan N, Scott DG. Mycophenolate mofetil for maintenance of remission in idiopathic retroperitoneal fibrosis. Rheumatology. 1999;38:1195.

60 Scheel PJ Jr, Feeley N, Sozio SM. Combined prednisone and mycophenolate mofetil treatment for retroperitoneal fibrosis: a case series. Ann Intern Med. 2011;154:31–6.

61 Marzano A, Trapani A, Leone N, Actis GC, Rizzetto M. Treatment of idiopathic retroperitoneal fibrosis using cyclosporin. Ann Rheum Dis. 2001;60:427–8.

62 Al-Harthy F, Esdaile J, Berean KW, Chalmers A. Multifocal idiopathic fibrosclerosis: treatment of 2 cases with cyclosporine. J Rheumatol. 2006;33:358–61.

63 Alberici F, Palmisano A, Urban ML, Maritati F, Oliva E, Manenti L, et al. Methotrexate plus prednisone in patients with relapsing idiopathic retroperitoneal fibrosis. Ann Rheum Dis. 2013;9:1584–6.

64 Harreby M, Bilde T, Helin P, Meyhoff HH, Vinterberg H, Nielsen VA. Retroperitoneal fibrosis treated with methylprednisolon pulse and disease-modifying antirheumatic drugs. Scand J Urol Nephrol. 1994;28:237–42.

65 Cogan E, Fastrez R. Azathioprine. An alternative treatment for recurrent idiopathic retroperitoneal fibrosis. Arch Intern Med. 1985;145:753.

66 Vega J, Goecke H, Tapia H, Labarca E, Santamaria M, Martinez G. Treatment of idiopathic retroperitoneal fibrosis with colchicine and steroids: a case series. Am J Kidney Dis. 2009;53:628–37.

67 Mertens S, Zeegers AG, Wertheimer PA, Hendrikz TR, van Bommel EF. Efficacy and complications of urinary drainage procedures in idiopathic retroperitoneal fibrosis complicated by extrinsic ureteral obstruction. Int J Urol. 2014;21:283–8.

68 Surcel C, Mirvald C, Pavelescu C, Gingu C, Carmen S, Emre H, et al. Management of idiopathic retroperitoneal fibrosis from the urologist’s perspective. Ther Adv Urol. 2015;7(2):85–99.

69 Fenaroli P, Maritati F, Yaglio A. Into clinical practice: diagnosis and therapy of retroperitoneal fibrosis. Curr Rheumatol Rep. 2021;23(3):18.

70 Wallwork R, Wallace Z, Perugino C, Sharma A, Stone JH. Rituximab for idiopathic and IgG4-related retroperitoneal fibrosis. Medicine. 2018;97:e12631.

71 Urban ML, Maritati F, Palmisano A, Fenaroli P, Peyronel F, Trivioli G, et al. Rituximab for chronic periaortitis without evidence of IgG4-related disease: a long-term follow-up study of 20 patients. Ann Rheum Dis. 2020 Mar;79(3):433–4.

72 Chanda A, Sharma AP, Pareek T, Devana SK, Bora GS, Masrudur RS, et al. IgG4-related retroperitoneal fibrosis: an emerging masquerader with a sinister presentation. Urology. 2019;133:16–20.

73 Fendler WP, Elber M, Stief CG, Herrmann K. A PET for all seasons: 18F-fluorodeoxyglucose to characterize inflammation and malignant in retroperitoneal fibrosis? Eur Urol. 2017;71:934–5.

74 Lee SJ, Eun JS, Kim MJ, Song YW, Kang YM. Association of retroperitoneal fibrosis with malignancy and its outcomes. Arthritis Res Ther. 2021;23(1):249.

75 Moroni G, Gallelli B, Banfi G, Sandri S, Messa P, Ponticelli C. Long-term outcome of idiopathic retroperitoneal fibrosis treated with surgical and/or medical approaches. Nephrol Dial Transpl. 2006;21:2485–90.

76 Liu H, Zhang G, Niu Y, Jiang N, Xiao W. Retroperitoneal fibrosis: a clinical and outcome analysis of 58 cases and review of literature. Rheumatol Int. 2014;34:1665–70.

77 Chomicka I, Kwiatkowska M, Lesniak A, Malyaszko J. Post-contrast acute kidney injury in patients with various stages of chronic kidney disease – is fear justified? Toxins. 2021;13(6):395.