Review paper

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Retroperitoneal fibrosis – the state-of-the-art

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Abstract

Retroperitoneal fibrosis (RPF) is a rare disease, hallmarked by inflammation and deposition of fibrous tissue around the abdominal aorta. This process may spread contiguously and involve adjacent structures, leading to many complications, among which the most frequent and most severe is ureteral obstruction. The condition usually has idiopathic origin (idiopathic retroperitoneal fibrosis – IRF), but can also develop secondarily to a number of factors. The etiology of the disease remains unclear. Current research suggests that about half of the cases of IRF may be a symptom of a recently discovered, clinically heterogeneous immunoglobulin G4-related disease (IgG4-RD). Corticosteroids are the first-line treatment for IRF, but effective attempts to use immunosuppressants are also made. This paper presents the current state of knowledge on the etiopathogenesis, clinical presentation, diagnosis and therapeutic possibilities in different forms of RPF. Based on the latest research, an analysis of the relationship between IRF and IgG4-RD was performed.

Key words: retroperitoneal fibrosis, Ormond's disease, IgG4-related disease, chronic periaortitis.

Introduction

Retroperitoneal fibrosis (RPF) is a rare disease based on an inflammatory process and deposition of fibrotic tissue around the abdominal aorta and the iliac arteries, which often spreads within the retroperitoneal space and involves surrounding structures. The origin of this condition may have idiopathic character (idiopathic retroperitoneal fibrosis – IRF), which covers about 2/3 of cases, or be secondary to various causes such as malignancies, drugs, infections, injuries, radiotherapy or surgery [1]. According to recent reports, approximately half of the cases of IRF can be a symptom of relatively newly described, clinically heterogeneous IgG4-related disease [2, 3].

The first description of the disease was made by the French urologist Joaquin Albarran in 1905. However, it was John Ormond who contributed to identifying RPF as an independent clinical entity with his hypothesis from 1948 claiming that bilateral ureteral obstruction was caused by retroperitoneal inflammation [4]. Therefore, RPF is also known as Ormond's disease. Significant progress has been made over the last half of the century, especially in terms of diagnostic methods and treatment. However, many questions about RPF still remain unanswered.

Epidemiology

The epidemiologic data about RPF are scarce. According to a study conducted in Finland [5], the annual incidence was estimated to be approximately 0.1/100 000, whereas the prevalence of RPF is at the level of about 1.4 per 100 000 inhabitants. However, more recent reports of van Bommel et al. [6] indicate 13-fold higher incidence (1.3/100 000 inhabitants). Such improvement in detection of the disease may result from wide availability of more sensitive diagnostic methods. The average age at diagnosis is between 50 and 60 years [1], but RPF can also occasionally occur in children [7]. Men are affected 2–3 times more frequently than women [1, 6].

Aetiopathogenesis

Idiopathic retroperitoneal fibrosis is one of three manifestations of chronic periaortitis (CP), which is characterized by deposition of fibroinflammatory, periaortic tissue within the retroperitoneal space. Chronic periaortitits can

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arise around an undilated or dilated aorta. In IRF the aortic diameter is normal, and the fibrotic mass can spread contiguously to entrap neighboring structures. Aneurysmal forms of CP include inflammatory abdominal aortic aneurysms (IAAAs), where the fibrosis covers the dilated aorta only, and perianeurysmal retroperitoneal fibrosis (PRF), where the involvement of surrounding structures is also observed [8, 9]. A schematic classification of chronic periaortitis is presented in Figure 1.

The pathogenesis of IRF remains unclear. The most popular theory, proposed by Mitchinson and Parums [8, 9], suggests a local inflammatory response to antigens present in the atherosclerotic plaque of the abdominal aorta. Oxidized low-density lipoprotein (LDL) and ceroid, contained in the plaque, are presented by macrophages to immunocompetent T and B lymphocytes, triggering the inflammatory reaction in the adventitia. Thinning or disruption of the aortic media, caused by advanced atherosclerotic plaque, is a prerequisite for development of the inflammation process. This theory is supported by the fact that immunohistochemical studies of aortic wall specimens taken from patients with CP revealed the antibodies (mainly IgG) in the neighborhood of the atherosclerotic plaque, whereas ceroid-laden macrophages can be detected in the adventitia [10]. Moreover, serum antibodies to oxidized low-density lipoproteins and ceroid are found in patients with chronic periaortitis. However, these were also detected in approximately half of the patients with ischemic heart disease and in elderly control individuals [9]. This theory does not explain the systemic nature of the disease: the presence of constitutional symptoms, elevated concentrations of inflammatory markers, often positive autoantibodies (especially ANA) and concomitance of other autoimmune conditions such as Hashimoto's thyroiditis, Graves' disease, ANCA-associated vasculitis or psoriasis [11–14]. It does not refer to cases of RPF among children and patients without apparent atherosclerotic changes in the aorta as well.

Nowadays, it is assumed that CP may arise as primary aortitis which, as a consequence, can trigger a fibroinflammatory process within the retroperitoneum. This theory is supported by the fact that the histopathologic pattern of CP is consistent with the one observed in vasculitis. In both cases, vasculitis of the vasa vasorum and lymphoid follicles with germinal centers, typically localized in adventitia, can be found. Moreover, due to the fact that CP can involve not only the aortoiliac region, but also other vessels, e.g. the thoracic aorta, renal, mesenteric or coeliac arteries, CP is considered to be a form of large vessel vasculitis [15, 16]. According to Palmisano et al. [14], in approximately one-third of patients with CP, the thoracic aorta and/or epiaortic arteries are also involved.

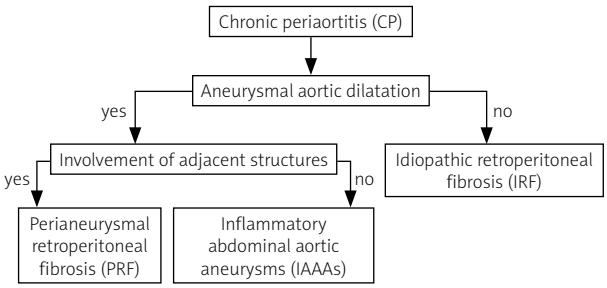


Fig. 1. Classification of chronic periaortitis.

There is no evidence of ethnic or familial predisposition in CP. There have been only incidental reports of RPF occurrence in twins or siblings [17]. However, several studies suggest that genetic factors may play a role in the pathogenesis of this condition. There are numerous cases of concomitance of IRF and seronegative spondyloarthropathies described in the literature. Nevertheless, the association between IRF and the HLA-B27 antigen is still unclear. However, a case-control study performed by Martorana et al. [13] shows that CP is strongly connected with the presence of HLA-DRB1*03 – an allele often encountered in other autoimmune diseases such as type 1 diabetes mellitus, Hashimoto's thyroiditis, and myasthenia gravis. The authors also suggest that the HLA system not only plays a role in susceptibility to CP, but may influence the intensity of the inflammatory response as well. However, more detailed studies concerning this aspect are necessary.

It has been proven that exposure to asbestos and tobacco smoke (presently or in the past) increases the risk of developing RPF. What is more, coexposure to these two factors has a multiplicative effect [1, 5, 18].

Secondary forms of RPF can be triggered by a wide range of factors such as drugs, medical interventions (e.g. radiotherapy, surgery), trauma, infections, malignancies, etc. Although the clinical picture often resembles IRF, the management of secondary RPF is focused on elimination of an appropriate cause. Hence, detailed differential diagnosis between primary and secondary forms is essential to institute an adequate therapy.

Drug-induced RPF was described in patients receiving: ergot derivatives (e.g. ergotamine, methysergide), dopamine agonists (e.g. pergolide, bromocriptine, cabergoline), methyldopa; nonselective (e.g. propranolol, sotalol) and β1-selective (metoprolol, atenolol) β-blockers; hydralazine; analgesics and non-steroidal anti-inflammatory drugs (aspirin, paracetamol, phenacetin) [19]. Ergot derivatives can induce fibrosis not only in the retroperitoneum, but also in the lungs, pleura or pericar-

dium. The mechanism of this process is not fully known; however, it is presumably associated with their serotonergic activity [20]. Recently, a report was published about RPF developing in two patients with rheumatoid arthritis, treated previously with etanercept for several years. It is a surprising phenomenon owing to the fact that biological agents (including TNF-α antagonists) have already been successfully used in RPF therapy. A similar, paradoxical effect of the disease induction, to which TNF-α inhibitor proves to be effective, has been repeatedly recorded in relation to other diseases, such as psoriasis, sarcoidosis, or inflammatory bowel diseases. Further research on the mechanism of this phenomenon and the safety of the possible use of etanercept in the treatment of RPF is required [21].

Retroperitoneal fibrosis is rarely a consequence of infectious diseases, such as tuberculosis, syphilis, histoplasmosis, actinomycosis and fungal infections [22].

Retroperitoneal fibrosis based on malignancy, which accounts for 8–10% [22] of all cases, is generated by desmoplasia (fibrous connective tissue formation in response to the presence of metastatic cells in the retroperitoneum), or is based on the primary retroperitoneal tumor, e.g. Hodgkin's lymphoma and non-Hodgkin's lymphoma, and various types of sarcomas. Metastases to the retroperitoneal space can originate from virtually every organ; the most frequently mentioned are the breast, stomach, colon, prostate, lung, and kidney. The clinical and radiological picture may deceptively resemble a mild form, then the retroperitoneal tissue biopsy is a conclusive examination. The prognosis in the case of confirmation of a proliferative base is not propitious, with an average survival period of 3–6 months from the time of diagnosis [23–25].

Retroperitoneal fibrosis can also be one of the symptoms of Erdheim-Chester disease (ECD), which is a form of non-Langerhans cell histiocytosis. This rare disease may affect multiple organs, among which the most frequent manifestations are skeletal, cardiovascular and central nervous system involvement, eye exophthalmos, diabetes insipidus, and interstitial lung disease. In contrast to IRF, ECD never encompasses the pelvic part of the ureters. Fibrosis most often covers the entire circumference of the aorta (which is referred to as a "coated aorta"), while in the case of IRF, its posterior wall is involved very rarely. A dense infiltration of perinephric fat, taking the appearance of "hairy kidneys", is very specific to ECD. Another characteristic radiographic finding includes symmetric diaphyseal and metaphyseal osteosclerosis, most often seen in the long bones of lower extremities. In the presence of these clinico-radiographic features, a biopsy is required to confirm the diagnosis [26].

IgG4-related disease and idiopathic retroperitoneal fibrosis

IgG4-related disease (IgG4-RD) is a recently discovered, fibro-inflammatory disease with a heterogeneous clinical picture, whose characteristic features include a tendency to the formation of tumefactive lesions; increased (in most cases, though not always) IgG4 levels in plasma and tissue infiltration of IgG4-positive plasma cells [27]. This disease may occur with the involvement of both single and multiple organs. The most common locations are lymph nodes, pancreas, salivary glands, kidneys, bile ducts, and lachrymal glands, but it may involve almost any organ or body region. Retroperitoneal involvement was reported in 20–56% of patients with IgG4-RD [3, 28, 29]. It is currently believed that a number of diseases, so far recognized as independent, may be included in the spectrum of IgG4-RD. These include autoimmune pancreatitis, Mikulicz's disease, Riedel's thyroiditis, Küttner's tumor, inflammatory pseudotumor, interstitial nephritis, interstitial pneumonia, inflammatory aneurysms of the aorta, sclerosing mesenteritis, and retroperitoneal fibrosis [30, 31].

Umehara et al. [30] proposed general diagnostic criteria for IgG4-RD, which are presented in Table I.

Table I. Diagnostic criteria for IgG4-RD

Criteria	Diagnosis		
	Definite	Probable	Possible
1. Characteristic diffuse/localized swelling or masses present in single or multiple organs	+	+	+
2. Increased concentrations of IgG4 in serum (> 135 mg/dl)	+	–	+
3. Histopathological picture: a) marked lymphocyte and plasmacyte infiltration with fibrosis b) infiltration of IgG4-positive plasma cell: ratio of IgG4/IgG-positive cells > 40% and > 10 IgG4-positive plasma cells per high power field	+	+	–

A definite diagnosis can be made when all three criteria, while excluding a proliferative process and other diseases, are met. The diagnosis is probable if criteria 1 and 3 are met, and possible if criteria 1 and 2 are fulfilled

In recent years, a few studies on the prevalence of IgG4-RD in patients primarily diagnosed with IRF were carried out; at the same time the studies were oriented on the presentation of the clinical characteristics of this group of patients. Immunohistochemical and histopathological examinations of retroperitoneal tissue showed lesions specific for IgG4-RD in about half (47–59%) of patients with IRF [2, 3, 32].

The absolute number of IgG4-positive plasma cells in specimens from the retroperitoneal tissue is lower than in other organs typically affected by IgG4-RD. This may be due to the low specific clinical picture of RPF and the consequent delay between the onset of the disease and the moment of diagnosis, when the biopsy material shows domination of fibrosis over cellular infiltration. Therefore, in the case of advanced fibrotic changes, the evaluation of the ratio of IgG4+/IgG+ cells is diagnostically more useful. Other histopathological characteristics of IgG4-RD, present in the material from the retroperitoneal tissue, which help to identify IgG4-related RPF include storiform fibrosis, lymphoplasmacytic infiltration, tissue eosinophilia, and obliterative phlebitis [2]. According to some authors, the concentration of IgG4 in the serum of patients with IgG4-related RPF is significantly higher than in patients with RPF unrelated to IgG4-RD. On the other hand, it is known that the concentration of IgG4 in the serum can be normal in up to 30% of patients with biopsy-confirmed IgG4-RD, and also elevated in other conditions. Therefore, this marker is helpful in the initial differential diagnosis, but it is insufficient to make a definitive diagnosis [3, 33–36].

According to Khosroshahi et al. [2] there are no significant differences in age, sex, laboratory and radiological findings among patients with IgG4-related and IgG4-unrelated RPF. However, 46–50% of cases of IgG4-related RPF show the involvement of organs located outside the retroperitoneal space; hence it is essential to distinguish these patients [2, 3]. Furthermore, the analysis of Koo et al. [32] revealed that a group with IgG4-related RPF had a significantly higher recurrence rate compared to IRF; therefore the authors suggest the need for more aggressive immunosuppressive therapy and longer duration of maintenance treatment.

Corticosteroids (CS) are the method of choice for the treatment of IgG4-RD. The response to therapy is usually rapid, but relapses are often observed after CS dose reduction [31].

Symptoms

Retroperitoneal fibrosis develops insidiously, because the initial symptoms are non-specific. The most common reports include low back, flank or abdominal pain, often radiating to the groin and/or side of the thigh [6, 23]. The pain is described as dull, persistent, with no decrease at rest. Initially, relief is brought by the use of non-steroidal anti-inflammatory drugs, but this effect is temporary. In the case of encasement of the ureters, the pain can have a colic character [37]. Patients often complain of constipation, and occasionally obstruction is observed due to the involvement of the duodenum. Less frequently reported symptoms related to compression of the retroperitoneally located lymphatic vessels and veins include swelling and deep vein thrombosis of the lower limbs, scrotal swelling, testicular pain, varicocele and hydrocele. Entrapment of arteries can result in renovascular hypertension, intermittent claudication or intestinal ischemia [12, 17, 18, 23, 38].

Patients may also show constitutional symptoms such as fatigue, fever, weight loss, lack of appetite, muscle and joint pain. Physical examination adds little to the diagnosis. Sometimes lumbar or abdominal tenderness is present, and very rarely a fibrous mass can be felt through the abdominal wall [12, 13, 17].

The non-specific clinical picture often significantly prolongs the time between the onset of symptoms and the correct diagnosis, which results in complications related to the advanced fibrotic process. The most frequent and, at the same time, the most severe complication is hydronephrosis, due to ureteral obstruction, which is found in 47–100% of patients [1]. In over 50% of cases, it has a bilateral character [1, 12].

Diagnostics

The laboratory findings are nonspecific to RPF. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated in more than half of the cases [12, 39, 40]. They can be helpful in monitoring treatment response, although it should be noted that their levels do not always correlate with disease activity assessed by imaging studies [38]. Approximately 40–50% of patients have raised serum creatinine levels at diagnosis, which is an indicator of renal complications [12, 38, 41]. Moreover, normocytic, normochromic anemia as a consequence of chronic inflammation and chronic kidney disease is frequently observed. Less common laboratory abnormalities include leukocytosis, eosinophilia, hypergammaglobulinemia, hypoalbuminemia, proteinuria and hematuria [17, 40]. Antinuclear antibodies (ANA) are positive in approximately 30–40% of patients [13, 18, 23]. Less frequently detected autoantibodies include antithyroid antibodies (anti-TPO, anti-TG), anti-smooth muscle antibodies (ASMA), rheumatoid factor, and anti-cytoplasmic antibodies (ANCA). Their presence is often, but not always, associated with the concomitance of autoimmune disease [12, 14, 18, 23, 40].

Abdominal ultrasonography often serves as a screening test, which is helpful in the initial diagnosis. Typically, RPF appears as a hypo- or anechoic, well-demarcated but irregular mass. In the case of ureteral entrapment, the ureterohydronephrosis can be visualized. Unfortunately, the sensitivity of the test is low, especially in the initial period of the disease, at approximately 25% [42].

Intravenous urography was once the modality of choice for the diagnosis of RPF, enabling the assessment of the location and degree of ureteral obstruction. However, nowadays the relevance of this technique is limited due to its low sensitivity and specificity in comparison to cross-sectional imaging studies [43].

Currently, a key role in diagnosis of RPF is played by computed tomography (CT) and magnetic resonance (MRI) imaging. Computed tomography most often shows RPF as a well-delimited, irregular, paraspinal mass, isodense to the psoas muscle. Typically, it is located at the level of L4–L5 vertebrae and spreads upwards towards the renal hila, or less frequently downwards, involving the pelvic organs. Over time, fibrosis envelops the aorta and inferior vena cava, and then, subsequently, covers the ureters and lumbar muscles [22]. The degree of enhancement after administration of a contrast agent, expressed in Hounsfield units (HU), depends on the activity of the inflammatory process. In the acute inflammatory phase it is higher than in the late, inactive period, which usually correlates with a better response to treatment [43]. According to Gao et al. [44] the baseline HU values and baseline transverse diameter of retroperitoneal tissue may serve as predictors of improvement in renal function after 12 months of treatment. In MRI, RPF typically shows the hypointensity of the T1-weighted signal. The intensity of the T2-weighted signal correlates with the activity of the inflammation, i.e. in chronic inactive fibrosis it is lower than in the early inflammatory phase [25].

Computed tomography and MRI enable very precise assessment of the extent of fibrosis, the degree of involvement of adjacent organs, as well as the activity of the inflammatory process. Unfortunately, they also have some limitations, e.g. they are not sensitive enough in differentiating benign and malignant forms of RPF. Some characteristics (e.g. the anterior displacement of the aorta and vena cava, exerting a mass effect on adjacent structures, atypical location, lobular or nodular structure) should lead to suspecting a malignant process. In such cases, the final diagnosis should be based on the histopathological examination of biopsies [42]. It should also be remembered that a large proportion of patients with RPF present complications such as obstructive uropathy and subsequent renal failure, which is a contraindication for the use of iodinated contrast media. With regard to MRI, the use of gadolinium-based contrast agents is associated with the risk of developing nephrogenic systemic fibrosis (NSF). Nephrogenic systemic fibrosis is a progressive, potentially fatal disease characterized by thickening and hardening of the skin and fibrosis of internal organs such as the lungs, heart, diaphragm, liver, or kidneys, leading to their failure. As the greatest risk concerns patients who are in the fourth and fifth stage of CKD, gadolinium-based contrast agents should not be used when GFR is less than 30 ml/min/1.73 m^2 [45, 46].

Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) and PET/CT are increasingly used in the diagnosis, as well as in evaluating the activity and extent of the RPF and the response to treatment [43, 47]. It can be a helpful tool in making therapeutic decisions, e.g. about removing the ureteral stent or reducing the dose of immunosuppressant [48]. In a high proportion of patients, despite a good clinical response and a decrease of inflammatory parameters, the imaging tests show a remaining residual mass. It can include both inactive remains of fibrous tissue, and persistent, latent inflammation. Positron emission tomography with 18F-fluorodeoxyglucose is a valuable source of information about its metabolic activity [49]. Unfortunately, this test is not appropriate in differentiation between idiopathic and malignant forms of RPF [47].

A biopsy is always mandatory in cases of atypical clinical, laboratory or radiological manifestation (especially in atypical location of the mass), which raise the suspicion of an underlying malignant cause, or in the absence of an adequate response to immunosuppressive therapy and in centers with little experience with diagnosis of RPF [1, 12, 43]. It also allows the differentiation of IgG4-related and IgG4-unrelated forms of RPF. Among the various techniques (open, laparoscopic, fine-needle, transcaval, CT-guided), a surgical biopsy remains the gold standard, with an opportunity to collect many deep specimens, which minimizes the risk of overlooking metastatic cells [24].

Treatment

Idiopathic retroperitoneal fibrosis treatment is focused on two principal objectives, namely, the inhibition of inflammation and fibrosis and, in the case of complications, the restoration of patency of the urinary tract. Most often, it is a combination of urological intervention with systemic treatment. Until now, the algorithm of IRF treatment has not been established. There is no doubt, however, that corticosteroids are still the first-line treatment. The initial dose based on prednisone is usually 0.5–1 mg/kg/day (30–60 mg/day); it is maintained for 4–8 weeks, and then gradually reduced within a few months to a maintenance dose of 5–10 mg/day. The duration of

treatment, suggested by different authors, ranges from 1 to 3 years [50, 51]. Most patients report relief in symptoms within the first two weeks of therapy. A little later, at an average of approximately 6 weeks, an improvement in laboratory parameters is observed: a decrease in ESR and CRP levels and creatinine concentration. The control CT/MRI after about 4–12 months of therapy shows in the majority of patients at least partial regression of fibrosis [50]. Although the rate of remission observed in the patients treated in this way is high (92–100%), often (even as much as in 72% of cases) a relapse occurs [50, 52].

To avoid relapses, as well as to reduce the risk of side effects associated with long-term intake of high doses of CS, attempts are made to use other immunosuppressive agents. However, the experiences are mainly based on observations of small groups of patients.

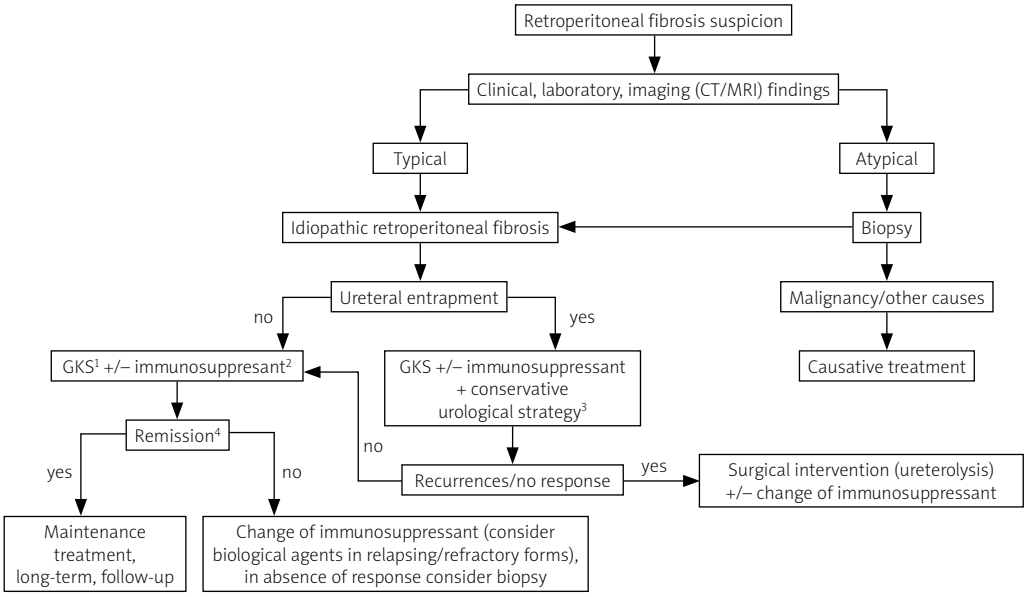
Some reports indicate that methotrexate in combination with prednisone in a gradually reduced dose may be effective in inducing remission in patients with frequent relapses, and when used in a low dose as a single agent this drug can be efficient in maintenance of remission [53, 54].

Promising results were presented by Adler et al. [55]: mycophenolate mofetil (MMF) in a dosage of 2 g/day used in conjunction with prednisone was effective in inducing long-term remission with relatively few side effects.

The combination of prednisone and azathioprine (AZA) or intravenous/oral cyclophosphamide (CYC) in different dosing regimens may also be effective as first-line therapy. AZA was also successfully used as remission-maintenance drug [56, 57]. Warnatz et al. [38] recommend the use of CS in combination with AZA at a daily dose of 2 mg/kg in mild and moderate cases, and CS together with monthly CYC pulses (15 mg/kg) in severe and recurrent forms.

Tamoxifen (TMX), due to its potentially anti-inflammatory and antifibroblastic properties, may provide an alternative to standard immunosuppressive therapy, although it seems to be less effective in the reduction of fibrosis and prevention of relapses as compared to CS. Its advantage lies in the relatively low toxicity. However, the possible, although rare but serious, adverse effects, primarily thromboembolic complications, should also be taken into account [52, 58].

Attempts to use biological agents in the treatment of the relapsing or refractory form of IRF have been made in recent years. The reports refer to isolated cases treated with rituximab (RTX), infliximab and tocilizumab; however, the results are promising [59–61]. Rituximab arouses particular interest in the context of IgG4-RD. It is a chimeric antibody directed against the CD20 antigen present on the surface of B lymphocytes. Treatment with RTX leads to depletion of circulating B cells, which are precursors of IgG4-producing plasma cells. Interestingly, it selectively affects the reduction of the concentration



[1]*Prednisone 0.5–1 mg/kg/day for 4–8 weeks, then gradually tapered to maintenance dose of 5–10 mg/day*
[2]*E.g. AZA, MMF, CYC, MTX, TMX*
[3]*Ureteral stenting or percutaneous nephrostomy*
[4]*Stable, reduced mass in CT/MRI; absence of hydronephrosis and clinical symptoms; normal inflammatory markers*

Fig. 2. Proposed algorithm for diagnosis and treatment of RPF.

of IgG4, whereas the concentrations of other IgG subtypes remain unchanged [31, 62]. Clinical improvement was observed after treatment with RTX in various forms of IgG4-RD, including IgG4-related RPF [62].

Because the majority of patients suffer from uni- or bilateral hydronephrosis at diagnosis, RPF usually requires a combination of systemic treatment and rapid urological intervention. A conservative strategy, consisting of temporary placement of a ureteral stent or percutaneous nephrostomy with subsequent systemic treatment, is generally effective and preferred over surgery [51, 55]. Ureterolysis, i.e. the surgical release of the ureters from fibrous tissue, should be reserved for recurrent cases, unresponsive to conservative treatment. The advantage of a surgical procedure includes the possibility of surgical biopsy, which is important to exclude a neoplastic process [42]. There are more and more reports about the effectiveness and safety of laparoscopic ureterolysis, including procedures performed with the assistance of a robot [24]. On the basis of the above discussed research results, the algorithm of RPF management was proposed, and schematically presented in Figure 2.

Summary

Although knowledge about RPF has significantly improved in recent years, it still remains an ambiguous condition. A lot of questions still need to be answered, especially about the pathogenesis. Further research on the relationship between IRF and IgG4-RD is required. It is also necessary to develop uniform guidelines for the diagnosis, treatment and monitoring of disease activity. Although there are more and more reports about the alternative to CS methods of treatment, not enough randomized studies on large groups of patients, comparing the effectiveness of different immunosuppressive drugs, are available. It can be expected that the coming years will bring us closer to solving these problems.

The authors declare no conflict of interest.

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