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Review

Idiopathic and secondary forms of retroperitoneal fibrosis: A diagnostic approach

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ABSTRACT

Retroperitoneal fibrosis (RPF) is an uncommon disease characterized by a fibrous reaction that takes place in the peri-aortic retroperitoneum and often entraps the ureters causing obstructive uropathy. RPF is idiopathic in the majority of cases, but can also be secondary to malignancies, infections, drugs, radiotherapy, and rare histiocytic disorders such as Erdheim–Chester disease. Idiopathic RPF is an immune-mediated disease, which can either be isolated, associated with other autoimmune diseases, or arise in the context of a multifocal fibro-inflammatory disorder recently renamed as IgG4-related disease. The differential diagnosis between idiopathic, IgG4-related and secondary RPF is crucial, essentially because the therapeutic approaches – especially of idiopathic vs. secondary RPF – can be dramatically different. This review focuses on the clinical, laboratory and imaging features of the different RPF forms, and also provides an overview of the available treatment options.

1. Introduction

Retroperitoneal fibrosis (RPF) comprises a spectrum of rare diseases hallmarked by the presence of an aberrant fibro-inflammatory tissue that usually develops around the infra-renal portion of the abdominal aorta and the iliac arteries and frequently entraps neighbouring structures such as the ureters and the inferior vena cava [1]. Retroperitoneal fibrosis may develop around an undilated or a dilated aorta, therefore "non-aneurysmal forms" and "peri-aneurysmal forms" of RPF can be distinguished.

Idiopathic RPF accounts for more than two thirds of the cases of RPF, the remaining third being secondary to other causes such as neoplasms, infections, trauma, radiotherapy, surgery, and intake of drugs [2]. The diagnosis is generally obtained by means of appropriate imaging studies (e.g., abdomen computed tomography, or magnetic resonance imaging) but, in patients presenting with a newly diagnosed RPF, it is mandatory to exclude malignancy with an age-appropriate cancer screening and, when there are clinical and radiological signs of underlying malignancies or infections, a retroperitoneal biopsy should be performed.

There are no standardized criteria to classify idiopathic RPF, but this is currently included in the spectrum of chronic periaortitis (CP) together with peri-aneurysmal RPF and inflammatory abdominal aortic aneurysms, as all of these forms have common histological features and a similar clinical presentation; recently, it has been proposed that CP is a form of large vessel vasculitis, especially in cases that also show thoracic aorta involvement [3]. Furthermore, idiopathic RPF (or CP) may be isolated or may develop in the context of a systemic immune-mediated disease.

Some authors argued that idiopathic RPF is part of the spectrum of immunoglobulin G4 (IgG4)-related disease (IgG4-RD) an immune-mediated disorder that may affect different organs (e.g., pancreas, gallbladder, salivary glands) and that is histologically hallmarked by a lymphoplasmacytic infiltrate rich in IgG4-bearing plasma cells, storiform fibrosis, tissue eosinophilia and obliterative phlebitis, and also characterised by increased levels of serum IgG4 in a significant proportion of cases [4,5]; some cases of idiopathic RPF have indeed such histological and clinical features, and can therefore be classified as being IgG4-related [6], although the exact proportion of IgG4-related out of the total number of idiopathic RPF cases is still unclear.

This review will focus on the clinical features of idiopathic RPF and will explore how to differentiate this entity from other diseases affecting the retroperitoneal space that can have a similar clinical presentation.

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2. Epidemiology

There are limited data about the epidemiology of this rare disease. One study from Finland showed an incidence of 0.1/100,000 inhabitants/year, and a prevalence of 1.4/100,000 inhabitants, whereas a more recent analysis performed in the Netherlands reported a 13-fold higher incidence, of 1.3/100,000 inhabitants/year [7,8]. This could mean that, with improved knowledge of the disease and greater accuracy of imaging techniques, the incidence of idiopathic RPF might turn out to be significantly higher than previously thought. The mean age at presentation is 50–60 years and there is a male predominance (male/female ratio 2:1 to 3:1). Pediatric cases are rare, with up to 30 patients described in the literature [9]. No clear data are available concerning the prevalence and incidence of secondary RPF [10].

3. Etiopathogenesis

Different mechanisms have been proposed to explain the pathogenesis of idiopathic RPF.

An early theory, proposed in the mid-1980s by Parums and Mitchinson, defined idiopathic RPF as a complication of advanced aortic atherosclerosis. These authors postulated that the fibro-inflammatory tissue may result from an initial processing of oxidized lipids by plaque macrophages, which migrate from the intima-media to the adventitia (especially when there is medial thinning as it occurs in atherosclerosis), where they present such lipids to lymphocytes and plasma cells, thus triggering adventitial and peri-adventitial inflammation and fibrosis [11]. However, this theory contrasts with the clinical evidence of idiopathic RPF in patients who do not suffer from atherosclerosis or have suffered no major cardiovascular events. In addition, this view cannot explain the complex systemic nature of idiopathic RPF, which in many cases presents with systemic symptoms, raised levels of inflammatory markers and concomitant autoimmune diseases involving other organs (e.g., Hashimoto's thyroiditis, small-vessel vasculitis, psoriasis and Sjögren's syndrome) [12,13].

Idiopathic RPF may instead be a manifestation of a systemic autoimmune disease, and may arise as a primary aortitis that subsequently elicits a peri-aortic fibro-inflammatory response. In keeping with this hypothesis is the observation that inflammation predominates in the adventitia, where vasculitis of *vasa vasorum* together with lymphoid follicles with germinal centers can also be found. Studies conducted on aortic biopsies showed the presence of gene transcripts of interferon-γ (IFN-γ), interleukin-1α (IL-1α), IL-2 and IL-4, suggesting lymphocytic activation [1,3,14]. Moreover, it has been reported that idiopathic RPF often affects other vascular segments (e.g., thoracic aorta, mesenteric arteries) that are usually spared by atherosclerosis [3,15]. Clinical findings such as the presence of systemic symptoms, the association with other autoimmune disorders as well as the good response to immunosuppressive therapies fit this systemic immune-mediated theory.

Multiple factors may contribute to this process. Martorana et al. [16] demonstrated a strong association between idiopathic RPF and HLA-DRB1*03, an allele linked to many autoimmune conditions such as type 1 diabetes, myasthenia gravis and autoimmune thyroiditis. A recent study also described an increased susceptibility to develop idiopathic RPF, especially its aneurysmal form, in patients carrying the delta 32 (Δ32) polymorphism of the CC-chemokine receptor 5 (*CCR5*) gene [17]. CCR5 is expressed on many immune cells, particularly Th1 cells, and acts by binding several chemokines, including RANTES, MIP-1α and MIP-1β. The *CCR5*Δ32 polymorphism creates a truncated, nonfunctional receptor and probably shifts the immune response toward a Th2 pattern.

Environmental factors also play a role in the susceptibility to idiopathic RPF. Occupational asbestos exposure and tobacco smoke are two important risk factors for the development of idiopathic RPF [7]. Goldoni et al. [18] have recently shown that the interaction between these two factors has a multiplicative effect rather than just an additive one: this translates into a markedly increased risk of developing idiopathic RPF (with an odds ratio > 10) when a patient is exposed to both factors [18].

The role of microbial agents as disease triggers is still elusive [19,20].

A broad range of factors may cause secondary forms of RPF, including drugs, infections, external-beam radiation and malignancies.

With regards to drugs, the most frequent associations are between RPF and derivatives of ergot alkaloids (e.g., methysergide, ergotamine), or with dopamine agonists (e.g., pergolide, methyldopa). Methysergide and the other ergotamine-derived agents increase the levels of endogenous serotonin and this has been suggested to lead to fibrotic reactions through proliferation of myofibroblasts and increase in collagen matrix deposition. This fibrogenic effect is not only limited to the retroperitoneum, but may also involve pericardium, pleura, and lungs [21]. Other medications reported as associated with RPF include β-blockers, hydralazine and phenacetin but whether there is a true causal relationship is still debated [1,22,23].

Recently, cases of RPF secondary to the use of biological agents have been reported, especially with the use of infliximab, a monoclonal antibody directed against tumor necrosis factor-α (TNF-α), and etanercept, a soluble receptor that acts as a TNF-α blocker [24,25]. How these drugs, widely employed in the treatment of rheumatic diseases, may trigger a fibrotic reaction in the retroperitoneum is still unclear, although it is well known that they may trigger a number of autoimmune conditions.

Malignancies are often listed as potential causes of secondary RPF. In most of these cases, RPF is the consequence of an exuberant desmoplastic response of retroperitoneal metastases (e.g., carcinoma of the prostate, breast, colon) or of a primary retroperitoneal tumor (e.g., Hodgkin's and non-Hodgkin lymphomas, inflammatory myofibroblastic tumour, well-differentiated liposarcoma sclerosing variant and various types of sarcomas) [26]. The only exception are carcinoids, that are likely to induce RPF in the absence of metastases, or primary localisations in the retroperitoneum, probably through a mechanism mediated by serotonin or by the release of profibrogenic growth factors such as platelet-derived growth factor, insulin-like growth factors, epidermal growth factor and the family of transforming growth factors α and β [27].

In case of infection-related RPF, the disease is usually secondary to the local spread of a contiguous infectious focus (e.g., spinal or paraspinal abscesses in patients with tuberculosis), or to an immune response triggered by a remote infection. In addition to *Mycobacterium tuberculosis*, which has often been reported as etiologic agent, actinomycosis or histoplasmosis can sometimes represent the primary infections [28].

Other potential causes of RPF include radiotherapy, trauma, major abdominal surgery, proliferative disorders such as Erdheim–Chester disease, a rare form of non-Langerhans cell histiocytosis, and other histiocytoses [29].

4. Pathology: gross and microscopic findings

In terms of macroscopic findings the idiopathic and secondary forms of RPF may look similar. RPF appears as a hard and grayish mass that infiltrates the retroperitoneal adipose tissue and does not have a fibrous capsule. In neoplastic forms the retroperitoneal