

Retroperitoneal Fibrosis: A Case Report of Five Patients and Short Review of the Literature



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Abbreviations: RPF: Retroperitoneal Fibrosis; IgG4-RD: IgG4-Related Disease; IRF: Idiopathic Retroperitoneal Fibrosis; CP: Chronic Periaortitis; IAAs: Inflammatory Abdominal Aortic Aneurysms; PRF: Perianeurysmal Retroperitoneal Fibrosis; LDL: Low-Density Lipoprotein; ANA: Anti-Nuclear Antibody; Ati-TPO: Anti-Thyroid Peroxidase; Anti-TG: Anti-Thyroglobulin; ASMA: Anti-Smooth Muscle Antibodies; ANCA: Anti-Neutrophil-Cytoplasmic Antibodies; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; CT: Computer Tomography; MRI: Magnetic Resonance Imaging; MMF: Mycophenolate Mofetil; AZA: Azathioprine

Introduction

Retroperitoneal fibrosis (RPF) is a rare disease characterized by inflammation and deposition of fibrotic tissue around the aorta and iliac arteries often spreading in the retroperitoneal space to adjacent structures and thus leading to various complications, of which the most severe is ureter obstruction [1,2]. The majority (cca.2/3) of RF cases are considered to be primary/idiopathic. Secondary causes of RF can be malignancies, drugs, medical interventions, trauma or infections [2]. About half of the idiopathic cases can be related to the newly discovered IgG4-related disease (IgG4-RD) [3,4].

IRF (idiopathic retroperitoneal fibrosis) is one of the three forms of chronic periaortitis (CP). The other two are the aneurysmal forms of CP: inflammatory abdominal aortic aneurysms (IAAs) with no involvement of periaortic structures and perianeurysmal retroperitoneal fibrosis (PRF) in which surrounding structures are also involved [5,6].

The pathogenesis of IRF is still largely unclear. The most accepted theory suggests a local inflammatory response, the oxidized low-density lipoprotein (LDL) and ceroid in the atherosclerotic plaques are presented by macrophages to T and B lymphocytes triggering an inflammatory reaction in the adventitia [6]. However, these changes are also found approximately in half of the patients with ischemic heart disease

and also in many elderly controls. Moreover, this theory cannot explain the generalized features of RF: the elevated inflammatory markers, positive auto antibodies (often antinuclear antibody, ANA) and concomitance of other autoimmune disease [7-10] and also cannot explain juvenile forms of IRF and IRF without atherosclerosis [2].

Lately, CP is thought to start as a primary aortitis which can trigger a fibro inflammatory process in the retroperitonium [2]. The finding, that histopathological features of CP and vasculitis are strikingly similar suggests that chronic periaortitis can be a form of large vessel vasculitis [11,12]. Several studies also suggest the role of genetic factors in the pathogenesis of CP, strongly associated with the presence of HLA-DRB1*03 [9].

The recently discovered IgG4 related disease is a clinically heterogeneous disease characterized by increased plasma IgG4 levels and tissue infiltration of IgG4-positive plasma cells, and may involve multiple organs. The most common locations are the pancreas, bile ducts, lymph nodes, lacrimal glands, kidneys and salivary glands [4]. The initial symptoms and laboratory findings are non-specific. Elevated serum IgG4 levels may indicate a more severe disease [13]. Inflammatory markers and ANA are positive in 30-40% of patients, with some less frequently detected auto antibodies including anti-thyroid antibodies [(anti-thyroid

peroxidase (anti-TPO), anti-thyroglobulin (anti-TG)], anti-smooth muscle antibodies (ASMA), rheumatoid factor, and anti-neutrophil-cytoplasmic antibodies (ANCA) [2].

Diagnosis of RPF is difficult as the laboratory findings are non-specific: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and increased serum creatinine. Normocytic, normochrom anemia is also frequently present as a consequence of chronic inflammation. Leukocytosis, eosinophilia, proteinuria and hematuria, hypoalbuminaemia, hyper gamma globulinaemia may also be found but much more rarely [14,15]. Abdominal ultrasonography is often used as a screening test. RPF shows as a hypo- or anechoic well-demarcated but irregular mass [16]. Currently, the key to diagnosing RPF is computer tomography (CT) or magnetic resonance imaging (MRI). CT scans typically show a demarcated mass at the level of the L4-L5 vertebrae [17], while MRI usually shows the hypo intensity of the T1-weighted signal [18]. Besides the diagnostic process, imaging techniques can be used to assess progression or therapy success. Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) and PET-CT can be helpful in making therapeutic decisions [19]. The final diagnosis should be based on the histopathological examination of biopsies [2,16].

Management of RPF is mainly based on the inhibition of inflammation and fibrosis, usually by using prednisone or even methotrexate in combination in some cases. There are some promising results with mycophenolate mofetil (MMF), combination of prednisone and azathioprine (AZA) or cyclophosphamide. Tamoxifen may provide alternative therapy. Rituximab in context of IgG4-RD, infliximab and tocilizumab are all promising [2].

Case Reports

Hereby we report our experiences with five patients admitted to the National Institute of Rheumatology and Physiotherapy, Department of Clinical Immunology, Adult- and Pediatric Rheumatology between 2010 and 2016 diagnosed with retroperitoneal fibrosis. Usually the first signs of RPF were pyelectasia, decreased GFR and/or symptoms of ureteral obstruction. RPF was diagnosed with CT and biopsy, in which no IgG4-positive case was found.

Results

The mean age of the patients was 59.2 years with male predominance (male: female ratio was 5:3). Our laboratory findings were elevated CRP, ESR, creatinine, and in one case proteinuria and ANA positivity.

We started 1-2mg/kg corticosteroid and 0.75-1g/m² cyclophosphamide as induction therapy. In case of the first patient the former therapy proved to be ineffective as the fibrosis progressed even to the mediastinum, so we switched to rituximab and later tocilizumab, which finally stopped the

progression. In case of the second patient retroperitoneal fibrosis showed regression after the cyclophosphamide treatment, and later the orally administered mycophenolate mofetil proved to be effective leading to remission. During cyclophosphamide infusions adverse events were candida endophthalmitis and urosepsis, successfully treated with antifungal and antimicrobial therapy.

Treatment led to regression in two patients, in one case the progression stopped and two patients are currently receiving treatment and awaiting further assessment.

Conclusion

Retroperitoneal fibrosis is a rare disease with largely unknown pathogenesis usually causing non-specific symptoms and laboratory markers. In our cases corticosteroids and cyclophosphamide treatments proved to be effective first line therapy. As in case of most (if not all) autoimmune diseases, the ultimate goal of curing all patients seems only possible with individualized therapy due to the heterogeneous pathophysiology underlying the similar clinical conditions. But until then, a zillion of questions still need to be answered.

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