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Retroperitoneal fibrosis: a case of a patient (63y/o) treated with low-dose methotrexate (mtx) and 6-methylprednisolone (6-mp)

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Abstract

Retroperitoneal fibrosis (RPF), is a rare fibroinflammatory disease. The pathogenesis of RPF is still unclear and numerous theories have been reported such as environmental factors, immunologic process, genetic component, local inflammation and advanced atherosclerosis.

RPF is characterized by the presence of a particular retroperitoneal fibrotic tissue which is white, woody and involving retroperitoneal structures such as the great vessels, ureters and psoas muscle. The main complication of RPF is the obstruction of local structures such as the ureters due to the fibrosis and the treatment of this aspect represents the main challenge for this pathology.

RPF medical treatment consists of corticosteroids or/and immunosuppressive therapy. We report a case of a patient (63y/o) affected by idiopathic RPF treated with low-dose methotrexate (MTX) and 6-methylprednisolone (6-MP) for two years, describing and confirming the effectiveness and safety of a long-term low-dose MTX and 6-MP treatment.

Key Words: Retroperitoneal Fibrosis, Case Report, Methotrexate, Methylprednisolone, PICO Strategy

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Introduction

Retroperitoneal fibrosis (RPF), also known as Ormond's disease, is a rare fibroinflammatory disease with uncertain etiology and its clinical features and diagnostic appearance are very different.

It was first described in 1905 by the French urologist Albarran, but it became fully recognized and established as a clinical entity only in 1948 by Ormond ^{1,2}. The true incidence of RPF is uncertain, anyway the literature reports a range from one case per 200,000 to 500,000 people per year and a male predisposition (3:1 male/female ratio) in the fifth and sixth decade of life ³.

RPF is characterized by the presence of a particular retroperitoneal fibrotic tissue which is white, woody and involving retroperitoneal structures such as the great vessels, ureters and psoas muscle. Usually it develops around the infrarenal part of the aorta and the iliac arteries, sometimes spread down to the pelvis and rarely it extends to the scrotum or up to the diaphragm ³. Retroperitoneal fibrosis is generally idiopathic (about 66% of cases), but can also be secondary to surgery, particular drugs, malignant neoplasms, radiation and infections ⁴. We can define a true idiopathic RPF when a potential specific cause or a multi-organ disease are not identified ⁵⁻⁸. The pathogenesis of RPF is still unclear and numerous theories have been reported such as environmental factors, immunologic process, genetic component, local inflammation and advanced atherosclerosis ⁹. Recent studies support the hypothesis that the disease may be caused by a chronic inflammatory state triggered and maintained by autoimmune responses ¹⁰. The surgical treatment of idiopathic RPF acts only on the ureteral

obstruction without preventing disease progression and relapses and the treatment of this aspect represents the main challenge for this pathology. The ureteral entrapment is often silent and progressive and the early patients' clinical manifestations are fever, abdominal or back pain, weight loss, asthenia, dysuria and oliguria¹¹. Since the Sixties of the last century, many medical therapies have been proposed such as corticosteroids and immunosuppressants. From the beginning of the Nineties, was introduced the tamoxifen, alone or as a second-line treatment because of its interference with the fibrogenic process¹⁷. We report one case of a patient affected by idiopathic RPF treated with low-dose methotrexate (MTX) and 6-methylprednisolone (6-MP) for two years, describing and confirming the effectiveness and safety of a long-term low-dose MTX and 6-MP treatment.

Case Series

In a 63 year old caucasian female was hospitalized in our Department due to persisting bilateral low back pain. The patient reported arterial hypertension in good control. She denied, autoimmune diseases, previous important infections or radiotherapy. Just recovered she was in good haemodynamic status, no fever but showing pain in both renal fossae and mild arterial hypertension (150/95 mmHg). The following blood abnormalities were present: erythrocyte sedimentation rate (ESR) 90 mm/hr; C-reactive protein (CRP) 50 mg/dl; serum urea nitrogen 72 mg/dl; serum creatinine 1.5 mg/dl; serum potassium 5.1 mEq/L; red blood cells 3,200,000/mm³; Hb 11.9 g/dl; albumin 50.2%; alfa-1 globulins 5.2%; fibrinogen 645 mg/dL. The abdominal ultrasound study showed severe right hydronephrosis with periaortic inhomogeneous hypoechoic tissue. Abdominal contrast-enhanced computed tomography (CT) scan revealed the presence of a gross, poorly-bordered, infiltrating tissue occupying pre-sacral and right obturator spaces, and extending along the mesorectal fascia (Fig. 1A-B, arrows). This tissue encased the right sciatic nerve, branches of the right internal iliac artery, the distal segment of right ureter with hydronephrosis upstream (Fig. C-D, arrows) and infiltrates the right postero-lateral corner of the bladder (Fig. 1A, arrowhead), the right ureteral opening and the body of uterus.

This inhomogeneous solid tissue (cross diameter of 5.7 cm, anteroposterior diameter of 3.4 cm) showed a slight enhancement after contrast agent injection in late phase and was compatible with the diagnosis of retroperitoneal fibrosis (Figure 1A-D).

Our team confirmed the clinical diagnosis of idiopathic RPF and required further blood tests before starting drug treatment. The patient had positive antinuclear antibodies (ANA). Then she started the therapy with low-dose MTX at a weekly dose of 10 mg and low-dose 6-methyl-prednisolone (6-MP) therapy (4 mg/daily). After ten days of treatment the patient was completely asymptomatic, all blood tests were normal and then she was discharged.

CT scan performed in march of 2015 after one year of treatment showed "subtotal resolution" of the fibrotic mass (Fig. 1 E-F) At two-years follow-up after the diagnosis of idiopathic RPF, the patient was completely asymptomatic and the abdominal CT scan has showed a complete regression of the retroperitoneal fibrotic mass without any sign of relapse.

Actually the patient is completely asymptomatic.

Discussion

RPF is a rare fibroinflammatory disease with uncertain etiology, characterized by the presence of a particular retroperitoneal fibrotic tissue which is white, woody and involving retroperitoneal structures such

as the great vessels, ureters and psoas muscle. When the fibrotic mass has a large extension, it can obstruct the ureters. Specimens collected early in the course of the disease are constituted by collagen bundles, fibroblasts, plasma cells and lymphocytes, confirming that the basis of the disease is an exuberant immunologic processes¹⁸. In the early phases, there is an inflammatory infiltrate of both B (CD 20+) and T (CD 4+) lymphocytes, plasma cells, macrophages (CD68+) and histiocytes and sometimes fibrinoid necrosis of medium-sized and capillary retroperitoneal vessels is also detected^{19,20}. As a possible genetic predisposition of idiopathic RPF, besides the old association with HLA-B27 antigen, a further clue has been studied because of its significant association with HLA-DRB1*03, an allele linked to other autoimmune diseases²¹. The most common symptoms are low back or abdominal pain and sometimes fever. Blood tests may often show raised acute phase reactants as ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), α_2 -globulins which reflect the disease activity, its natural course and the eventual relapses²². The laboratory tests include the complete blood count, renal function profile (creatinine levels, serum electrolyte concentration), the assay of antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), anti-thyroglobulin antibodies, anti-smooth muscle antibodies (ASMA), rheumatoid factor, and furthermore IgG and IgG4 serum levels^{23,24}. To reach the correct diagnosis CT and MRI are very useful²⁵ and in doubtful cases a biopsy is performed¹¹. More recently FDG-PET and PET/CT are feasible and suitable imaging methods useful to reach a correct diagnosis and to monitor the response to therapy²⁶. In complicated cases or unresponsive to therapy, the ureteral stenting may not be sufficient and then a surgical treatment is necessary. The surgical treatment of choice is laparoscopic or open ureterolysis; the ureter is dissected free from the fibrotic mass laterally or intraperitoneally. There is also an alternative technique through which the ureter is wrapped with omentum to avoid the entrapment by the fibrosis²⁵. Currently with the introduction of robotic surgery, some surgeons have begun to use it for the ureterolysis²⁷. The surgical or endoscopic (ureteral stenting) treatment must be combined with drug therapy in order to avoid relapses of disease³³. Some Authors combine corticosteroid and immunosuppressive therapy. Others give only

corticosteroid or immunosuppressive agents²⁵. Kiesel B et al²⁸ showed azathioprine to be particularly effective in the treatment of RPF. Multi-targeted bio-therapy as TNF- α blocking antibodies, Jaks-STATs complex inhibitors and anti-human CD20 antibodies, either alone or combined with steroids/immunosuppressants, could represent an interesting and challenging approach for the management of idiopathic RPF²⁹. Actually, there are many studies about the therapeutic potential of F8-IL10 (antibody F8 fused to anti-inflammatory IL10) and the use of phosphodiesterase-4 (PDE4) inhibitors^{30,31}. As reported from Alberti, in the last two decades we did not have any interesting innovation about diagnosis and therapy of RPF but only many pathogenetic news³². The prognosis of RPF is surprisingly good with treatment. However, the disease may be very insidious with unpredictable progression. All the authors agree that RPF may persist or recur also some years later and a strict follow-up is necessary all life long. The rapid clinical and laboratory improvement and the progressive reduction of the fibrotic tissue, shown by CT scan, in this case report, lead us to affirm and confirm (as in our first experience of 1995)¹² that long-term low-dose MTX and 6 MP therapy is a particularly safe and effective therapy on idiopathic RPF which avoids more invasive surgical treatments.

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