Idiopathic Retroperitoneal Fibrosis – a Long Time Challenge. Case Report and Review of the Literature

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Abstract

Introduction
Idiopathic retroperitoneal fibrosis (IRF) is a rare benign pathology, consisting of fibrous inflammatory tissue formation in the retroperitoneal space, surrounding main vessels and often involving nearby anatomic structures, such as the ureters, leading to obstruction and renal function impairment. Diagnosis is challenging, based upon high clinical suspicion, correct differential diagnosis and imagistic evaluation. Biopsy is required to confirm the non-malignant nature of the retroperitoneal mass. Medical immunosuppressive treatment is reasonable for moderate disease, whereas surgical treatment is indicated in advanced stage. Follow-up is mandatory but there is no consensus upon a surveillance schedule.

Material and Methods
We present a case of a male patient treated for a left retroperitoneal tumour destructive for the left renal unit, which was partially removed alongside the kidney, and turned up to be IRF and consequently immunosuppressive therapy was administered with 5 years normal follow-up. 8 years after the first event, IRF recurred on the right side of the retroperitoneum, obstructing the solitary kidney. Ureterolysis with omental wrapping was performed with optimal results and immunosuppressive therapy was reinitiated, with good response and normal check-ups to present day.

Results and Conclusions
IRF can prove to be a real challenge, as knowledge on its origin, optimal diagnostic, treatment and follow-up protocols is still building up. It is a potentially curable disease if managed correctly. Bilateral ureterolysis in unilateral disease could be taken into consideration from the start as late recurrence can occur. Follow-up should be conducted for a long period of time, maybe for the rest of the patient’s life.

Keywords: idiopathic retroperitoneal fibrosis, medical treatment, ureterolysis, recurrence, follow-up

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Introduction/Epidemiology
Idiopathic retroperitoneal fibrosis (IRF), also called Ormond's disease, is a chronic condition which was first documented as a clinical entity by John Kelso Ormond in 1948. It consists of a chronic inflammation and inappropriate formation of fibrous tissue in the retroperitoneal space, surrounding the abdominal aorta and iliac arteries but also around other retroperitoneal organs, especially the ureters, often leading to ureteral obstruction. The prevalence of the disease is about 1.38 per 100,000 persons/year. The incidence is between 0.1 and 1.3 cases per 100,000 persons/year. IRF affects men two to three times more often than women, but it appears that the forms which involve the thoracic aorta, predominantly affect females. The disease is diagnosed in the 5th-6th decade of life in most of the patients, but paediatric cases are also reported.

Pathogenesis
Etiopathogenesis of IRF is not yet established, but its autoimmune origin was proposed due to the association with other autoimmune diseases and the mild elevation of the nonspecific inflammatory markers (such as ESR and CRP) which is found in most of the cases. Also, an association between IRF and some environmental factors such as exposure to asbestos, use of drugs like ergot alkaloids, beta-blockers or dopamine agonist, has been reported.

Clinical Presentation
Clinical presentation of IRF is commonly nonspecific and characterized by a localized spectrum of signs and symptoms (caused by the fibrous mass), associated or not with systemic manifestations. The most frequent symptom is low back pain or pain in the flank, abdomen or into the groin. Other symptoms are related to the lymphatic or venous obstruction due to the retroperitoneal compression, such as oedemas of the inferior limbs, deep vein thrombosis. Other signs that had been reported are hydrocele, constipation, dysuria, oliguria, haematuria, anejaculation. The systemic symptoms may include malaise, low-grade fever, anorexia, weight loss, arthralgia and myalgia.

Diagnosis
The diagnosis is based on a high clinical suspicion and exclusion criteria because there are no clear guidelines regarding IRF management. However, the primary suspicion is based on clinically and laboratory tests, corroborated with the imagistic findings. To date, CT-scan and MRI seem to be the investigation of choice with equivalent diagnosis value. The suggestive CT-signs for diagnosis consist of entrapment of the retroperitoneal structures with a periaortic mass with frequently involvement of the inferior vena cava (IVC) and the ureters (uni- or bi-lateral). The fibrous plaque usually starts at renal hilum (at the L2-L4 vertebra level) spreading to the bifurcation of the iliac arteries. 18F-FDG PET-CT was proven not to be very accurate in the diagnosis of IRF because of its low specificity, despite the fact that it has a great sensitivity and it is used as an effective diagnostic tool in oncology. However, 18F-FDG PET-CT appears to be useful in assessing the response to immunosuppressant therapy, by providing information about the metabolic activity of the fibrotic tissue, which can lead to a better therapeutic management.

IRF imagistic aspect is very similar to the secondary form of retroperitoneal fibrosis, so only few signs might differentiate them, such as the anterior displacement of the aorta and IVC, adenopathy located posterior to the great vessels and the nodular aspect of the mass, signs with low specificity and sensitivity. The cranial extension of the mass is also not specific for IRF; even if the retroperitoneal lymphomas are frequently located above the renal hilum, there are also IRF cases extending above L2 vertebra. For this reason, biopsy and histological exam seems the reasonable way to diagnose this disease. It can be performed surgically (open or laparoscopic) or CT guided biopsy. Pathology report usually shows a fibroblast proliferation and a perivascular inflammatory tissue with lymphocytes, macrophages, plasma cells and eosinophils. Still, other studies show that not all of the patients would need biopsy. Biopsy becomes necessary when the clinical and laboratory findings along with imagistic interpretation can’t make the differential diagnosis with a malignant tumour.

Given that IRF is an exclusion diagnosis, it is necessary to rule out all other possible diagnostics. Commonly, the differential diagnosis includes the secondary forms of retroperitoneal fibrosis such as inflammatory aortic aneurysm, tuberculosis affecting the retroperitoneum, retroperitoneal fibrosis caused by some drugs, radiotherapy, surgery or other retroperitoneal benign lesions. The most important differential diagnosis that has to be made is with malignant retroperitoneal tu-
mours, particularly lymphomas and sarcomas, due to the similarity in clinical presentation and the cross-sectional imaging aspects.\textsuperscript{16,21,22,23}

**Treatment**

Choosing the best treatment strategy may be a challenge for the clinician because of the wide range and non-specificity of clinical manifestations. So treatment has to be adapted to the situation, mainly because there are no generally accepted guidelines regarding IRF treatment.\textsuperscript{11,24} The aim of the treatment is to stop the progression of the fibrous mass, preventing or treating the obstruction of the ureters.\textsuperscript{16}

For mild disease, without severe urinary obstruction, medical treatment appears to be the first choice. Glucocorticoids are the fundamental medical therapy for IRF.\textsuperscript{16,22,25} Other drugs that had been used in combination with steroids are a large spectrum of immunosuppressant drugs, such as cyclophosphamide, methotrexate, mycophenolate mofetil, and also the use of tamoxifen. These drugs help reducing the dose of steroids, but they also had been used as second-line therapies.\textsuperscript{16,18,22,24}

Severe IRF leads to ureteral obstruction and eventual renal failure with severe uremia; in this case the approach should be urologic, by placing ureteral stents or percutaneous nephrostomy tubes for restoring the renal function. In case of medical treatment failure, or sometimes from the beginning, definitive surgical treatment should be initiated. The procedure of choice is ureterolysis with peritonealisation of the ureter when ever possible and omental wrapping, either via open or laparoscopic approach. The moment of surgery is also appropriate for taking multiple biopsies.\textsuperscript{11,16,24}

**Case Report**

We present a case of a 52 years old male patient, who was admitted in our institution complaining of mild back pain, nonspecific abdominal discomfort, moderate weight loss, constipation. CT-scan revealed a left retroperitoneal tumour mass, partially entrapping the lower lumbar aorta and the left ureter, with stage V hydronephrosis and non-functional left kidney. The mass was limited to the lateral side of the aorta, having an infiltrative aspect, with normal aspect of the right retroperitoneal space, and a normal right ureter and kidney.

Consecutively, he underwent surgery that partially removed the tumour, en block with the left kidney. The pathology report showed a high probability of a low grade non-Hodgkin malignant lymphoma, but immunohistochemistry staining revealed the benign non-specific inflammatory nature of the tumour.

Afterwards, the patient was given an immunosuppressive regimen consisting of Prednisone, at initial dose of 1mg/kg/day, which was tapered at a dose of 10 mg/day during the first 3 months and then discontinued after a total treatment period of two years. Clinical and imagistic response was good, with initial decrease of the remaining retroperitoneal mass, then with stabilisation of the disease, during a 5 years surveillance period. Follow-up was conducted with medical consultations, initial quarterly, with clinical and bioumoral evaluation and 6 months and 1 year CT-scan, and then annually in the same manner for the next 4 years, when it was interrupted.

On July 2014, 8 years after the initial diagnosis, the patient was admitted again in our institution for right lumbar pain and nonspecific abdominal discomfort. Initial investigation showed mildly elevated CRP, fibrinogen and ESR levels, and a serum creatinine of 1.4 mg/dl. Abdominal ultrasound revealed mild right hydronephrosis. Subsequent CT-scan was performed and it showed a retroperitoneal mass encasing lower lumbar aorta and IVC, with caudal extension to the common iliac vessels and right ureteral entrapment, with stage I-II right hydronephrosis (Fig. 1).

![Fig. 1. CT-scans revealing the retroperitoneal mass](image)

After endoscopic placement of a double J ureteral stent on the solitary kidney, the patient underwent open right ureterolysis with intraperitonealisation of the ureter and omental wrapping (Fig. 2). Multiple biopsy specimens were prelevated from the mass.
Pathology report showed a polymorphous inflammatory tissue, composed mainly of lymphocytes, macrophages and neutrophils, suggestive for the benign nature of the mass.

Immunosuppressive regimen consisting in 1 mg/kg/day of Prednisone was initiated soon after surgical recovery and 6 weeks later the JJ catheter was removed. The dose of immunosuppressive agent was slowly tapered to a 10 mg/day, the maintenance dose.

Control at 3 months showed normalisation of renal function, with decrease of inflammatory markers. CT scan at 6 months and 1 year showed minimal decrease of the mass, with constant aspect at 2 years follow-up.

Discussion
IRF is a rare condition, with unknown causes and unspecific clinical presentation. Diagnosis can be a real challenge, being in essence a matter of excluding malignancy and other pathologic conditions, and it depends upon a high clinical suspicion. Management of IRF should be conducted by a multidisciplinary team, as it is potentially curable if managed correctly.

Advanced fibrosis is often leading to severe uremia and it should be referred to an urology department for initial desobstruction of the kidneys. Immunosuppressive therapy might then stabilise or even reduce the fibrous plaque. In case of medical treatment failure, definitive surgical treatment is indicated. Current data suggests that the optimal surgical treatment for IRF is ureterolysis, with peritonealisation of the ureter and ommental wrapping, performed either open or laparoscopic.

Data on the optimal follow-up schedule is currently inconsistent. Present therapeutic approach suggests a 2 years immunosuppressive regimen, and after the disease is stabilised there is no clear protocol for follow-up. Our case shows an unexpected recurrence 8 years after the initial episode, which means that follow-up should be recommended for a long period, perhaps even lifelong.

If IRF is predominant only in one retroperitoneal side, involving only one ureter and initial surgical treatment is performed, it seems reasonable to think that maybe ureterolysis should be performed bilaterally from the beginning, as our case showed contralateral involvement after a long period of time.

Future research is needed to establish an optimal management of IRF, regarding diagnostic protocols, optimal medical or surgical treatment and the right follow-up schedule.

References