Retroperitoneal Fibrosis: A Case Report and Review of the Literature

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Abstract

Retroperitoneal fibrosis (RPF) is a rare disease characterized by inflammatory fibrotic processes affecting the retroperitoneal structures. To date, there are no guidelines for the diagnosis of or therapy for the disease. The presence of autoantibodies and histological similarities with vasculitis support the hypothesis of autoimmune processes that plays a role in causing the disease. If untreated, the disease may be fatal. The diagnosis becomes easier only at a later stage, when both the ureters are affected by fibrosis with the consequent development of symptoms of urinary obstruction or renal failure. Initial therapy aims at restoring the function of the affected hollow organs through the application of (ureteric) stents, followed by immunosuppressive therapy. Life-long observation of the patients is necessary, as the disease may be chronic and relapsing. Interdisciplinary and nationwide cooperation is of crucial importance to further investigate this disease.

We describe the case of a 46yr-old patient with 5 years long history of untreated hypercholesterolemia who was admitted in the Internal Medicine Service with fever 38.6 C, oliguria, diffuse abdominal pain and de novo arterial hypertension (190/90mmHg). Diagnosis representative blood analysis was: serum urea 153.97 mg/dl, serum creatinine 13.88 mg/dl, without proteinuria, serum potassium 6.48 mmol/l. serum cholesterol 313. 24 mg/dl, acid uric 10.57 mg/dl, hematocrit 29.50%, hemoglobin 9,2 g/dl , white cells 7,40 /mm^3 , erythrocyte sedimentation rate (ESR) 63mm/1 h, C-reactive protein (CRP) 103.6 mg/l .Sonography reported a bilateral ureteral hydronephrosis (right stage III and left stage II) with proximal hydroureter and, abdominal-pelvic scan showed a periaortic retroperitoneal mass which included both ureters and appeared to trigger the obstruction. Into the Urology Service a right percutaneous nephrostomy tube was inserted as an emergency and it was implanted a bilateral "double J" catheter, while diagnostic laparoscopic biopsy was perfected into the surgery service The biopsy and immunohistochemical staining showed a specific type of retroperitoneal fibrosis .Due to the failure of the previous measures and as a last therapeutic recourse when one year had passed from the diagnosis, a continuous regimen with prednisone in dose of 40 mg/day initially from 3 month and after 5-7,5mg/day since 12 months was started, which began a progressive remission in the size of the observed mass by scan (CT) and magnetic resonance (MR). The treatment was completed with high dose of statins Atorvastatin 80 mg/day during 12 months and, in this time, the levels of blood cholesterol, urea nitrogen and creatinine were reduced gradually too. Finally, at the end of the treatment with Atorvastatin and Prednisone and no more immunosuppressive treatment, the magnetic resonance demonstrates the complete disappearance of the fibrosis and one question enforces: is retroperitoneal fibrosis a consequence of a local autoimmune reaction against atherosclerotic plaque antigens?

Key Words: *Retroperitoneal Fibrosis, Hydronephrosis, Immunoglobulin G4-related Disease*

INTRODUCTION

Retroperitoneal fibrosis is an uncommon disease, characterized by the replacement of normal retroperitoneal tissue with fibrosis and/or chronic inflammation. In two thirds of the cases retroperitoneal fibrosis is idiopathic (IRF), whereas in the remaining ones it is secondary/associated to cancer, infections, drugs, autoimmune disease and vasculitis. IRF appears as a dense, fibrous plaque that usually arises between the level of the lower aorta and the common iliac arteries. As the plaque progresses, it engulfs the adjacent structures (e. g., ureters). In its early stages IRF is characterized by a rich infiltrate of lymphocytes, plasma cells and macrophages interspersed within fibroblasts and collagen bundles. In its advanced stages it becomes relatively avascular and acellular with abundant collagen bundles and scattered calcifications. The pathogenesis is still poorly elucidated, but few evidences supports the hypothesis that the disease may be the result of an inflammatory state triggered by autoimmune responses [1,2,3]. Parum *et al*. [1], considering the high correlation of IRF with atheromatous peri-aortitis, postulated that the disease may be due to an immune reaction to some components of atherosclerotic plaques such as low-density lipoprotein (LDL) and ceroid.

CASE REPORT

We describe the case of a 46-yr-old patient with 5 years long history of untreated hypercholesterolemia who was admitted in the Internal Medicine Service because of abrupt decline of the renal function and de novo arterial hypertension (190/90 mm Hg). Two months before hospital admission the patient experienced mild, diffuse abdominal pain non-responsive to anti-inflammatory drugs with renal laboratory tests normally. On the hospital entry patient presented with fever 38.6°C, anorexia, nausea, vomiting, oliguria: all of these were for 3 days. There was no history of hypertension, dysuria, hematuria, urolithiasis, hematochezia, melena, low dorsal and/or pain radiation with muscle weakness, tuberculosis or exposure to it or to asbestos, and no family history of renal diseases or malignant tumors. The temperature was 38.6°C, the pulse was 88, and the respirations were 28; the blood pressure was 190/90 mm Hg. On physical examination the patient was normal wight, no lymphadenopathy was found, mild peripheral edema, no xanthelasma or xanthomas, lungs clear, tachycardia 88/min, no cardiac arrhythmias, no turgescent jugular artery. Rectal examination was negative. On the abdomen examination there was diffuse pain with maximum of intensification in the right posterior lumbar site. No urine test was performed hospital admission because oliguria. An electrocardiogram showed a sinusal rhythm at a rate of 88, with evidence of an antero -septal ischemia. Radiographs of the chest were normal. The laboratory values are presented in **Table 1.** Diagnosis representative blood analysis were: serum urea 153.97 mg/dl, serum creatinine 13.88 mg/dl, without proteinuria, serum potassium 6.48 mmol/l. serum cholesterol 313. 24 mg/dl, uric acid 10.57 mg/dl, hematocrit 29.50%, hemoglobin 9,2 g/dl , white cells 7,40 /mm^3 , erythrocyte sedimentation rate (ESR) 63mm/1 h, C-reactive protein (CRP) 103.6 mg/l .A specimen of blood was obtained for culture. Sonography reported a bilateral ureteral hydronephrosis (right stage III and left stage II) with proximal hydroureter and no abnormalities of dimensions or parenchymal structure of prostate. In view of the absence of previous biochemical data of renal failure, we considered possible reasons which start with an acute pattern. In initial evaluation, pre-renal etiology was not seen (no history high blood pressure, right cardiac systole function). The absence of prostatic syndrome and sonography discovery did not justify a diagnosis of urinary tract obstruction. It was necessary an uncontrasted abdominal-pelvic scan that showed a periaortic retroperitoneal mass which included both ureters and appeared to trigger the obstruction. **(Figure 1 a).**

VARIABLE	ON ADMISSION	1 week after admission START PREDNISONE **40mg/Kg**	3 months after start Prednisone 40mg/Kg START PREDNISONE **7,5mg/day**	9 months after start Prednisone 7.5 mg/day **STOP PREDNISONE**
UREA mg/dl	**153.97**	35.40	29	31.08
CREATININA mg/dl	**13.88**	1.63	1.02	1.12
PROTEINURIA	NEG	NEG	NEG	NEG
POTASIUM mmol/l	**6.48**	5.03	3.96	4.71
CHOLESTEROL mg/dl	**313. 24**	**355.90**	**299**	**256**
HEMATOCRIT	**29.50**	**31.60**	48.30	45.50
HEMOGLOBIN	**9.2**	**9.6**	15.60	14.90
URIC ACID mg/dl	**10.57**	6.22	3.97	5.40
ESR mm/1 h	**63**	**89**	33	23
CRP mg/l	**103.6**	**110.66**	13.95	8
WBC per mm^3	7,40	4,65	10	8,24
PSA ng/ml	1.73	1.73	1.73	1,45

Table 1. The Laboratory Values

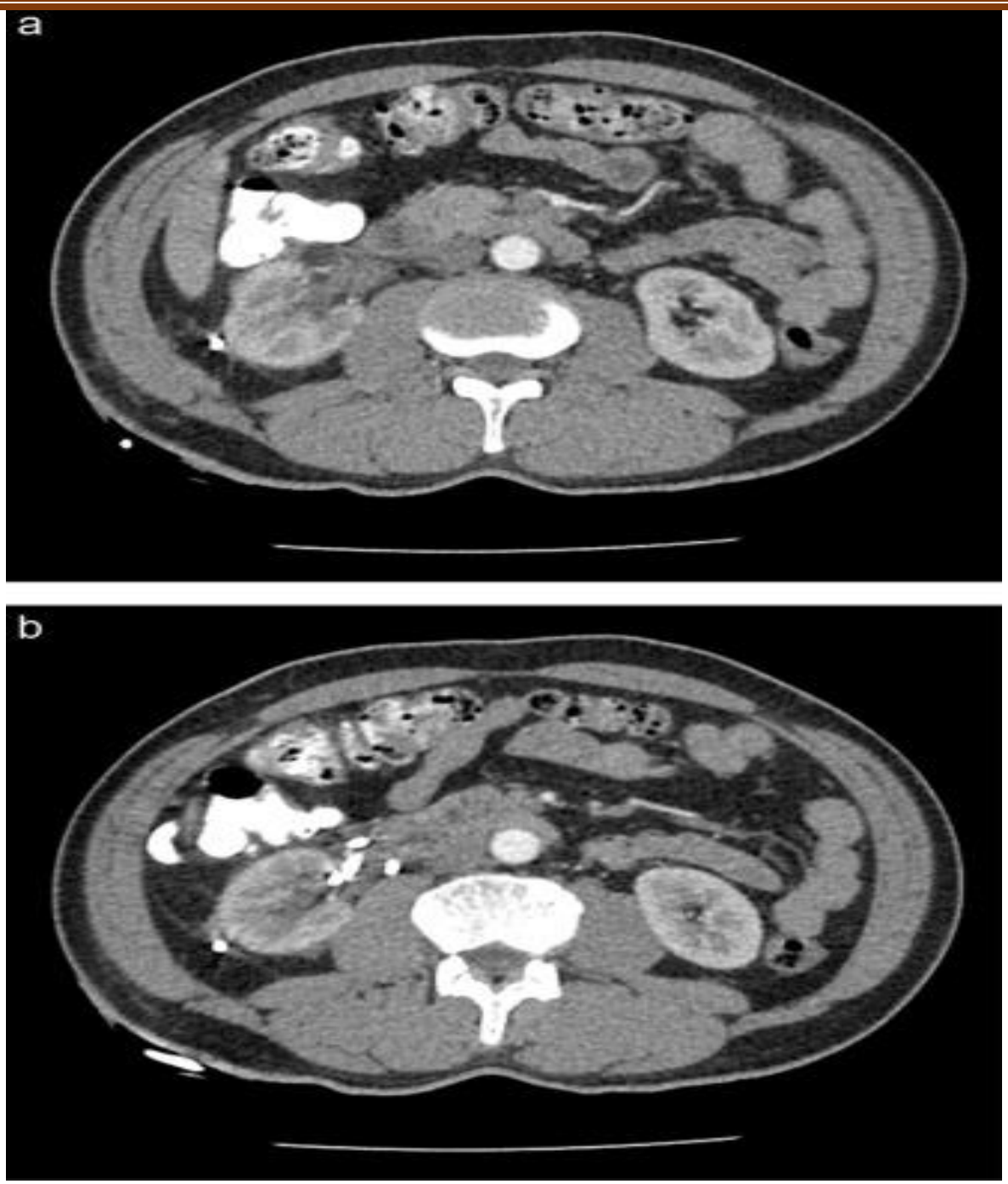

Figure 1. **CT Examination** demonstrating:

(a) Mass at the level of the renal hilum.

(b) Mass at the level of the renal hilum – nephrostomy visible in proximal ureter.

Into the Urology Service a right percutaneous nephrostomy tube was inserted as an emergency, and the patient's renal function subsequently decreased to : serum urea 35.40 mg/dl, serum creatinine 1.63 mg/dl, serum potassium 5.03 mmol/l. uric acid 6.22 mg/dl, but increased serum cholesterol to 355.90 mg/dl. **Table 1.** Intravenous urography demonstrated a dilated right ureter down to L3 with complete cut off **(Figure 2).**

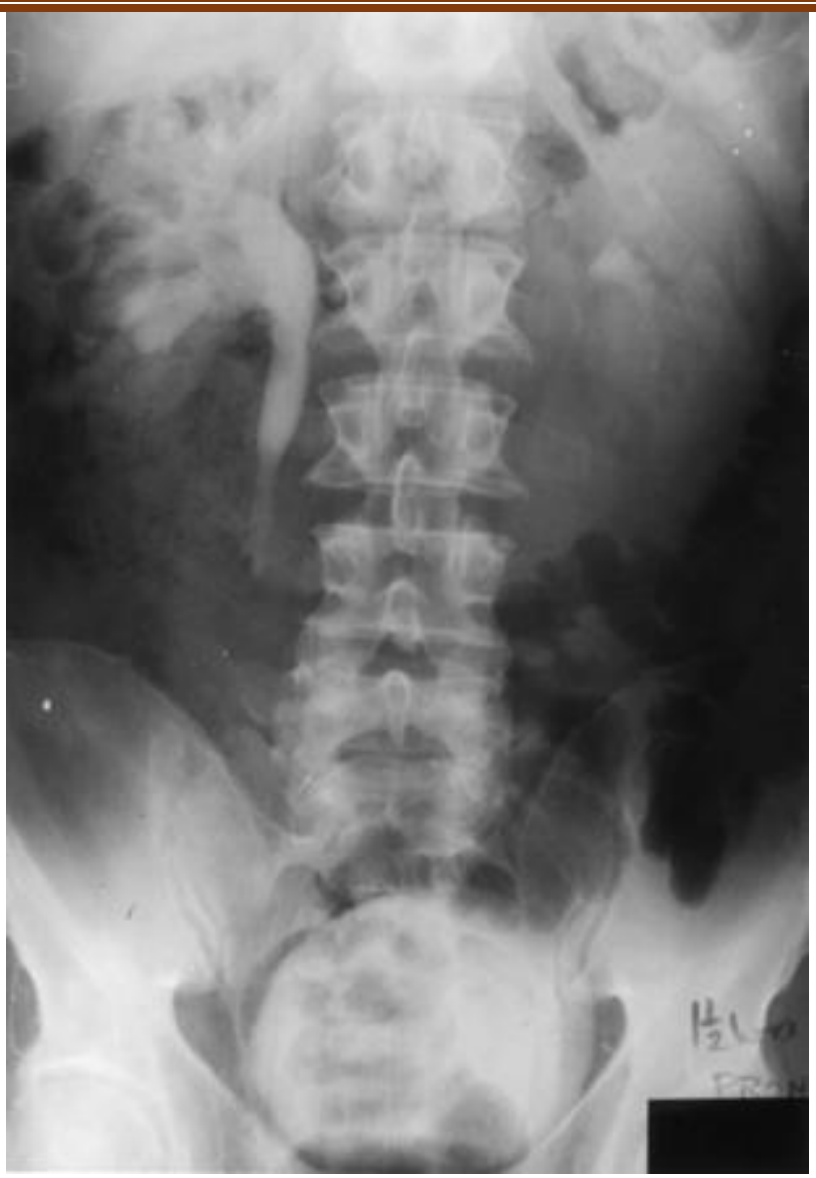

Figure 2. Intravenous urography demonstrating a dilated right ureter down to L3, with a complete cut off

A retrograde pyelogram showed right upper tract dilatation and complete obstruction, which seemed to be extramural. It was implanted a bilateral "double J" catheter, while diagnostic laparoscopic biopsy was perfected into the surgery service **(Figure 1 b).** The percutaneous nephrostomy tube, as well as the DJ stent were both removed within 6 weeks of the ureterolysis procedure when the patient had normal renal function and was currently asymptomatic .The patient was also started on high-dose oral glucocorticoid therapy due to the CT features and raised ESR suggesting RPF. Low-power magnification view of a retroperitoneal biopsy showed an admixture of moderate numbers of large elongated mononuclear cells of uncertain type (fibroblasts) and small numbers of mast; cells abundant and irregular fibrosis replacing normal retroperitoneal soft tissues, and inflammatory infiltrates are organized into lymphoid aggregate that is centered around a small retroperitoneal artery. The most common aspect consists into diffuse pattern of the inflammatory infiltrate, mainly consisting of lymphocytes and plasma cells that are diffusely interspersed within collagen bundles. In adipose tissue just outside the fibrotic area there were frequently small collections of lymphocytes, but no evidence of necrosis, vasculitis, or lymphatic blockage. Adipose cells appeared to break down only after being encircled by collagen. All of these aspects are suggestive for retroperitoneal fibrosis **(Figure 3 A,**

B, C, D).

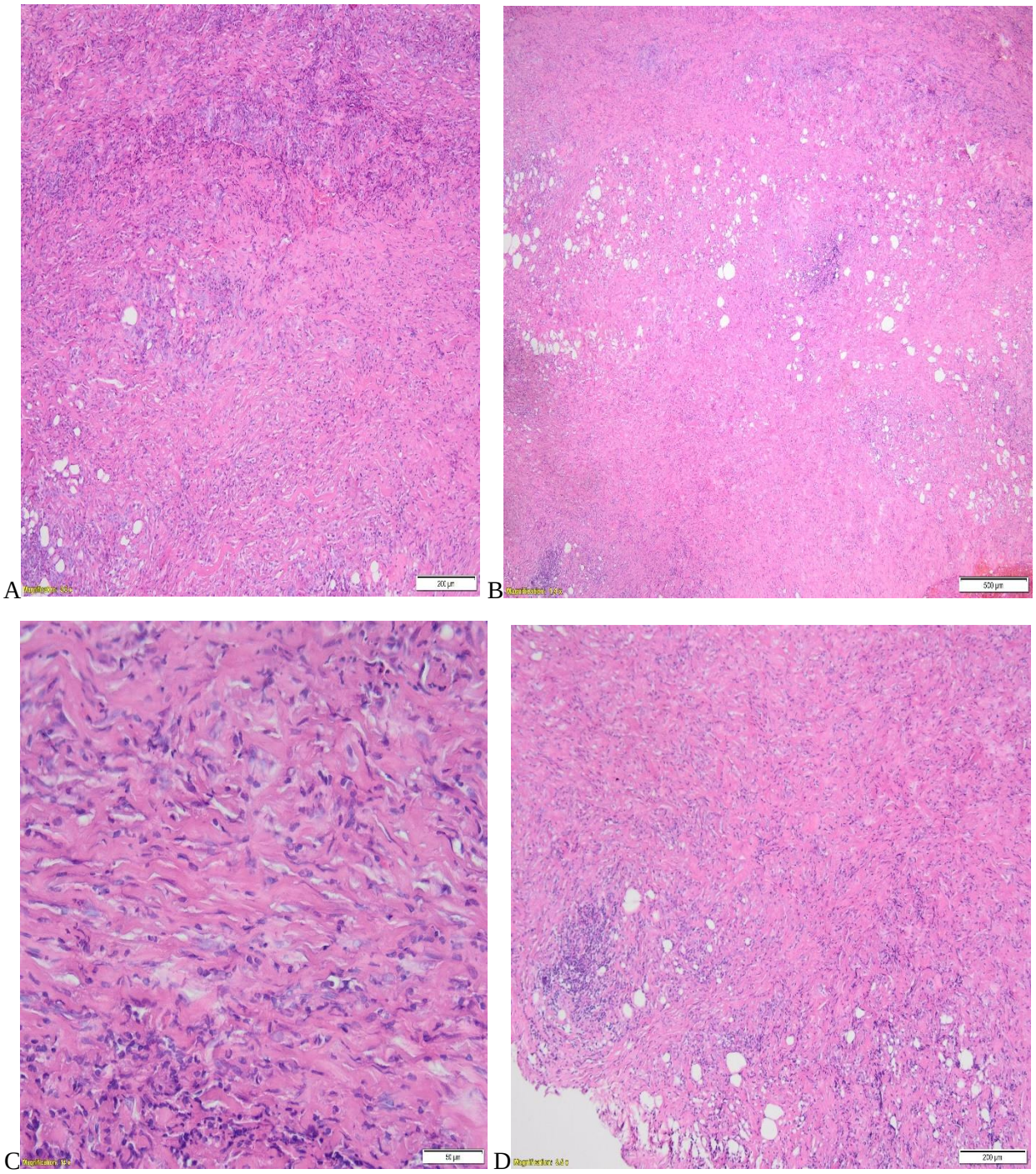

Figure 3. Histopathology demonstrating: (A) Low-power magnification view of a retroperitoneal biopsy showing abundant and irregular fibrosis replacing normal retroperitoneal soft tissues; diffuse and nodular inflammatory infiltrate with residual adipocyte cells (4x) (B) Conjunctive tissue with collagen aggregate, diffuse inflammatory and rare adipocyte cells (10x) (C) Abundant fibrosis with diffuse pattern of the inflammatory infiltrate diffuse and nodular (10x) (D) Fibrosis with collagen bundles and diffuse inflammatory infiltrate (arrows) (40x): Hematoxylin and eosin (A–D).

Immunohistochemical staining showed a specific type of retroperitoneal fibrosis consists in: Beta-Catenin positive into fusiform cells; Actin positive into abundant fusiform cells; CD30 positive into rare PMN; CD20

positive into lymphoid aggregate; Ki67 positive ~10%; ALK positive into fusiform cells.
The diagnosis of retroperitoneal fibrosis was based on intravenous urography and abdominal ultrasound: the patient was found to have right-sided hydronephrosis and proximal hydroureter findings of uretero-hydronephrosis and extrinsic ureteral compression, considered pathognomonic of retroperitoneal fibrosis. The diagnosis of retroperitoneal fibrosis was supported by CT scan findings and confirmed laparotomy findings and histology.
Glucocorticoids were rapidly effective, and the imagistic response was seen in the first weeks of treatment. Glucocorticoids was the first- and the only -line therapy, with initial doses of 0.75–1 mg/kg per day of prednisone for 3 months, gradually tapered to 5–7.5 mg/day within 9 months) , which began a progressive remission in the size of the observed mass by scan (CT) and magnetic resonance (MR). The treatment was completed with high dose of statins Atorvastatin 80 mg/day during 12 months and, in this time, the levels of serum cholesterol were reduced gradually too. The treatment during 12 months and in this time, the levels of blood urea nitrogen and creatinine were reduced gradually too.

Finally, at the end of the treatment, the magnetic resonance demonstrates the complete disappearance of the fibrosis. Behind of a 46-yr-old patient with history of severe untreated hypercholesterolemia who develop an obstructive renal failure due to periaortic retroperitoneal mass completed reversible with Atorvastatin and Prednisone and no more immunosuppressive treatment one question enforces: is retroperitoneal fibrosis a consequence of a local autoimmune reaction against atherosclerotic plaque antigens?

DISCUSSION

Epidemiology

Retroperitoneal fibrosis is a rare disease: occurs in 1 in 200,000 to 500,000 people per year, and the mean age is approximately 64 years [4]. The disorder occurs approximately twice as often in men as it does in women, but the reason for this difference is unclear. Most cases of retroperitoneal fibrosis are sporadic, which means that they occur in people with no apparent history of the disorder in their family. In rare cases, the condition has been reported to occur in a few members of the same family, but the inheritance pattern is unknown.

In one Finnish study, the incidence of the idiopathic form of the disease was estimated from hospital discharge data to be 0.1 per 100,000 person-years and its prevalence 1.4 per 100,000 inhabitants [5]. However, in a subsequent population-based study performed in the Netherlands, the reported annual incidence was approximately 10-fold higher (i.e., 1.3 per 100,000 inhabitants per year) [6]. The latter study probably provides a more accurate estimate of the incidence given the complexity of the diagnosis and requirement for prolonged follow-up that would not have been possible in a study of hospital discharge codes [7]. Inflammatory abdominal aortic aneurysms represent 4 to 10 percent of all abdominal aortic aneurysms [8]. No data are available about the incidence of secondary retroperitoneal fibrosis. Idiopathic disease most commonly occurs in individuals 40 to 60 years of age [6,9,10,11]. Most studies have suggested a 2:1 to 3:1 male-to-female predominance [6,9,10.11], although this is not reported in all studies [12,13]. There may also be a higher frequency of disease among people aged >60 years as compared with those who are younger [13].

Etiology

Retroperitoneal fibrosis may be idiopathic or secondary to other causes. Idiopathic retroperitoneal fibrosis is an immune-mediated disease, which can be either isolated, associated with other autoimmune diseases, or arise in the context of a multifocal fibroinflammatory disorder, named immunoglobulin G4-related disease (IgG4-RD). Although there are no standardized criteria of classification, idiopathic retroperitoneal fibrosis is part of the disease spectrum of chronic periaortitis, a condition characterized by inflammation and fibrosis surrounding the aorta and iliac arteries [12,14,15]. Chronic periaortitis (CP) also includes inflammatory

abdominal aortic aneurysms and perianeurysmal retroperitoneal fibrosis, two entities that are grouped together because of similar clinical and histologic characteristics, although pathogeneses and epidemiology may differ [5,6]. In approximately one-third of cases of CP, the perivascular tissue is not limited to the abdominal aorta and the iliac arteries but also involves the thoracic aorta and the origin of the epiaortic arteries (diffuse periaortitis), lending support to the hypothesis that CP is a large-vessel inflammatory disease [13].

Etiology of retroperitoneal fibrosis is summarized into:

1. idiopathic: Ormond disease (70% benign)
2. radiation
3. medication
    a. hydralazine
    b. beta blockers
    c. methyldopa
    d. ergotamine
    e. methysergide (a restricted medication for intractable headaches)
4. inflammation: pancreatitis, pyelonephritis
5. malignant: desmoplastic reaction, lymphoma
6. prolonged exposure to asbestos
7. retroperitoneal bleeding, e.g. after trauma or medical procedure
8. immune-mediated inflammation: sclerosing cholangitis, Riedel's thyroiditis ,ankylosing spondylitis ,uveitis ,systemic lupus erythematosus ,rheumatoid arthritis, ANCA-associated vasculitis, psoriasis , GN membranous nephropathy (MN) [18].

Clinical Presentation

The presenting signs and symptoms are non-specific; systemic manifestations (fever, anorexia, weight loss), often associated with local symptoms, are usually found to be related to the entrapment of retroperitoneal structures. The most common local symptom is lumbar and/or abdominal pain which is not position-dependent and has a transient relief with oral non-steroidal anti-inflammatory drugs. If the ureters are involved may develop a ureteric colic pain.

Laboratory Findings

Investigations include blood work-up, with a serum creatinine, a WCC and an ESR as the initial tests to be performed [18]. These are non-specific tests, but RPF tends to be associated with raised inflammatory markers, including a high ESR, as well as a raised C-reactive protein (CRP) level [19], [20]. *Although high baseline acute-phase reactants are associated with a more symptomatic disease, these parameters poorly predict response to therapy and do not correlate with mass regression.* [32,33] *Additionally, relapses commonly occur when acute-phase reactants are still normal*[34].

Is RPF an immune-mediated and autoimmune mechanisms play relevant pathogenic roles?

Blood tests that may be considered in RPF include those for autoimmunity work-up, such as anti-double-stranded DNA, anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies, and recently, raised IgG4 levels. IgG4 levels have been found to be increased with RPF, and a IgG4:total IgG has also been proved to be useful in that a higher ratio confirms the diagnosis [21]. Serum IgG4 levels may or may not be

raise*d: the exact proportion of patients with high serum IgG4, as well as the prognostic significance of this biomarker are still unknown.* Serum IL-6 is also high, reflecting an acute-phase response; its correlation with disease activity or prognosis is unexplored. Experimental studies on small cohorts showed that serum chemokines such as chemokine (C-C motif) ligand 11 (CCL11)/eotaxin-1 [35]. and CCL18[36]. are increased during active disease; CCL18 correlates with RPF thickness variations after therapy [36]. These patients also tend to present with features of autoimmune disease as opposed to the classical symptoms associated with RPF, including constitutional symptoms alone, generalized painless lymphadenopathy, autoimmune pancreatitis and sialadenitis [22], [23]. Renal dysfunction in these patients may also be caused by IgG4-related tubulo-interstitial nephritis, as opposed to the obstruction from RPF itself [9].It is becoming apparent that more cases that were previously labelled idiopathic RPF are actually IgG4-related RPF [24], [25]. The true importance of this finding is yet to be confirmed. However, given that many patients with IgG4-related RPF have associated autoimmune symptoms, it is important to specifically look for these symptoms in order to optimize overall patient care.

Idiopathic RPF, as part of the spectrum of chronic periaortitis, was initially viewed as a localized reaction to antigens contained in the atherosclerotic plaques of the abdominal aorta such as oxidized low-density lipoproteins [37]. Such antigens would be presented by plaque macrophages to lymphoid cells residing in the adventitia, where they would elicit a fibro-inflammatory response [38]. But: the disease can develop in patients without atherosclerotic lesions or involve vascular territories spared by atherosclerosis [39] and this theory cannot explain the complex clinical spectrum of idiopathic RPF, particularly the associations with autoimmune or fibro-inflammatory diseases involving other organs. These need an answer: is or not the pathogenesis of the disease multifactorial? The immunopathogenesis of idiopathic RPF are many arguments :$CD4^+$ T cells are abundant in idiopathic RPF biopsies [40]; in IgG4-RD lesions they show a T-helper 2 (Th2)-polarization and produce IL-4, IL-5, and IL-13, although regulatory T cells are also found [41]. In idiopathic RPF, it has been shown that T cells also locally produce IL-6, which can activate B cells and fibroblasts. B lymphocytes account for a high proportion of infiltrating cells and may be precursors of plasma cells; Th2 cytokines may induce the enrichment of the $IgG4^+$ plasma cell subset, although this has not yet been proven in RPF.The pathogenic importance of the IL-6–mediated axis and of B cells was confirmed *in vivo* by the efficacy of therapies targeting the IL-6 receptor (tocilizumab) [42] and the B cell marker CD20 (rituximab) [43] but it must be acknowledged that these data are limited to small case series. Th2 responses are often characterized by tissue eosinophilia, which is also observed in idiopathic RPF and IgG4-RD. Tissue recruitment of eosinophils can be driven by chemokines such as CCL11/eotaxin-1, whose tissue expression and serum levels are high in idiopathic RPF. Eotaxin-1 also induces recruitment of mast cells, which have been found in idiopathic RPF lesions. Notably, in idiopathic RPF biopsies, eosinophils and mast cells strongly express CCR3, the receptor for CCL11/eotaxin-1[35]. Eosinophil and mast cell products (*e.g.*, eosinophil granule proteins, tryptase) stimulate fibroblast proliferation and collagen production. [35]. Fibroblasts can also be activated by CCL18, a chemokine whose serum levels are increased in idiopathic RPF[36].

Radiographic Features

Contrast-enhancing fibrosis encasing the retroperitoneal structures causing ureteric and vascular obstruction and displacement. Displacement of the aorta and IVC anteriorly away from the vertebral bodies is suggestive of malignant etiology. Invasion and disruption of bone and/or soft tissue structures suggests an aggressive process - infection or malignancy. Multiple sub centimeter lymph nodes are frequently seen in non-malignant RPF, probably reactive secondary to the disease process, and should not be confused for malignancy [2,4,12,16,17,19].

- Fluoroscopy: IVU

While largely superseded by cross-sectional imaging techniques, a classic triad is described [2,4,16,17.19]:

1. medial deviation of the middle third of the ureters
2. tapering of the lumen of one or both ureters in the lower lumbar or upper sacral region
3. proximal unilateral or bilateral hydroureteronephrosis with delayed excretion of contrast material (reported in over half of cases and thought to be due to impaired peristalsis)

- CT

Retroperitoneal fibrosis is visible as a soft tissue density mass located around the aorta and iliac arteries. Classically, it develops around the aortic bifurcation and spreads upwards where it can envelop the renal hila. It encases but does not invade or stenose the ureters or vessels. However, ureteric obstruction and venous thromboses can occur. In early or active stages variable enhancement can be seen with intravenous contrast while no enhancement may be seen in the quiescent disease [16,17, 18, 21].

- MRI

MRI has been reported to be as sensitive as CT in its assessment of retroperitoneal fibrosis with the added advantage of high contrast resolution between closely apposed retroperitoneal structures. It can evaluate the urinary tracts using fast T2 weighted spin-echo sequences without requiring intravenous contrast in patients with impaired renal function. The soft tissue mass is usually dark on T1W and T2W unless there is an active inflammation whereby the T2W images can be hyperintense [17, 18, 21].

- FDG-PET

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) uptake will be seen in active inflammation and absent in metabolically inactive disease [17, 18, 21], but has little diagnostic utility because many infectious, inflammatory, or neoplastic lesions also accumulate ^{18}F-FDG.

Retroperitoneal biopsy is usually performed (via open, laparoscopic, or CT-guided approaches) in cases with atypical localization (*e.g.*, periureteral, perirenal) [44], or with clinical or imaging findings consistent with neoplastic RPF[45] . The percentage of biopsy-proven cases varies widely among series, with a range of 24%–77%[46]. In the early stages of retroperitoneal fibrosis, there is active chronic inflammation. Large numbers of lymphocytes, plasma cells, and macrophages are interspersed in a framework of fibroblasts and collagen bundles. In late stages, there is progression to fibrous scarring. The tissue becomes avascular and acellular with scattered calcification amongst collagen bundles. Ureteral, nerve, aortic and iliac artery compression is frequently described.

Differential diagnosis

Imaging differential considerations include:

- retroperitoneal lymphoma: non-lymphomatous RPF is often seen centered at L4/5 level; if the disease is centered cranially to L4/5, consider lymphoma [2,12,16,17].
- retroperitoneal sarcomas and retroperitoneal metastases from various types of carcinomas [49]: *carcinoids* can cause RPF– through as yet unclear mechanisms– even without metastasizing to the retroperitoneum[50] .
- retroperitoneal Erdheim-Chester disease: a non-Langerhans histiocytosis that – unlike idiopathic RPF – tends to infiltrate the perirenal space [47].
- retroperitoneal extramedullary hematopoiesis (rare)
- pelvic actinomycosis may mimic pelvic RPF and should be suspected particularly in women with a history of intrauterine device use[48].

- tuberculosis can spread into the retroperitoneum from neighboring foci or be disease-triggering when located distantly[51] .
- recent reports described RPF developing during anti-TNFα therapy for rheumatoid arthritis[52]
- Takayasu and giant-cell arteritis can cause diffuse aortic thickening and thus mimic RPF, but they lack retroperitoneal diffusion and ureteral involvement[13]
- radiotherapy, major abdominal surgery, and trauma are uncommon causes of RPF.

Treatment and prognosis

Both surgical and medical managements have been used in RPF. The first goal of treatment is the relief of ureteral obstruction. Surgical ureterolysis with intraperitonealization and omental wrapping of the ureters is no longer the first-line approach, and conservative procedures (*e.g.*, double-J stent or nephrostomy placement) followed by medical therapy are preferred [53].Ureteral stenting allows better quality of life than does nephrostomy and is usually successful; however, stents and nephrostomies have comparable complication rates (*e.g.*, infection, obstruction). [54] Although no guidelines exist, when ureteral obstruction is mild and there is no kidney function impairment, it seems advisable to start medical therapy without urinary drainage. Steroids may also reverse the ureteral obstruction within a few days and may improve the biological markers of inflammation and the systemic symptoms of the disease [26]. For these reasons, steroid therapy is often associated with ureterolysis, but uncertainty still exists as to the optimal dosage and duration of steroid therapy. Medical management includes the use of high-dose steroids initially, and then tapering to chronic low-dose continuation therapy [19,27]. However, much controversy exists regarding the optimal dosage and dosing schedule. One regimen that has been suggested involves using 60 mg of prednisolone on alternate days for 2 months, and then tapering down to 5 mg on alternate days over the following 2 months [27]. A successful treatment regimen is regarded as improved symptoms, as well as regression of the mass and normalization of the ESR [19,27].

Other methods of medical management have been used, including: azathioprine, tamoxifen, and pulses of methylprednisolone ,mycophenolate mofetil[18], [21], [28]. Rituximab has been used for IgG4-related disease in an off-label capacity [23]. Actually, there are 10 medical studies ongoing reported by Clinical Trial. Gov involving Sirolimus, Prednisone versus Tamoxifen, Methotrexate, Rituximab, Rituximab and Revlimid, Leflunomide as new alternative for the treatment of retroperitoneal fibrosis. Tamoxifen, an anti-estrogen agent with potential antifibrotic activity, has been proposed as an alternative to glucocorticoids particularly in patients experiencing steroid-related toxicity or when there are contraindications to glucocorticoids [55]. However, in a randomized controlled trial, an 8-month treatment with tamoxifen was significantly less effective than a treatment with prednisone of equal duration in maintaining remission in patients treated with prednisone induction (1 mg/kg per day for 1 month) [56]. Therefore, to date, the efficacy of tamoxifen is not supported by controlled trials and its superiority to other agents is unproven.

In the presence of a urinary obstruction, the aim of the initial management should be to restore the patency of the urinary tract and to improve renal function. Placement of stents or nephrostomy may be used as an emergency treatment, followed by ureterolysis that may be performed either by open surgery or by laparoscopy. The advantages of surgery are the relief of obstruction with a recovery of renal function in about 70% of cases [29] and the possibility of taking samples of the invading mass to rule out lymphomas or metastatic cancer. However, obstruction may recur in about 22% of responders [30]. Moreover, surgery does not relieve the systemic manifestations of the disease that affect the majority of patients. Therefore, corticosteroids alone or together with immunosuppressive agents have been used either in association with surgery or to avoid the use of ureterolysis [21,23,24].

Follow-up routines also vary, but include symptom assessment and ESR monitoring every 3–6 months, laboratory examinations, periodic ultrasound (to monitor hydronephrosis and aneurysmal dilatation) and CT/MRI studies [27] (able to accurately define size and morphologic changes of RPF) to allow early detection of relapses. There are few data about residual renal insufficiency after surgical or medical treatment. By

reviewing some of the most representative articles, we found that 27–50% of patients recovered only partial renal function [20, 22, 31].

CONCLUSION

Retroperitoneal fibrosis (RPF) is a severe and an immune-mediated disease, that may progress until completely blocking the ureters and the blood vessels involved by the process. Idiopathic RPF, as part of the spectrum of chronic periaortitis, was initially viewed as a localized reaction to antigens contained in the atherosclerotic plaques of the abdominal aorta such as oxidized low-density lipoproteins .Such antigens would be presented by plaque macrophages to lymphoid cells residing in the adventitia, where they would elicit a fibro-inflammatory response But: the disease can develop in patients without atherosclerotic lesions or involve vascular territories spared by atherosclerosis and this theory cannot explain the complex clinical spectrum of idiopathic RPF, particularly the associations with autoimmune or fibro-inflammatory diseases involving other organs. These need an answer: is or not the pathogenesis of the disease multifactorial?

To date, there are no guidelines for the diagnosis of or therapy for the disease. If untreated, the disease may be fatal. A prompt diagnosis is an early diagnosis, but it is as difficult as it is important. Retroperitoneal fibrosis should be considered in the differential diagnosis whenever diffuse abdominal pain is associated with ureteral or great vessels compression. Due to the rare nature of the disease, and the variability in patient response to treatment, it is difficult to truly assess which treatment regimen is optimal.

Life-long observation of the patients is necessary, as the disease may be chronic and relapsing. Interdisciplinary and nationwide cooperation is of crucial importance to further investigate this disease.

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