Retroperitoneal fibrosis

Demographic, clinical and pathological findings

Kamal E. Bani Hani, *MD, FRCS,* ***Ibrahim H. Bani Hani,*** *MBChB, FRCS,* ***Hussein A. Al-Heiss,*** *MBChB, FRCS,* ***Hamza Z. Omari****, MBChB, FRCR.*

ABSTRACT

Objectives: To describe the clinical characteristics of patients with retroperitoneal fibrosis including the etiopathogenesis, clinical features, diagnostic criteria and effective treatment of the disease.

Methods: This study was carried out at Princess Basma Teaching Hospital, Irbid, Jordan, during the year 2001. Records of 15 patients with retroperitoneal fibrosis were retrospectively reviewed. Demographic, clinical and pathological criteria was evaluated and analyzed.

Result: From 1990 to 2000, there were 15 patients seen with retroperitoneal fibrosis (10 men and 5 women; the mean age was 55.8 years, ranging between 39 years to 75 years). Nine cases were idiopathic and 6 were secondary. Risk factors of the idiopathic group were cigarette smoking (6 patients) and arterial hypertension (4 patients). Etiologic factors of the secondary group were aortic abdominal aneurysm (3 cases including one following abdominal aortic surgery), radiation therapy for seminoma (one case), ergot-derivative treatment (one case), retroperitoneal non-Hodgkin lymphoma (one case). Main presentations were abdominal or back pain, or both. Treatment performed was medical in 5 cases, medical and endourological in 3 cases and 7 patients received surgical treatment. Medical treatment induced remission in 3 patients, while endourological and surgical treatment resulted in complete recovery in 9 patients (including the 2 patients who failed medical treatment). In the remaining 3 patients treatment failed and the disease relapsed.

Conclusions: An awareness of this rare disorder is important to prevent misdiagnosis. Retroperitoneal fibrosis remains a difficult therapeutic challenge. Aggressive medical, endourological or surgical treatment, or both are equally good modalities for its treatment.

Keywords: Retroperitoneal fibrosis, fibrosis, retroperitoneum.

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Retroperitoneal fibrosis (RPF) is an uncommon fibro-inflammatory disease of the retroperitoneum that is being diagnosed with increasing frequency.[1,2] It is characterized by development of extensive fibrosis throughout the retroperitoneum that leads to consecutive obstruction of adjacent organs. The etiology, clinical presentation, diagnostic criteria and the proper treatment are still debatable. Herein this disorder is retrospectively reviewed in 15 patients in order to report on the features of the disease and its treatment.

Methods. Medical records of patients with proved RPF who were managed at Princess Basma Teaching Hospital in Irbid, Jordan between 1990 through to 2000 were retrieved, to assess the etiology, clinical presentation, diagnostic work up, treatment modality and follow-up. The study was carried out during the year 2001 at Princess Basma Teaching Hospital, Irbid, Jordan. According to protocols of Surgical/Urological Departments, all suspected cases supposedly had biochemical evaluation of renal function, urine analysis and

From the Department of Surgery, (K. Bani-Hani, Al-Heiss), Department of Urology, (I. Bani-Hani), and the Department of Radiology, (Omari), Princess Basma Teaching Hospital, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan.

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Address correspondence and reprint request to: Dr. Kamal E. Bani-Hani, Associate Professor, Department of Surgery, Faculty of Medicine, Jordan University of Science and Technology, PO Box 1055, Irbid 22110, Jordan. Tel. +962 (79) 500014. Fax. +962 (2) 7060300. E-mail: kamal@just.edu.jo

culture, renal ultrasound evaluation and intravenous urography. If RPF was suspected, computerized tomography (CT) scan was carried out to elucidate possible causes and to classify the case to either idiopathic retroperitoneal fibrosis (IRF) or secondary to other pathology. For the idiopathic group, the treatment modalities were medical with immunosuppresion agents or tamoxifen. For the other cases including those who failed the medical treatment, endourological or surgical intervention, or both were contemplated. Follow up was at the outpatients' clinics of surgery and urology.

Results. Records of 15 patients with RPF were identified, 10 men and 5 women, the mean age was 55.8 years, ranging from 39 years - 75 years. Nine cases were idiopathic and 6 secondary. **(Table 1 & 2)** Etiologic factors of the secondary group were perianeurysmal (3 cases, one of them following an aorto-femoral dacron graft bypass), radiation therapy for stage one seminoma (one case), ergot-derivative treatment (one case), and retroperitoneal non-Hodgkin lymphoma (one case). Of the idiopathic group, 6 were smokers, while 4 were hypertensive. The main presentation was abdominal or back pain, or both. Eight patients demonstrated unilateral and 5 cases had bilateral hydronephrosis with impairment of renal function, in the remaining 2 patients no dilatation was observed. Twelve patients received oral immunosuppressive agents (prednisolone one mg/kg, azathioprine one mg/kg/day), and the remaining 3 patients received tamoxifen 20mg/day, for 3 months before re evaluation was performed. In the case of complete remission, medication was continued for another 3 months, in the case of stable disease or progression, surgery was performed. Treatment performed was medical in 5 cases and endourological in 3. Surgical intervention was required in the remaining 7 patients in addition to the 2 patients that did not respond to medical treatment. In 12 cases (6 primary RPF, 6 secondary RPF) with hydronephrosis the initial management consisted of DJ-stent placement, whereas in one case (primary RPF) percutaneous nephrostomy had to be placed.

Three out of the 5 patients demonstrated complete remission after oral prednisolone/azathioprine (2 patients), or tamoxifen one patient, and CT scan showed a significant decrease of the fibrotic periaortic mass at 12 months, we then stopped medical treatment. Three patients had endourologic treatment in addition to the medical therapy, and all of them showed complete remission. Patients who were subjected to surgical intervention received preoperative corticosteroid treatment. In 5 cases (4 primary RPF, one secondary RPF) ureterolysis with intraperitoneal displacement and omental wrapping was performed; in another one case bilateral ileal replacement of the ureters had to be performed, nephrectomy was performed in one patient. In 2 cases in which the medical treatment failed, ureterolysis with intraperitoneal displacement was performed. The ureterolysis was performed intraperitoneally in 5, and by placement of the ureter in a lateral extraperitoneal position in 2 cases. Three cases remained on DJ-stents and nephrostomy. Postoperatively, all patients were continued on immunosuppressive medication for another 3 months. After a follow-up of 10 to 115 months only 3 patients developed a retroperitoneal recurrence and were treated by unilateral nephrectomy (N=one) or DJ stent placement (N=2). The only patient with

Table 1 - The characteristics of the 9 patients with idiopathic retroperitoneal fibrosis.

Sex	Age	Risk Factor	Main Presentation	Hydronephrosis	Treatment
Male	45	Smoking	Abdominal pain and hematuria	Unilateral	Medical
Male	65	Hypertension	Abdominal mass	No	Medical*
Female	42	Smoking	Abdominal pain	No	Medical
Male	52	Smoking	Obstructive acute renal failure	Bilateral	Ureteric stents
Female	70	Smoking and Hypertension	Left hydronephrosis	Unilateral	Percutaneous nephrostomy
Male	42	Hypertension	Right hydronephrosis	Unilateral	Ureterolysis
Male	51	Smoking	Left hydronephrosis	Unilateral	Ureterolysis
Male	55	Smoking	Left hydronephrosis	Unilateral	Ureterolysis
Female	63	Hypertension	Right hydronephrosis	Unilateral	Ureterolysis
* - Medical treatment failed in this patient, and he subsequently had ureterolysis					

Table 2 - The characteristics of the 6 patients with secondary retroperitoneal fibrosis.

Sex	Age	Etiology	Main Presentation	Hydronephrosis	Treatment
Male	39	Radiation/Seminoma	Left hydronephrosis	Unilateral	Medical*
Female	52	Ergot	Abdominal pain	Bilateral	Medical
Female	46	Lymphoma	Obstructive acute renal failure	Bilateral	Ureteric stents
Male	69	AAA	Intermittent claudication	Bilateral	Ureterolysis
Male	71	Aortic graft	Incidental retroperitoneal mass	Unilateral	Nephrectomy
Male	75	AAA	Intermittent claudication	Bilateral	Bilateral ileal replacement

* - Medical treatment failed in this patient, and he subsequently had ureterolysis, AAA - abdominal aortic aneurysm

malignant retroperitoneal fibrosis survived only for 5 months despite medical care and chemotherapy.

Discussion. Retroperitoneal fibrosis is an uncommon collagen vascular fibro-inflammatory disorder of the retroperitoneum that leads to development of dense fibrous mass throughout the retroperitoneum which usually involves the periureteric area **(Figure 1)** more often than the periaortic region **(Figure 2)** and often leads to ureteral entrapment and subsequently ureteral obstruction and hydronephrosis **(Figure 3)**.[1-4] Up to 15% of patients have additional fibrotic processes outside the retroperitoneum.[1] The clinical course of this disease is insidious, although it can sometimes take an acute course. It occurs at any age, but the peak incidence is between 40 years and 60 years of age.[5] The clinical features are not specific, but back pain is a common finding.[4] Hypertension could be the presenting feature in patients with RPF as a result of renal insult, as illustrated in 4 of our patients, in whom RPF was diagnosed during evaluation of their hypertension. Hypertensive encephalopathy was reported in patients with RPF.[6] Retroperitoneal fibrosis should be included in the investigative protocols in hypertension management. The renin-angiotensin system plays an important role as angiotensin 2 is known to induce renal fibrosis associated with increased transforming growth factor beta (TGF)-beta and the appearance of myofibroblasts.[7] As a result of periureteral encasement, acute renal failure secondary to obstructive nephropathy occurs. This is illustrated in our patients as 8 of them demonstrated unilateral and another 5 had bilateral hydronephrosis with impairment of renal function. In addition to ureteric obstruction, RPF can cause arterial or iliac vein occlusions, duodenal obstruction, intrinsic common bile duct stricture, and testicular encasement.[8-12] Deep venous thrombosis can be an unusual manifestation.[13] Rupture of the renal pelvis, subcapsular urinoma, and encasing of the left renal vein with secondary renal vein hypertension causing dramatic gross hematuria has been reported as a complication of IRF.[14-16] On

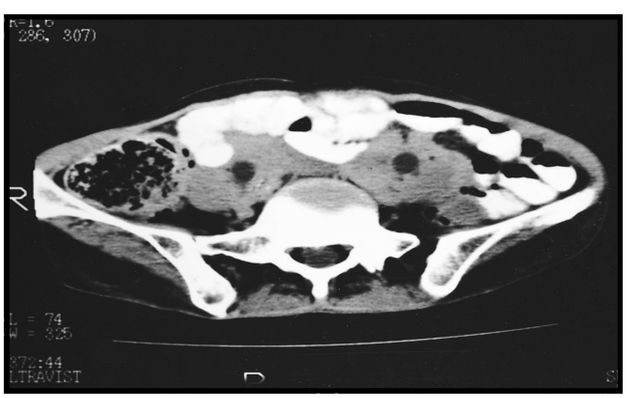

Figure 1 - Abdominal computerized tomography scan showing bilateral periureteric dense fibrosis.

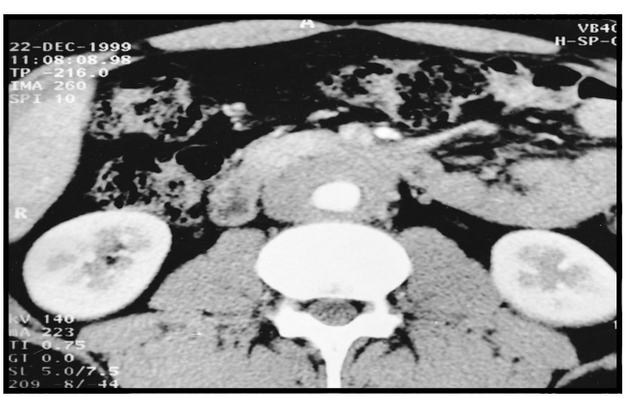

Figure 2 - Abdominal computerized tomography scan with intravenous contrast showing periaortic dense fibrosis.

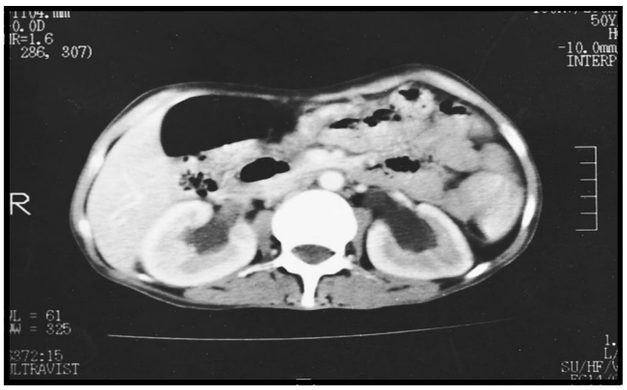

Figure 3 - Abdominal computerized tomography scan for the same patient as Figure 1 showing bilateral hydronephrosis as a result of ureteral entrapment and obstruction.

the other hand RPF can be part of the Erdheim-Chester disease.[17]

The etiology of RPF has not been clearly established up to now. Retroperitoneal fibrosis has been observed to be associated with Riedel's thyroiditis, immune complex membranous glomerulonephritis, chronic sclerosing sialadenitis, breast sclerosing lobulitis, Sjogren's syndrome, antiphospholipid syndrome, primary biliary cirrhosis, carcinoid tumor, seronegative spondylarthropathy with iritis and a number of different possible inciting factors.[5,18-25] These associations might result from a particular systemic immune response to an unknown antigen.[19] It is suggested that the fibrosis process is an exaggerated reaction to an inciting inflammatory event.[26] An autoimmunological mediated process has been suggested in which an antigen derived from atherosclerotic plaques penetrate into the periaortal space through the atheromatic wall of the aorta.[23] There is a well-established relationship between the atherosclerotic abdominal aorta and RPF.[27] Fifty percent of our patients in the secondary group developed perianeurysmal RPF (3 out of 6 cases, one of them following an aorto-femoral Dacron graft bypass). The association of RPF with inflammatory aortic aneurysm has been reported.[28] The RPF patients had a higher percentage of abdominal aortic aneurysms, however, atherosclerosis as determined by abdominal aortic calcifications is not enough to provoke IRF.[3] Two of our patients had malignancy, one developed RPF secondary to radiation therapy for stage one seminoma, and the 2nd patient had retroperitoneal non-Hodgkin lymphoma. Malignant RPF was reported in 20% of patients in one series.[1] Retroperitoneal fibrosis secondary to radiation has been also reported before.[2]

In one of our patients, RPF was secondary to pergolide treatment. Pergolide and other agents such as cocaine, intraperitoneal chemotherapy, barium, methysergide, and other dopamine agonists can be complicated with RPF.[29-34] Drug induced RPF is usually silent and needs on average 2 years to develop, which necessitates a high index of suspicion, regular monitoring and meticulous follow up.[29] The lack of specificity of the symptoms of RPF makes early diagnosis difficult and abdominal CT scan with intravenous contrast or magnetic resonance imaging (MRI) is essential for differential diagnosis of abdominal masses.[35] The association of fibrous periaortic tissue with high erythrocyte sedimentation rate supports the diagnosis and the histology will confirm it and differentiate between benign and malignant RPF.[4] The diagnosis of IRF by fine needle aspiration requires supportive clinical and radiologic data and systematic evaluation of entities in the differential diagnosis.[36]

There is so far no optimal treatment for RPF as there is no consensus on the current standard therapy. Medical treatment (tamoxifen, corticosteroids or immunosuppressive drugs), endourological procedures, or surgery, each in its own, or in combination are proposed. Tamoxifen has been shown to inhibit the proliferation of fibroblasts cultured from keloid biopsies.[37] Treatment of RPF with tamoxifen has been reported, but the duration and effectiveness of treatment are still unclear as few cases have been reported in the literature.[38] Corticosteroids, in conjunction with surgery when needed, are the mainstay of therapy. Heidenreich et al[2] reported that combination of both immunosuppressive medication and surgical management results in an excellent long-term outcome in IRF with a recurrence rate of only 8% and primary reconstructive surgery appeared to be the most promising approach in secondary RPF with a recurrence rate of only 5%. Breems et al[3] evaluated the relapse rate of surgery versus medical treatment in 9 patients with IRF, and they reported that no superiority of corticosteroids over surgical treatment could be demonstrated. However, their study was too small and retrospective. Messinetti et al[27] suggested that surgical therapy plays a fundamental role in the management of RPF, but the use of medical treatment is to be considered extremely promising. Seven of our patients had ureterolysis (intraperitoneally in 5, and extraperitoneally in 2 cases). There were no differences in the outcome between the 2 approaches. Similar findings were reported before and the intraperitoneal approach was considered as an unnecessary manoeuvre.[39] Recently laparoscopic approach for the treatment of RPF has been reported.[40]

In this retrospective study we reported on the management of 15 cases of RPF. The current concepts with respect to RPF etiology, pathogenesis, associations and management are summarized. A review of the literature is also presented.

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