Management of Idiopathic Retroperitoneal Fibrosis, a Retrospective Study at Prince Hussein Urology and Organ transplantation center (PHUO), Jordan

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Introduction. to study the presentation, clinical course, laboratory results, imaging findings, medical and urological treatments of idiopathic retroperitoneal fibrosis at our institution.
Methods. Between January 2006 and December 2017, medical records and operatives' notes of 116 patients with idiopathic retroperitoneal fibrosis (IPRF) were reviewed retrospectively. Diagnosis was done by clinical and radiological imaging that fulfilled a strict criterion. All patients were initiated on Prednisolone 60 mg for two months, and reduced until reaching 10 mg daily, with a total duration of 24 months in the responding patients. Renal drainage was done in cases of obstructed kidneys. To assess response, both laboratory results and imaging studies at initiation and after 4 months were reviewed and compared.
Results. Of 116 patients diagnosed with IRPF, eighty five (73.3%) were male and thirty one (26.7%) female, with mean ± SD age at presentation was (50.5 ± 10.6) years. 79% of the patients complaint of abdominal and low back pain, 27% uremic symptoms, 10.3% had a new onset of hypertension, 3.4% presented with anejaculation, and 13.8% were totally asymptomatic. Uretric obstruction had been resolved in 132 ureters after a mean of 152 days of treatment. Almost 30 % reduction in the fibrotic mass size was achieved in 82 % of patients.
Conclusion. Glucocorticoids is the the mainstay of treatment. The renal function tests, of the vast majority of patients, normalized with treatment. Relapse may occur, so a follow-up over a long period of time is required. A high index of suspicion is needed for diagnosis in asymptomatic patients.

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INTRODUCTION

Retroperitoneal fibrosis (RPF) is an uncommon pathology with an unknown pathogenesis.[1] It is characterized by development of fibrosis in the retroperitoneum. The etiology is unknown in the majority of the cases, thus it is called idiopathic RPF. The disease is characterized by gradual onset of non-specific systemic symptoms and low back pain or dull flank pain that is generally not responding to simple analgesics.[2] Both medical and surgical managements are being used,[3] but until now, there is no consensus regarding the

appropriate treatment of this disease. In this retrospective study, we described the clinical presentation, laboratory and imaging results, medical and urological managements, and the outcomes of patients with IRP who were treated by urologists in our institution.

MATERIALS AND METHODS

We looked into the medical files of 132 patients who were diagnosed with IRF and managed at our institution from January 2006 to December 2017, retrospectively. Patients were identified using the International Classification of Disease Tenth Revision Code. Patients were enrolled in this study if they fulfilled the following criteria determined by a contrast enhanced abdominal computed tomography, which was used by Scheel PJ:[4] (1) a soft tissue mass enchasing the infrarenal aorta or iliac vessels, (2) absence of infrarenal aortic aneurysm, (3) no intra abdominal or pelvic mass apart from periarrtoritis, (4) no suspicion of malignancy based on history and physical examination. Sixteen patients were excluded because initially they were diagnosed and treated as retroperitoneal fibrosis and later found to have retroperitoneal malignancy based on CT scan guided biopsy results.

Patients' admission notes, follow-up notes, operative notes, initial laboratory results, imaging findings, and treatments were reviewed retrospectively. All patients were followed up monthly through complete blood count (CBC) and kidney function tests (Cr, BUN) and serum electrolytes. Non-enhanced abdominal computed tomography (CT) scans with intravenous contrast were performed during the first visit and every 3-6 months afterwards (A contrast enhanced CT scan was done if creatinine was less than 1.5 mg/dL).

All patients were treated with Prednisolone 60 mg/d for two months. If imaging findings and laboratory results showed improvement, then the dose was decreased to 40 mg/d. After that, steroid was tapered by five milligrams every two weeks until up to 10 mg/d achieved. The total duration of Prednisolone use was nearly 24 months. Regular follow-ups were done until the patient either missed a follow-up at our outpatient urology clinic or passed away; whichever came first.

The initial contrast enhanced CT-scans were reviewed by experienced radiologists blinded to the final diagnosis. At least two measurements were obtained for each mass at each imaging phase, and their mean attenuation values were recorded. Lesions found to be on one side of the aorta were regarded to be a unilateral location. The contrast enhanced abdominal CT-scans performed after completion of therapy were compared to the initial CT-scans, and the mean ± SD of mass size was calculated and compared.

Patients who presented with unilateral or bilateral ureteral obstruction underwent either a retrograde ureteral stent insertion, or ultrasound fluoroscopic guide percutaneous nephrostomy tube insertion in prone position if not fit or a candidate for general anesthesia. Patients who presented with acute renal failure and symptoms of uremia or hyperkalemia, underwent urgent dialysis followed by percutaneous nephrostomy tube insertion and later antegrade ureteral stent insertion size 6F. The decision for ureteral stent removal was based on laboratory results and resolution of obstruction in the imaging study. Patients who showed sustained ureteral obstruction for more than six months, underwent cystoscopy with retrograde ureteric stent change under C arm fluoroscopy. After 24 months of Prednisolone therapy, the initial Cr, ESR, mean hematocrit values, patient symptoms, and retroperitoneal fibrotic mass size were compared.

We got approval from the ethical and research committee in our institution for publication. Oral informed consents were taken from all patients. We used SPSS software (version 24) for all statistical analyses. Most of the data was presented in the form of descriptive statistics. For categorical data analysis, we used chi-square tool. Paired t-test was used to compare mean initial and post medical treatment values. *P* values were considered statistically significant when < .05.

RESULTS

Out of 116 patients diagnosed with IRF, 85 (73.3%) were males, and 31 (26.7%) were females, with a 2.7:1; male:female ratio. The mean ± SD age at diagnosis was 50.5 ± 10.6 (28-68) years and the mean ± SD duration of therapy was 24.5 ± 1.68. With regards to the most presenting symptoms, abdominal and low back pain accounted for 79%, acute renal failure and uremic symptoms for 27%, new onset hypertension for 10.3%, and anejaculation for 3.4% while 13.8% of patients were totally asymptomatic.

Table 1. Shows the Laboratory Data at Baseline and After Completion of Medical Therapy

Lab Tests	Presentation		Follow-up		
	Range	Mean (± SD)	Range	Mean (± SD)	*P*
ESR	40 - 85	63.3 ± 11.0	8 - 18	11.8 ± 3.3	< .001*
Hct, %	28 - 40	33 ± 3.3	32 - 45	38.9 ± 2.44	< .001*
CR	1.0 - 16.1	3.95 ± 4.1	0.6 - 2.0	1.01 ± 0.26	< .05*

**P* value is considered statistically significant when < .05.

The Cr, ESR, and Hct values showed significant improvement and returned to normal after 24 months of therapy in almost all patients (Table 1).

At presentation, 68 patients (58.6 %) were found to have bilateral ureteral obstruction; 44 patients (37.9%) underwent bilateral retrograde ureteral stents insertion, while 28 patients (24.1%) underwent urgent dialysis followed by bilateral nephrostomy tube insertion and later by antegrade ureteral stents insertion. 24 patients (20.6%) were found to have a unilateral uretral obstruction and underwent unilateral ureteral stent insertion. Only 20 patients (17.2%) had no obstruction. 132 ureters were free of obstruction after mean ± SD of therapy (152, 5) days.

The initial abdominal CT-scan with intravenous contrast showed a retroperitoneal soft tissue mass surrounding the aorta in all patients (Figure 1), a regular margin in more than three fourth of patients, suprarenal extension in less than one third of patients, and medial uretric bowing in two thirds of patients, while a unilateral location was seen in a fifth of the patients. Homogenous enhancement was seen in the vast majority of patients (Table 2).

Table 2. Show the Initial Contrast Abdominal CT-scan Findings and the Initial and Follow-up Mean Paraaortic Lesion Size

Initial Contrast Enhanced Abdominal CT-scan Findings	Number of Patients/ total number of patients (%)
Retroperitoneal Soft Tissue Lesion Surrounding the Aorta	116/116 (100%)
Regular Margin	104/116 (84.6%)
Suprarenal Extension	20/116 (17.2%)
Medial Uretric Bowing	84/116 (72.4%)
Unilateral Location	24/116 (20.6%)
Homogenous Enhancement	108/116 (93 %)
Initial and Follow-up Paraaortic Lesion Size (mean ± SD); respectively, cm	1.92 ± 0.2, 0.88 ± 0.22

After 24 months of Prednisolone therapy, more than 82% of patients achieved 30% reduction in paraaortic fibrotic mass (Figure 2).

Sixteen patients developed relapse after discontinuation of treatment, but once medical treatment commenced again, the disease was controlled. Ten patients developed hypertension during treatment and were controlled by one antihypertensive medication and a reduction of the dose. Eight patients developed impaired glucose tolerance and were controlled by regular insulin

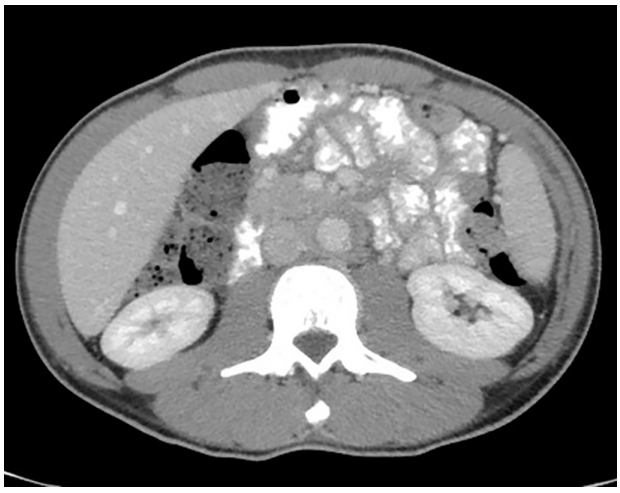

Figure 1. It shows the contrast enhanced abdominal CT scan of a patient demonstrating retroperitoneal fibrosis.

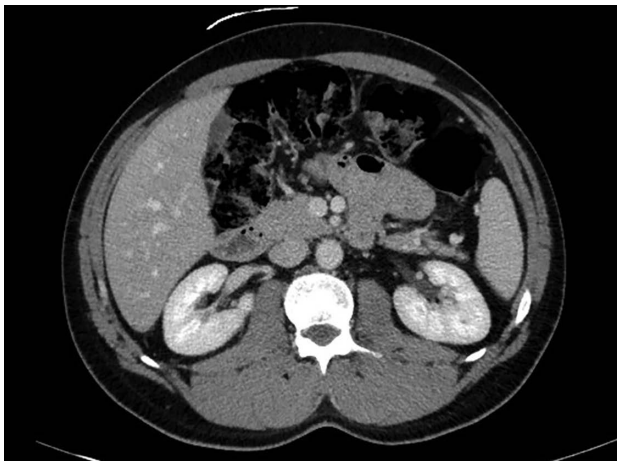

Figure 2. A contrast enhanced Axial computed tomography image of the abdomen showing complete resolution of the retroperitoneal mass after 12 month of treatment.

and a reduction of the dose. No major steroid side effects were seen, and none of the patients developed end stage renal disease.

DISCUSSION

Although the ideal medication has yet to be elucidated, this study confirms initial observation that prednisone with dose of 60 mg/d can alleviates the symptoms (abdominal and low back pain, weight loss, and poor appetite) and normalizes laboratory values (CR, ESR, Hct) associated with IRF.[5] In a study published by Van Bommel EF and colleagues in 2009, 53 patients with RPF were included. The incidence of RPF was 1.3/100,000 populations. Mean age was 64 ± 11.1 yr; male:female ratio was 3.3:1.0. Median duration of symptoms was 6.0 months (IQR 3.0-12.0), and the most common complaints were abdominal pain and back pain.[6] Non-specific systemic symptoms such as poor appetite and weight loss often preceded the disease onset, and were usually associated with abdominal, flank, and back pain. Pain was difficult to define, had no relation to change in position, and responded partially to non-steroidal anti-inflammatory drugs (NSAIDS); patients with ureteral involvement usually had renal colic. Other urologic symptoms that were common included: testicular discomfort associated with varicocele and/or hydrocele due to spermatic vein obstruction by RPF, ejaculation disorders, and impotence. Dysuria, frequency, and blood in the urine were less common. Inflammation due to ceroid and oxidized low-density lipoproteins was suggested.[7,8] Systemic autoimmune disorders proposed by other associated symptoms, including systemic symptoms, presence of other autoimmune diseases, presence of auto antibodies such as ANA,[9,10] usually patients have elevated erythrocyte sedimentation rate and they are anemic,[11] baseline ESR was elevated in about 77 % of patients,[12] more than two third of patients have been shown by some studies to have elevated inflammatory markers.[6,11,13] In another two studies, less than half of participants had elevated markers. Based on those results, normal inflammatory marker levels do not exclude the disease. Accordingly, other diagnostic tools such as CT and magnetic resonance imaging (MRI) have great diagnostic values.[14,15] A study published by Paul J. Scheel Jr in 2012 included thirty-one patients with retroperitoneal fibrosis. Abnormal initial ESR, serum Cr, and hemoglobin levels returned to normal in all patients.[16] The diagnosis of IRF was carried out by exclusion of other retroperitoneal lesions. Biopsy of the masses was the gold standard for diagnosis which was confirmed by the improvement in steroid therapy. CT scans or MRI was important diagnostic tools that helped physicians to diagnose and monitor the progress of the disease.[17] Abdominal Computed tomography usually showed a uniform mass encompassing the anterolateral sides of the abdominal aorta and surrounding the common iliac arteries (medial ureteral deviation and/or obstruction and inferior vena cava encasement were common). The mass had a similar density to that of the muscle and had varying degrees of contrast enhancements.[18,19] When the mass had a bulky appearance, inhomogeneous intensity continued beyond the renal arteries origin, or pushed the aorta to an anterior location on MRI; those features were in favor of malignancy rather than RPF. Also, idiopathic RPF caused midline ureteral deviations more frequently than malignant RPF.[20] A study published by Shuai Zhang and colleagues showed that computed tomography scans based on certain CT scan features and mass size can help on discriminating. While this is differentiation based on attenuation values in different CT contrast phase is hard to be made.[21] The first step in management was relief of ureteral obstructions. Surgical uretrolysis with ureteral transposition to intraperitoneal location and omental wrapping of the ureters is rarely used nowadays, and relieving the obstruction with ureteral stent (e.g., double-J stent or nephrostomy placement) followed by medical therapy is better and non-invasive. Both ureteral stents and nephrostomy have similar success rates and complications; however, ureteral stents provide a better quality of life in comparison with percutaneous nephrectomies.[22] There is no standard treatment for RPF yet. A combination of many agents is usually used with glucocorticoids, tamoxifen, and methotrexate being the most common.[23] Glucocorticoids are usually the initial drug of choice, with the initial dose of prednisone ranging from 0.75 to 1 mg/kg/d then being gradually tapered to 5 to 7.5 mg/d within 6 to 9 months. Remission is considered when symptoms have subsided, ureteral obstruction has resolved, acute phase reactant values have

normalized, and disease has regressed on imaging studies. Steroid therapy induces remission in the vast majority of patients; with the mass being reduced to less than half its original size. Glucocorticoids are shown to be rapidly effective since after only one week of treatment, a large number of patients had radiological improvements.[7] Immunosuppressive agents have been used in combination with Glucocorticoids; however, it is still uncertain if they actually have a synergistic effect or function as steroid-sparing agents. Mycophenolate mofetil is a commonly used immunosuppressive agent, especially since it is well tolerated and not contraindicated in patients with renal impairment.[5,24] Despite its chronic-relapsing course, idiopathic RPF has a benign course. Studies with more than four to five years of follow up showed mortality rates of 3.3% to 7.3%. Different degrees of renal impairment occur in about a third of patients, but end-stage renal disease is uncommon.[7,25]

The main strengths of our study include the large number of patients, the perspective being from urologists, the long-term follow-up, and the study being the first of its kind done at a military hospital. The limitations of the study include the lack of biopsy and the fact that it was a retrospective single center study.

CONCLUSION

IRF is usually seen more in males, and this finding was confirmed in our study. Renal impairment at presentation is common among patients with retroperitoneal fibrosis. Some patients are asymptomatic and a high index of suspicion is needed for diagnosis. Glucocorticoids are still the mainstay of treatment, with a few minor side effects. Due to the relapsing nature of the disease, long–term follow-up is warranted. End stage renal disease is uncommon. A contrast enhanced CT scan criteria reviewed by experienced radiologists showing good response to Glucocorticoid therapy can help in the diagnosis of the disease. Biopsy is the gold standard for diagnosis.

SOURCE OF SUPPORT

None declared.

CONFLICT OF INTEREST

None declared.

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