Conservative treatment in retroperitoneal fibrosis

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ABSTRACT

Background: Retroperitoneal fibrosis is classified as idiopathic or secondary. It was discovered by Albarran (1905) and described by Ormond (1948) as a fibrotic process tending to affect the ureter.

Objective: To present a case of idiopathic retroperitoneal fibrosis and its conservative management.

Materials and Methods: The case of a patient with idiopathic retroperitoneal fibrosis with bilateral ureteropyelohydrenephrosis and acute renal insufficiency is presented.

Results: After exploratory laparoscopy, and supported by immunohistochemistry, definitive diagnosis was idiopathic retroperitoneal fibrosis. Treatment was initiated with 20 mg daily of prednisone that was gradually reduced to 5 mg daily, serum creatinine and urea were improved and there was no retroperitoneal fibrosis reactivation at 3-year follow-up.

Discussion: Retroperitoneal fibrosis can be managed with medical treatment based on steroids and immunosuppressors or surgery.

Conclusions: A steroid regimen may be used as first line treatment for the majority of patients with a minimum of complications, along with periodic evaluation for the remainder of their lives.

RESUMEN

Antecedentes: La fibrosis retroperitoneal se divide en idiopática y secundaria, descubierta por Albarán (1905) y Ormond (1948) describiéndola como un proceso fibrótico que tiende a atrapar los uréteres.

Objetivo: Presentar un caso de fibrosis retroperitoneal idiopática y su manejo con tratamiento médico conservador.

Material y métodos: Se presenta el caso de una paciente con fibrosis retroperitoneal idiopática con ureteropielohidronefrosis bilateral e insuficiencia renal aguda.

Resultados: Se realiza laparotomía exploradora con diagnóstico definitivo de fibrosis retroperitoneal idiopática apoyado en inmunohistoquímica, se agrega prednisona 20 mg diarios, la cual se disminuyó en forma gradual hasta 5 mg diarios, mejorando sus azoados, con seguimiento a tres años sin reactivación de la fibrosis retroperitoneal.

Discusión: La fibrosis retroperitoneal se puede manejar con tratamiento médico a base de esteroides e inmunosupresores o quirúrgico.

Conclusión: El esquema con esteroides puede ser usado como primera línea de tratamiento para la mayoría de los pacientes con mínimas complicaciones, así como una evaluación periódica por el resto de su vida.

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Key words: idiopathic retroperitoneal fibrosis, immunohistochemistry, immunosuppressors, prednisone, Mexico.

INTRODUCTION

Of the pathologies affecting the retroperitoneum, not including intrinsic pathology of organs situated in this space, the following are the most frequent: idiopathic retroperitoneal fibrosis (IRF), retroperitoneal abscesses and primary tumor pathology. Albarran in 1905 and John K. Ormond in 1948 described retroperitoneal fibrosis as a fibrotic process that tends to affect the ureters.1,2 Retroperitoneal fibrosis is divided into idiopathic (IRF) or secondary (SRF) to certain drugs, malignancies, infections and other factors leading to the disease.3 Principal IRF epidemiological characteristics were evaluated in a 2004 study from Finland that reported an annual incidence of 0.1 per 100 000 individuals and a prevalence of 1.4 per 100 000 individuals. Peak incidence is in 40- to 60-year-old patients and is predominant in men with a man:woman ratio between 2:1 and 3:1.4,5 SRF represents less than one third of retroperitoneal fibrosis (RF). There are different conditions and potential causes of SRF such as the use of certain medications (methysergide, alkaloids derived from ergotamine, dopamine agonists), primary retroperitoneal cancer (lymphoma, sarcoma), retroperitoneal metastatic disease (carcinoids, carcinomas), trauma, radiotherapy, major abdominal surgery and infections.3,4 SRF does not have identifiable causes although it has been reported in patients presenting with inflammatory and autoimmune diseases involving other organs or structures such as autoimmune thyroiditis, autoimmune pancreatitis and systemic lupus erythematosus.5

IRF is a rare chronic inflammatory process that develops fibrous plaque localized in the retroperitoneum that extends caudally from the renal pedicles to the pelvic floor and laterally to the external edge of the psoas muscles. Ureteral obstruction is its most striking symptom. It is distributed around the aorta although it does not completely surround it, and is able to reach the aortic bifurcation and common iliac vessels.

There are atypical IRF cases in which the fibrous mass is not centered in the aorta but tends to be situated just to the side of the aorta or surrounding an important artery or vein such as the celiac artery or the vena cava.6 Fibrosis is associated with an inflammatory infiltrator that has particular histopathological aspects such as being rich in lymphocytes, plasmatic cells and macrophages. It is also associated with the human leukocyte antigen (HLA) system (HLA-DRB1-03).7,8 It has been suggested that this process originates due to an autoimmune reaction to an antigen that is located in the atheromatous plaque of the aorta and infrarenal and common iliac vessels.9 An insoluble lipid (ceroid) passes to the periaortic tissue inducing an immune response mediated by immunoglobulin G (IgG).

CASE PRESENTATION

The patient is a 71-year-old woman with no important medical history whose present illness began in July 2004. She presented with frontoparietal and occipital headache, vertigo of 24-hour progression, photophobia, nausea and vomiting. She had clear-colored diarrhea, diffuse abdominal pain in lower hemiabdomen and general malaise.

Blood pressure was 220/110, respiratory rate (RR): 18x’, heart rate (HR): 98x’, temperature 36.8º C. Patient was conscious, oriented, non-febrile and with no cardiopulmonary alterations. Abdomen was soft, palpable, and there was diffuse pain in the lower hemiabdomen. There were no signs of peritoneal irritation and peristalsis was normal. Laboratory results from July 29, 2004 showed: Hb 11.7 g, leukocytes 5800/mm³, platelets 228000/mm³, partial thromboplastin time (PTT) 31.5 sec, glucose 86 mg/dL, creatinine 6.17 mg/dL, urea 145 mg/dL, glutamic-oxaloacetic transaminase GOT 15, alanine transaminase (ALT)16, gamma-glutamyl transferase (GGT) 33, Na 147 mEq/L, K 5.8 mEq/L, cholesterol 189 mg/dL, triglycerides 88 mg/dL, alkaline phosphatase 165, total proteins 6.9. Electrocardiogram was unaltered. Chest x-ray showed cardiomegaly with pinching of both costophrenic sinuses. Echocardiogram from August 2004 showed ejection fraction 68%, mild mitral stenosis with mild tricuspid regurgitation, slight increase of pulmonary pressure and mild pericardial effusion.
Computed axial tomography (CAT) of the head done July 2004 was normal. Abdominal ultrasonography from August 2004 revealed bilateral ureteropyelohydronephrosis that was more important in the right kidney. Bladder characteristics were normal. Abdominal CAT from August 2004 showed bilateral ureteropyelohydronephrosis that was more accentuated in the right excretory system. At iliac bifurcation the mass surrounded the aorta including the inferior vena cava and both ureters (Image 1). Right double-J catheter was placed and patient was treated with calcium antagonist.

**MANAGEMENT**

Exploratory laparotomy was done and intraoperative biopsy of retroperitoneal mass reported lymphoproliferative process with fibrosis, consistent with lymphoma. Left double-J catheter was put in place. Definitive histopathological study was carried out in which connective tissue with fibrotic zones and thick collagen bands were observed. Within this tissue, isolated and aggregated lymphoid cells of varied form and size with occasional formation of germ cell centers were also found. Macrophages and aggregates of plasma and eosinophil cells were also observed along with fat necrosis with focal accumulation of neutrophils. Immunohistochemical study was done to confirm the polyclonality of the lymphoid infiltrate, obtaining positive stains for lymphocytes with CD45, CD20 and CD3. In eosinophils and isolated neutrophils, positivity to CD15 was obtained. Macrophages were positive to CD68 and plasma cells to CD30, kappa and lambda. Pan-cytokeratin and BCL2 results were negative, ruling out the possibility of both Hodgkin and non-Hodgkin lymphoma as well as the possibility of carcinoma. Twenty milligrams daily of prednisone were added to treatment and this dose was gradually reduced to 5 mg/day, resulting in improved laboratory work-up carried out on April 2007: creatinine 1.31 mg/ml, BUN 24.3 mg/ml, uric acid 6.76 mg/ml, hemoglobin 15 g, hematocrit 44.2% and platelets 179 000/mm³. At 3-year follow-up there has been no reactivation of retroperitoneal fibrosis (Image 2).

**DISCUSSION**

Retroperitoneal fibrosis (RF) is an uncommon disease in which the fibrotic process involves the retroperitoneum, surrounding the aorta from below the level of the renal arteries. Etiology of idiopathic retroperitoneal fibrosis (IRF) remains unclear, but certain drugs such as methysergide, hydrazaline, beta blockers and alkaloids derived from ergotamine have been associated with this disease. Pathological findings have presented as inflammatory infiltrate containing macrophages, lymphocytes, plasma cells and occasionally, eosinophils. Macrophages are often a lipidic layer and the majority of lesions contain areas of perivascular lymphocytic infiltrate made up of type T and B cells. In the present case, the pathology report stated lymphocyte germ cell centers accompanied by macrophages and plasma and eosinophil cells were determinants in RF diagnosis, which was reinforced by the immunohistochemical study of those cells. It is possible that periaortitis develops as an immune reaction to atherosclerotic plaque components. These compounds can include low-density lipoprotein oxidation and ceroid material. The presence of IgG at the rupture of atherosclerotic plaque lends support to this possibility. The most frequent initial symptom is pain in 90% of cases. Lumbar pain present in 40-60% and abdominal pain in 50%. Pain is dull and insidious. Other early stage manifestations include asthenia, anorexia, weight loss and fever. Late stage clinical symptoms are attributable to progressive ureteral obstruction which can lead to anuria. General malaise, weakness, weight loss and gastrointestinal disturbances may constitute the first signs of disease secondary to progressive uremia. In the present case, IRF presented with uremia data including important
elevation of creatinine and urea. Alterations in laboratory work-up results tend to be unspecific, erythrocyte sedimentation rate is above 30 mm/h and levels of creatinine and urea are elevated. Ultrasonography is the first diagnostic technique used on these patients. It is very sensitive for detecting pyelocaliceal dilatation, as in our report, but it is not very sensitive for detecting fibrotic plaque. CT is the most useful technique for confirmation diagnosis. Disease location varies – it can be in the center, symmetrical or asymmetrical, well or poorly defined or extensive. With intravenous contrast medium the image may be captured to a greater or lesser degree, depending on vascularization. Various medications such as corticosteroids, tamoxifen, aziathropine and cyclophosphamide have been recommended for this purpose. Ross and Tinkler reported success with corticosteroids based on the presence of inflammatory cells in the fibrous plaque. Currently, treatment with corticosteroids is the principal treatment for IRF but the majority of studies on this are retrospective and non-controlled. At any rate, there is no consensus in the literature as to steroid dose and therapy duration. Various steroid regimens using 20 – 60 mg have been proposed, especially as initial treatment. In a series of 11 patients, glucocorticoids were administered at an initial dose of 60 mg daily on alternating days during the first 2 months. Dose was gradually reduced to 5 mg daily. This protocol added alpha-blockers and calcium supplements in an effort to prevent side effects from high doses of steroids. In a recent study on a large cohort of patients, glucocorticoids were administered at an initial dose of 60 mg daily for a period of 6 weeks and reduced over the following 2-3 months to 10 mg daily. Mean treatment duration was 1 year. Twenty-two of the twenty-four selected patients reported significant symptom reduction and 19 patients experienced partial or complete regression of the mass. Disease recurrence presented in 13 patients when glucocorticoids were suspended. Although there was no previous case-control study, our treatment regimen consisted of 20 mg of prednisone daily for 3 months. Dose was gradually reduced to 5 mg daily over a 9-month period with satisfactory results. Glucocorticoids may be used as primary treatment for IRF with a satisfactory response in the majority of patients. Follow-up should include tomography at 3 and 6 months in order to evaluate mass regression. In a small number of patients (8.3%), retroperitoneal mass does not regress and surgical ureterolysis may be required. Higgins and collaborators suggest two distinct groups: patients who are seriously ill who respond poorly to surgery and steroid therapy and patients who develop ureteral obstruction that is often unilateral early on and who may have a better response to steroid treatment.

## CONCLUSIONS

IRF is an uncommon disease that has many etiologies. It is generally diagnosed in advanced stage presenting with important obstructive uropathy (unilateral or bilateral) and on occasion with established renal insufficiency. Medical treatment may be useful in the initial stages, but surgical treatment supported with endourological maneuvers is indicated when disease is in advanced stage. Steroid regimen may be used as first line treatment for the majority of patients with a minimum of complications and follow-up should be continued throughout the patient’s lifetime.

## BIBLIOGRAPHY