CASE REPORT

IgG4-related retroperitoneal fibrosis: A case report and review of literature

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Abstract

Idiopathic Retroperitoneal fibrosis is a rare clinical condition recently identified as an autoimmune process related to Immunoglobulin G4 (IgG4) deposition. Herein we report a case of a 46 year old male presenting with 4 months history of backache, fever, flank pain and leg swelling for 2 weeks. Investigations revealed acute kidney injury diagnosed as a result of bilateral ureteric obstruction. This was later confirmed to be retroperitoneal fibrosis on CT scan and biopsy. Histopathology was consistent with IgG4 related disease. Treatment with immunosuppressive agents showed reduction in the fibrosis and normalization of the kidney functions. We discuss the IgG4 related retroperitoneal fibrosis in detail along with its varied presentations.

Keywords: IgG4-related disease, Retroperitoneal fibrosis, Ureteric obstruction, Acute renal failure.

Introduction

Retroperitoneal fibrosis (RPF) is an uncommon clinical condition with estimated prevalence of 1.38 per 100,000 people, which affects middle aged individuals 40 to 60 years of age with male predominance of 3:1.[1] It is characterized by inflammation and fibrosis of retroperitoneal tissues usually involving anterior surface of 4th and 5th lumbar vertebrae with encasement and obstruction of retroperitoneal structures like ureter, aorta and other abdominal organs.

Etiology of RPF in most of the cases is unclear and termed as idiopathic RPF. Up to one third of the cases are related to malignancy, surgery, radiation, medications and certain chronic infections. In some recent studies it has been claimed that approximately 60% of RPF is IgG4 related disease.[2] The IgG4 related RPF differs from non IgG4 related fibrosis in histopathologic aspect and involvement of other extra retroperitoneal organs. The presentation may be an isolated IgG4 related retroperitoneal fibrosis however IgG4 related extra retroperitoneal lesions may occur synchronously or metachronously.[2] We report a case of isolated RPF presenting as AKI that was managed successfully.

Case Report

A 46 years old male presented in our outpatient department at Fatima Memorial Hospital in February 2014 with complaints of low back pain for last 4 months and low grade fever, bilateral flank pain and bilateral leg swelling for last 2 weeks. He had type 2 diabetes for the last 6 years with fair control on Insulin and recently was found to have hypertension a month ago. His blood pressure was controlled on ACE-Inhibitor therapy. He had also been taking multiple Non-Steroidal Anti Inflammatory Drugs for backache for the last 4 months. On examination, he had generalized pallor, mild bilateral pitting pedal oedema and bilateral flank tenderness. Rest of the examination was unremarkable.

His lab investigations showed: Hb. 8.6 gm/dl, Urea 62 mg/dl, Cr 5.7 mg/dl, K 5.6 mmol/l, Total Calcium 9.8 mg/dl and Albumin of 3.4 gm/dl. Urine examination was insignificant and negative for Bence-Jones protein. Inflammatory markers ESR and CRP were 62 mm/1st hour and 74.9 mg/l respectively while serum ferritin was 298 ng/ml. Ultrasound of abdomen was performed which revealed bilateral mild ureteric obstruction at vesicoureteral junction raising suspicion of post obstructive renal failure, however no renal calculi or mass was appreciable in the ultra-sonogram.

CT pyelogram showed diffuse circumferential soft tissue mass encasing the infrarenal abdominal aorta up to

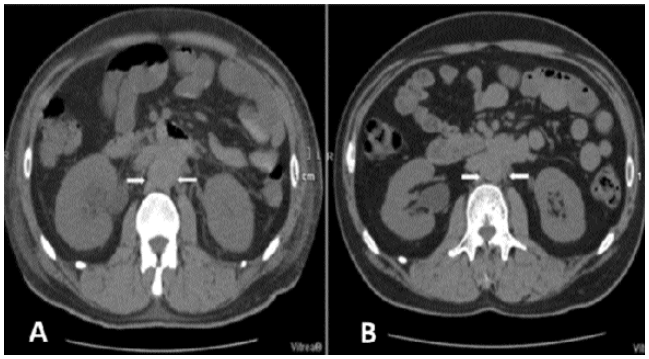

Figure-1: CT Scan Abdomen. A) Before Steroid Treatment. B) After Steroid Treatment.

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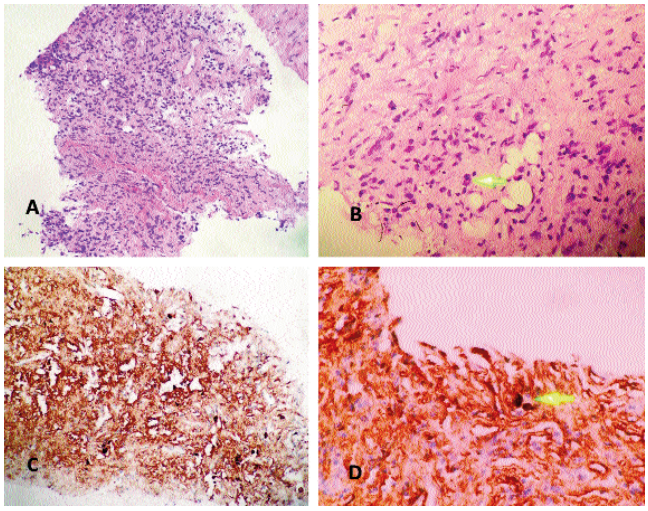

Figure-2: Histopathology of the retroperitoneal mass. A) and C) showing low power view of Hematoxilyn & Eosin stain and immunostaining for IgG4 respectively. B and D are the high power view with yellow arrows showing the plasma cells and the IgG4 stained plasma cells respectively.

bifurcation of iliac vessels. This mass also entrapped both ureters and was highly suggestive of retroperitoneal fibrosis (Figure-1 A).

His creatinine rapidly increased with anuria requiring haemodialysis. Bilateral ureteric stenting was performed resulting in good urine output and kidney function improved markedly resulting in discontinuation of dialysis after three sessions.

Biopsy from the retroperitoneal mass showed hyalinized fibrous tissue and lymphoplasmacytic chronic inflammation with increased IgG4 positive plasma cells suggestive of IgG4 related sclerosing lesion (Figure-2). Only an IgG4 immuno-histochemical stain was performed since IgG stain was not available, so an IgG4/IgG ratio could not be determined. However, since IgG4 was positive in ~70% of total plasma cells in the infiltrate with >30 positive cells per high power field, findings were diagnostic.

Methylprednisolone bolus was given for 3 days and then oral prednisolone was started initially at 1 mg/kg dosage. It was tapered down to maintenance dose of 5 mg/ day in following 3 months. Mycophenolate Mofetil was advised, he however discontinued it himself due to nausea and vomiting. His stents were removed 5 months later. Follow-up CT scan at 6 months (Figure-1 B) showed interval decrease in the soft tissue mass, however he developed arthralgia, back pain and low grade fever. Methotrexate was therefore started at 10 mg weekly and he was advised strict compliance. A repeat ultrasound at one year follow-up again showed normal pelvicalyceal system and normal serum creatinine. He was asymptomatic and was advised good compliance and control of his blood sugars.

Discussion

IgG4 related diseases are a newly recognized spectrum of autoimmune disease related to a minor subclass of immunoglobulin IgG, named as IgG4. This constellation of autoimmune diseases was initially recognized as autoimmune pancreatitis in 2001 and by 2003, extra pancreatic tissue and virtually any organ or system of the body involvement was documented.[3]

IgG4-related disease is a fibro inflammatory condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, and, often but not always elevated serum IgG4 concentrations.[4]

These fibro inflammatory processes involve different cytokine cascade and result in extensive fibrosis, sclerosis and obliterative phlebitis of the involved organ.

Regardless of the cause RPF may present clinically with dull vague abdominal pain and backache along with nonspecific constitutional symptoms of fever, myalgia, anorexia and weight loss, as in our patient.[5] However, half of the patients may remain asymptomatic and as the disease advances it may cause ureteric obstruction leading to renal insufficiency of variable degree. In our patient ultrasound revealed hydronephrosis to be minimal whereas on CT the presence of fibrosis was identified as the clue to diagnosis. In fact ureteric obstruction is found in 60 % to 80% of patients with Ig G4 related RPF.[6]

Diagnosis of RPF is based on radiological findings, histopathology of the fibrotic mass biopsy and serum IgG4 levels if available.[5]

In our patient the clinical scenario, CT scan findings and histopathology of the biopsy specimen from the fibrotic mass was diagnostic. Serum IgG4 levels were not available at that time and were not done.

Ultra-sonogram may or may not provide information about the mass but it can readily establish the degree of obstruction of ureters and kidneys.[7] Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are considered as a reliable modality to assess the extent of the mass. On CT RPF appears as periaortic soft tissue density extending from the level of renal artery to iliac vessels with frequent medial deviation and obstruction of ureters. MRI can further elaborate the RPF masses as low to intermediate signal intensity on T1

weighted images and variable intensity (according to inflammation) on T2 weighted images.[8]

Nonspecific acute phase reactants as CRP and ESR are usually elevated.[1] IgG4 levels are found to be elevated in majority of patients with Ig G4 related disease but approximately 30% patients exhibit normal serum IgG4 level despite having classical histopathological and immunochemical findings.[9] IgG4 level of more than twice i.e. more than 280mg/dl (normal 135mg/dl) is highly specific of IgG4 related disease,[5] however serum concentration of IgG4 depend on number of organ involvement and it tends to decrease with treatment with steroids.

The IgG4-related diseases are histologically characterized by lymphoplasmacytic inflammation with a predominance of IgG4-positive plasma cells and CD4+ T lymphocytes, accompanied by storiform fibrosis, as in our patient[3] (Figure-2). The presence of IgG4-positive plasma cells should be increased (> 30 cells/high power field). To avoid over diagnosis, the ratio of IgG4/IgG-positive plasma cells is calculated which should be at least over 40%, typically over 70%.[10] In our patient 70% of total plasma cells were IgG4 positive confirming the diagnosis.

The management of RPF involves urgent attention to obstructing organs such as ureters requiring stenting and surgery for obstructive bowel or vascular structures and immunosuppressive medications. Patients with mild unilateral hydronephrosis can be managed without surgical intervention and can monitor closely on medical therapy alone.[7]

Immunosuppressive medications include the initiation of glucocorticoids, which are started at a dose of 0.6-1 mg/kg of body weight per day for 4 weeks and later tapered over a period of 3 to 6 months to 5 mg per day continuing for 3 months to 3 years.[4] Glucocorticoid sparing drugs namely azathioprine, mycophenolate and methotrexate are also frequently used widely as maintenance therapy or in cases where long term use of glucocorticoids is contraindicated. However, due to rarity of the disease, there is no data suggesting the effectiveness of various immunosuppressive agents.[4] In resistant cases anti CD20 antibody, Rituximab has shown its efficacy by B cell depletion.[4]

Disease progression can be monitored by regular evaluation of ESR, CRP and Creatinine levels and radiological imaging with MRI, CT scan or ultrasound. Prognosis is usually good with relapse rate of less than 10 to 30 % after discontinuation of treatment. However there is no predictor of response to treatment or relapse.[4]

Conclusion

IgG4 related retroperitoneal fibrosis is a rare cause of acute renal failure and can be treated successfully with release of obstruction and initiation of immunosuppressive medications. Follow-up serial ultrasound, CT or MRI and serum IgG4 levels are needed to monitor the disease activity.

References

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