IgG4-related Retroperitoneal Fibrosis: An Emerging Masquerader With a Sinister Presentation

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OBJECTIVE Retroperitoneal fibrosis (RPF) is a rare proliferative fibro-inflammatory disease involving the soft tissues of the retroperitoneum. IgG4 related retroperitoneal fibrosis is an emerging entity which needs to be distinguished from idiopathic RPF. We describe a clinical case of IgG4 related RPF highlighting the importance of clinching this diagnosis.

METHODS A 70 year old female was referred to the outpatient department of our institute with complaints of fatigue, bilateral flank pain and loss of appetite for the past 1 month. The CT and PET scan demonstrated a uniformly enhancing bulky retroperitoneal mass causing bilateral hydroureteronephrosis. The biopsy from the mass lesion revealed IgG4 related disease. The patient was started on corticosteroids after percutaneous nephrostomy placement.

RESULTS Three months post induction of therapy, repeat PET-CT shows resolution of the mass with no FDG avid lesion. Serum IgG4 levels were reduced to normal (27 mg/dL) suggestive of response to treatment. The percutaneous nephrostomies were removed and the patient is doing well on maintenance dose of corticosteroids for her disease.

CONCLUSION The availability of serum IgG4 levels for monitoring treatment response and follow-up can curtail the repeated radiological imaging and associated contrast exposure as compared to idiopathic RPF. Secondly, the diagnosis of IgG4-related RPF shall alert the clinician to look out for extra-retroperitoneal diseases on follow up of this multi-organ disease. UROLOGY 133: 16–20, 2019.

CASE PRESENTATION

A 70-year-old female was referred to the outpatient department of our institute with complaints of fatigue, bilateral flank pain, and loss of appetite for the past 1 month. She also complained of shortness of breath and decreased urine output for the past 7 days. Previous surgical and medical history of the patient was unremarkable. She was thin built and undernourished with a BMI of 17 kg/m^2. On examination, the patient had bilateral pedal edema and fine crackles on respiratory examination. The cardiovascular examination of the patient was essentially normal. The abdomen was soft on palpation with no abnormality noted. The laboratory investigations of the patient revealed a raised serum urea and creatinine; 172 mg% and 8.4 mg/dL, respectively (increase from baseline of 1.2 mg/dL), hemoglobin of 9.0 gm/dL, and total leukocyte counts of 4500/mm^3. Peripheral blood smear was normal.

Abdominal ultrasound revealed bilateral gross hydronephrosis with dilated upper ureters. A contrast-enhanced CT scan was performed outside (after adequate hydration) at local hospital before referral to us. It demonstrated a uniformly enhancing bulky mass extending from the lower pole of bilateral kidneys to the level of the sacrum, encasing the lower part of the abdominal aorta, inferior vena cava, and iliac vessels and medially displacing both the ureters (Fig. 1B,C). The mass was causing bilateral hydroureteronephrosis (HDUN) (right more than left), with dilated ureters seen up to the lower part of the abdominal aorta (Fig. 1A). To manage obstructive uropathy, in view of suspicion of malignant pathology causing extramural compression and logistical issues, percutaneous nephrostomy were placed in both the kidneys (right followed by left) and the urine output and creatinine levels were measured serially. Taking into account the age of the patient and the rapid onset of the disease, there was a high suspicion of a malignant disease at play. A FDG-PET scan was performed demonstrating an ill-defined FDG avid (SUVmax 8.34) soft tissue mass (2.5 × 3.3 × 6.5 cm) arising from the retroperitoneum encasing the abdominal aorta and its branches as well as bilateral ureters (Fig. 2). No significant FDG avidity was noted elsewhere in the body.

Conflicts of interest: *None.*

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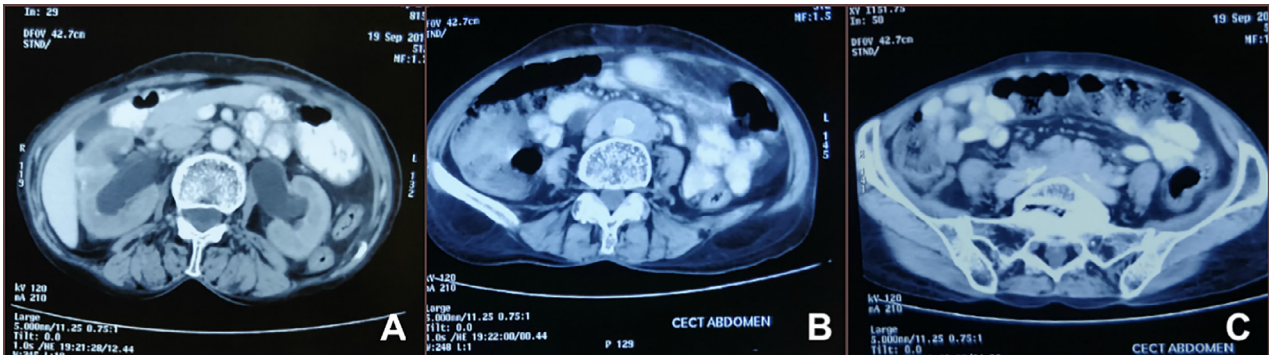

Figure 1. (**A**) CECT abdomen demonstrating bilateral hydroureteronephrosis. (**B**) Uniformly enhancing, bulky soft tissue mass enveloping the abdominal aorta and IVC. (**C**) Extension of the mass into the pelvis with encasement of the iliac vessels. (Color version available online.)

The 2 major differential diagnoses in this patient were kept as lymphoma and retroperitoneal fibrosis (RPF), the former having a grave prognosis as compared to the later.[1] The patient underwent a CT-guided biopsy of the mass exhibiting the presence of storiform fibrosis, patchy aggregates of plasma-rich infiltration admixed mature lymphocytes and histiocytes, with an evidence of obliterative phlebitis (Fig. 3A,B). No fungal elements, granulomatous, or neoplastic pathology were seen on histopathologic examination. Immunostaining of the tissue demonstrated IgG4 staining of the plasma cells (>40 per HPF) suggesting the diagnosis of IgG4-related RPF (Fig. 3C,D). Serum IgG4 levels were assessed and were raised (220 mg/dL), confirming the diagnosis. The erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) levels were raised, while antinuclear antibody (ANA) levels were normal.

The patient was started on oral prednisolone (1 mg/kg) for 4 weeks, which was tapered over the next 4 weeks to 7.5 mg/d. Three months post induction of therapy, repeat PET-CT shows resolution of the mass with no FDG avid lesion (Fig. 4). Serum IgG4 levels have reduced to normal (27 mg/dL) suggestive of response to treatment. The percutaneous nephrostomies were clamped after ensuring sterile culture and the serum creatinine has stabilized to 1.3 mg/dL. They were removed as patient did not mount any fever or flank pain and had adequate per urethral urine output. The ESR and CRP levels have also normalized. The patient is doing well and is on maintenance dose of corticosteroids for her disease. She is planned for regular follow-up by means of serum IgG4 levels every monthly as a surrogate for disease activity and FDG-PET scan after 6 months.

DISCUSSION BY ADITYA P SHARMA

RPF is a rare proliferative fibroinflammatory disease involving the soft tissues of the retroperitoneum. Idiopathic RPF has a prevalence of about 1.3 per 100,000 population with male predominance.[2] Although idiopathic

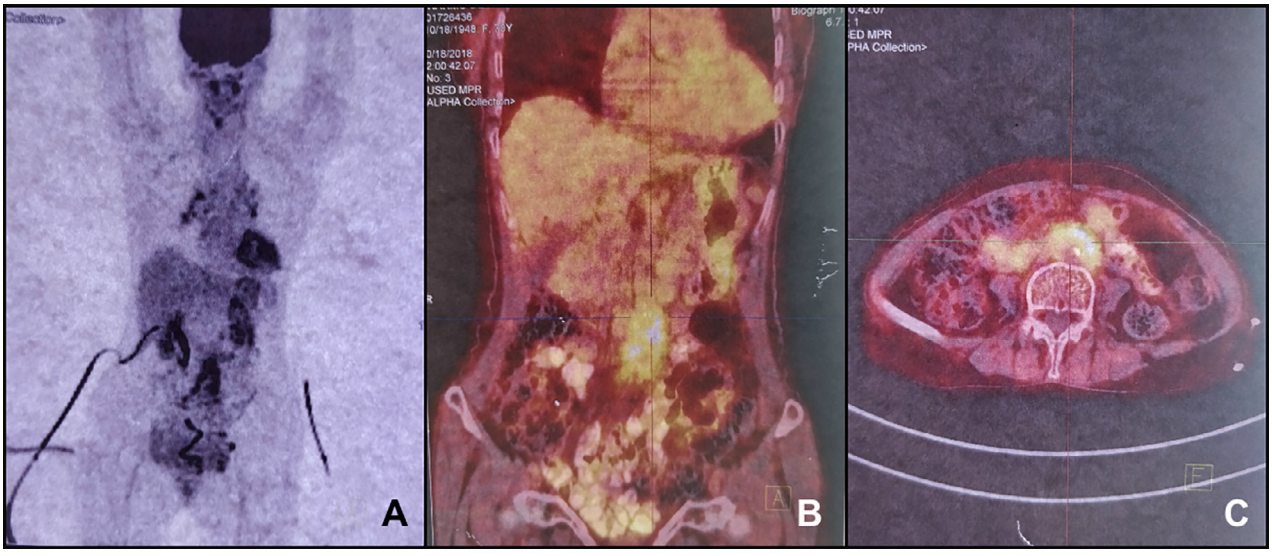

Figure 2. (**A** and **B**) FDG avid retroperitoneal mass around the abdominal aorta and IVC. Bilateral PCN in situ. (**C**) Cross-sectional imaging demonstrating encasement of the aorta and IVC. (Color version available online.)

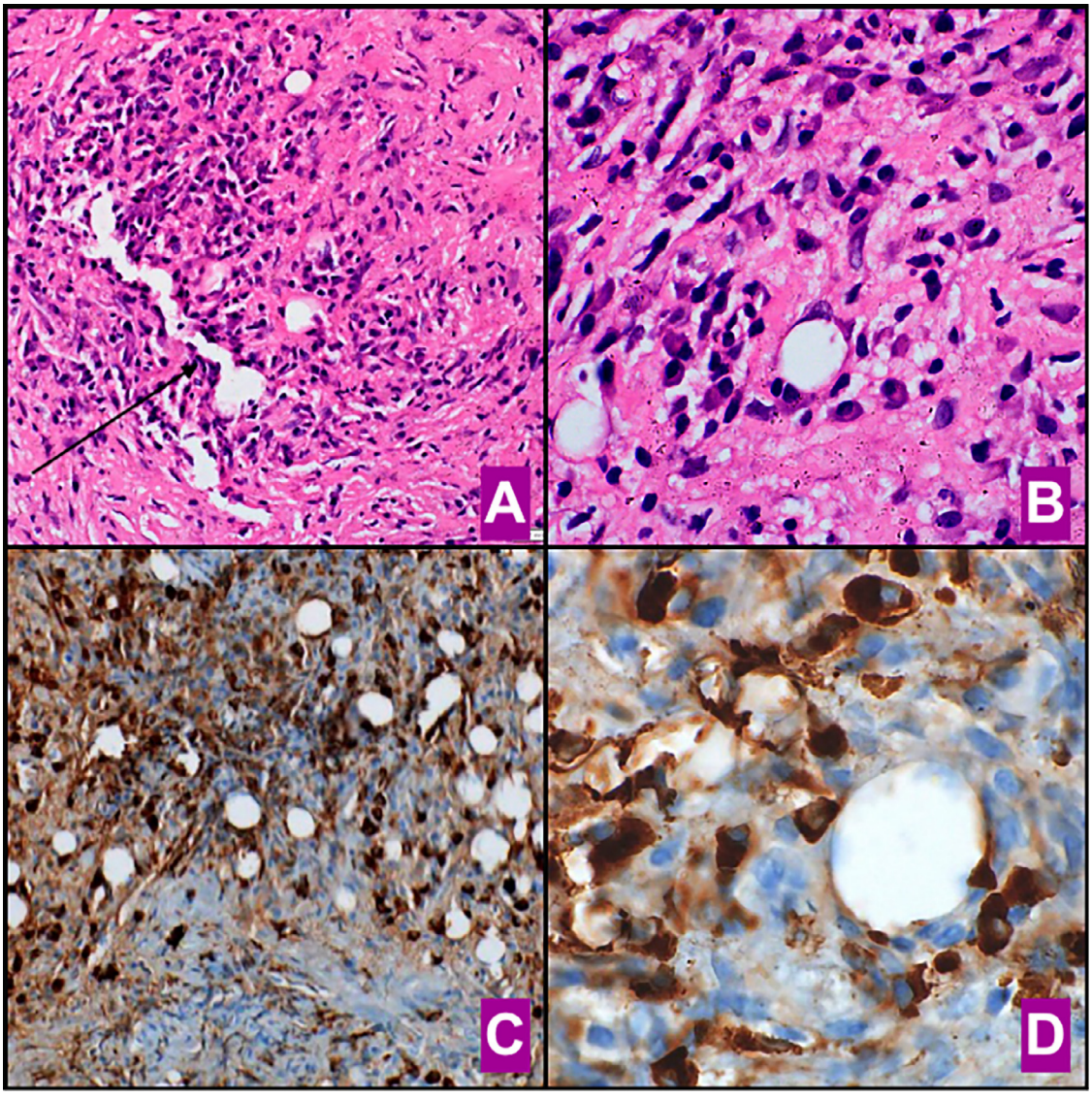

Figure 3. (**A**) Areas of storiform fibrosis and obliterative fibrosis (arrow). (**B**) High power magnification demonstrating numerous plasma cells showing eccentrically placed nuclei with perinuclear halo (white arrow). (**C** and **D**) IgG4 positivity of the plasma cells with >30 plasma cells/HPF. (Color version available online.)

RPF was first recognized by Ormond in 1948,[3] the etiopathogenesis of this disease still remains an enigma. Local inflammatory response to antigens present in atherosclerotic plaque of the abdominal aorta is considered the most plausible pathology underlying this disease. Malignant RPF accounts for 10% of all cases but is associated with a poor prognosis, making it imperative to differentiate it from benign etiology at the very onset. Lymphoma,

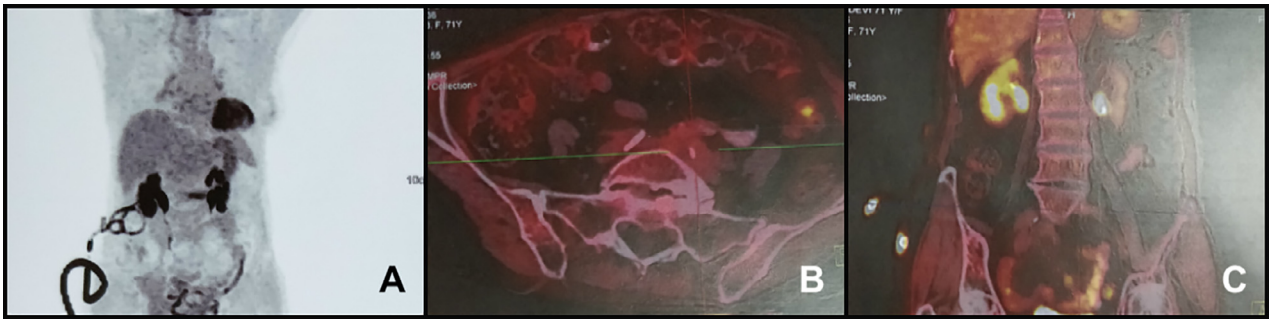

Figure 4. No FDG avidity noted in follow-up FDG-PET scan after 3 months of glucocorticoid therapy demonstrating complete response. (Color version available online.)

retroperitoneal sarcoma, carcinoid tumor, and metastatic involvement of primary tumors are predominant causes of malignant RPF.[4]

Another recently described fibroinflammatory disease with heterogeneous clinical picture is immunoglobulin G4-related disease (IgG4-RD). It is characterized by systemic involvement of multiple organs including the pancreas, lacrimal duct, lungs, bile duct, kidneys, and retroperitoneum.[5] A multitude of diseases are now part of gamut of IgG4-RD. These include autoimmune pancreatitis, Mikulicz disease, Kuttner's tumor, interstial nephritis, and idiopathic RPF among others.[5] About half of the patients (47%-59%), previously classified and treated as idiopathic RPF may be reclassified as IgG4-RD ever since the discovery of this disease. Around 10% patients with IgG4-RD have evidence of retroperitoneal involvement while isolated involvement of the retroperitoneum is much rarer. Forty-six to fifty percent cases of IgG4-related RPFs demonstrate involvement of organs located outside the retroperitoneum.[6] The disease is much more common in middle aged and older men except when it involves head and neck which has female preponderance.

Clinical presentation of RPF (both idiopathic and IgG4-related) varies from nonspecific symptoms such as malaise, anorexia, weight loss, lower back pain to much sinister inflammatory aneurysms, and their ruptures. Compression of retroperitoneal veins and lymphatics may present with deep vein thrombosis and lower limb edema. Ureteral involvement is found in 47%-100% patients with bilateral involvement in more than 50% of these cases, presenting with obstructive uropathy as in the present case.[2,6]

Laboratory findings (rise in ESR and CRP) essentially remain nonspecific and do not differentiate malignant forms of RPF. Concomitantly, ANA levels must be measured to rule out the presence of autoimmune disorders.[2] IgG4 is the most sparse (<5% of the total) subclass of IgG antibodies. IgG4 is elevated in a majority of patients with IgG4-RD (typically >135 mg/dL). The index patient also had elevated levels (220 mg/dL) of serum IgG4. However, it cannot be used as an isolated marker to diagnose 1gG4-RD as normal serum concentrations have been reported in 3%-30% patients.[6,7] Besides, serum IgG4 elevation has been demonstrated in non-IgG4-related pancreatic and biliary disorders, chronic respiratory infections like sinusitis and bronchiectasis, skin diseases like atopic dermatitis and pemphigus vulgaris as well as 5% of the normal population.[8,9]

Cross-sectional imaging remains the cornerstone in diagnosis of RPF whether IgG4 related or idiopathic. CT and magnetic resonance (MR) imaging allows comprehensive evaluation of the location and extent of RPF. The quintessential imaging finding is a well-defined, irregular enhancing mass encasing the major blood vessels at the level of L4-L5 vertebrae with upward extension toward the renal hilum more often than downward extension to the pelvis. The level of enhancement correlates with the activity of the disease. MR imaging typically demonstrates T1 hypointensity and T2 hyperintensity which correlates with disease activity.[4] Zhang et al investigated the role of multidetector row CT scans in differentiating between RPF and lymphoma. The lymphomas presented as larger masses (3.9 ± 1.2 vs 1.8 ± 0.6 cm). Pelvis extension and medial ureteral bowing were identified as predictors of RPF while suprarenal extension and involvement of additional lymph nodes predicted lymphomas.[1] FDG-PET has demonstrated a promising role and fared better in identification of multiorgan involvement in comparison to conventional imaging. It also assisted in assessing treatment response and guiding therapeutic intervention on the basis of F^{18}-FDG uptake in patients with IgG4-RD. However, PET-CT fails to differentiate IgG4-RD from malignancies like lymphoma at the very outset. A rapid response to steroid therapy (>80% decrease of avidity) on follow-up PET-CT scan (after 2-4 weeks), as has been proposed by Zhang et al, may serve as a useful guide to exclude possible malignancies.[10]

Histopathologic examination is indispensable in diagnosing IgG4-related RPF and to exclude other malignant and benign causes.[6,7] Umehara et al[11] proposed a comprehensive diagnostic criterion for IgG4-RD:

1. Characteristic diffuse/localized swelling or masses in single or multiple organs
2. Elevated serum IgG4 concentrations (>135 mg/dL)
3. Histopathologic examination showing (a) marked lymphocyte and plasmacyte infiltration and fibrosis, (b) infiltration of IgG4+ plasma cells: IgG4/IgG ratio >40% and >10 IgG4+ plasma cells/HPF

The diagnosis of IgG4-RD is classified as definite (1 + 2 + 3), probable (1 + 3), and possible (1 + 2). The index case classifies into definite disease on the basis of this criteria. In contrast to IgG4-related RPF, non-IgG4-RPF has more remarkable fibrosis on histopathology.

Glucocorticoids are considered as the first-line agents for treatment induction (1 mg/kg).[7] Maintenance therapy is essential to prevent relapse in these patients, for they suffer a high rate (30%-60%) of relapse after induction therapy. There is no consensus on the maintenance agent and its duration. Maintenance therapy may consist of low-dose glucocorticoids or any steroid-sparing drug like azathioprine, mycofenolate mofetil, methotrexate, or a combination regimen. Optimal duration of maintenance therapy varies, ranging from 1 to 3 years.[2,6,7] Rituximab, an anti-CD20 monoclonal B-cell depleting antibody, has shown promising results with response rates of 93.5%.[12] It selectively acts on plasmablasts and plasma cells producing IgG4, as CD20 is exclusively present on the surface of the cells. Hence, it leads to a significant decrease in concentration of IgG4, without affecting other subclasses. Response to treatment is assessed in terms of improvement in overall clinical status, reduction in serum IgG4 levels, and disappearance/diminution of radiological abnormalities.[12] In cases refractory to the medical management, surgical option of ureterolysis can be used similar to that for idiopathic RPF.[13]

Although the treatment modalities of IgG4-related RPF do not differ much from idiopathic RPF, differentiation between the 2 diseases is essential. The availability of serum IgG4 levels for monitoring treatment response and follow-up can curtail the repeated radiological imaging and associated contrast exposure. Second, the diagnosis of IgG4-related RPF shall alert the clinician to look out for extraretroperitoneal diseases on follow-up of this multiorgan disease.

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