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CASE REPORT

IgG4 Related Disease Associated Retroperitoneal Fibrosis: A Rare Cause of Chronic Back Ache

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ABSTRACT

Title of the article: Immuno-globulin G4 related disease associated retroperitoneal fibrosis: A rare cause of chronic back ache.

Introduction: Retroperitoneal fibrosis is an uncommon presentation of IgG4 – Related Disease, often presenting with non-specific symptoms leading to delayed diagnosis and management.

Case report: This case report describes a 67-year-old female who presented to the emergency department with complaints of gradually worsening back ache in the last 3 months; associated with urinary hesitancy and fever with chills; not resolving with antibiotics and analgesics. Contrast Enhanced Computed Tomography abdomen was suggestive of left pyelonephritis and retro-peritoneal inflammatory fibrosis. IgG4 sub class level of 1.71 (Reference range: 0.1 – 1.2). The patient was started on glucocorticoid therapy resulting in rapid symptoms resolution. Maintenance therapy with Tab. Mycophenolate mofetil 500mg once daily was started to prevent relapse.

Conclusion: When lower back pain is present with symptoms like abdominal pain and obstructive urinary tract symptoms retroperitoneal fibrosis should be considered in the differential diagnosis. Recognizing the association is crucial for initiating appropriate therapy to prevent progression.

KEYWORDS

• Retroperitoneal fibrosis • IgG4 related disease • Lower back pain • Obstructive urinary tract symptoms • Glucocorticoid therapy Emergency department

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KEY MESSAGE

- When lower back pain is present with symptoms like abdominal pain or obstructive urologic symptoms in the Emergency Department, retroperitoneal fibrosis should be considered in the differential diagnosis, as gglucocorticoid therapy alone usually results in rapid symptoms resolution.
- Retroperitoneal fibrosis has a relatively common association with IgG4 related disease – a rare fibro-inflammatory disease.

INTRODUCTION

Immunoglobulin G4-Related Disease is a rare, multi-organ, fibro-inflammatory condition with tumefactive lesions of unknown aetiology and characteristic histopathological features.[1]. It involves an aberrant immune response, including the activation of T-helper 2 cells and regulatory T-cells, resulting in IgG4 production and fibrosis[2]. Although the disease can affect virtually any organ, there are strong predilections for certain organs. These include the major salivary glands, the orbits and lacrimal glands, the pancreas and biliary tree, the lungs, the kidneys, the aorta and retroperitoneum, the meninges, and the thyroid gland[3]. The exact incidence and prevalence of IgG4-RD is not known due to low awareness, recent discovery, and an indolent clinical course. According to available data, the incidence of IgG4-related disease (IgG4-RD) in India appears to be relatively understudied, but case series from tertiary care centres suggest a significant presence, with a pattern of frequent orbital, periorbital and retroperitoneal involvement, and a younger patient population compared to global trends. The exact prevalence remains unknown due to limited research, but studies indicate a growing recognition of the disease in the region.[4][5] The 2020 Revised comprehensive diagnostic (RCD) criteria for IgG4-RD[6]:

1. **Clinical and radiological features:** One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted.
2. **Serological diagnosis:** Serum IgG4 levels greater than 135 mg/dl.
3. **Pathological diagnosis:** Positivity for two of the following three criteria:
   - Dense lymphocyte and plasma cell infiltration with fibrosis.
   - Ratio of IgG4-positive plasma cells / IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high powered field
   - Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis

Definite: 1) +2) +3)

Probable: 1) +3)

Possible: 1) +2)

Recent studies on Immunoglobulin G4-related disease (IgG4-RD) reveal that abundant infiltration of IgG4 positive plasma cells is found in biopsies on the mass of RPF of some Idiopathic RPF patients, which is identified as IgG4-related RPF[7]. IgG4-RPF is the most common manifestation of IgG4-RD. Approximately 9.6–27.0% of patients with IgG4-RD are found to have this lesion. The most common symptoms include abdominal, back, flank, or lumbar pain, lower extremity oedema, decreased urinary excretion, low grade fever, appetite loss, and weight loss [8]. The diagnosis of IgG4-RD RPF poses a clinical challenge due to its insidious onset and overlapping features with other causes of RPF, such as malignancy or infections.

We present here a case report of a 67-year-old female who developed retroperitoneal fibrosis in response to IgG4 related disease (RD). We believe this case to be of clinical relevance because IgG4-RD associated RPF can lead to significant morbidity due to the involvement of vital structures, including the ureters and vascular systems - recognizing the association, therefore is crucial for initiating appropriate therapy to prevent progression and irreversible organ damage.

CASE REPORT

A 67-year-old female presented to the emergency department with complaints of gradually progressive, dull aching, middle to lower **back ache** in the last 3 months.

She had taken several consults from different departments before presentation to the ER:

She was first initiated on analgesics by her **Orthopaedician**.

The patient then developed low grade persistent **fever with chills** 1 month ago for which she was given Tab. Paracetamol, Tab. Norflox and Inj. Amikacin 2gms IM by her **Gastroenterologist**.

Her symptoms were temporarily relieved.

One week later, the patient developed radiation of pain to the left flank region and complained of **decreased frequency of micturition with an associated burning sensation**. Urine C/S done at an outside lab was suggestive of E. coli for which she was given Tab. Levofloxacin by her **Gynecologist**.

The patient had no history of similar episodes in the past.

She had Type 2 Diabetes Mellitus; Hypothyroidism; diverticulae in the sigmoid and descending colon.

She was a non-smoker and non-alcoholic.

There was no history of recent travel.

Family history was negative for any similar complaints.

On examination:

Vitals:

Heart rate: 120/min

Blood pressure: 110/70 mmHg

Respiratory rate: 20/min

SpO2 on room air: 98%

Pain score: 7

Abdominal examination: Tenderness in the left lumbar region.

Back and spine examination: There was mild para-spinal tenderness in the dorso-lumbar region.

Neurological examination: GCS: 15/15; Bilateral lower limbs showed no motor or sensory deficits.

An initial provisional diagnosis of left pyelonephritis with urinary tract infection and lower urinary tract symptoms was made and in lieu of that CECT abdomen was advised.

Contrast Enhanced Computed Tomography of the abdomen was suggestive of:

1. B/L tiny concretions in the lower pole calyces.
2. Mild luminal narrowing in infra-renal aorta which shows irregular, circumferential enhancing wall thickening extending inferiorly to the common iliac arteries on both sides up to the bifurcation of left common iliac artery – suggestive of **infra-renal aortitis**.
3. Peri-aortic inflammatory changes in the retroperitoneum predominantly involving the pre and left para-aortic locations – suggestive of **retroperitoneal fibrosis**.
4. Thickening of left anterior perirenal, left posterior perirenal fascia along with left side perinephric stranding – suggestive of **left pyelonephritis**.

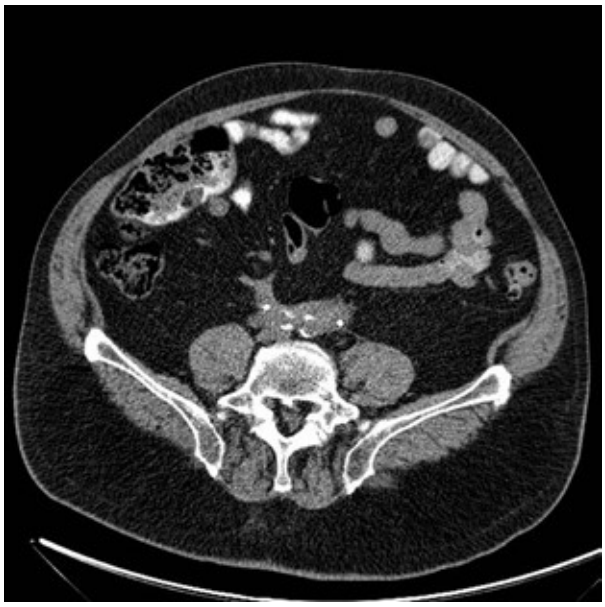

Figure 1: Patient's contrast enhanced CT scan suggestive of retroperitoneal fibrosis and infra-renal aortitis

Lab investigations showed elevated inflammatory markers (ESR: 30; CRP: 38.87).

ANA LIA, Vasculitis LIA, IgA and IgM levels came back negative.

However, patient had an IgG4 sub class level of 1.71 (Reference range: 0.1 – 1.2).

To make a definitive diagnosis of IgG4-RD associated RPF, patient was advised to undergo biopsy for histopathological confirmation. However, the patient did not provide consent for the same.

To rule out malignancy/vascular inflammation/infection as the etiology

for the RPF and peri-aortitis, FDG (Fluorodeoxyglucose)-PET CT scan was done which showed multiple non-FDG avid, sub centimeter sized enhancing pre-aortic and para-aortic lymph nodes. No significant FDG avid lesion in the body surveyed.

Based on clinical, serological and radiological findings a diagnosis of **possible IgG4-RD associated RPF** was made as per the 2020 Revised comprehensive diagnostic (RCD) criteria for IgG4-RD[8].

The patient was started on glucocorticoid therapy – Tab. Prednisolone 60mg for 10 days, 40 mg for 10 days, 30 mg for 10 days, 20 mg for 1 month, 15 mg for 1 month, 10 mg for 3 months and lastly 5 mg for 6 months.

She was also initiated on immunosuppressive therapy with Tab. Mycophenolate Mofetil 500mg.

The patient was followed in the outpatient department of the hospital and was inquired about the intensity of her symptoms.

Within one month of therapy initiation, the patient reported resolution of her urinary hesitancy with minimal improvement in the intensity of the lower back ache.

At her 3 month follow up, the patient reported marked improvement in her pain and no recurrence of the lower urinary tract symptoms.

The patient refused to consent for a follow up CT scan which was advised to check for RPF regression.

Management challenge: Patient's refusal for invasive procedures and follow up scans.

DISCUSSION

RPF is a rare disorder characterized by the presence of chronic inflammation and fibrosis in the retroperitoneal space. Two thirds of the cases are idiopathic.

It can present with a variety of non-specific symptoms, including:

i. **Pain:** dull pain in the lower back, abdomen, flank, groin, or scrotum. The pain can be colicky if the ureters are partially or completely obstructed.

ii. In a study of 185 patients with RPF, the most common presenting symptoms were **back pain (38%) and abdominal pain (40%)**[12].

iii. **Systemic symptoms:** Fatigue, anorexia, weight loss, fever, nausea or vomiting.

iv. **Urologic manifestation:** Decreased urine production or urinary hesitancy can indicate renal or ureteral involvement.

Rhys D.R. Evans conducted a retrospective observational study of patients with IgG4-RKD and IgG4-RPF in a multicentre IgG4-RD cohort. In an analysis of 154 patients with IgG4-RD 28 patients (18.2%) had renal or retroperitoneal involvement. Fourteen patients (9.1%) had intrinsic renal disease, **10 (6.5%) had RPF (Figure 1)**, and 4 (2.6%) had both intrinsic renal disease and RPF.

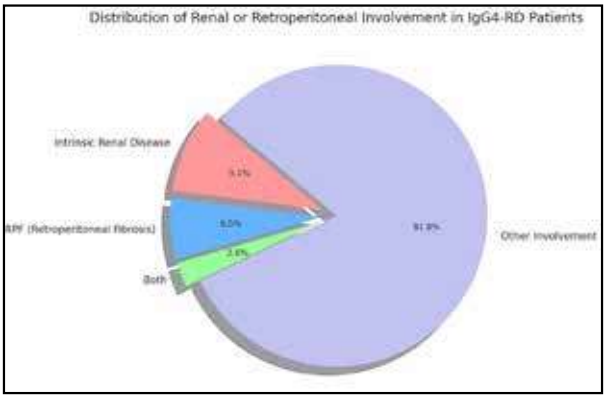

Figure 2: Clinical Manifestations and Long-term Outcomes of IgG4-Related Kidney and Retroperitoneal Involvement in a United Kingdom IgG4-Related Disease Cohort (Rhys D.R. Evans et. Al): In a cohort of 154 patients with IGg4-RD, 10 patients (6.5%) had RPF

A study by Pucar and Hinchcliff[11] presented the highest quality evidence regarding the potential value of dedicated[18] F-fluorodeoxyglucose PET-CT examinations for the detection of vascular inflammation in patients with IgG4-RD. Para-aortic tissue can be a challenging area to access for biopsy and is a high-risk procedure owing to the potential arterial complications. As in our case, absence of avid FDG lesions in the FDG-PET scan in conjunction with the radiological and serological report consistent with IgG4-RPF led us to initiating corticosteroid therapy for our patient. It resulted in rapid resolution of symptoms. Our article brings into notice that in a developing country like India, lack of awareness and financial constraints may deem it impossible for clinicians to obtain histopathology and immunochemistry reports for a definitive diagnosis. We can probably include FDG PET scans and the resolution of symptoms upon corticosteroid therapy in our diagnostic criteria for definitive IgG4-RPF.

CONCLUSION

Chronic back pain, a common clinical complaint, is often attributed to musculoskeletal or degenerative causes. This case demonstrates how atypical imaging findings prompted further investigations, leading to the identification of IgG4-RD as the underlying aetiology.

According to available medical literature, a significant portion of people experiencing lower back pain will not have retroperitoneal fibrosis.

However, when lower back pain is present with symptoms like abdominal pain, difficulty urinating, or unexplained weight loss, retroperitoneal fibrosis should be considered in the differential diagnosis, with studies indicating around 38% of individuals diagnosed with retroperitoneal fibrosis present with back pain as their primary symptom; making it a substantial percentage among those diagnosed with the disease.

This case contributes to the growing understanding of IgG4-RD and RPF; its varied clinical manifestations and the importance of considering it in atypical presentations of chronic back pain.

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