How to Manage Retroperitoneal Fibrosis?

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Patient Case:

A 42-year-old man of Iranian descent presented originally with peri-umbilical discomfort. He had a computed tomography (CT) scan in Iran showing soft tissue attenuation surrounding the aorta from the infrarenal vessels to the common iliac bifurcation. This mass measured 5.7 cm x 3.0 cm x 5.9 cm. He received a course of prednisone empirically but, when he was completely weaned off steroids, his mass recurred. He underwent a CT-guided biopsy which showed chronic inflammation enriched with lymphocytes, plasma cells and eosinophils, consistent with retroperitoneal fibrosis. He was restarted on prednisone and then placed on mycophenolate which he continued taking at presentation to us.

His labs in Canada showed normal kidney function, with a creatinine of 81 µmol/L (normal 60-155 µmol/L) and an estimated glomerular filtration rate of 103 ml/min (normal is >59 ml/min). His complete blood count, electrolytes, liver enzymes, and urinalysis were normal. His C-reactive protein (CRP) was elevated at 19.1 mg/L (normal <3.1 mg/L). His total protein was elevated at 84 g/L (normal 62-80 g/L). His IgG4 level was normal at 0.719 gram/L (normal 0.052-1.25 g/L).

The patient was referred for recommendations on the diagnosis and management of his retroperitoneal fibrosis.

Introduction

Retroperitoneal fibrosis (RPF) was first described by John Ormond, an American urologist in 1948.[1] He described it as sclerotic tissue in the retroperitoneum, commonly peri-aortic or peri-iliac, and encasing adjacent structures. Common presenting symptoms include abdominal, back and/or flank pain along with constitutional symptoms.[2] Patients may also present with acute renal failure due to ureteric obstruction, with retroperitoneal fibrosis found on abdominal/pelvis CT scanning. Peripheral edema may also be present due to compression of the iliac veins in the pelvis.[3]

RPF is a rare disease; for example, a Dutch study reported an incidence of 1.3/100,000.[2] There is a male predominance, and the median age of onset is 64 years old.[2] Patients were historically managed by urology with serial monitoring for hydronephrosis and serial ureteral stenting.[3]

A definition of RPF by Scheel et al. has been proposed that is not reliant on pathology. This includes: 1) identification by computed tomography (CT) or magnetic resonance imaging (MRI) of a soft-tissue density surrounding the infrarenal or iliac vessels; 2) absence of aneurysmal dilation of the infrarenal aorta; 3) absence of an intra-abdominal or pelvic mass; 4) lack of suspicion of malignancy from history and physical examination; and 5) negative age-appropriate cancer screening.[4] A radiographic-focused definition is important but does not precisely address the etiology of RPF, as management differs depending on the underlying cause. The pattern of aortic involvement, ureteric involvement, presence of lymph nodes or extension into the pelvic wall are not predictive radiographically of the underlying disease.[5]

What Are the Causes of RPF?

The pathogenesis of RPF is not known.[6] However, when pathology is obtained from surgical or CT-guided biopsies, certain patterns emerge. Unfortunately, there have been no prospective analysis of biopsy results in retroperitoneal fibrosis. There is a high prevalence of both idiopathic and IgG4-related RPF in cases of RPF reported.[5] In Khosroshahi's study, any patients who carried a prior diagnosis of malignancy were excluded. This fits with the literature in which the association or causal relationship of RPF and malignancy is hard to quantify.[6] It is safe to say that IgG4-related disease is the cause of RPF 30-57% of the time.[6] Determining whether the patient has IgG4-related disease may represent one of the most important considerations, as it is a systemic disease that may progress over time.

Table 1

Causes of Retroperitoneal Fibrosis

Immune-mediated

- Erdheim Chester disease
- Giant cell arteritis
- Granulomatosis with polyangiitis
- Idiopathic retroperitoneal fibrosis
- IgG4-related retroperitoneal fibrosis
- Sarcoidosis

Infection

- Actinomyces
- Mycobacterium

Malignant

- Inflammatory myofibroblastic tumor
- Lymphoma
- Metastatic carcinoma
- Plasmacytoma
- Sarcoma

Contributors to this list include the following experts: Drs. Luke Chen, Emmanuel Della Torre, Arezou Khosroshahi, John H. Stone, and Zachary Wallace

There have been associations proposed between RPF and other conditions such as atherosclerosis, certain medications, and connective tissue disease.[3] In cases where the tissue clearly shows one of these conditions, then one can make a case for causality. This occurs with lymphoma, for example, where the retroperitoneal soft tissue infiltration shows B-lymphocyte clonal proliferation.[7] Similarly, when the adventitia of the aorta shows granulomatous infiltration and antineutrophil cytoplasmic antibodies are positive, this is consistent with granulomatosis with polyangiitis.[8] The list in Table 1 represents a more tailored differential diagnosis for RPF based on histopathologic evidence and expert opinion.

What Is the Appropriate Work-up of RPF?

Due to the high prevalence of IgG4-related disease with retroperitoneal fibrosis, a full clinical work up for systemic IgG4-related disease makes sense (Table 2). The systemic nature of IgG4-related disease makes pattern recognition difficult when making a clinical diagnosis. Similarly, the IgG subclasses are an unreliable biomarker for diagnosis, with a specificity of 90% and sensitivity of 60% in one single centre study.[9] The typical pattern of IgG4-related disease has been defined in recent American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria.[10] However, these classification criteria remain heavily reliant on histopathology and, therefore, most cases of IgG4-related disease require biopsy confirmation.[11] IgG4-related RPF is defined by storiform fibrosis and enrichment of IgG4-positive plasma cells with a IgG4/IgG ratio of >40%. By contrast, idiopathic RPF shows lymphoid follicles, extensive non-storiform fibrosis and a low IgG4/IgG ratio. The idiopathic RPF patients also have no extra-abdominal involvement.

In RPF, as in IgG4-related disease, a CT-guided or surgical biopsy is often necessary. If there is another organ site that is suggestive of IgG4-related disease, such as a submandibular gland, then the more easily accessed organ would be biopsied preferentially. Given the various causes of RPF listed in Table 1, management would be very different, depending on whether an immune-mediated condition, malignancy or infection is present.

The index patient was assessed in clinic for IgG4-related disease. He was asymptomatic at that time. His physical exam was notable for bilateral submandibular swelling. On CT scan of his neck, chest, abdomen, and pelvis he was found to have bilateral submandibular gland enlargement, and bilateral mediastinal and hilar lymphadenopathy. The RPF mass had decreased in size and now measured 5.1 cm x 2.7 cm x 5.2 cm. Figure 1 shows the characteristic axial view of RPF showing soft tissue encasement of the abdominal aorta at the level of the renal vessels. Histopathology slides of the retroperitoneal mass that he brought from Iran were reviewed at the British Columbia Cancer Agency. The pathology was found to be diagnostic of IgG4-related disease, notably with lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis with an IgG4/IgG ratio of >40%. This patient was diagnosed as having IgG4-related disease after this biopsy review.

Table 2
IgG4-related Disease Manifestations

Organ Manifestation	Symptoms	Physical Exam Findings	Imaging
Pachymeningitis	Headaches Focal neurologic deficit	Abnormal neurologic exam	MRI enhancement of the pachymeninges
Orbital Pseudotumor	Visual changes Eyelid swelling New eye protrusion	Extraocular muscle palsies Enlarged lacrimal glands Proptosis	Extraocular muscle myositis Dacryoadenitis Pseudotumor
Sialadenitis	Sicca symptoms Cheek swelling	Submandibular enlargement Parotid enlargement	Glandular enlargement Glandular enlargement
Riedel's thyroiditis	Neck swelling	Goiter	Diffuse enlargement of the thyroid gland
Pulmonary inflammatory pseudotumor	Cough Shortness of breath	Normal lung exam Decreased breath sounds at site of mass	Diffuse pulmonary nodules Pulmonary mass
Pericarditis	Asymptomatic Chest Pain	Pulsus parodoxus (rare) Friction Rub	Pericardial effusion Pericardial thickening
Autoimmune pancreatitis	Nausea and vomiting Right upper quandrant abdominal pain Pancreatic insufficiency	Epigastric tenderness Right upper quadrant tenderness Jaundice	Pancreatic mass especially at pancreatic head Diffuse pancreatic swelling "sausage-shaped pancreas" ERCP* shows stricture(s) of the pancreatic duct Pancreatic atrophy
Sclerosing cholangitis	Pruritis Jaundice	Hepatomegaly	ERCP shows "beading" of the intra and extrahepatic ducts Dilated intra and extrahepatic ducts
Tubulointerstitial Nephritis	Constitutional symptoms Oliguria	Peripheral edema	Multiple kidney opacities
Retroperitoneal Fibrosis	Nausea and vomiting Constitutional symptoms Flank/back/abdominal pain	Abdominal mass Abdominal or femoral bruits Peripheral edema	Peri-aortic soft tissue infiltration
Sclerosing mesenteritis	Nausea and vomiting Abdominal pain	Diffuse or focal abdominal tenderness Palpable abdominal mass(es)	Peritoneal mass or masses Diffuse peritoneal thickening
Lymphadenopathy	Often associated with constitutional symptoms Pain from lymph node swelling	Lymphadenopathy ranging from mild to massive in any lymph node chain commonly cervical, axillary, and inguinal	Lymphadenopathy commonly seen in the following chains: cervical, mediastinal, hilar, axillary, abdominal, retroperitoneal, pelvic, and inguinal
Rash	Asymptomatic	Flesh coloured papules on face and upper chest	None

*ERCP: Endoscopic Retrograde Cholangiopancreatography

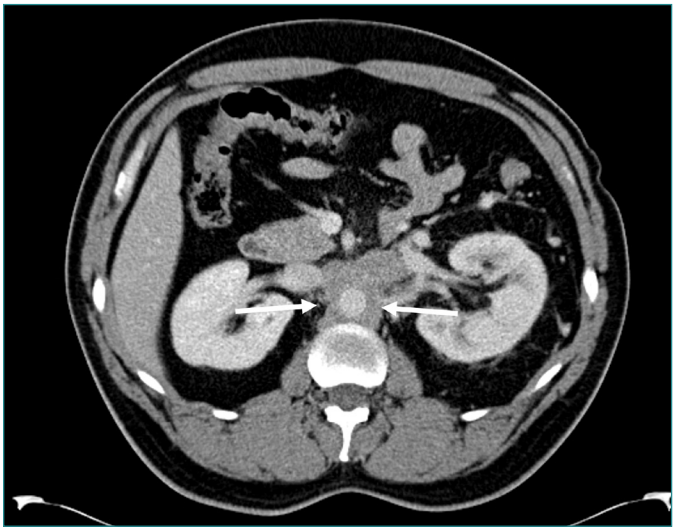

Figure 1: Axial CT with contrast showing maximal 2.5 cm soft tissue thickening encasing the aorta indicated between 2 white arrows.

What is the Appropriate Management of IgG4-related RPF?

The proper treatment of IgG4-related disease is emerging. The mainstay of therapy is prednisone.[12] Other options for IgG4-related disease include disease modifying anti-rheumatic drugs, of which mycophenolate is the most favoured.[13,14] Rituximab has been observed to be effective in both IgG4-related disease and idiopathic retroperitoneal fibrosis.[15,16,17] Ongoing studies are being done with respect to newer agents specifically for IgG4-related disease.

The index patient was refractory to both prednisone and mycophenolate. He was commenced on rituximab, but after one course of treatment, he was lost to follow up.

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