Multifocal Idiopathic Fibrosclerosis Mimicking Tuberculosis of the Abdomen

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Abstract
We present a 13 year old girl from Assam who had been treated as abdominal tuberculosis for 2 years due to the presence of refractory lymphocyte-predominant ascites and multiple small bowel strictures associated with significant anorexia and weight loss. On evaluation she was found to have retroperitoneal fibrosis with hydroureteronephrosis, mediastinal fibrosis and a retro-orbital pseudotumour. Based on these findings the diagnosis of Multifocal Idiopathic Fibrosclerosis (MIFS) was made. Ascites and multiple bowel strictures have been only rarely been described in association with MIFS. The other unique features in this patient were the early age of presentation, the presence of mediastinal fibrosis in association with retroperitoneal fibrosis, extensive soft tissue fibrosis of the neck, axillae and the presence of trismus. In a country like ours where Tuberculosis is commonplace, one would not think twice about treating such a case with antituberculous therapy. However, with a constellation of findings suggestive of a diffuse fibrotic process, MIFS should be an important consideration.

INTRODUCTION
Idiopathic Retroperitoneal fibrosis (also known as Ormond’s Disease) on occasion forms a part of the rare disseminated process of Idiopathic Multifocal Fibrosclerosis (MIFS), in varying association with fibrosis of other tissues in the body such as mediastinal fibrosis, Riedel’s thyroiditis and sclerosing cholangitis. Characteristically it may be associated with a pseudotumour of the orbit, which may be locally invasive and requires differentiation from neoplasia.1,2 The association of retroperitoneal fibrosis, Riedel’s thyroiditis and orbital pseudotumour was first described by Barret due to the similarity in histopathology. Less commonly, it may be associated with Dupuytren’s contracture, lymphoid hyperplasia, Peyronie’s disease, vasculitis, pachymeningitis, autoimmune pancreatitis, pancreatic fibrous pseudotumour, parotid, lacrimal and pulmonary fibrosis.1,3 Presentations may also include exophthalmos, visual loss secondary to optic nerve involvement or reduced renal function due to ureteric obstruction and hydroureterosis as a result of retroperitoneal fibrosis; hence the patient may present to an ophthalmologist or urologist at the outset.

CASE HISTORY
A 13 year old girl from Assam presented in February 2003 with history of progressive weight loss for 3 years associated with anorexia, occasional low grade fever and intermittent abdominal distension. In April 2000 she had presented to a local hospital with features of an acute intestinal obstruction. The surgeon at that time observed multiple intra-abdominal adhesions and small bowel strictures, and went on to perform an ileo-transverse anastomosis. Following the surgery, she developed refractory lymphocyte-predominant exudative ascites requiring repeated abdominal paracentesis. She was treated with multiple adequate courses of anti-tuberculous drugs including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide which she took regularly. Over the next 2 years, on treatment, she had no resolution of symptoms. Over the 6 months prior to presentation at our centre, she developed progressive inability to open her mouth resulting in significant malnutrition.

At presentation, she was grossly emaciated. She was noticed to have induration of the tissues of the neck and axilla, with significant restriction of movement of the neck. She was unable to open her mouth beyond one finger breadth. Her left eye was prominent as compared to the right. She had a firm enlarged thyroid but was clinically euthyroid. She had bilateral pitting pedal oedema but no lymphadenopathy. She had no clinical features to suggest an autoimmune disorder as sclerodactyly, rash, oral ulcers, Raynaud’s phenomenon or arthritis. Abdominal examination revealed a tense ascites with no features of peritonitis and no organomegaly. Respiratory, cardiovascular and central nervous system examination was unremarkable.
Investigations revealed a haemoglobin of 7.1 gm/dl (Mean Corpuscular Volume 62.7 fl), and a total White Blood Cell count of 15,000 cells/mm³ with a differential count of - Neutrophils 92%, Lymphocytes 7%, Monocytes 1%, Eosinophils (NIL). Serum creatinine was 0.5 mg/dl, and liver function tests revealed severe hypoalbuminemia with reversal of the albumin/globulin ratio. Inflammatory markers were elevated with an ESR of 178 mm/1hr and CRP of 150mcg/l. The thyroid function tests were normal (Serum T4 – 9.5mcg%; Free Thyroxine Concentration - 1.5 mcg %). An autoimmune workup which included antinuclear antibody, anti double stranded DNA, Direct Coombs Test and rheumatoid factor did not show any significant positive result. The patient had no features as cavitory lesions in the lung, glomerulonephritis, neuropathies, asthma or eosinophilia to suggest an Anti-neutrophil cytoplasmatic antibody (ANCA) associated vasculitis and hence serological testing for these antibodies was not conducted. A biopsy of the pseudotumour (via a Caldwell-Luc approach) revealed fibrosis with non-specific chronic inflammation. Tissue biopsy of the cervical induration also revealed focal fibrosis and perivascular atrophy. There was no evidence of vasculitis (granulomatous or non-granulomatous) on any of the biopsies taken. Fibrosis of the tissue was the predominant component in all biopsies of the sinuses, skin and fascia.

Ascitic fluid analysis revealed a lymphocyte-predominant exudate; cytology for malignant cells, fluid cultures and TB PCR were negative. Fluid analysis for chylomicros was also negative ruling out a possible chyous ascites. The ECG, Chest X-ray and Echocardiogram were all normal. Both the ECHO and the CT Thorax showed no evidence of pericardial fibrosis or features of constrictive pericarditis.

A Barium meal follow through (BMFT) study revealed mid and distal ileal strictures with proximal ileal loop dilatation and a patent mid ileo-transverse colon anastomosis.

Abdominal Doppler studies were negative for portal hypertension and Budd Chiari syndrome. Computed Tomography (CT) of the abdomen revealed significant retroperitoneal fibrosis encasing both ureters causing moderate hydro-ureteronephrosis and encasing the iliac and mesentric vessels with significant ascites (Fig. 1). A CT of the orbit showed a destructive, partially sclerotic, 2.5 cm lesion in the floor of the left orbit, extending into the maxillary antrum and infratemporal fossa, suggestive of a pseudotumour (Fig. 2). CT scans of the lower neck and thorax revealed mediastinal fibrosis (Fig. 3) and significant fibrosis of the tissues of the neck with diffuse thyroid enlargement (Fig. 4). A bone scan revealed diffuse uptake in all joints including the temporo-mandibular joint. Renal Scintigraphy & Renogram showed bilateral hydro-ureteronephrosis with no evidence of urinary extravasation and significant reduction of GFR in the right kidney. Based on the findings of retroperitoneal, mediastinal fibrosis and retro-orbital pseudotumour, a diagnosis of Idiopathic Multifocal Fibrosclerosis was made. Bilateral ureteric DJ-stents were placed and she was initiated on Prednisolone at 1 mg/kg body weight for 3 months. The steroid protocol was subsequently changed to an alternate day regime with a plan to taper of 5 mg every month to a baseline of 15 mg on alternate days. There was minimal ascites on the last follow-up at one year and the restriction of mouth opening and restriction of tissues around the neck had resolved significantly. There was remarkable improvement in terms of weight gain and appetite, with significant improvement in nutrition, and decrease in inflammatory markers (Table 1).

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Fig. 1 : Contrast-enhanced CT scan of the abdomen showing retroperitoneal soft tissue encasing the aorta, IVC and ureters [long thick arrow] with resultant bilateral hydroureteronephrosis [short thick arrow], and encasing the mesentric vessels [short thin arrow] with ascites.

Fig. 2 : Contrast-enhanced CT scan of the orbits revealing a destructive mixed lytic and sclerotic lesion with mildly enhancing soft tissue in the floor of the left orbit, extending into the maxillary sinus and infratemoral fossa [arrow].
DISCUSSION

The aetiology of the disease is not known, though the association with other inflammatory diseases, elevated inflammatory markers, auto-antibodies, tissues infiltrated by inflammatory cells and importantly the remarkable improvement with steroids tends to suggest an immunological mechanism. It is important in such cases to embark on a thorough search for underlying infections and malignancies such as retroperitoneal sarcomas, as well as remove possible drugs that could induce fibrosis.

Retroperitoneal proliferation of fibrous tissue can range from marked chronic inflammation with an exuberant cellular response to differentiated fibrous tissue with occasional inflammatory cells. In most cases, dense fibrocollagenous stroma with vasculitis and a non-specific chronic inflammatory infiltrate are evident. [3] Unusual changes in the small and medium sized veins in the fibrous tissue in the thyroid and the retroperitoneum best designated as “occlusive phlebitis” seem to be characteristic of Multifocal Fibrosclerosis. [2] IgG4 has been suggested as a possible marker for fibrosclerotic lesions in these cases and may also predict sensitivity to steroids. [4, 5] This proliferation of fibrous tissue encroaches upon surrounding structures like the ureters, blood vessels and lymphatics resulting in a myriad of manifestations. Gross appearance of the fibrosclerotic process is that of a grey-white plaque-like tissue.

This patient had multiple bowel strictures which have only been rarely described in Retroperitoneal Fibrosis. The strictures were probably a result of ischemia due to vascular compromise secondary to inflammation (vasculitis) and mechanical occlusion due to fibrosis. The persistent ascites was probably multi-factorial. Few cases of ascites have been documented in retroperitoneal fibrosis, the primary culprits being a chylous ascites and urinary ascites secondary to ureteric rupture. [6] Our patient had severe hypoalbuminemia which was probably due to a combination of chronic disease and underlying protein losing enteropathy secondary to bowel ischemia. It is also possible that the persistent ascites was a sequel to significant irreversible lymphatic obstruction though there was no evidence of chylous ascites. Hence, her presentation had closely mimicked abdominal tuberculosis for a long period of time but was refractory to Anti tuberculous therapy. It subsequently responded dramatically to steroids. Another factor of interest in this patient was the inability to open the mouth as well as marked soft tissue fibrosis of the neck and axillae which, to the best of our knowledge, have not been described previously. This problem was probably a result of inflammation of the temporo-mandibular joint as documented on the bone scan as well as restriction of movement due to fibrosis of the surrounding tissues.

The treatment of choice is steroids, with good response in the majority of cases, though surgery, radiotherapy and systemic chemotherapy, including cyclosporine, have been advocated and may play a role in more aggressive forms of the disease. Medroxy-progesterone acetate, progesterone, and tamoxifen have also been used with some success in

Table 1

<table>
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<tr>
<th>Date</th>
<th>Haemoglobin g/L</th>
<th>Albumin g/L</th>
<th>Globulin g/L</th>
<th>ESR (1 hour)</th>
<th>Ascites estimation</th>
<th>USG abdomen</th>
<th>Mouth opening</th>
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<tr>
<td>Feb 2003</td>
<td>7.1</td>
<td>1.9</td>
<td>6.9</td>
<td>128</td>
<td>Massive</td>
<td>USG abdomen</td>
<td>1 finger breadth</td>
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<tr>
<td>Nov 2003</td>
<td>14.6</td>
<td>4.1</td>
<td>2.5</td>
<td>30</td>
<td>Moderate</td>
<td>USG abdomen</td>
<td>2 finger breadth</td>
</tr>
<tr>
<td>(6 months of steroids)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apr 2004</td>
<td>14.6</td>
<td>-</td>
<td></td>
<td>12</td>
<td>Mild to Moderate</td>
<td>Almost complete</td>
<td>Mouth opening</td>
</tr>
<tr>
<td>(&gt;1 year of steroids)</td>
<td></td>
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Fig. 3: Contrast-enhanced CT scan of the thorax showing enhancing mediastinal soft tissue encasing the aortic arch [arrow], as well as great vessels [not shown].

Fig. 4: Contrast-enhanced CT scan of the neck revealing diffusely enlarged thyroid [short arrow], ill-defined enhancement and thickening of the sternomastoid & strap muscles [long arrow], and diffuse loss of normal fat planes in the neck.
refractory cases. Once therapy has been initiated these patients require close follow-up. Serial CT scans and ESR measurements for monitoring of disease activity have been suggested as has Positron Emission Tomography.

In a country where tuberculosis of the abdomen is rampant, one may not think twice about assuming it to be the diagnosis in a patient such as ours and initiating treatment. However, in patients who are refractory to antituberculous therapy, and in those that have any of the protean manifestations of diffuse fibrosis as described, Idiopathic Multifocal Fibrosclerosis may be a rare but important consideration for the treating doctor.

REFERENCES