IgG4 related sclerosing disease - a case report
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Abstract:
IgG4 related sclerosing disease is an immune mediated disorder that affects multiple systems. This disorder is characterized by elevated serum IgG4 levels, IgG4 rich lymphoplasmacytic infiltration of various organs and typical imaging features that have since been described in literature. IgG4 related sclerosing disease is characterised by IgG4 positive plasma cell infiltration of various target organs resulting in fibrosis of the involved organs. Autoimmune pancreatitis of lymphoplasmacytic type is one of the most common manifestations of this disease. In this paper, we present a case report of a 66 year old lady who presented with pyrexia of unknown origin and low grade obstructive jaundice who on imaging was discovered to have features of autoimmune pancreatitis in addition to other imaging features of IgG4 disease as described in literature.

Keyword: IgG4 related sclerosing disease, autoimmune pancreatitis

A sixty six year old lady presented to the geriatric clinic in our institution in June 2011 with complaints of intermittent high grade fever for duration of one and a half years. She also complained of recent onset anorexia and significant weight loss. There was no history of localizing systemic symptoms like cough, expectoration, abdominal pain, loose stools, melena, joint pains, skin rash or oral ulcers.

Past medical history:
She underwent a laparoscopic cholecystectomy elsewhere in October 2010 for asymptomatic cholelithiasis. She underwent oesophago-gastro-duodenoscopy on two occasions; no significant abnormality was noted on either of these occasions. Ultrasonography in March 2011 revealed mild to moderate intrahepatic biliary radicle dilatation and common bile duct dilatation (CBD). Subsequently a magnetic resonance cholangiography (MRCP) was performed and the CBD dilatation was interpreted as a Type I choledochal cyst. Biochemical tests performed elsewhere also revealed elevated serum alkaline phosphatase and direct hyperbilirubinemia suggestive of obstructive jaundice. She had no history of diabetes, hypertension or heart disease.

Clinical examination:
General physical examination revealed severe emaciation (weight: 36.6 kg). She was afebrile and in no obvious distress. Pulse was 100/min and blood pressure was 190/70 mmHg. Respiratory examination revealed bibasal crackles. Abdominal examination revealed moderate hepatomegaly. The liver was palpable 5 cm below the right costal margin.

Central nervous system and cardiovascular system examination were normal. In view of the hepatomegaly, past history of cholecystectomy and intrahepatic biliary radicle dilatation combined with dilated CBD, a clinical diagnosis of obstructive jaundice was made and the differentials considered were iatrogenic common bile duct stricture related to possible bile duct injury at the time of laparoscopic cholecystectomy and a neoplastic process causing compression of the common bile duct / intraluminal common bile duct neoplasm. Baseline biochemical tests and hematological tests were then performed and repeat Computed Tomography (CT) of the abdomen and magnetic resonance cholangiopancreatogram (MRCP), ultrasonography of the abdomen and endoscopic ultrasound were advised. Blood tests revealed elevated ESR (90 mm at 60'), mild anemia (Hb: 10 g/dl), normal total and differential white blood cell counts. Basic fever work up including Widal test for salmonella typhi, Brucella antigen test, blood smear for microfilariala and plasma ia species were negative. Liver function test revealed a total serum Bilirubin level of 2.3 mg/dl and direct Bilirubin level of 2.0 mg/dl, the serum alkaline phosphatase level was 873 units/litre. The findings of the various imaging studies performed are enumerated below.

Ultrasonography:
Ultrasonography of the abdomen revealed:
1. Enlarged, hypoechoic pancreas, there was no evidence of intra-pancreatic or peri-pancreatic fluid collection
2. Moderate intra-hepatic biliary radicle dilatation and dilated CBD with cylindrical configuration and abrupt cut-off of the CBD at the level of the pancreatic head, no detectable intra-luminal calculus or mass at the distal end of the common bile duct
Computerized tomography of the abdomen:
1. Diffusely enlarged, “sausage shaped” pancreas with mild reduction in the degree of enhancement, continuous rim of hypodensity surrounding the entire pancreas
2. Markedly dilated CBD with moderate intra-hepatic biliary radicle dilatation, no obvious mass lesion in the region of the head of the pancreas
3. Enlarged left para-aortic lymph node
4. Well defined, enhancing soft tissue density lesion in the presacral region with no obvious extension into the neural canal, no widening of the neural foraminae was noted on the bone windows

**Hypoenhancing pancreatic head and body with thick rim of hypoattenuating tissue**

**Dilated CBD, laparoscopic cholecystectomy clips, bulky hypoenhancing pancreas**

**Bilobar intrahepatic biliary radicle dilatation**

**Left lower para-aortic node**

**Pre-sacral enhancing nodal mass**

High resolution CT of the thorax was performed in view of the bibasal crackles noted on clinical examination in order to rule out the possibility of interstitial lung disease

The findings on HRCT thorax were as follows:
1. Mild diffuse ground glass opacity with fine randomly distributed nodules in both lungs
2. Mild inter and intralobular septal thickening
3. Mild multifocal, peripheral cylindrical bronchiectasis with mild bronchial wall thickening

**HRCT thorax with diffuse mild ground glass opacities and fine randomly scattered nodules**

**HRCT thorax with mild ground glass opacities and mild peripheral cylindrical bronchiectasis**

Endoscopic ultrasound:
1. Diffusely enlarged, hypoechoic pancreas with a mottled, heterogeneous, predominantly hypoechoic echotexture
2. Margin of the pancreas demonstrated the presence of a hypoechoic rim, the main pancreatic duct was of normal caliber, there was no obvious mass lesion in the pancreas
3. Markedly dilated CBD in the supra-pancreatic region, the course of CBD within the pancreas could not be identified

Endoscopic ultrasound guided, fine needle aspiration for cytology from the head of the pancreas and biopsies for the ampulla were obtained. The imaging features thus far were suggestive of autoimmune pancreatitis, however, the para-aortic and pre-sacral enhancing lesions were deemed to be of indeterminate etiology and tumours of mesenchymal and neurogenic origin were considered as differentials. Serum ANA was weakly positive and serum IgG4 (1850 U/L) levels were markedly elevated. Imaging studies were reviewed in view of the elevated IgG4 level. The cylindrical dilatation of the common bile duct, moderate intra-hepatic biliary dilatation, the left para-aortic and presacral enhancing soft tissue lesions and the presence of ground glass nodules within the lung – all fitted with a pattern of possible IgG4 related sclerosing disease. Immuno-histochemical proof of IgG4 could not be obtained (the ampullary biopsy sample obtained during the endoscopic ultrasound was considered inadequate for immuno-histochemistry studies). In view of the imaging features and elevated serum IgG4 levels, a diagnosis of “possible IgG4 related sclerosing disease” was considered most likely. The patient was started on high dose systemic steroid therapy. The patient was followed up 3 months after the initiation of systemic steroid therapy to assess disease response and repeat imaging of the abdomen was undertaken. Repeat imaging revealed resolution of the intrahepatic biliary radicle dilatation with mild reduction in the dilatation of the CBD. The para-aortic lymph node and presacral nodal mass remained relatively unchanged, however there was no progression with regards to size or extent of involvement. The patient also reported a reduction in the intensity and frequency of febrile episodes, constitutional symptoms like anorexia and weight loss were reported to have improved and she remained asymptomatic as at the time of initial presentation with regard to the respiratory system.

**HRCT thorax with diffuse mild ground glass opacities and fine randomly scattered nodules**

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Th1-predominant immune reaction, similar to that seen in Sjogren’s sclerosing disease and such elevations of serum IgG4 level can be elevated in up to 5% of the normal population. (5, 6).

IgG4-related sclerosing disease is a systemic disease that is characterized by extensive infiltration of various organs by IgG4-positive plasma cells and T-lymphocytes which induce tissue fibrosis with obliterator phlebitis. Clinical manifestations are apparent in the pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, kidney, lung, and prostate. Autoimmune pancreatitis (AIP) is thus not a separate pathological entity but the pancreatic manifestations of systemic IgG4-related sclerosing diseases. The spectrum of organ involvement in this disease includes AIP, sclerosing cholangitis, cholecystitis, sialadenitis, retroperitoneal fibrosis, tubulointerstitial nephritis, interstitial pneumonia, prostatitis, inflammatory pseudotumor and lymphadenopathy. The most common manifestation of IgG4-related sclerosing disease is autoimmune pancreatitis, however, there have been reports of cases without involvement of the pancreas. The disease occurs predominantly in older men and responds well to steroid therapy.

Clinical features:
A male to female ratio of 4:1 has been reported in one series. (7) The most common clinical presentation is that of obstructive jaundice due to the presence of sclerosing cholangitis. (7) Upto 50% of patients may manifest features of endocrine pancreatic dysfunction like glucose intolerance. (7)

Pathogenesis:
This spectrum of sclerosing disorders may be mediated by a Th1-predominant immune reaction, similar to that seen in Sjogren’s syndrome or primary sclerosing cholangitis (PSC). (8)

Pathology:
Histological findings in various extranodal sites include lymphoplasmacytic infiltration, lymphoid follicle formation, sclerosis and obliterator phlebitis, accompanied by atrophy and loss of the specialized structures of the involved tissue (such as secretory acini in pancreas, salivary gland, or lacrimal gland).

Diagnosis criteria:

1. Serum IgG4 elevation
2. Clinical and/or radiologic evidence of lesions consistent with IgG4-related disease in one or more organs as described in the literature
3. IgG4 immuno-histochemical staining showing greater than 10 IgG4+ cells/high-power field and IgG4+/IgG+ ratio greater than 40% in the presence of lymphoplasmacytic infiltration and fibrosis. Elevated serum levels of IgG4 are not diagnostic of IgG4-related sclerosing disease and such elevations of serum IgG4 level can be encountered in other diseases such as pancreatic cancer, (1) atopic diseases (2), and infections (3,4). Serum IgG4 level is elevated in up to 5% of the normal population (5, 6).

In the absence of immuno-histochemical proof of IgG4 lymphoplasmacytic infiltration, based on elevated serum IgG4 levels and typical imaging features a diagnosis of “possible IgG4 related sclerosing disease” can be considered. (9)

Imaging features of IgG4 relating sclerosing disease:
Organ specific imaging features are discussed below:

**Pernicous:**
Delayed enhancement of an enlarged bulky pancreas with a so called “sausage” appearance (10) A capsule-like rim may be noted to surround the pancreas, this capsule has a low density in CT and is the result of inflammatory and fibrous changes involve the peripancreatic adipose tissue.(10,11). Patterns of pancreatic involvement in autoimmune pancreatitis diffuse, focal and multifocal.

**Types of involvement:**
Diffuse disease is the most common type, with a diffusely enlarged sausage like pancreas with a sharp margin, loss of the lobular contour of the pancreas, and an absence of pancreatic clefts seen at imaging. (10, 11)

**Biliary system:**
Biliary disease in IgG4 related sclerosing disease manifests as sclerosing cholangitis. The intrapancreatic segment of the common bile duct is involved most commonly and results in proximal biliary dilatation and obstructive jaundice (12). Multifocal intrahepatic biliary strictures may occur, but they are less common than in typical primary sclerosing cholangitis (13). At cross-sectional imaging, a symmetrical, circumferential thick ring of tissue that encases the affected duct is indicative of IgG4-related sclerosing cholangitis.(15).

**Lymphadenopathy:**
IgG4-related lymph node enlargement is characterized by dense infiltration of IgG4-positive plasma cells within the lymph nodes.

**Pulmonary disease:**
IgG4-related pulmonary disease has been reported in approximately 13% of patients with autoimmune pancreatitis (16).

The spectrum of imaging findings in pulmonary involvement of IgG4 related sclerosing disease includes
- - solid parenchymal nodules or mass like lesions
- - bronchovascular pattern, which may be mistaken for sarcoidosis
- - round area with ground-glass opacification that may mimic bronchioloalveolar carcinoma
- - alveolar interstitial pattern, such as bronchiectasis and honeycombing
- - areas of diffuse ground-glass opacification that resembles nonspecific interstitial pneumonia

(14) Other systemic manifestations of IgG4 relating sclerosing disorders include sclerosing sialadenitis, sclerosing cholecystitis, renal involvement, retroperitoneal fibrosis, sclerosing mesenteritis, arteritis and inflammatory bowel disease.(14)

**Conclusions:**
IgG4 related sclerosing disorders are a group of immune mediated sclerosing disorders that has been described relatively recently.
This group of disorders is eminently treatable with high dose steroids. Patients with imaging features of autoimmune pancreatitis may have other organ involvement that has to be actively sought out during the process of radiological reporting, associated findings may support a diagnosis of IgG4 related sclerosing disorders. Even in the absence of immune-histochemical proof, a combination of imaging findings described above and elevated serum levels of IgG4 are not diagnostic to arrive at a diagnosis of “possible IgG4 related sclerosing disorder” (9) and this may be regarded as...
adequate justification for institution of high dose steroid therapy as was done in this case.