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Autoimmune Pancreatitis Mimicking Carcinoma of Head of Pancreas

Farrukh Iqbal, Misbah-uz-Zehra and Uzma Nasim Siddiqui
Department of Medicine, Shaikh Zayed Postgraduate Medical Institute, Lahore

ABSTRACT

Autoimmune Pancreatitis is a rare cause of chronic pancreatitis of unknown etiology and can mimic carcinoma of head of pancreas. We report a case of 63 years old man who presented with obstructive jaundice due a mass in the head of pancreas. He underwent laparotomy after the CT and MRI and raised carbonic anhydrase 19-9 (CA 19-9). He had concurrent heavy infection with *H. pylori* and normal levels of immunoglobulin G-4 levels. Histopathological examination of pancreatic tissue samples taken during surgery revealed fibro inflammatory changes with numerous IgG-4 rich plasma cells consistent with the diagnosis of autoimmune pancreatitis. At laparotomy the mass was found un resectable and palliative choledocho-jejunostomy was performed. He was treated successfully with systemic corticosteroids and responded well with remarkable results. There is a hypothesis suggesting that molecular mimicry between bacterial and pancreatic carbonic anhydrase antigens may be a reason for autoimmunity in genetically predisposed individuals.

Keywords: Autoimmune pancreatitis, immunoglobulin G-4 levels, H. pylori, carbonic anhydrase, molecular mimicry.

INTRODUCTION

Autoimmune pancreatitis is a rare form of pancreatitis. It was first ever described in the history by Sarles as pacreatitis with hypergammaglobulinemia.[1] However it was not untill 1995 when Yoshida et al described it as a form of pancreatitis with autoimmune basis.[2] It accounts for 4.6 to 6% of all cases of pancreatitis and is associated with other forms of autoimmune diseases particularly Sjogrens' syndrome.[3] The disease can involve bile ducts (sclerosing cholangitis), gall bladder (lymphoplasmacytic sclerosing cholangitis), kidney (interstitial nephritis) and can form inflammatory masses in the lungs.[4] it occurs in both sexes but at least twice as common in men compared to women and most patients are older than 50 years old.[5,6]

Due to its presentation, it can easily be missed and diagnosed as carcinoma of head of pancreas and can present as a dilemma for the physician or a surgeon.

CASE REPORT

A 63-year-old man with essential hypertension developed abdominal pain and epigastric burning which rapidly deteriorated in one week despite treatment with proton pump inhibitors and gastric prokinetic drugs. He was tested serologically for *helicobacter pylori* (*H. pylori*) which came out to be strongly positive. (Patient value 4.17 U/ml {n: less than 0.9 U/ml}).

He was given amoxicillin 2 gms 12 hourly, clarithromycin 500 mg 12 hourly, metronidazole 400 mg 12 hourly along with omeprazole and itopride to eradicate H. pylori infection for two weeks. One day later he developed clay colored stools and dark urine along with yellow discoloration of skin and sclera but he continued his treatment till 14th day; despite this his symptoms kept deteriorating. He developed extreme nausea and weakness, so he consulted his physician who diagnosed him as having drug induced hepatitis, stopped all medications and advised complete blood count (CBC) and liver function tests (LFT). His CBC was normal but LFT's were deranged and were as follows:

ALT: 161 IU/L (n: < 45 IU/ L); ALP: 168 IU/L (n: 45-129 IU/L); Gamma GT: 377 IU/L (n: <55 IU/L); Total bilirubin: 4.6 mg/dL (n: 0.1-1.2 mg/dL); Direct bilirubin: 3.7 mg/dL (n:0-0.2

mg/dL); Indirect bilirubin: 0.9 mg/dL (n: 0.1-0.8 mg/dL)

Viral serology for hepatitis A, B, C was non reactive. Ultrasound abdomen showed a fatty liver. CT abdomen was also done which pointed towards a bulky enlarged head of pancreas (Fig. 1) and MRI was advised. His serum amylase at that time was 228U/L. MRI showed 62mm pancreatic head/ uncinate process mass and tiny regional lymph nodes. There was also significant biliary and pancreatic duct dilatation. Carcinoembryonic antigen (CEA) was normal (2.55ng/mL). His carbonic anhydrase levels (CA 19-9) were also elevated 275 U/mL (n:3 U/mL). His IgG-4 levels were also done and found to be normal, 9.75G/L (n:6-15.6). Meanwhile his jaundice kept on worsening and total bilirubin reached to 10.23 mg/dL with direct bilirubin 8.88 mg/dL. ALP at that time was 187 U/L. His blood sugar levels which were initially normal also started rising and his HbA_1c was 6.7% (n: 4.8-5.9). Then he was admitted to the hospital about one month after the onset of symptoms with the initial diagnosis of carcinoma of the head of pancreas. He lost about 10 kg during this one month period. He underwent staging laparoscopy followed by laparotomy. His perioperative findings were as follows:

- Head of pancreas was felt as large and nodular mass with a hard and nodular body.
- Edema of tissues all around the pancreas with an inflammatory reaction around the superior mesenteric vein and portal vein.
- Large fleshy lymph nodes behind the duodenum and all along the hepatic artery.
- Distended gall bladder with a grossly distended common bile duct.

In view of the advanced nature of the disease a curative resection was not possible therefore cholecystectomy and palliative choledocho-jejunostomy was performed. True cut biopsy of the head of pancreas was taken for histopathological diagnosis. He made a smooth post operative recovery and was discharged home after one week.
Histopathological examination revealed (Fig. 2 and Fig. 3):

- Pancreatic parenchyma with preserved lobular architecture

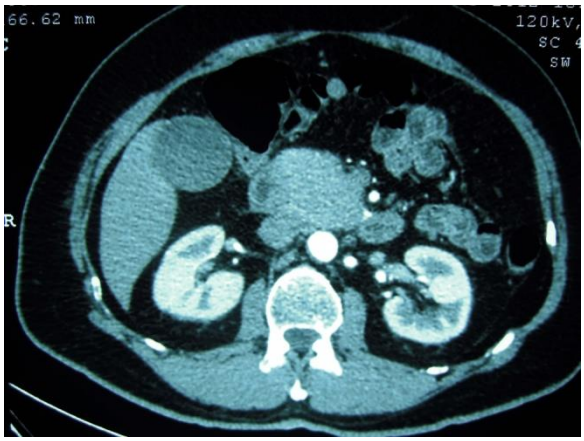

Fig. 1: Axial section of contrast enhanced CT abdomen showing enlarged pancreatic head including uncinate process and small volume para aortic lymph nodes.

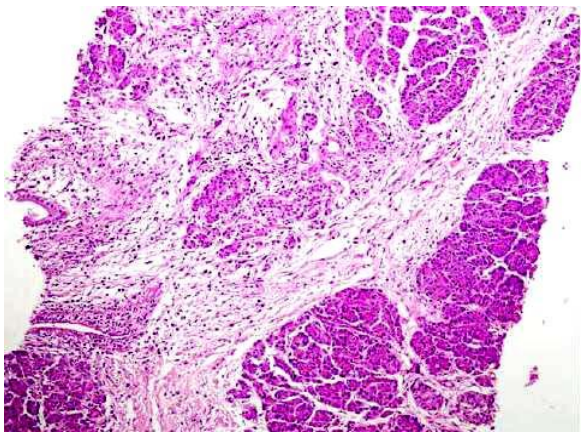

Fig. 2: Photomicrograph showing pancreatic parenchyma with preserved lobular architecture, areas of acinar atrophy and fibrosis (H&E x 40)

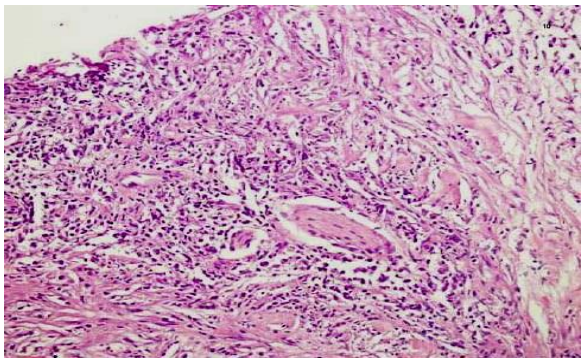

Fig. 3: Photomicrograph showing marked perineural and periductal lymphoplasmacytic inflammatory infiltrate with obliterative venulitis (H&E x 40)

- Areas of acinar atrophy and stromal fibrosis
- Marked periductal and perineural lymphoplasmacytic inflammatory infiltrates
- Prominent obliterative venulitis
- Immunostain for IgG 4 showed numerous IgG4 positive plasma cells (more than 50 cells per high power field)
- No evidence of invasive carcinoma was seen

These features were strongly suggestive of autoimmune pancreatitis. Other markers of autoimmunity including anti nuclear antibodies (ANA), anti smooth muscle antibodies (ASMA), antimitochondrial antibodies (AMA) were all negative.

Magnetic resonance cholangio-pancreatography (MRCP) showed mass lesion in the head of pancreas distorting common bile duct and pancreatic duct in the region of head of pancreas with filling defects in common bile duct.

On the basis of histological findings diagnosis of autoimmune pancreatitis was made and patient was started on systemic corticosteroids. His condition dramatically improved and steroids were eventually tapered off. Patient is leading a normal life till date.

DISCUSSION

Autoimmune pancreatitis (AIP) is a benign disease of pancreas which can occur as type 1 as a part of systemic disease associated with elevations in the levels if immunoglobulin-G4 producing plasma cells[7] or as type 2 which does not show the immune mediated diseases that are observed in about 20 to 40% of patients with IgG4 related disease[8], instead they commonly suffer from chronic inflammatory bowel disease like ulcerative colitis or Crohn's disease[9].

The pancreatic disease may present as a focal mass or enlargement which may be difficult to distinguish from pancreatic cancer[10], strictures of pancreatic duct and chronic or recurrent abdominal pain; recurrent acute pancreatitis in the absence of biliary involvement is not a typical presentation of autoimmune pancreatitis[11]. Clinical presentation varies according to subtype of AIP, however the most common feature is obstructive jaundice, which occurs in 75% of patients with type 1 AIP and 50% of patients with type 2 AIP[9]. Type 2 AIP may also present as with abdominal pain (68%) and acute pancreatitis (34%)[12]. Patients may also present with manifestations due to other organ involvement like sclerosing cholangitis, sclerosing sialadenitis, lung nodules, interstitial nephritis and retroperitoneal fibrosis[12]. Biliary tract involvement includes strictures involving proximal portions of intrahepatic and extrahepatic ducts, all due to generalized IgG4 infiltration[12]. It is sometimes called IgG4 sclerosing cholangitis (IgG4-SC) which is distinguished from primary sclerosing cholangitis (PSC) by large segmental strictures in IgG4-SC and short band like strictures with diverticulae formation and beaded appearance typical of PSC on cholangiograms[13].

AIP was previously diagnosed using HISORt criteria which was based on prospective study of 29 patients at Mayo clinic who met the histological criteria for AIP[14]. It was based on:

- Diagnostic Histology
- Characteristic **I**maging
- Elevated IgG-4 levels on **S**erological testing
- **O**ther organ involvement
- **R**esponse to Steroid **t**herapy

However in 2010, International Consensus Diagnostic Criteria (ICDC) was developed which focused on distinction between type 1 and type 2 AIP.[11]

It is also based on the clinical profile of AIP including characteristic histology, imaging, serum IgG4 levels, extra pancreatic lesions and response to steroids; each criterion has two levels of evidence. Level 1 is typical or highly suggestive while level 2 is indeterminate.[11] According to ICDC type 1 AIP can be diagnosed noninvasively using combination of various criteria but type 2 AIP can only be diagnosed by histology.[11]

Histology remains the gold standard for the diagnosis of AIP. [15] Type 1 AIP demonstrates classically periductal lymphoplasmacytic infiltrates rich in IgG4, storiform fibrosis and obliterative venulitis; whereas in type 2 AIP there is neutrophilic infiltration in ductal epithelium with duct destruction and micro abscess formation; classically ductal granulocyte epithelial lesion (GEL) is

seen.[15,16]

Although exact pathogenesis of AIP is not clear but it is hypothesized that it evolves as a biphasic mechanism consisting of "induction" and "progression".[17] It is induced by naïve regulatory T cells (Tregs) and T helper (Th) 1 cells in response to self antigens like lactoferrin, carbonic anhydrase II , carbonic anhydrase IV, pancreatic secretory trypsin inhibitor and α-fodrin and molecular mimicry to H.pylori, which leads to release of proinflammatory cytokines (interferon-gamma, interleukin -1, interleukin-2, and tumor necrosis factor α).[17] Progression is supported by increased memory Tregs and Th2 immune responses.[17]

Possession of the HLA DRB1*0405-DQB1*0401 genotypes confers a risk for the development of AIP.[18] H. pylori infection could trigger AIP through several different and probably cooperating mechanisms including molecular mimicry between bacterial and human carbonic anhydrases.[19] Such molecular mimicry has been proven in past to be a trigger for several autoimmune diseases in genetically predisposed individuals.[20,21] The human pancreatic carbonic anhydrase and alpha carbonic anhydrase of H. pylori have proven to contain a homologous segment which has a binding motif for the HLA DRB1*0405, strengthening the hypotheses that H.pylori can trigger AIP in genetically predisposed individuals.[22]

The characteristic findings of AIP on CT or MRI consist of a diffusely enlarged pancreas with loss of lobular architecture or typically a sausage shaped pancreas with delayed enhancement, with or without rim like enhancement and minimal peripancreatic stranding.[23,24] A focal pancreatic mass may be seen in 30-40% of patients mimicking pancreatic cancer as in our case.[25] Specific ERCP findings include long stricture greater than one third of the length of pancreatic duct, multiple strictures, lack of upstream dilatation from the stricture and/or side branches arising from the stricture site.[26,27] MRCP though less invasive but also less accurate alternative in evaluating these pancreatic ductal changes.[28]Intraductal ultrasonography can help to differentiate AIP from cholangiocarcinoma which has irregular luminal surface and eccentric wall thickening in comparison to concentric wall thickening with smooth luminal surface seen in AIP.[26]

AIP is associated with elevations in gammaglobulins and autoantibodies. Serum IgG4 levels >140 mg/dL has a sensitivity of 76% and specificity of 93% in diagnosing AIP.[29] A meta analysis of seven studies demonstrate a variation in sensitivity and specificity ranging from 67-94% and 89-100%, respectively.[30] However raised IgG4 levels are not typically seen in type 2 AIP,[31] therefore they are not sufficient for accurate diagnosis of type 2 AIP. Also antibodies to lactoferrin, carbonic an anhydrase II and IV isoforms, pancreatic secretory trypsin inhibitor (PSTI or SPINK) as well as less sensitive markers of autoimmunity such as ANA and rheumatoid factor are invariably found in AIP.[32]

The major indication of treatment in AIP is the presence of symptoms; for which initial prednisolone dose of 0.6mg/kg/day is recommended which is tapered off to a maintenance dose over a period of three to six months.[33] The relapse rate in type 1 AIP ranges from 30 to 50% whereas type 2 AIP does not relapse.[31] Due to high relapse rate some centre advocate a prolonged steroid treatment for up to 2 to 3 years.[33] Relapses are treated with a second course of steroids.[34] The use of IgG4 as an indicator of relapse is still a subject of debate.[34] Steroid-sparing immunomodulators can also be used to maintain remission after first or second relapse.[34] Patients may need prolonged maintenance therapy to prevent further relapses.[34]

In patients refractory to steroids azathioprin, cyclophosphamide and mycophenolatemofetil have all been tried in addition to or instead of steroids.[35,36,37]

As AIP is an emerging disease entity therefore there is very limited data on long term follow-up of patients with AIP. However some studies show that there is increased risk of malignancy including colonic cancer, lung cancer and lymphoma occurring at a frequency of 3.5 times greater than the general population.[38] There is also slightly increased risk of pancreatic cancer in patients with AIP.[39] However despite increased risk of malignancy long term survival in patients with either type 1 AIP or type 2 AIP, was similar to age and gender matched controls.[31]

CONCLUSION

Autoimmune pancreatitis is a rare and benign form of pancreatitis with a good response to steroids. Therefore it should be considered when treating pancreatitis with no obvious cause. Also it has variable presentations in terms of serology and clinical features so diagnosis should always be confirmed via histology. As far as clinical features are concerned, it can mimic cancer of the head of the pancreas as in our case initially. Because of strong association between H. pylori infection and AIP, the hypothesis of molecular mimicry between human and bacterial carbonic anhydrase enzymes should be further evaluated to Improve our understanding and knowledge of AIP.

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The Authors:

Farrukh Iqbal
Professor and Head Division of Medicine
Shaikh Zayed Postgraduate Medical Institute,
Lahore.

Misbah-uz-Zehra
Trainee Registrar
Department of Medicine
Shaikh Zayed Postgraduate Medical Institute,
Lahore.

Uzma Nasim Siddiqui
Senior Registrar
Department of Medicine,
Shaikh Zayed Postgraduate Medical Institute,
Lahore.

Corresponding Author:

Farrukh Iqbal
Professor and Head Division of Medicine
Shaikh Zayed Postgraduate Medical Institute,
Lahore.
E-mail: fiqbal-56@hotmail.com