Title-autoimmune pancreatitis in pancreatic resections done for presumed pancreatic malignancies-An experience of tertiary centre from North India

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Abstract

Background: Autoimmune pancreatitis (AIP) can present as pancreatic mass mimicking malignancy. However, it has specific histomorphology and immunohistology which in clinical context can be diagnostic.

Aim: To retrospectively analyze pancreatic resections done for pancreatic head masses to identify cases of autoimmune pancreatitis.

Methods: Hematoxylin and eosin stained slides of pancreatic resections (n=142) done for pancreatic masses (2004-2012) were reviewed. Immunohistochemistry for IgG4 was done in cases suggestive of AIP. As controls, 30 pancreatic carcinomas (n=30) and plasma cells rich chronic pancreatitis (n=25) were stained with IgG4. Clinical records were retrieved.

Results: There were 5/142 cases (3.5%) of autoimmune pancreatitis among pancreatic resections done for presumed pancreatic tumors. There were 3 females and 2 males and age range was 35-65 (mean 51). Presenting symptoms were painless jaundice (n=4), with adult onset diabetes (n=1) and feature of gastric outlet obstruction (n=1). Histomorphology of all the five masses was of Type I autoimmune pancreatitis showing lobulocentric plasma cell rich inflammation and storiform fibrosis. IgG4 positive plasma cells (>10 per high power field) in all the cases diagnosed as autoimmune pancreatitis; though few IgG4 positive plasma cells were positive in controls. Venulitis and veno-oblitrative changes, neural hyperplasia, neuritis were present in all. Serum IgG4 levels done immediately after surgeries in three patients were elevated.

Conclusion: Incidence of autoimmune pancreatitis in pancreatic resections done for pancreatic masses is 3.5%. All the five cases were of Type 1 autoimmune pancreatitis with significant number of IgG4 positive plasma cells using >10 positive cells per high power field as cut off.

Keywords: Autoimmune, IgG4 positive plasma cells, pancreatitis, pancreatic masses

Introduction

Autoimmune pancreatitis is the only form of chronic pancreatitis where histopathology has been considered to be diagnostic by the most of the authors involved in defining this entity [1-4]. Chronic pancreatitis occurring in autoimmune settings like that of systemic lupus erythematosus has been known for long [5-7]. However, autoimmune pancreatitis as a distinct entity with classical clinicopathological [8] criteria supported by relevant radiology and serology has evolved over the last decade [9].

Autoimmune pancreatitis is part of spectrum of IgG4 related sclerosing disease where subset histomorphological changes supported by requisite number of IgG4 positive cells and relevant autoimmune serology in an appropriate clinical setting are diagnostic of organ specific sclerosing disease [10]. Other organ systems may be involved synchronously or metachronously in a subset of autoimmune pancreatitis, which may be symptomatic or can be identified by relevant...
investigations. Various organ specific IgG4 related sclerosing disease have been identified in the past recognized by distinct names like Mikulicz’s disease, Kuttner’s tumor, Riedel’s thyroiditis, orbital pseudo tumor and inflammatory pseudo tumors in various locations [1]. In all these organs, including pancreas, often they have been recognized as tumor masses which have been surgically excised. Histopathology has been important in defining the auto immune pancreatitis and now considered essential in diagnosis of one of the variants i.e., Type II (Granulocytic Epithelial lesions-type) and morphology of Type I (lympho-plasmacytic sclerosing pancreatitis-LPSP) is diagnostic whenever histopathology is available [5].

Incidence of AIP is higher in western countries as compared to Asian countries where otherwise incidence of chronic pancreatitis is higher than the western countries [11]. There is paucity of data from India. We analyzed retrospectively surgical material available from pancreatic resections done for presumed pancreatic malignancies in our tertiary care hospital to identify cases of autoimmune pancreatitis.

Materials and methods
Retrospective analysis of 142 pancreatic resections done for pancreatic head masses during 9 years (2004-2012) at a tertiary institute from North India were retrieved from the records of department of Histopathology. Clinical details including radiology were retrieved from records of department of Gastroenterology and Surgery. Hematoxylin and eosin stained slides of all the cases were re-examined and cases with diagnostic histomorphology of autoimmune pancreatitis were immunostained with IgG4 (Invitrogen, mouse monoclonal antibody, clone: HP6025). After endogenous blockage of peroxidase using hydrogen peroxide (0.2%) heat induced antigen retrieval was done using citrate buffer (pH6). Primary antibody was used in 1:50 dilution and slides were incubated for 2 hour, followed by incubation with HRP labeled universal secondary antibody (Dako) for 1 hour. DAB (Diamino benzene) as chromogen was used to develop the color, brown coloration of cytoplasm was taken as positive. Numbers of IgG4 plasma cells were counted per high power field. Cut off value for significant number of IgG4 plasma cells for the diagnosis of auto-immune pancreatitis was taken as 10 positive cells per high power field (HPF) [12,13]. Pancreatic tumors (n-30) rich in plasma cells and plasma cells rich pancreatitis (n-25) from pancreatic tissues removed during head coring for chronic pancreatitis were selected as controls for staining with IgG4 immunostain. The pathologist was blinded to the clinical details while evaluating immunohistochemistry for IgG4 in cases with presence of plasma cells. Masson’s trichrome and elastic von gieson stains were done on selected sections to assess fibrosis and oblitrative vascular changes.

Pancreatic masses which did not show tumor were analyzed extensively. Sections were examined for presence of dilatation of ducts (intra or interlobular) and any alteration in epithelium. Ductal concretions/plugs/calculations were looked for. Presence of peri or intralobular fibrosis was assessed by Masson’s trichrome stain. Nature of inflammatory cells i.e., lymphocytes, plasma cells, mast cells eosinophils and neutrophils were noted. Veno-oblitration, changes, arterial occlusion/vascularitis, neural hyperplasia/hypertrophy, peri-neuritis were assessed using Elastic von geison stain. Areas of calcification, fat infiltration and islet cell atrophy was also looked for. Serum for IgG4 was done in three cases; early after surgery (first week on presumptive diagnosis) in three cases and three weeks after in one case at the time of review of the case.

The investigations performed on patients were part of routine diagnostic work required for diagnosis and patient management. The study was approved by institute’s ethics committee.

Results
There were five patients (2 males and 3 female) and two of them were younger than 50 years (35, 42, 60, 55, and 65 years). Clinical symptoms at the time of presentation were of painless jaundice (n-4), along with adult onset diabetes (n-1) and feature suggestive of gastric outlet obstruction as pain and recurrent vomiting (n-1). Liver function tests in cases with jaundice were suggestive of obstructive jaundice. Radiology (CT scan and MRCP) were suggestive of localized pancreatic masses with irregularities of ductal system. Upper gastrointestinal endoscopy and biopsies were normal in case with features suggestive of gastric outlet obstruction. Gross examination of pancreatic resections revealed firm–hard mass like lesions in pancreatic parenchyma with adjacent areas of fibrosis. There were no calculi in the ducts. There was evidence of calcification in the parenchyma in one case with gastric outlet obstruction. Histomorphological features in all the five cases where no tumor was found showed fibro-inflammatory changes. Ducts were normal. There was no ductal dilatation/concretions/mucin plugs and epithelium did not show hyperplasia/metaplasia/dysplasia. There was lobulocentric and periductal inflammation composed of lymphomononuclear cells including plenty of plasma cells and eosinophils. There were no granulocytic epithelial lesions. There was extensive fibrosis with storiform pattern in the interlobular regions. Intralobular lymphoplasmacytic infiltrate, edema and fibrosis of varying extents was seen. Venulitis and veno-occlusive changes was seen in all the five cases. Oblitrative arteritis was present in one case only. All the cases showed extensive neural hyperplasia and neuritis in areas of storiform fibrosis and peripancreatic regions. Occasional lymphoid follicle in peripheral fat was seen in two cases. There were areas of calcification in one case.

Immunohistochemistry showed >10 IgG4 positive plasma cells (n-15-25)/HPF in all the five cases of AIP whereas in
controls (pancreatic tumors and chronic pancreatitis) the number varied from 4-7 per HPF. Four out 30 cases of pancreatic malignancies and 3 out of 25 cases of chronic pancreatitis (idiopathic pancreatitis-18, alcoholic pancreatitis-7 showed 4-7 IgG4 positive cells/HPF. Distribution of these plasma cells was patchy in cases of pancreatic malignancy.

Overall impression based on histomorphology i.e., plasma cell rich inflammatory infiltrate with normal ducts, storiform pattern of fibrosis, veno-occlusive venulitis, obliterative arteritis and supported by >10 IgG4 positive plasma cells/HPF, a diagnosis of IgG4 positive type I autoimmune pancreatitis was made (Figure 1). The clinicians were requested for IgG4 serology in three cases within first week after surgery and were elevated (1022µl/l, 620µl/l and 422µl/l). It was less than 200µl/l (172µl/l) in one case which was done after 3 weeks of surgery when the case was re-examined on review. One patient did not agree for the test.

Since these cases were presumed to be pancreatic masses, sections taken as resection limits of pancreatic masses also showed features of pancreatitis, thereby indicating presence changes beyond recognizable masses. Sections from duodenum in case presenting with gastric outlet obstruction showed extension of fibro inflammatory process into the adventitial aspect of the duodenum extending to submucosa in some areas (Figure 2).

Pancreatic tissue of patient with recent onset diabetes did not show excessive loss of islets in the pancreatic mass or rest of pancreatic tissue included in the specimen. The case which presented with gastric outlet obstruction had extensive fibro inflammatory changes extending from adventitial aspect of the duodenum up to submucosa (Figure 2). One of the cases showed mild diffuse neutrophilic infiltrate in an area as seen in type II AIP. There were reactive follicles in peripancreatic tissue in three cases. There was no evidence of multisystem disease based on history or radiology including PET scan in four cases. One case showed evidence of renal parenchymal disease on PET scan.

Discussion

Autoimmune pancreatitis has emerged as distinct entity in the last decade for which various diagnostic criteria were proposed from America, Asia especially Japan and Europe [1-6]. The difference was mainly due to variable diagnostic protocols which were influenced by available diagnostic facilities and their interpretation laboratory cut off standardized for those study populations. International meetings of representatives of these leading groups came out with consensus internationally acceptable diagnostic criteria which would felicitate international studies and
comparisons. Accordingly autoimmune pancreatitis is classified as type I [5] (earlier LPSP) [2] or lobulocentric [3]) which can be part of systemic IgG4 related sclerosing disease where elderly patients present with painless jaundice, pancreatic mass or adult onset diabetes [12]; type 2 [5] (earlier Idiopathic duct centric pancreatitis-IDCP [2]) with granulocytic epithelial lesions or duct centric [3] which affects young patient who present with pain abdomen [12]. According to these criteria, histopathology is mandatory for type 2 AIP which is not a systemic disease and does not have diagnostic serology. In experience of all these study groups, mass lesions of type I AIP have been mistaken as pancreatic tumors and resected, from where classic descriptions of AIP type I emerged. Since histomorphology of AIP type 1 is classic, we analyzed our all presumed pancreatic tumors over 9 years to identify AIP mistaken as pancreatic tumors. There were 5 cases of AIP out 142 (3.5%) pancreatic resections done for tumors. One case with feature of upper pain abdomen had mainly features of type I AIP with fibro inflammatory process involving duodenum from adventitial aspect up to sub mucosa and some areas which were like type II AIP. Radiology of all these cases pre-operatively was considered to be consistent with malignancy, thereby warranting surgery.

Results of another study conducted in Asian population by Trans et al., were quite similar to present study. Tran et al., [13] analyzed Hawaii’s Asian-dominant population through a retrospective review of 65 pancreaticoduodenectomy cases performed between 2000 and 2010 and found only three of the 65 pancreaticoduodenectomies (4.6%) diagnosed with autoimmune pancreatitis, and 3 additional cases were diagnosed prior to surgery. Imaging of these patients in their study showed findings typical of pancreatic malignancy with distal bile duct stricture and pancreatic head mass. All patients in their series were males and present obstructive jaundice (n-6), weight loss (n-5), and epigastric pain and elevated serum lipase (4). All six patients showed elevated serum IgG4 levels.

There is literature from other countries as well this form of pancreatitis have been operated upon as they where presumed to be malignant based on extensive radiologic workup. A study from Netherlands [14] documents incidence of AIP to be 2.6% in patients who underwent pancreaticoduodenectomy (n=274) for presumed malignancy over a 9-year period (2000 and 2009) in a tertiary referral centre. Post-operative diagnosis was reassessed in all cases where no evidence of malignancy was found. Overall prevalence of benign disease in 274 pancreaticoduodenectomy was 8.4%; AIP constituting approximately one third of their cases. Onda et al., [15] documented a case of histopathologically proven AIP mimicking pancreatic cancer, pre-operatively presumed as neuroendocrine tumor in a 53-year-old man. He was detected to have a pancreatic mass on ultrasonography at a medical check-up which was confirmed as a 15-mm hypo echoic mass located in the pancreatic body by repeat abdominal ultrasonography. Further radiological confirmation was done by computed tomography and magnetic resonance imaging. Endoscopic retrograde cholangiopancreatography showed only mild dilatation of a branch of the pancreatic duct without stricture of the main pancreatic duct. The common bile duct was within normal limits. Based on clinical suspicion and supported by radiology a diagnosed of a non-functioning NET or malignant neoplasm was presumed and, laparotomy was performed. Histopathology of enucleated mass showed features of AIP.

Whereas overall incidence of chronic pancreatitis is relatively high in Indian patients (114-116/100,000) as compared to data available from USA, Europe and Japan, incidence of AIP reported from India–histopathology proven or serology based is less than that reported from other Asian countries like Japan. Overall incidence of AIP as reported from western literature is 3-4% [16]. The prevalence of AIP in the United States is documented to 2.4%-11%. Japanese series have quoted the prevalence of disease between 5% and 6% of all patients who have chronic pancreatitis [17]. Since there was paucity of data from Asian countries, a multicentre trial was conducted where 10 centers from Japan, China, Korea, Taiwan and India pooled their data [18,19]. It was questionnaire based data collection using Asian diagnostic criteria and a total of 327 AIP cases were identified. Radiology and histology of all cases were reviewed at 3 major referral centers with experience to diagnose AIP. For diagnosis of AIP, the imaging criteria consisting of enlargement of pancreas and irregular narrowing of the main pancreatic duct was considered must along with the serological criteria (elevated serum immunoglobulin IgG or IgG4 levels or detection of auto antibodies) and or histological criterion (lymphoplasmacytic sclerosing pancreatitis). There were 137 patients from Japan, 118 from Korea and 47 from Taiwan and 25 cases of from China. There was only one patient out of 1181 cases of chronic pancreatitis from India (two other tertiary care centers excluding our centre). There are occasional case reports from India [20] and Thailand [21,22]. In present study, we have retrospectively identified cases of AIP which presented as pancreatic masses, which is only one of the symptoms of AIP. Now with the awareness about this entity, we hope to identify more cases of AIP using clinicoradiologic criteria so as to avoid surgery.

Type II autoimmune pancreatitis (IDCP-GEL) affects younger patients, present with pain abdomen, frequently associated with ulcerative colitis, have negative serology and no systemic sclerosing disease and needs histological confirmation. [22] However, in present study as study design emphasized on pancreatic mass lesions we did not find any case of type II AIP. Even rest of the surgical material examined as control group (chronic pancreatitis) had no case of type II AIP. Prevalence of type II AIP is less both in USA, Asia as compared to Italian series. There were only 5 cases of histologically confirmed cases of IDCP in the Asian mult-centre trial (4 cases from Korea and 1 from Japan) and were not
included in their study [19]. Frequency of this subtype in USA is also infrequent. Italian study documents almost 40-50% cases of LPSP and IDCP with their diagnostic criteria.

Present study validates the cut-off value of 10 IgG4 positive plasma cells per HPF as being diagnostic in an appropriate histopathological context for making diagnosis of autoimmune pancreatitis [4,23]. In cases of controls, 4-7 IgG4 positive cells/HPF were found in patchy distributions in 4 out 30 cases of pancreatic malignancies and 3 out of 25 cases of chronic pancreatitis (idiopathic pancreatitis-18, alcoholic pancreatitis-7) [24,25].

Another observation that pancreatic tissue away from the mass lesions also showed fibro-inflammatory changes indicate changes are rather diffuse and focally exaggerated to form masses as is being demonstrated on radiology [26]. Presence of diabetes in such cases again supports the fact that changes must be rather diffuse with focal head masses. Beta cells are concentrated in the islets of tail region and must be damaged significantly in presence of head mass to present as diabetes [27].

Patient profile is also varying in different studies. Comparison of data of Western, European and Asian countries revealed that Italian patient had no predilection for elderly male subjects, had frequent association with ulcerative colitis, weak association with other sclerosing diseases, and low frequency of serum IgG4 elevation. Two patients in present study were younger and there were more number of females. Multisystem involvement with AIP is seen in 60-90% cases; however. There was no evidence of multisystem disease based on history or radiology including PET scan in four cases. Only one case was suspected to have renal parenchymal disease. Kidneys and salivary glands were especially looked for IgG4 levels were suspected to have renal parenchymal disease. Kidneys and salivary glands were especially looked for IgG4 levels were normalized when disease is not systemic. Since, it was retrospective study, one patient when contacted did not agree for IgG4 serology as he was doing well; radiology was reviewed in all histologically suspected cases.

Since AIP responds dramatically to steroid therapy, accurate diagnosis of AIP can avoid unnecessary laparotomy or pancreatic resection [26,27]. In a patient with fluctuating obstructive jaundice with elevated serum IgG4 levels, presence of other organ involvement such as bilateral salivary gland swelling, retroperitoneal fibrosis and hilar or intrahepatic sclerosing cholangitis; negative work-up for malignancy including endoscopic ultrasound-guided fine needle aspiration a diagnosis of AIP can be suspected. Classic radiologic features (like diffuse enlargement of the pancreas with delayed enhancement and presence of a capsule-like rim on dynamic computed tomography; low apparent diffusion coefficient values on diffusion-weighted magnetic resonance image; irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography; less upstream dilatation of the main pancreatic duct on magnetic resonance cholangiopancreatography) are considered diagnostic in such appropriate setting.

Conclusion
AIP is not uncommon in India. Awareness and multi-disciplinary approach might help in identifying cases to give them benefit of therapy with steroids to which they consistently respond and avoid major surgical operations.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

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Publication history
Editor: Lingyan Wang, Oregon Health & Science University, Portland.
EIC: Giuseppe Musumeci, University of Catania, Italy.
Received: 24-Aug-2014 Final Revised: 24-Sep-2014
Accepted: 09-Oct-2014 Published: 17-Oct-2014

References

Citation: