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IgG4 Related Disease Masquerading as Periampullary Carcinoma with Surgical Obstructive Jaundice

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Abbreviations:

AIP: Auto immune pancreatitis; ALP: Alkaline phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate aminotransferase; CECT: Contrast enhanced computed tomography; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic Ultrasonography; FNAC: Fine needle aspiration cytology; ICDC: International consensus diagnostic criteria; IDCP: Idiopathic duct centric pancreatitis; IgG4: Immunoglobulin G 4; LPSP: lymphoplasmacytic sclerosing pancreatitis; MRCP: Magnetic resonance cholangiopancreatography); RCIPD: Research Committee of Intractable Pancreatic Diseases; RFT: Renal function test; SMV-PV: Superior mesenteric vein-portal vein

1. Abstract

IgG4 related disease is rare and can mimic pancreatic cancer clinically and radiologically. Having a strong clinical and radiological suspicion is essential as it can only be diagnosed with raised serum IgG4 levels and core biopsy. Response to steroid therapy is dramatic however requires long duration steroid therapy. We present a case of IgG4 Related disease mimicking borderline resectable periampullary malignancy for which Whipple's procedure was done and confirmed to have IgG4 related disease on histopathology. Post operatively raised serum IgG4 levels supported the diagnosis and patient was started on steroids.

2. Introduction

AIP is a rare disease all over the world. More common being type 1 is pancreatic manifestation of IgG4 related systemic disease, has male preponderance (M: F = 2:1) and often associated with extra pancreatic lesions. Type 2 affects younger patients with no gender preponderance. Raised serum IgG4 levels along with radiological and pathological findings are required to diagnose AIP [1]. Most commonly presenting as painless obstructive jaundice, can mimic pancreatic cancer [2,3]. Although elevated CA 19-9 levels are typical of pancreatic cancer it is rarely elevated in AIP.

3. Case Report

67-year-old known hypertensive presented with epigastric abdominal pain and progressive jaundice for 2 months with significant loss of appetite and weight. On examination, icterus was present. Hepatomegaly of 4 finger breadths and palpable gall bladder was present. Relevant blood investigations are depicted in Table 1. Ultrasonography was suggestive of dilated common bile duct, intrahepatic biliary radical dilatation, overdistended gall bladder with an ill-defined lesion in pancreatic head. MRCP (Magnetic resonance cholangiopancreatography) was suggestive of mass in head of pancreas 46 x 37mm with abrupt cut off of common bile duct at ampulla, upstream dilatation of common bile duct 19mm and prominent main pancreatic duct of 3.4mm (Figure 1). Contrast enhanced computed tomography (CECT) scan was suggestive of bulky head of pancreas with an ill-defined enhancing lesion of 1.5 cm in ampullary region abutting SMV-PV, multiple sub centimetric peripancreatic lymph nodes and mild prominence of main pancreatic duct (Figure 1).

Suspecting periampullary carcinoma, Whipple's procedure was planned. Intra operatively, 4x4 cm hard mass in pancreatic head was present which was densely adherent to SMV-PV (superior mesenteric vein-portal vein) junction. Whipple's procedure with sleeve resection of SMV-PV confluence was done. Post operatively, patient did well, had no post operative complications and was discharged on post operative day 8. Histopathology report was suggestive of IgG4 related disease which was reviewed. However, raised IgG4 serum levels 4.55 (0-2.0 g/L) and pathologist review confirmed IgG4 related pancreatitis (Figure 2). Subsequently, patient was started on steroids (tablet Wysolone 40mg/day for 4 weeks) and is currently six months post op and has been on tapering dose of steroids.

Table 1: Laboratory investigations

Lab investigations	Value	Reference Range	Units
Haemoglobin	11.2	13-17.5	gm/dl
Total leucocyte count	8000	4000-11000	10^6/L
Platelets	324	150-450	10^9/L
Total bilirubin	13	0.2-1.2	mg/dl
Conjugated bilirubin	10	0-0.3	mg/dl
AST	173	Feb-40	U/L
ALT	175	Feb-41	U/L
ALP	680	42-128	U/L
CA 19.9	108	<37	IU/ml
CEA	3.42	04-Jul	ng/ml
Serum IgG4	4.55	0-2	g/L

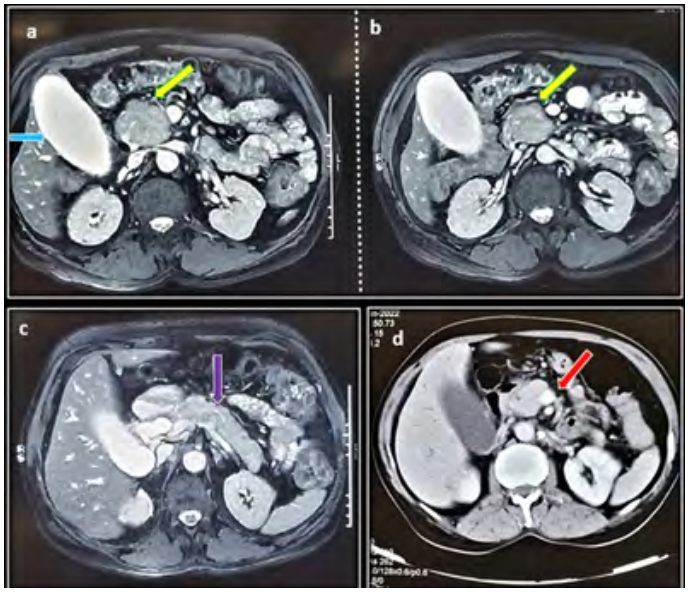

Figure 1: a & b. Mass present in head of pancreas with upstream dilated common bile duct (yellow arrow), overdistended gallbladder (blue arrow).
c. Prominent main pancreatic duct (violet arrow).
d. SMV-PV abutment (red arrow).

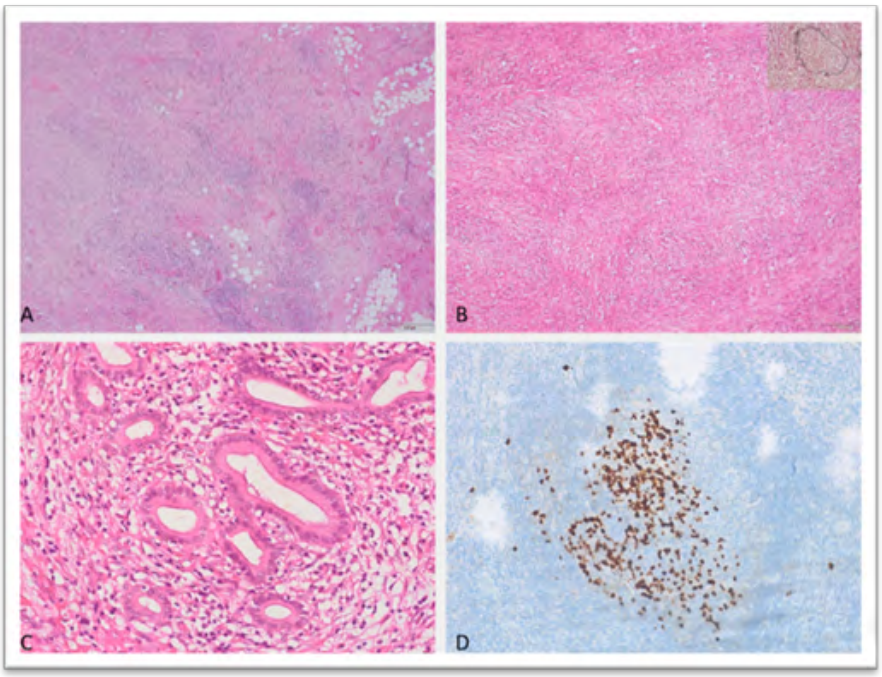

Figure 2: Histopathology Slides- A. Extensive acinar loss which is replaced by storiform and interlobular fibrosis accompanied with inflammation extending into peripancreatic soft tissue; B. Obliterative phlebitis (EVG stain in inset); C. The benign pancreatic ducts surrounded by plasma cell rich infiltrate admixed with lymphocytes; D. IgG4 immunostain highlighting the collections of IgG4 positive plasma cells.

4. Discussion

Differentiating AIP from periampullary cancer is difficult and the published literature is evident of the same [4-7]. IgG4 disease can present with multi-organ system involvement having constellation of non-specific symptoms, leading to diagnostic delay. Most common manifestations are autoimmune pancreatitis, salivary gland disease, orbital/lacrimal gland disease and retroperitoneal fibrosis [8]. AIP most commonly presents with painless obstructive jaundice, thereby mimics pancreatic cancer, thus differential diagnosis is challenging and in cases of diagnostic uncertainty, maybe confirmed following surgical resection [9].

9% pancreatic cancer patients also have high serum IgG4, thus serum levels should only be done if a strong clinical and radiological suspicion of AIP is present [10]. Contrastingly, retrospective analysis of histopathology of resected pancreatic cancer showed 40% of AIP coexisting with pancreatic cancer [11]. In another study, about 27% Whipple resections performed for suspicious pancreatic adenocarcinoma masqueraded AIP [12]. As our patient presented with progressive jaundice, significant weight loss and appetite, high CA 19-9 levels along with evidence of pancreatic mass in CECT, first differential was pancreatic cancer and no specific autoimmune workup or pre-operative biopsy was performed. On retrospective analysis of our case, associated salivary gland, lacrimal gland disease and other extra pancreatic disorders were absent.

Characteristic findings on computed tomography (CECT) are sausage like pancreas, low density rim borders and diffuse narrowing of pancreatic duct. MRCP findings are long pancreatic duct stricture (more than one-third of the pancreatic duct), presence of multiple strictures, strictures resulting in side branch ectasia with absence of upstream dilatation [13]. On endoscopic retrograde cholangiopancreatography (ERCP) long, narrow duct stricture or multiple non-continuous strictures may be present [14]. On EUS, (Endoscopic Ultrasonography) pancreas appears diffusely enlarged, hypoechoic with echogenic interlobular septa and narrowing of main pancreatic duct [14]. EUS guided FNAC (fine needle aspiration cytology) alone has low sensitivity (up to 40%) when compared to combination of FNAC and trucut biopsy (accuracy up to 85%) [14].

Diagnosis requires HISORt criteria which includes Histology, Imaging, Serology, Other organ involvement and Response to therapy (steroids) [4]. ICDC 2011 criteria uses Parenchymal imaging, Ductal imaging, Serology, Other Organ Involvement, Histology and Response to therapy(optional) to classify AIP in type 1 and type 2 [15]. Intraoperative evaluation of AIP and its differentiation from malignancy can be difficult and even invasion or encasement of surrounding vasculature is seen [6]. As in our case, mass was firm to hard and densely adherent SMV-PV junction. In AIP, pancreas is diffusely firm to hard and the vascular dissection is difficult [6]. This may preclude resection or may lead to extensive surgery for a benign disease which is not necessary. In such cases, presence of chronic inflammatory cells with abundance of plasma cell infiltration on intra op frozen sections can alert surgeon to consider diagnosis of AIP. Although, pancreatic transection being the irreversible step and uncinate dissection off of SMV being the last step, it may be a little too late when surgeon faces such a situation.

Alternatively, relationship between AIP and carcinoma is not clear

[16]. Chronic inflammation due to chronic pancreatitis and autoimmune cholangiopathy is major determinant of biliopancreatic malignancies and a well-established risk factor [17]. Therefore, causal association in the natural history of AIP and possible development carcinoma may be discovered in future.

Steroids are the treatment of choice for AIP. Initial high doses are given for 4 weeks followed by gradual tapering after the symptoms of jaundice regresses. Surgical resection is usually not recommended and can only be planned in cases of diagnostic uncertainty or cases misdiagnosed as malignancy.

5. Conclusion

The diagnosis of AIP from carcinoma is difficult or even impossible without a thorough histological examination of surgical specimen. Radiological clues and serum IgG4 levels can help to distinguish if there is a strong suspicion preoperatively but in spite of all efforts, distinguishing from malignancy can still be impossible. Operative findings of a hard pancreas in its entirety should alert the surgeon and if available, frozen section can help avoid a major resection. On the other hand, non-operative management must be exercised with caution to avoid treatment of a resectable periampullary malignancy.

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