Intraductal Papillary Mucinous Neoplasm (IPMN) and Chronic Pancreatitis: Overlapping Pathological Entities? Two Case Reports

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ABSTRACT

Context Intraductal papillary mucinous neoplasms (IPMNs) are a recently classified pancreatic neoplasm with an increasing incidence. IPMN is often misdiagnosed as chronic pancreatitis because of symptoms of relapsing abdominal pain, pancreatitis, and steatorrhea and imaging findings of a dilated pancreatic duct of cystic lesions that are frequently confused with pseudocysts. Early recognition of IPMN allows for prompt surgical resection before malignant transformation. Case reports We report two cases of patients with long histories of chronic pancreatitis (more than 15 years) that went on to develop IPMN. Both patients presented with symptoms of abdominal pain, nausea, steatorrhea and eventually weight loss. Biochemical and radiological findings were suggestive of chronic pancreatitis although no clear causes for this were identified. Both patients were followed up with multiple repeat scans with no reported sinister findings. Many years after the initial diagnosis of chronic pancreatitis, radiological investigations identified pathological changes suggestive of neoplastic development and histology confirmed IPMN. Conclusions The cases demonstrate the ongoing challenges in diagnosing and managing IPMN effectively; highlights the important aspects of epidemiology in differentiating chronic pancreatitis and IPMN; continues the discussion surrounding the relationship between IPMN and chronic pancreatitis.

INTRODUCTION

The World Health Organization (WHO) classifies IPMNs as intraductal mucin-producing neoplasms with tall, columnar, mucin-containing epithelium with, or without papillary projections [1]. They extensively involve the main pancreatic duct and/or major side branches and lack the ovarian stroma characteristic of mucinous cystic neoplasms [1]. A sub classification has been proposed with non invasive and invasive IPMN (tubular, colloid, mixed and anaplastic) [2]. The disease progression is not clearly understood but has been hypothesized to follow the more well defined pancreatic ductal adenocarcinoma; IPMN adenoma to borderline IPMN with dysplasia to IPMN with carcinoma in situ and finally to invasive IPMN [2, 3, 4]. The time of progression from adenoma to invasive carcinoma appears to be slow but up to 30% of non invasive IPMN may eventually become invasive and metastasize [2, 5]. In contrast to the ductal adenocarcinoma, IPMNs have in general a better clinical prognosis with a 5-year survival of 77% for non invasive IPMN and 43% for invasive IPMN with no difference between the different forms of non invasive IPMN [2]. The clinical presentation of IPMN and chronic pancreatitis are often indistinguishable. Talamini et al. prospectively followed up 473 patients with chronic pancreatitis, including 45 cases of IPMN, and revealed approximately 12% of patients with IPMN have a history leading to a diagnosis of chronic pancreatitis and roughly 2% of all chronic pancreatitis diagnoses are associated with IPMN [6]. Abdominal pain, jaundice, weight loss, nausea and vomiting are often seen in both conditions [7, 8]. The misdiagnosis of IPMN as chronic pancreatitis can lead to serious delays in the appropriate management with possible curative surgery available if detected early. The following case discussions highlight the interrelationship between IPMN and chronic pancreatitis and illustrate the challenges in establishing an early diagnosis of IPMN.

CASE REPORTS

Case #1

A 53-year-old man initially presented in 1992 with recurrent episodes of acute pancreatitis. The principal
symptoms were epigastric pain, nausea and weight loss with high levels of serum and urine amylase. He was a non smoker, moderate alcohol consumption and had no history of diabetes. Abdominal ultrasound (US) showed gallbladder sludge and subsequent CT imaging showed only mild findings of pancreatitis with oedematous changes of the peripancreatic fat. There was never any evidence of cystic lesions or dilated ducts. The patient was treated conservatively. One year later he underwent a cholecystectomy after a similar episode of pancreatitis. Over the subsequent sixteen years he was admitted to hospital seven times with recurring unretractable abdominal pain, nausea, steatorrhoea and weight loss. CT and magnetic resonance imaging (MRI) demonstrated progressive pancreatic gland atrophy and calcification. Although he underwent extensive investigations to establish the cause of his recurring pancreatitis no identifiable factors were identified. In addition, no pancreatic masses or peripancreatic lymph nodes were seen in multiple US, CT, MRI, magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP). In 2008, after the last episode of pancreatitis the patient’s CT scan showed dilatation of the main pancreatic duct and a cystic lesion in the head of pancreas. These findings were not noted on imaging two years earlier and were confirmed on subsequent MRI and MRCP. The patient underwent an endoscopic ultrasound (EUS) and fine needle aspiration of the cystic mass. Cytology showed mucinous type epithelium and the presence of intracellular mucin, as well as mild nuclear atypia. The differential diagnosis included well differentiated mucin secreting pancreatic adenocarcinoma, IPMN and mucinous cystic pancreatic neoplasm. All tumor markers were normal. The patient subsequently underwent a pancreaticoduodenectomy (Whipple procedure). Histology revealed a 1.5 cm intra-papillary mucinous tumor in the head of the pancreas which arose from a branch duct and involved the major pancreatic duct. The mucous secreting epithelium was characterised by mild nuclear atypia. Four peripancreatic lymph nodes presented no signs of malignancy. The patient remains free of symptoms and with no signs of recurrence in the imaging two years after the operation.

Case #2

A 70-year-old lady, with a 15-year history of chronic pancreatitis initially presented with persistent abdominal pain, nausea and steatorrhoea. She was a non smoker with modest alcohol consumption and had a first degree relative with a history of pancreatitis. During exacerbations serum amylase and lipase were elevated. Gallstone disease was never identified. Over time the patients’ main symptoms evolved into weight loss and chronic abdominal pain with CT and MRI imaging showing signs of fibrotic changes to the pancreatic gland with minimal calcification. Aside from the family history, there were no other clear identifiable causes for her chronic pancreatitis. She had attended regular review under the physicians but presented acutely to the emergency department with an acute exacerbation of epigastric pain, fatigue and weight loss. She proceeded to have a CT and an MRI scan which revealed a non-homogeneous cystic mass in the head of pancreas with maximum transverse diameter of 4.4 cm, suspicious for a malignant tumor. These findings were not present on scans performed two years earlier. The pancreatic cyst was in communication with a clearly dilated main pancreatic duct. The imaging findings were compatible with the diagnosis of an IPMN and surgical resection was decided. Intraoperatively widespread extensive microcystic lesions and fibrotic alterations were demonstrated throughout the pancreas and a total pancreatectomy was deemed the most appropriate surgical option (Figure 2b). Macroscopically the pancreatic parenchyma was replaced by a firm whitish tumoral mass 11 cm in diameter. Sectioning revealed several cystic areas measuring 0.2-0.5 cm containing colloidal mucinous material while the rest of the tumour was solid. Microscopically the cystic areas were lined by mucus-secreting columnar epithelium forming well-developed

Figure 1. Intraoperative and histological findings for Case #1. a. Intraoperative findings of the Whipple surgical specimen. b. Histological slide showing intra ductal papillary mucinous neoplasm with a major duct filled with tall, complex, papillary structures lined by mucin-producing cells.
papillae with fibrovascular cores, small ductular structures and cords of highly atypical neoplastic cells (Figure 2c). The tumour invaded the muscularis propria of the duodenal wall. From the above we concluded that the tumour originated from an IPMN lesion which progressively gave rise to an infiltrating adenocarcinoma. Metastatic deposits were found in three peripancreatic lymph nodes.

DISCUSSION

There has been a dramatic increase in the incidence of IPMN in the last decade and this increase is most likely due to a combination of factors [9, 10]. The grouping of previously autonomous tumours, such as mucin-producing tumours of the pancreas, papillary carcinomas and villous adenoma, as well as improved diagnostic imaging undoubtedly has a central role here [9, 10]. It is unclear whether these two patients had indeed chronic pancreatitis which developed into IPMN or whether the diagnosis of IPMN was undetected during follow-up assessment. The advancement of radiological investigations and the higher incidence of IPMN may have raised the suspicion of the diagnosis earlier if presenting now; however the lack of imaging and histological changes throughout suggests the outcome would have been similar.

In the early stages of IPMN there are usually only subtle changes with mild duct dilation and papillary hyperplasia. The delay in identifying this pathology can postpone the diagnosis and in turn increase the risk of malignant change. Interestingly the cases discussed here showed no pathological signs of IPMN for the majority of their investigations but did show multiple clinical and radiological findings suggestive of chronic pancreatitis. Several studies have proposed mechanisms whereby IPMN produces a chronic obstructive pancreatitis picture through mucin blockade of the pancreatic ducts. [6, 11] Talamini et al. discuss two cases of chronic obstructive pancreatitis who later were diagnosed with IPMN after reoccurrence of obstructive symptoms several years after a pancreaticojejunostomy [6]. The importance in recognising the different epidemiological factors to distinguish chronic pancreatitis, chronic obstructive pancreatitis and IPMN are highlighted. Age, sex, alcohol consumption and smoking history appear to be the most significant factors with IPMN presenting more frequently in older (63.1±11.0 years) females with low to moderate alcohol and smoking usage [6]. Chronic pancreatitis patients are more commonly male with a diagnosis of chronic pancreatitis on average 20 years earlier than IPMN and have high alcohol consumption and smoking history. However, an earlier study by Traverso et al. demonstrates a greater risk of malignancy in IPMN when there is a clinical history of alcohol abuse [12]. The development of insulin dependent diabetes mellitus in chronic pancreatitis may also be an important factor as it appears to correlate with progression to malignant transformation in a similar fashion to ductal adenocarcinoma [13].

There is evidence that radiological imaging can differentiate between invasive and non invasive IPMN. Nevertheless, surgical resection is necessary as almost
all benign main branch duct IPMNs have the potential for invasive transformation and the 5-year survival for resection of non invasive IPMN is excellent [5, 14, 15, 16]. Reoccurrence of non-invasive and invasive IPMN has been shown after apparent complete resection of the tumour and so careful follow-up and surveillance is required [6]. One study demonstrated no reoccurrence of non invasive IPMN following total pancreatectomy and this has led to suggestions for total pancreatectomy in managing non invasive IPMN [5]. Whether the physiological consequences of this outweigh the benefit of reoccurrence is up for debate. When elderly patients present with chronic pancreatitis with modest histories of smoking and alcohol consumption, and development of insulin dependent diabetes mellitus there should be a low threshold for considering other causes of the clinical presentation, namely a pancreatic tumour. Detection of IPMN in the early phases of transformation can permit prompt surgical referral often with positive outcomes [2]. Sohn et al. show a 5-year survival of 77% in non-invasive IPMN and 43% for invasive cancer [2].

Tumour markers have been employed to aid in differentiating between benign and malignant IPMN. Correa-Gallego et al. reviewed cystic carcino-embryonic antigen (CEA) and report levels over 200 ng/mL having a sensitivity of 47% and specificity of 40% for differentiating benign vs. malignant IPMN [17]. Pais et al. reviewed cystic carbonic anhydrase 19-9 (CA19-9) over 10,000 U/mL and report sensitivity of 80% and specificity of 50% for classifying IPMN into malignant vs. benign [18]. The latest developments in the area involve identifying potential biomarkers for classifying IPMNs. Analysis of cyst fluid cytokines have identified elevated IL-1beta and IL-8 with high grade IPMN compared to low grade IPMN [19]. Analysis of T-regulatory cells from peripheral blood and resected tumor has shown that patients with no recurrence had low peripheral T-regulatory cells compared with those who have recurrence [20].

The opportunity to review patients with chronic pancreatitis and to assess for the potential of IPMN can be achieved during follow-up clinics. Follow-up in chronic pancreatitis is often dependent on the recurrence of attacks and the presence of complications. In any case, an initial clinic appointment, 4-6 weeks after the most recent hospital discharge, and subsequent 6 monthly and finally, yearly assessments are warranted. The presence of complications such as ongoing abdominal pain, strictures to the main pancreatic duct or duodenum, calcification deposits and suspected pancreatic pseudocysts may alter the follow-up strategy; with pancreatic cystic lesions carrying a 10% risk of malignancy. In these instances, 6 monthly radiological review with or without biopsy may be warranted. In this cases report we demonstrate the challenges in recognising and diagnosing IPMN in the context of chronic pancreatitis. This ultimately stems from the overlapping clinical presentations and delay in macroscopic radiological findings in IPMN. The recognition of unique epidemiological characteristics may play an important role in early identification, treatment and prevention of the development of invasive IPMN.

Conflict of interest The authors have no potential conflict of interest

References


