Recurrent Acute Pancreatitis Secondary to Alpha-1-Antitrypsin Deficiency

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ABSTRACT

We present the first reported case of recurrent acute pancreatitis occurring with alpha-1-antitrypsin deficiency (PI*ZZ phenotype). Despite evidence of a clinically significant association between alpha-1-antitrypsin deficiency and other inflammatory diseases, the literature surrounding the causal relationship with pancreatitis is less well-documented and currently remains inconclusive. It is important to explore this association as a substantial proportion of recurrent acute pancreatitis is ‘idiopathic’. Alpha-1-antitrypsin deficiency is often under-diagnosed as many patients do not present with classic respiratory and/or hepatic dysfunction hence it is not routinely investigated in the work-up of recurrent acute pancreatitis. Concurrently, there is interest in the role of alpha-1-antitrypsin replacement beyond augmentation therapy. If a true genetic association exists, it may justify routine testing for alpha-1-antitrypsin deficiency in patients with recurrent acute pancreatitis of unknown aetiology and may warrant further studies in to alpha-1-antitrypsin replacement as a novel therapeutic target for a subset of patients with troublesome pancreatitis.

Introduction

Acute Pancreatitis (AP) is an inflammatory condition of the pancreas in which activation of intra-acinar pancreatic enzymes leads to autodigestive injury that damages pancreatic tissue, activates the complement system and triggers the resultant inflammatory cascade that causes AP [1]. The incidence of AP is rising in the UK, ranging from 1.50 to 420 cases per million population, with Severe AP (SAP) having a mortality rate of approximately 20% [2-4,7] In the UK, the most common aetiologies of AP are gallstone disease and alcohol abuse. Other risk factors include hyperlipidaemia, hypercalcaemia and trauma [4]. Nonetheless, 10% of cases achieve no causal factor, rising to 30% in recurrent AP (RAP) [5]. An effort to investigate rarer causes of RAP is a worthy process given the greater risk of these patients developing chronic pancreatitis (CP) [6].

Alpha-1-antitrypsin deficiency (AATD) is an uncommon genetic disorder inherited in an autosomal co-dominant fashion affecting around 1 in 3,000 to 1 in 4,000 people in the UK [7,8]. It is caused by mutations in the SERPINA1 gene located on the long arm of chromosome 14 (14q31-32.3) [9]. Deficiency states cause a shortage of the primarily liver-produced enzyme alpha-1-antitrypsin (AAT), which protects against aberrant proteinase activity [10]. Amongst the 90 protein variants (referred to as PI* types), the deficiency...
phenotype PI*ZZ is associated with greater disease severity in AATD including early-onset emphysema, liver cirrhosis and panniculitis of the skin [10,11]. An association between AATD and a number of inflammatory disorders has been outlined in the literature, however a causal relationship to pancreatitis remains unclear [12,13]. Although some studies have found no significant difference in AAT phenotype in patients with pancreatitis, [1,14-17] there are reports suggesting that imbalance between proteases and their inhibitors in patients with AATD contribute to the development of pancreatitis [18-23]. In a study by Witt et al [14], no difference was found in incidence but there were no PI*ZZ patients included; given that the manifestation of other phenotypes of AATD (such as that of the emphysema in the lung) is co-dominant in nature, the addition of our PI*ZZ case to the literature is valuable, since PI*ZZ patients might have a different phenotype to those with lower risk genotypes. The proportion of patients identified is influenced primarily by local and national practice as it is usually unsuspected and not routinely investigated in the workup of RAP [11]. Therefore, it is possible that a number of patients presenting with RAP of unknown aetiology have undiagnosed AATD. Hence, there is growing interest in determining whether a true causal relationship exists between AATD and pancreatitis and whether AAT replacement may have future therapeutic utility in these patients [24].

Here we present the first reported case of a patient experiencing RAP in whom extensive investigations attribute the episodes to her PI*ZZ AATD phenotype.

Case Presentation

A 30-year-old Caucasian woman presented to hospital with acute onset abdominal pain with nausea and vomiting. She denied any preceding systemic or constitutional symptoms and did not recall any particular rich meals preceding the episode or previous abdominal trauma. The patient was genetically screened and confirmed to have AATD (PI*ZZ type) as a child after her brother was diagnosed in infancy. Notwithstanding, she had no current evidence of active lung or liver disease secondary to her AATD. Apart from a high BMI (42), she was medically fit and well and was not on any regular medications or recreational drugs. Although her maternal uncle died of liver cancer aged 32, she had no family history of pancreatitis or hyperlipidaemia. The patient had no history of alcohol excess and was a current smoker with a 17-pack-year history. On examination, she had marked epigastric tenderness radiating to her right upper quadrant with localised guarding. Her abdomen was otherwise soft and non-distended with normal bowel sounds on auscultation. Chest examination was unremarkable. She remained afebrile and haemodynamically stable but was subsequently admitted to hospital with 4 further episodes over the following year.

Investigations

Blood tests revealed an amylase of 1420 U/L (30-110) with normal liver and kidney function including an albumin of 43g/L (35-50), urea 4.4mmol/L (2.5-7.8) and alanine aminotransferase (ALT) 40iu/L (2-53). Lipase levels, although more sensitive and specific for pancreatitis, were not available at the patient’s medical facility. Full blood count was normal demonstrating a white cell count (WCC) of 8.6x10^9/L (4-11), neutrophils 6.46x10^8/L (1.6-7.5) and C-reactive protein (CRP) 5mg/L (0-10). The patient also had an unremarkable lipid profile, serum biochemistry and bone profile including normal adjusted calcium levels (2.3 mmol/L), triglycerides 0.79mmol/L (0-2), cholesterol 3mmol/L (<5.2), glucose <10mmol/L and PaO2>8kPa. Based on these values and the modified Glasgow score, a prognostication tool used for pre-empting AP-associated severity and mortality, she was diagnosed with mild AP. Investigations in to the underlying aetiology of the recurrent attacks included negative autoimmune serology and normal immunoglobulins including an IgG4 of 0.19g/L. An USS of the abdomen was unremarkable (Figure 1). Computerized Tomography (CT) of the abdomen further confirmed a diagnosis of pancreatitis and also ruled out pancreatic pseudocysts and pancreatic necrosis (Figure 2). A Magnetic Resonance Image (MRI) and
magnetic resonance cholangiopancreatography (MRCP) ruled out gallstones, pancreatic strictures and congenital abnormalities such as pancreatic divisum (Figure 3). In order to exclude hereditary diseases, serum AAT was rechecked demonstrating a level of 0.19g/L (1.23-2.17), clinching the diagnosis. Chlorine levels in sweat and the existence of a mutation for Cystic Fibrosis (CF) was not tested because the patient did not have evidence of bronchiectasis, or other features of CF (eg liver disease or diabetes). In this context screening was not felt applicable when an alternative diagnosis had been made and ongoing fibro scans, chest imaging and spirometry throughout this period remained unremarkable.

Figure 1: Ultrasound image of the gallbladder showing no gallstones and no cholecystitis.

Figure 2: Axial CT image through the pancreas in portal venous phase demonstrating pancreatic inflammation with surrounding fluid.

Figure 3: MRCP coronal image showing no gallstones, no microlithiasis, non-dilated common bile duct and non-dilated pancreatic duct. Conventional pancreatic anatomy is also demonstrated.

Treatment

The acute management was primarily supportive with IV fluids, IV morphine and IV anti-emetics. No antibiotics were given. On review in clinic 2 weeks after her third admission, although her symptoms had subsided, she was commenced on exocrine supplements and a Proton Pump Inhibitor (PPI) for long-term management: Creon 25,000 2 capsules TDS and Lansoprazole 30mg OD, respectively.

Outcome and Follow-Up

Although our patient initially responded well to exocrine supplementation with a PPI, she unfortunately developed a further 2 episodes of AP. The aforementioned investigations were repeated and remained unremarkable. Based on these normal results bar an AAT level of 0.19g/L (1.23-2.17), the only possible aetiological factor identifiable was her AATD hence she was diagnosed with recurrent pancreatitis secondary to AATD. Since her last episode of pancreatitis in October 2016, she has been discharged from the care of the pancreatic and hepatobiliary specialists. Our patient also remains stable from an AATD point of view with no changes in her on-going liver and lung investigations as part of routine follow-up.
Discussion

We describe the first report of RAP in a patient with PI*ZZ AATD. Although gallstone disease and alcohol abuse are the predominant causes of AP in Western countries, these were ruled out early in our investigations. The risk of developing RAP even in the presence of these risk factors remains extremely low which suggests that other factors may be at play, emphasizing the role of individual susceptibility and the need to explore rarer associations [25].

Given our patient’s high BMI and current smoking status with a 17-pack-year history, it is pertinent to consider these as independent risk factors. To date, there is limited data related to BMI and smoking as the aetiology for AP [26,27]. A greater duration of smoking increases the risk of non-gallstone-related AP however data regarding the role of smoking in RAP is lacking [26]. One meta-analysis of 5 studies found a statistically significant association between higher BMIs and the development of AP [27]. The mechanism by which obesity increases the risk of developing AP is unclear, but in the presence of a normal lipid and metabolic profile, it is difficult to ascertain how relevant it is in our case. Nevertheless, given that our patient was thoroughly assessed, with several tests being repeated over the course of 2 years to rule out other aetiopathological factors and that she was assigned her diagnosis by an appropriate specialist (pancreatic surgeon), we believe the diagnosis of RAP secondary to AATD to be accurate.

Supporting this conclusion, in comparison to a recently proposed algorithm for approaching patients with RAP, avenues extensively investigated ruled out microlithiasis, infection, malignancy, drugs/toxins, autoimmune disease, metabolic disease and anatomical variations (Figures 1-4.) [25]. The outstanding assessment for sphincter of Oddi dysfunction with ERCP (Figure 1), is reserved for patients with highly debilitating symptoms with no response to standard treatment, which our patient did not fit the criteria for [25].

The relationship between AATD and inflammatory conditions has been well documented [13]. AAT is one of the most important serum inhibitors of proteolytic enzymes such as trypsin, chymotrypsin, pancreatic elastase, leukocyte proteases and bacterial proteases, protecting mucosal tissue from their proteolytic effects [28]. It has been hypothesized that decreased antiprotease activity in the bowel may promote local injury and progression to inflammatory bowel disease [13]. Similarly, there is a hypothesis that increased levels of pancreatic proteinases or a decrease in pancreatic antiproteinases in AATD can lead to pancreatitis [1,28].

Consistent with this, several studies have found an association between various AATD alleles and pancreatitis [18-23], in particular PI*SZ and PI*SS genotypes, with negative studies generally being limited in the conclusions they could draw due to their small size [14-17]. Furthermore, several in vitro and in vivo studies have demonstrated AAT’s pivotal role in modulating local and systemic inflammatory responses through...
various mechanisms including anti-TNFα effects and neutrophil superoxide inhibition [10,12]. Thus, a lack of AAT may account for the severity of episodes and/or the individual’s exacerbation potential, which could explain the frequency of events that our patient experienced [18]. Supporting the idea that AAT might modulate, if not cause pancreatic problems, Kavutharapu et al found that lowered AAT results in altered immunity and defence in CP resulting in an increase in trypsin and chymotrypsin, which later promotes progression of the disease [28]. The role of genetic mutations in other serine protease inhibitors such as Kazal type 1 (SPINK1), a pancreatic trypsin inhibitor, which has been linked to CP, lends further weight to the possible implication of AATD phenotypes in the occurrence of RAP [29].

It is interesting to speculate on the potential for therapeutic changes if AATD is proven to be a cause of RAP. AAT replacement is a common treatment for AATD worldwide, most commonly used commercially in PI*ZZ AATD patients with lung disease [30], although it is also used intermittently in AATD related panniculitis [10,12], implying that use in recurrent inflammatory conditions is effective, and thus might reduce morbidity (perhaps mortality) in RAP. To our knowledge, there have been no reports of off-license AAT replacement in the management of RAP, thus AAT augmentation in this setting remains an area for future research.

Conclusion

Although the literature remains inconclusive at present, our case raises three questions: Is there a true causal association between PI*ZZ AATD and RAP? And if so, is it distinct from the association reported between other AATD alleles and CP? If additional evidence were to emerge in support of this, it would strengthen the argument for AATD screening in RAP of unknown aetiology. Finally, might AAT augmentation be of use as a therapy in RAP? Further research is needed to answer these questions.

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References