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CASE REPORT

Type 2 autoimmune pancreatitis: case report of a 9-year-old female and a review of the literature

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Abstract We report a case of autoimmune pancreatitis in a 9-year-old female who presented with persistent epigastric pain for 3 weeks. Magnetic resonance cholangiopancreatography (MRCP) showed both intrahepatic and extrahepatic biliary ductal dilatation. The common bile duct, along with the pancreatic duct, was noted to be dilated. Labs showed normal IgG and IgG4 levels and negative for autoimmune antibodies. Endoscopic ultrasound revealed the pancreatic head to be enlarged and surrounded by hypoechoic and lobulated lymph nodes. Biopsy of the pancreatic head showed chronic mildly active inflammation with fibrosis, acinar atrophy, and lymphocytic infiltrate. A diagnosis of autoimmune pancreatitis (AIP) was made, and she was treated with prednisone. The patient's symptoms improved quickly, and follow-up MRCP showed resolution of inflammatory changes and intrahepatic and pancreatic ductal dilatation.

Keywords Autoimmune pancreatitis · Epigastric pain · Corticosteroids

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Introduction

The most common causes of pancreatitis in adults are excessive alcohol use and gallstones. In children, however, pancreatitis is usually due to gene mutations, anatomic anomalies of the pancreatic duct (PD), biliary tract disease, and lipid disturbances [1]. Autoimmune pancreatitis (AIP) makes up approximately 1.9 % of the pancreatitis cases in adults, and is more commonly reported in males [2, 3]. The prevalence of AIP in children is unclear as it is a rare phenomenon. We report here a case of type 2 AIP in a 9-year-old-female that was successfully treated with methylprednisolone.

Case report

A 9-year-old-female presented to the emergency department with a three-week history of intermittent epigastric pain that worsened with meals. The pain was associated with nausea, nonbilious emesis, dark urine, and diarrhea. She reported decreased appetite with a weight loss of 1 kg. Her past medical history was significant for constipation and tonsillectomy. Her review of systems was negative for fever or chills. She denied any recent travel or sick contacts. Medications included polyethylene glycol for constipation, and she was recently started on a proton pump inhibitor. She had no relevant family history. On physical examination, vital signs were normal. She was not jaundiced, and the abdominal examination was normal without tenderness, rebound, or guarding.

Laboratory tests revealed amylase 118 U/L (37–121), peaking at 174 U/L during her admission, lipase 420 U/L (5.6–51.3), total bilirubin 3.4 mg/dL (0.2–1.1), direct bilirubin 2.8 mg/dL (0–0.5), alanine transaminase 275 IU/L

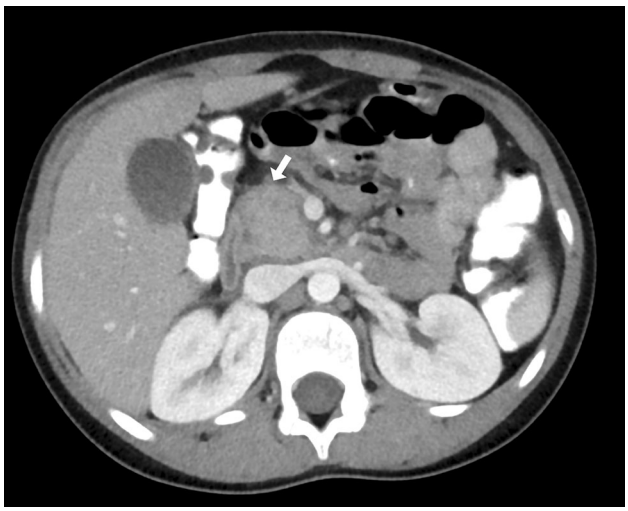

Fig. 1 CT image demonstrating a prominent heterogenous pancreatic head (*arrow*) with mild fat stranding, compatible with pancreatitis

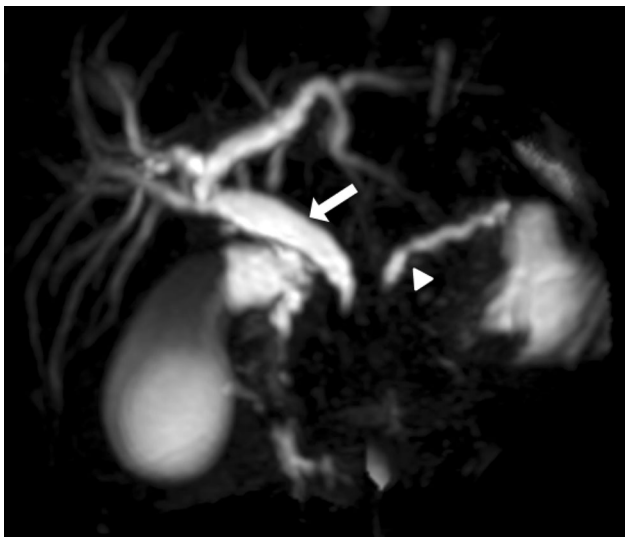

Fig. 2 Reconstructed MRCP image demonstrating 7-mm dilated CBD (*arrow*) and 3-mm dilated PD (*arrowhead*) with a bead-like pattern. The tapering of the ducts demonstrates an area of possible mass obstruction rather than a filling defect suggestive of a gallstone

(4–36), aspartate transaminase 131 IU/L (13–39), alkaline phosphatase 377 IU/L (25–100), gamma-glutamyl transpeptidase 479 IU/L (6–41), erythrocyte sedimentation rate 26 mm/h (1–30), and C-reactive protein 1.90 mg/L (<3.0).

Right upper quadrant ultrasound showed a liver normal in size and echogenicity, measuring 13.1 cm. The common bile duct (CBD) was mildly dilated at 8 mm, and there was minimal intrahepatic and extrahepatic biliary duct dilatation with no sludge or gallstones. The PD was also dilated to 3 mm. Computed tomography (CT) of her abdomen/pelvis with intravenous contrast also demonstrated minimal

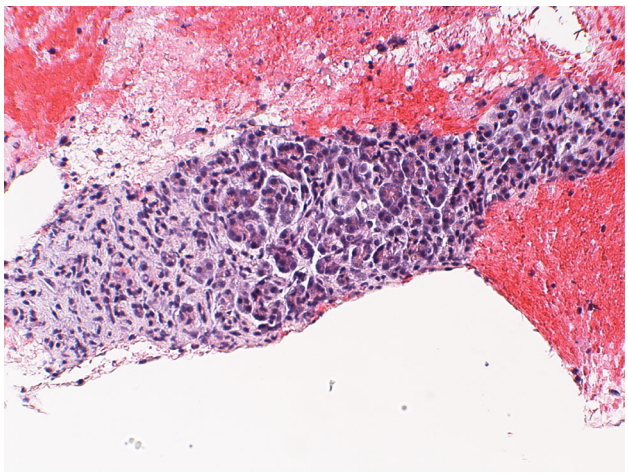

Fig. 3 FNA biopsy of the pancreatic head showing benign pancreatic parenchyma with fibrosis (*left*), scattered inflammation and acinar atrophy

intrahepatic biliary ductal dilatation, and minimal CBD/PD dilatation. Peri-pancreatic edema was noted (Fig. 1). Magnetic resonance cholangiopancreatography (MRCP) without contrast showed intrahepatic and extrahepatic biliary duct dilatation with the CBD measuring 7 mm. The PD was noted to be dilated to 3 mm with a beaded appearance (Fig. 2). There was an abrupt cut-off of the CBD and disappearance of the PD at the level of the pancreatic head, raising suspicion of a pancreatic 'mass'. Again, edema was noted around the pancreatic head.

Despite being on bowel rest, the patient's liver function tests (LFTs) continued to remain elevated. Endoscopic ultrasound (EUS) was performed for further evaluation. The major papilla appeared moderately protuberant. The head of the pancreas appeared enlarged, with hypoechoic and lobulated lymph nodes surrounding the pancreas. The bile duct was dilated at 7 mm and the PD was dilated at 3 mm. A 25-gauge needle was used to perform fine-needle aspiration (FNA) of the ampulla, peri-pancreatic lymph nodes, and pancreatic head. Histology revealed marked fibrosis, active inflammation, and acinar atrophy of the pancreatic head, i.e, findings consistent with chronic mildly active pancreatitis (Fig. 3). No granulocytic infiltration of the duct wall was seen. Immunostaining of the pancreatic head was negative for immunoglobulin (Ig) G. Autoimmune work-up revealed normal IgG and IgG_4 levels, negative endomysial antibody IgA, and negative tissue transglutaminase IgA. The patient was initially treated with bowel rest and intravenous fluids. Her diet was advanced, and she remained pain free prior to discharge.

One week later, she was admitted again for epigastric pain and pruritus. She was found to have elevated LFTs—total bilirubin 3.8 mg/dL, alanine transaminase 275 IU/L, aspartate transaminase 155 IU/L, alkaline phosphatase

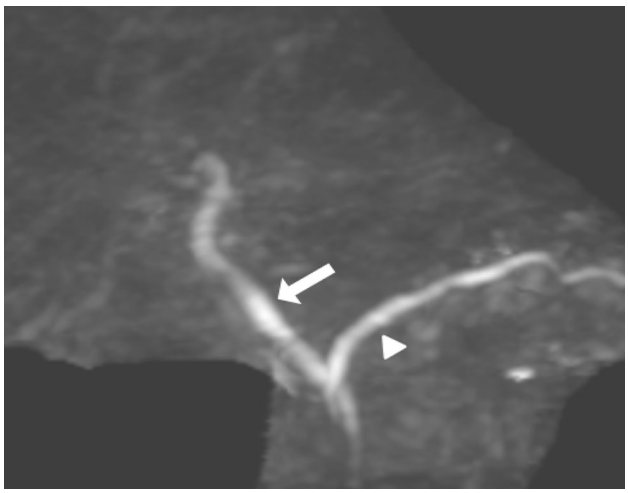

Fig. 4 Follow-up MRCP 1 month after her initial presentation demonstrates normal CBD (*arrow*) and normal PD (*arrowhead*). The ducts can be seen converging and the previous abrupt disappearance of the ducts is no longer present

408 IU/L, amylase 361 U/L and lipase >1,000 U/L. She was started on intravenous methylprednisolone 15 mg three times daily for rapid progression of possible AIP and was transitioned to oral prednisone 40 mg once daily, tapered over 2 weeks. Her symptoms improved rapidly, and she was discharged 5 days later, confirming the diagnosis of type 2 AIP. An outpatient MRCP showed a marked decreased in the caliber of the CBD (3 mm) and PD (1 mm) with no significant intrahepatic biliary duct dilatation. There was resolution of pancreatic edema and inflammatory changes adjacent to the pancreas (Fig. 4).

Discussion

The frequency of AIP in children is unknown as it is a rare phenomenon. Since 2014, our review of the literature found only 16 reported cases of autoimmune pancreatitis in children based on International Consensus Diagnostic Criteria (ICDC) for AIP (discussed further below) [1, Table 1]. There are two variants of AIP—type 1 and type 2. Type 1 AIP is seen in 85 % of adults, usually older males, and these patients typically present with painless obstructive jaundice, fatigue, and weight loss [1, 4]. A common finding is cholestasis secondary to obstructive jaundice from pancreatic/ampullary inflammation [5]. There is an association with diabetes mellitus and other autoimmune diseases, such as sclerosing cholangitis and Sjogren's syndrome [2, 6]. Patients may also have hypergammaglobulinemia with elevated levels of IgG_4 in 68 % of cases [7].

Table 1 Reported cases of autoimmune pancreatitis in pediatrics [1]

Type of autoimmune pancreatitis	No. of reported cases
Definitive cases of type 2 AIP	8
Definitive cases of type 1 AIP	2
Probable type 2 AIP	1
Unspecified AIP	5

Type 2 is seen in younger individuals, with an equal sex distribution, has no serological markers, and has no systemic signs [8]. There is an association with inflammatory bowel disease (IBD), especially ulcerative colitis [1, 8]. These patients are more likely to present with abdominal pain and less likely to have obstructive jaundice. In both variants of AIP, amylase levels are usually elevated and there is hyperbilirubinemia with a predominance of the conjugated bilirubin [3, 5].

The differential diagnoses for AIP includes pancreatic cancer, primary sclerosing cholangitis, and cholangiocarcinoma [9]. In 2010, an international panel of experts proposed ICDC for autoimmune pancreatitis to help distinguish AIP from other diagnoses [10]. There are 5 cardinal features of AIP—parenchymal and ductal imaging, serology, other organ involvement, histology of the pancreas and response to steroid. ICDC further classifies type 1 and type 2 AIP as definitive and probable AIP. Each feature is also categorized as level 1 and level 2 criteria [10].

Pancreatic imaging can be performed with ultrasound, CT scan, or EUS/endoscopic retrograde cholangiopancreatography (ERCP). Ultrasound will frequently show stenosis of the intrahepatic and extrahepatic biliary ducts [11]. CT will reveal either diffuse or localized enlargement of the pancreas giving it a 'sausage-like' appearance [12]. The pancreas is heterogenous and hypoechoic in appearance and shows signs of atrophy or inflammation [5]. In addition, there will be 'diffusely decreased enhancement of the pancreas, a capsule-like rim, and bile duct enhancement', which is more consistent with AIP rather than with a pancreatic tumor [13]. ERCP will demonstrate irregularity or narrowing of the PD [12]. On EUS, AIP findings include hypoechoic pancreatic enlargement, bile duct thickening and peripancreatic hypoechoic margins [9].

Serology, specifically IgG_4, can facilitate the diagnosis. Approximately 35 % of AIP patients will have elevated IgG_4 levels (>140 mg/dL) [12]. Elevated IgG_4 levels have been shown to have 95 % sensitivity and 97 % specificity in differentiating AIP from pancreatic cancer [12]. In type 1 AIP, the IgG_4 levels are elevated (>150 mg/dL) which may indicate involvement of other organs [7, 8]. In contrast, type 2 AIP patients have low IgG_4 levels (<128 mg/dL), and this is associated with localized pancreatic disease [7, 8]. Elevated serum IgG_4 levels and/or the presence of abundant IgG_4-positive cells in other organs are criteria for diagnosis of AIP. Autoimmune antibodies can be seen in

Table 2 Diagnosis of patient based on ICDC for AIP [10]

Parenchymal imaging	Level 1 (typical): diffuse swelling
Ductal imaging	Level 2: segmental/focal narrowing without marked upstream dilatation (duct size <5 mm)
Serology	–
Other organ involvement	–
Histology	Level 2: granulocytic and lymphoplasmacytic acinar infiltrate, absent or scant (0–10 cells/hpf) IgG_4-positive cells
Response to steroids	Radiologically demonstrable resolution and marked improvement in manifestations
Diagnosis	Type 2 probable

58 % of AIP cases, indicating a possible association with other autoimmune diseases [1, 14].

In addition to AIP, elevated serum IgG_4 levels and positive IgG_4 immunostaining have been associated with other diseases [15]. Extrapancreatic findings in AIP may include hilar/intrahepatic biliary strictures, persistent distal biliary strictures, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, or retroperitoneal fibrosis [15].

Histologic findings in AIP vary between type I AIP and type 2 AIP. Type 1 AIP is characterized by 'periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis with an abundance of (>10 cell/high-power field [hpf]) IgG_4-positive cells' [12]. The lymphoplasmascytic infiltrate consists primarily of CD8- and CD4-positive lymphocytes [16]. In type 2 AIP, the pancreas shows ductal granulocyte epithelial lesions [4, 8, 9]. It has recently been proposed that the term 'type 2 AIP' should be replaced by 'idiopathic duct-centric pancreatitis' [8].

The response of AIP patients to corticosteroids has also been used in diagnosing AIP. These patients will usually show improvement within 2 weeks of starting corticosteroids [2]. The rapid resolution helps differentiate AIP from other pancreatic conditions. The typical starting dose is 1 mg/kg/day, tapering down by 2.5–5 mg/week [2]. Some patients may require a long-term maintenance dose of 5–10 mg/day. Patients with extrapancreatic manifestations may also need azathioprine, rituximab, mycophenolate mofetil or cyclophosphamide [8, 12].

Our patient met many of the criteria for type 2 AIP as seen in Table 2. Histology revealed reactive lymphocytic infiltration, and biopsy of the pancreas showed marked fibrosis, acinar atrophy and active inflammation. EUS showed an enlarged pancreatic head with dilatation of the PD. Her serological markers were within normal limits. She had a dramatic response to steroids with marked symptomatic improvement and decreased pancreatic inflammation and resolution of the intrahepatic and extrahepatic biliary dilatation. Although type 2 AIP is associated with IBD, our patient did not report any diarrhea or rectal bleeding which may suggest the presence of ulcerative colitis.

The overall prognosis for AIP patients is dependent on multiple factors. Patients with only focal pancreatic swelling who are seronegative for IgG_4 and have no obstructive jaundice and/or diabetes mellitus are more likely to have spontaneous remission [17]. Patients with diffuse pancreatic swelling are more likely to have relapse pancreatitis [17]. For type 1 AIP patients, the relapse rate is 30–50 %, while for type 2 AIP patients there is usually no relapse [8, 9]. Both type 1 and type 2 patients are at an increased risk of pancreatic insufficiency [11]. They also have an increased risk for malignancies, such as pancreatic cancer, colon cancer, lung cancer, and lymphoma, compared to the general population [4, 9].

In conclusion, AIP in children is a rare phenomenon as it is a 'disease of adults' [4]. It should be included in the differential diagnosis when evaluating a child found to have a pancreatic 'mass' on imaging or who presented with abdominal pain or pancreatitis of unclear etiology. The overall prognosis is good, and it can be treated effectively with steroids.

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Compliance with ethical standards

Conflict of Interest: Dr. Zinal Patel, Dr. Suril Patel, Dr. James Grendell, and Dr. Tuvia Marciano declare that they have no conflict of interest.

Human/Animal Rights: All procedures were followed in accordance with the Helinski declaration of 1975.

Informed Consent: Informed consent was obtained from the patient to be included in the study.

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