Autoimmune Pancreatitis and IgG4 Related Disease in Three Children

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ABSTRACT
We report 3 children who presented with fever and abdominal pain, deranged liver function tests, and on abdominal ultrasound were found to have an enlarged pancreas, substantial abdominal lymphadenopathy, and extrahepatic biliary duct dilatation. After ruling out malignancy, probable immunoglobulin G4-related disease (IgG4RD) associated with autoimmune pancreatitis was considered. This condition was first described in the adults and often mimics pancreatic cancer. It can involve multiple organs, either synchronously or metachronously, and is rarely reported in children. The disorder mostly responds to corticosteroid therapy and other immune suppression. We highlight the difficulty in diagnosing autoimmune pancreatitis/IgG4-related disease in children and illustrate the difference between pediatric and adult presentation.

INTRODUCTION
Classification of autoimmune pancreatitis (AIP) has been difficult and only recently international consensus diagnostic criteria have been agreed upon in adults. Type 1 is more common in elderly Asian males, involves other organs and is associated with a raised immunoglobulin G4 (IgG4). Type 2 has been described in a younger population from Europe and North America, with a normal serum IgG4 and is more commonly associated with the development of ulcerative colitis. Each type has distinctive histopathology on biopsy of the pancreas. There is limited global experience of AIP in pediatrics, and only 25 children with AIP have been reported in the literature to date. Autoimmune pancreatitis in association with IgG4-related disease (IgG4RD) or type 1 AIP in children is even rarer.

CASE REPORT
Case 1: A 14-year-old boy of Ethiopian origin presented with a 2-week history of fever, abdominal pain, and weight loss. He was not jaundiced and did not complain of arthralgia, rashes, or mouth ulcers. His liver function test showed an alanine transaminase of 222 IU/L (normal, 10-35 IU/L) and gamma-glutamyl transpeptidase of 305 IU/L (normal, 10-40 IU/L). Lipase was normal. C-reactive protein was 148 mg/L (normal, <6 mg/L) and had a positive anti-nuclear antibody and p-anti-nuclear cytoplasmic antibody. An abdominal ultrasound (US) demonstrated hepatomegaly, mildly dilated bile ducts, and a bulky pancreatic head and body with enlarged lymph nodes at the porta hepatitis. His magnetic resonance cholangiopancreatography (MRCP) demonstrated high T2 and low T1 signal material surrounding the head and neck of the pancreas with restricted diffusion and post contrast enhancement.
(Figure 1). The common bile duct was dilated without any irregularity of the bile ducts. A possibility of a lymphoma, primary pancreatic malignancy or tuberculosis was considered. Workup for tuberculosis and bone marrow aspiration was negative. For a tissue diagnosis, he underwent a laparotomy and a lymph node biopsy, which showed follicular hyperplasia, interfollicular expansion with abundant plasma cells, and focal progressive transformation of germinal centers with positive staining of IgG4 plasma cells ranging from 80 to 90/high power field. His serum IgG4 level was elevated (3.70 g/L [normal, 0.8 - 1.4 g/L]) together with eosinophilia. A diagnosis of probable AIP/IgG4RD was suspected. However, as they refused corticosteroid treatment, he was started on ursodeoxycholic acid alone. This resulted in an improvement of liver function tests but not the MRCP findings. He developed colitis 6 months after the initial symptoms, which on evaluation was consistent with ulcerative colitis on endoscopy and histology, and was commenced on treatment including corticosteroids. As he had a frequent relapse of symptoms, he was also started on azathioprine a year and a half later. His latest MRCP showed a normal pancreas; however, the biliary changes, although improved, are persisting.

Case 2: An 11-year-old Caucasian girl presented with a 6-week history of abdominal pain, fever, and anorexia associated with weight loss. Examination revealed hepatomegaly and bilateral cervical and inguinal lymphadenopathy. She was not jaundiced and there was no splenomegaly. Her liver enzymes were deranged with a raised lipase. Autoantibodies were positive and serum IgG4 level was elevated (6.16 g/L). There was portal and mesenteric lymphadenopathy with a bulky pancreas on US. Magnetic resonance cholangiopancreatography was the same as case 1 but also showed mild irregularity and beading of intrahepatic biliary ducts. Liver biopsy showed portal inflammation with increased IgG4 plasma cells (11-12/high power field). A few weeks later, she developed diarrhea. Endoscopy showed a patchy colitis and with histological features suggestive of inflammatory bowel disease.

Corticosteroids were commenced with an initial response, which was not sustained, and azathioprine was introduced, but she developed symptomatic pancreatitis. Subsequent to this, for her bowel symptoms, she was started on tacrolimus and then subsequently infliximab and methotrexate, to which she responded with complete resolution of gastrointestinal disease (normal endoscopy). The MRCP findings with respect to the pancreatic mass have improved dramatically; however, the biliary ducts continue to show mild changes.

Case 3: A 7-year-old Caucasian boy presented with a 2-month history of progressive pallor and intermittent abdominal pain. Clinically, he was febrile and not jaundiced with mild hepatosplenomegaly. Laboratory examination demonstrated a normochromic normocytic anemia with a positive direct Coomb’s test. He was diagnosed to have autoimmune hemolytic anemia. He also had eosinophilia, and his liver enzymes were deranged with raised lipase. Ultrasound confirmed mild hepatosplenomegaly with a diffusely enlarged pancreas and peri-pancreatic lymph nodes. The MRCP findings were almost identical to previously described cases. A normal positron emission tomography showed reactive lymph nodes only, and this was further supported by fine needle aspiration of the lymph nodes. Liver biopsy showed a chronic cholangitic pattern with focal interface hepatitis and >10 IgG4 positive plasma cells/high-power field were found in the portal tracts. His IgG4 level was normal (1.09 g/L). Anti-nuclear antibody and antiliver kidney microsomal antibody were negative, but the antismooth muscle antibody was positive. He was treated initially with steroids and ursodeoxycholic acid, and then subsequently azathioprine was added. His liver function tests improved. From an initial peak of up to 876 IU/L his ALT improved to 48 IU/L in his last visit. GGT normalized. A recent US demonstrated complete resolution of pancreatic enlargement with normal pancreatic and biliary ducts. He has recently developed diarrhea and is being evaluated for a possible inflammatory bowel disease.

DISCUSSION

All our patients presented with fever, abdominal pain, and biochemical evidence of hepatobiliary disease, raised inflammatory markers, and peripheral eosinophilia, and there was accompanying radiological evidence of pancreatic swelling and biliary duct dilatation. Initially, malignancy was suspected (in particular a lymphoma) and after this was ruled out, a referral to our service was made, and a diagnosis of AIP/IgGdRD was considered.
The international consensus diagnostic criteria classification from 2011 has suggested 2 types of AIP with differing clinical profiles, histopathology (presence or absence of granulocytic epithelial lesions), associations (IgG4 and ulcerative colitis), and clinical course. In fact, because of their distinct nature, in a recent publication, there has been a suggestion to classify the 2 types as separate entities, with type 1 being referred to as AIP and type 2 being called as idiopathic duct centric pancreatitis.

It is difficult to classify our patients accurately without pancreatic histopathology. Almost all children that have been reported to date appear to have type 2 disease, which is pancreas specific and occurs in the younger age group and is associated with a normal serum IgG4. Type 1, on the other hand, is the pancreatic manifestation of a multisystem involvement seen in IgG4RD. Ulcerative colitis, although more commonly reported with type 2, has also been seen in type 1 as well. All 3 children in our cohort had a multisystem involvement. To the best of our knowledge, only a handful of children with AIP/IgG4RD have been reported before in literature. Unlike adults, pancreatic neoplasm is rare in children. Unfortunately, in the past, because of lack of recognition, children with AIP have been subjected to a Whipple procedure or pancreatectomy. We must urgently recognize this condition in children and establish separate diagnostic algorithms.

DISCLOSURES

Author contributions: R. Bolia collected data, reviewed the literature, wrote the manuscript, and is the article guarantor. S. Y. Chong conceived and wrote the manuscript and collected data. L. Coleman and D. MacGregor reviewed and reported the radiological findings. W. Hardikar collected data and reviewed the manuscript. M. R. Oliver collected data and edited the manuscript.

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Informed consent was obtained from the patients’ parents.

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