Autoimmune pancreatitis characterized by predominant CD8+ T lymphocyte infiltration

She-Yu Li, Xiang-Yang Huang, Yong-Tao Chen, Yi Liu, Sha Zhao

Autoimmune pancreatitis (AIP) is a rare form of pancreatitis characterized by prominent lymphocyte infiltration and pancreatic fibrosis resulting in organ dysfunction. The pathogenesis and pathology of AIP remain unknown. A 64-year-old Chinese man presented with symptoms and signs of bile duct obstruction diffuse enlargement of the head of pancreas, elevated IgG levels, and negative autoimmune antibody responses. A pylorus-preserving pancreateoduodenectomy was performed and a pancreatic tumor was suspected. However, periductal lymphoplasmacytic infiltration and fibrosis were found in the head of pancreas and nearby organs instead of tumor cells. Four months after surgery, the patient was readmitted because of reoccurrence of severe jaundice and sustained abdominal distension. Prednisone 30 mg/d was administered orally as an AIP was suspected. One and a half months later, the symptoms of the patient disappeared, and globulin, amino-transferase and bilirubin levels decreased significantly. Over a 9-mo follow-up period, the dose of prednisone was gradually decreased to 10 mg/d and the patient remained in good condition. We further demonstrated dominant CD3+/CD8+ populations, CD20+ cells and a few CD4+ cells in the pancreatic parenchyma, duodenum and gallbladder wall by immunohistochemical assay. This AIP case presented with significant CD8+ T lymphocyte infiltration in the pancreas and extra-pancreatic lesions, indicating that this cell population may be more important in mediating AIP pathogenesis than previously known and that AIP might be a poorly defined autoimmune disease with heterogeneous pathogenesis.

Key words: Autoimmune pancreatitis; Pancreas; Prednisone; CD8+ T and CD4+ T lymphocytes; CD20; Inflammatory cell; Infiltration

Peer reviewers: Basil Ammori, MD, Department of Surgery, Salford Royal Hospital, Stott Lane, Salford, Greater Manchester, M6 8HD, United Kingdom; Dr. Thiruvengadam Muniraj, MBBS, MD, PhD, MRCP (UK), University of Pittsburgh Medical Center, 100 Chatham Park Drive, Apt 511, Pittsburgh, PA 15220, United States

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Abstract
Autoimmune pancreatitis (AIP) is a rare form of pancreatitis characterized by prominent lymphocyte infiltration and pancreatic fibrosis resulting in organ dysfunction. The pathogenesis and pathology of AIP remain unknown. A 64-year-old Chinese man presented with symptoms and signs of bile duct obstruction diffuse enlargement of the head of pancreas, elevated IgG levels, and negative autoimmune antibody responses. A pylorus-preserving pancreateoduodenectomy was performed and a pancreatic tumor was suspected. However, periductal lymphoplasmacytic infiltration and fibrosis were found in the head of pancreas and nearby organs instead of tumor cells. Four months after surgery, the patient was readmitted because of reoccurrence of severe jaundice and sustained abdominal distension. Prednisone 30 mg/d was administered orally as an AIP was suspected. One and a half months later, the symptoms of the patient disappeared, and globulin, amino-transferase and bilirubin levels decreased significantly. Over a 9-mo follow-up period, the dose of prednisone was gradually decreased to 10 mg/d and the patient remained in good condition. We further demonstrated dominant CD3+/CD8+ populations, CD20+ cells and a few CD4+ cells in the pancreatic parenchyma, duodenum and gallbladder wall by immunohistochemical assay. This AIP case presented with significant CD8+ T lymphocyte infiltration in the pancreas and extra-pancreatic lesions, indicating that this cell population may be more important in mediating AIP pathogenesis than previously known and that AIP might be a poorly defined autoimmune disease with heterogeneous pathogenesis.

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Introduction
Autoimmune pancreatitis (AIP) is a rare form of pancrea-
Autoimmune pancreatitis with CD8+ T lymphocyte infiltration

A 64-year-old Chinese man was admitted to the West China Hospital on May 8, 2004 with a history of 1-mo abdominal distension and 3-d jaundice. He was examined with blood biochemical tests, including direct bilirubin (DB, 114.71 µmol/L), indirect bilirubin (IB, 44.9 µmol/L), alanine amino transferase (ALT, 70 IU/L), aspartate amino transferase (AST, 51 IU/L), globulin (45.8 g/L) and fasting plasma glucose (FPG, 6.1 mmol/L) (Figure 1). Computed tomography (CT) showed a 3 cm × 3 cm mass at the head of the pancreas suspected to be a pancreatic tumor. Therefore, a pylorus-preserving pancreaticoduodenectomy was performed on May 11 and a 3 cm × 3 cm mass was identified at the head of the sclerified pancreas, with cholestatic changes in the liver and gallbladder hydrop with dilation of the common bile duct (1.5-2 cm; the normal range is 0.3-0.8 cm). Pathological examination showed chronic inflammation with fibrosis in the pancreatic and common bile ducts as well as moderate to severe epithelial dysplasia (Figure 2). Adenopithelial hyperplasia but not tumor cells were found in the pancreatic parenchyma. The patient was discharged 2 wk after surgery when jaundice symptoms abated.

Four months later on September 13, 2004, the patient was readmitted to the West China Hospital due to a recurrence of severe jaundice and sustained abdominal distension. No obvious abnormal findings were identified following physical examination other than jaundice in the skin and sclera. Blood biochemical results (Figure 1) demonstrated the levels of DB at 91.5 µmol/L, IB at 37.7 µmol/L, ALT at 41 IU/L, AST at 59 IU/L, globulin at 60.4 g/L, FPG at 6.1 mmol/L; AST: Aspartate amino transferase; ALT: Alanine amino transferase; DB: Direct bilirubin; IB: Indirect bilirubin.

Figure 1  Blood biochemical analyses. Pre- and post-prednisone treatment levels of (A) immunoglobulin, (B) aminotransferase and (C) bilirubin. The black arrow indicates the start of prednisone treatment. ALT: Alamine amino transferase; AST: Aspartate amino transferase; DB: Direct bilirubin; IB: Indirect bilirubin.

Based on the hypergammaglobulinemia and elevated IgG levels observed, this patient was suspected to have pancreatitis of autoimmune origin. Prednisone 30 mg/d was administered orally beginning on November 2, 2005. One and a half months later, the patient was discharged from the hospital after the jaundice and abdominal distension disappeared and the globulin (Figure 1A), aminotransferase (Figure 1B) and bilirubin (Figure 1C) levels decreased significantly. Over a 9-mo follow-up period, the dose of prednisone was gradually decreased to 10 mg/d and the patient remained in good condition without the presentation of either jaundice or abdominal distention and his globulin (Figure 1A), aminotransferase (Figure 1B) and bilirubin (Figure 1C) levels were within the nor-
AIP, also described as chronic pancreatitis of autoimmune origin, is clinically similar in presentation to pancreatic carcinoma. AIP patients may undergo pancreatoduodenectomy as a consequence of treatment. It is reported that 2.5%-11% of the patients diagnosed with pancreatic malignancy actually had a benign pancreatic disorder confirmed by pathological examination after surgery and 9.9% of the patients underwent pancreateoduodenectomy following a diagnosis of pancreatitis. 38% of them were reported to be caused by autoimmune responses.

AIP is characterized by an irregular narrowing of the main pancreatic duct, massive lymphoplasmacytic inflammation of the pancreatic parenchyma, hypergammaglobulinemia and a fair response to glucocorticoid treatment. The case presented in this report was mainly characterized by symptoms and signs of bile duct obstruction, diffuse enlargement of the head of pancreas, elevated IgG levels, negative autoimmune antibody responses and periductal lymphoplasmacytic inflammation and fibrosis. After a strict treatment regimen of prednisone, the patient recovered quickly and his globulin, amiotransferase, and bilirubin levels returned to normal for more than half a year. In our case, AIP was diagnosed based on the criteria established by the Japan Pancreas Society.

AIP presentation has recently been divided into either subtype type 1 or 2. In Asia, type 1 AIP presents at a higher frequency and is also referred to as lymphoplasmacytic sclerosing pancreatitis or AIP without granulocyte epithelial lesions (GELs). Type 2 AIP is referred to as idiopathic duct-centric pancreatitis or AIP with GELs. The case presented here with periductal lymphoplasmacytic infiltration (without granulocytes), fibrotic proliferation and pancreatic ductal atrophy is consistent with the histopathological features of type 1 AIP.

It was previously reported that infiltrating cells in AIP cases predominantly consisted of CD4+ T lymphocytes with few detectable CD8+ T lymphocytes and B lymphocytes. T helper imbalance (Th1 vs Th2) is believed to be associated with the initiation of AIP and elevated Th1 responses were reported in both pancreatic and extra-pancreatic lesions in AIP patients. CD4+CD25+ regulatory T lymphocytes have also been demonstrated to contribute significantly to the pathology of AIP-associated lesions compared to lesions resulting from other pancreatic disorders. In animal AIP disease models, administration of amylase-sensitized CD4+ T lymphocytes elicited autoimmune pancreatitis, suggesting that CD4+ T lymphocytes may be the most important components in mediating disease pathogenesis. This observation is supported by the cases presenting with a reduced number of infiltrating CD4+ T lymphocytes in AIP lesions.

In contrast, our case presented with infiltrating CD8+ T (primarily cytotoxic T lymphocytes) instead of CD4+ T lymphocytes in both pancreatic and extra-pancreatic lesions. Since CD4+ T helper lymphocyte is believed to be indispensable in mediating various types of immune responses, we hypothesize that CD4+ T lymphocytes may have originally infiltrated these tissues and then recruited more CD8+ T lymphocytes functioning as effector cells of AIP pathogenesis. These data demonstrated that the presence of CD8+ T lymphocytes in AIP lesions may be

DISCUSSION

To further characterize the pathogenesis of AIP in this case, histopathologic and immunohistochemical analyses were carried out to determine the CD3, CD4, CD8 and CD20 positive profiles in paraffin sections taken from the head of the pancreas, duodenum and gallbladder. Hematoxylin and eosin staining of the head of pancreas showed ductal atrophy and periductal lymphocytic infiltration with fibrotic proliferation (Figure 2), and high levels of CD3+ cells were identified in the periductal region of the head of the pancreas (Figure 3A), duodenal villi (Figure 3B) and the gallbladder wall (Figure 3C). Interestingly, CD4+ cells were present at low levels in the specimens from the head of the pancreas (Figure 3D), duodenum (Figure 3E) and the gallbladder wall (Figure 3F). Parallel to the CD3 expression levels, CD8+ cells were detected at high levels in the periductal region of the head of the pancreas (Figure 3G), duodenal villi (Figure 3H) and the gallbladder wall (Figure 3I). The CD20 was expressed at low levels in the periductal region of the head of the pancreas (Figure 3J) and focally expressed in the duodenal villi (Figure 3K). No CD20 expression was detected in the gallbladder wall (Figure 3L).

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more important than previously thought and that elicitation of AIP may have heterogeneous origins. A limitation in these observations is that they have only been reported in a single case, more investigations about the role of
CD8+ T lymphocytes are required to further understand the pathogenesis of AIP. In summary, we identified a significant number of CD8+ T lymphocytes infiltrating in both pancreatic and extra-pancreatic AIP lesions, instead of CD4+ T lymphocytes as commonly expected. It suggests that AIP might possess heterogeneous autoimmune origins.

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