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Two cases of autoimmune pancreatitis with diabetes and literature review

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Abstract

OBJECTIVE: To investigate the clinical features of autoimmune pancreatitis (AIP) with diabetes as the first manifestation, improve our understanding of the disease and highlight the recognition of special types of diabetes.
METHODS: A retrospective analysis was performed on 2 AIP patients diagnosed with diabetes at the First Affiliated Hospital of Anhui Medical University.
RESULTS: Two elderly patients with new-onset diabetes mellitus were admitted to the hospital with weight loss and yellowing of the skin. Imaging showed pancreatic enlargement, bile duct dilatation, and cholestasis. Auxiliary examination followed by histopathology or experimental hormone therapy revealed elevated IgG4 levels, and the patients were eventually diagnosed with AIP.
CONCLUSION: For elderly diabetic patients with atypical clinical characteristics, such as unexplained gastrointestinal symptoms or weight loss, IgG4 levels should be examined to rule out diabetes secondary to AIP.

CASE REPORT

INTRODUCTION

In 1889, von Mering and Minkowski confirmed that pancreatic resection can cause diabetes. Indeed, pancreatogenic diabetes is a type of secondary diabetes that is often misdiagnosed as type 1 (T1DM) or type 2 (T2DM) diabetes, and studies have reported that approximately half of these patients are misdiagnosed with T1DM or T2DM.

Autoimmune pancreatitis (AIP) is an immune-mediated pancreatic inflammatory disease. In 2011, the International Association of Pancreatology (IAP) defined the diagnostic criteria and classification of AIP, with type 1 being lymphocytic sclerosing pancreatitis (LPSP) and type 2 being idiopathic catheter-type pancreatitis (IDCP) (Shimosegawa *et al.* 2011). Most cases of the former occur in China (Editorial Board of Chinese Journal of Pancreatology, 2012). Clinically, patients often suffer from abdominal pain, diarrhea, weight loss, obstructive jaundice and other symptoms. A small number of patients with impaired pancreatic endocrine function, i.e., abnormal glucose metabolism, are likely to be misdiagnosed. This article reports two cases of clinical diagnoses of AIP with the first symptom being diabetes. The aim is to deepen our

understanding of AIP and improve the diagnosis and treatment of specific types of diabetes.

METHODS

Ethics

This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University and that the two patients gave their informed consent to participate.

Case report

Case 1: A 56-year-old male was admitted to the hospital with the complaint of "increased blood sugar for 2 years and weight loss for half a year." Two years previously, physical examination revealed a fasting blood glucose level of 8.01 mmol/L. He was prescribed oral metformin and gliclazide, after which his fasting blood glucose was approximately 6~8 mmol/L. The patient lost approximately 15 kg over the course of six months and experienced pain in the right upper abdomen but no diarrhea, anorexia, vomiting or other discomfort. He had a history of tuberculosis that had been cured. He had a history of smoking and alcohol consumption. There was no family history of diabetes. There were no obvious signs on physical examination. Laboratory tests showed the following: fasting blood glucose 9.43 (3.9~6.1) mmol/L; glycosylated hemoglobin 7.6 (4 ~ 6)%; triglyceride 0.81 (0.4~1.6) mmol/L; CA-199 166.2 (0.0~39.0) U/ml; CEA 3.72 (0.0~3.4) ng/ml; and IgG 24.6 (7.0~16.0) g/L. His liver and renal function and levels of hemodiastase and urease amylase were normal, and autoantibodies were not detected. Abdominal B-ultrasound showed extrahepatic biliary obstruction, a right upper abdomen mass, pancreatic head enlargement, and pancreatic duct dilatation. On pancreatic computed tomography (CT), the pancreas was swollen, the pancreatic duct was dilated, and the pancreatic tail and especially the head were spotted with calcification (Fig. 1a). Magnetic resonance cholangiopancreatography (MRCP) revealed that the head of the pancreas was enlarged, and the signal was uneven; the pancreatic duct was also dilated, rough, and unevenly thick. The left hepatic duct, the common hepatic duct and the common bile duct were dilated (Fig. 1b, 1c). Endoscopic ultrasound (EUS) indicated calcification of the tail of the pancreas. The dilated pancreatic duct could be seen and had a diameter of approximately 5 mm. Several stones were visible in the pancreatic duct, most of which were approximately 1.5 mm in diameter. The observed calcification mainly affected the pancreatic head, though the pancreatic duct was also clearly calcified. The pancreas was slightly smaller than normal. No abnormalities were observed in the liver or surrounding tissues. Pancreatic puncture pathological return showed pancreatic acinar atrophy and disappearance, fibrous tissue hyperplasia, and lymphocyte and plasma cell infiltration (Fig. 2a). Immunohistochemical staining was positive for CD38+ and CD138+, and the IgG4 level was >10/HPF (Fig. 2b), which is in line with the diagnosis of IgG4-related AIP.

Case 2: A 56-year-old male was admitted to the hospital with the complaint of "increased blood sugar for half a year, and yellow skin and sclera for 2 months". Six months prior to this admission, a physical examination revealed increased blood sugar levels; he was prescribed intermittent oral metformin and glimepiride, with periodic blood sugar measurements. The jaundiced skin and sclera appeared two months previously, and his urine was dark brown. His stool was clay-like, and he experienced skin itching, bloating, diarrhea, fatigue, and weight loss of 5 kg in 2 months. Examination upon admission showed deep-yellow skin and sclera, pronounced tenderness in the right upper abdomen and the xiphoid process near the gallbladder, with no pain in the gallbladder; the examination was otherwise normal. Auxiliary examinations revealed the following: fasting blood glucose 8.88 mmol/L (3.9 ~ 6.1 mmol/L); glycosylated hemoglobin 8.8 (4 ~ 6)%; ALT 145.7 U/L; AST 77.6 U/L; GGT 708.4 U/L; TBIL 78 μmol/L; DBIL 59.3 μmol/L; CA-199 51.99 U/ml; IgG 20.0 (7.0 ~ 16.0) g/L; and IgG4 18.2 (0.03 ~ 2.01) g/L. Abdominal ultrasound showed intrahepatic bile duct dilatation, cholestasis, common bile duct dilatation, pancreatic head enlargement, and echo reduction. Upper abdomen enhanced CT revealed a lump in the head of the pancreas with a clear boundary; scan of the arterial phase indicated slight enhancement (Fig. 3a). MRCP showed gallbladder enlargement, effusion, low biliary obstruction, and lower biliary stricture. Despite the possibility of AIP, the patient refused to undergo a needle biopsy and received oral prednisone 15 mg twice daily. After 2 weeks, his biochemical indicators had improved, as follows: ALT 61U/L; AST 18U/L; GGT 474U/L; TBIL 19 μmol/L; DBIL 12.5 μmol/L; and CA-199 22.7 U/ml (Table 1). An upper abdominal scan showed intrahepatic and extrahepatic bile duct dilatation and a reduction in the size of the mass in the uncinate process of the head of the pancreas (Fig. 3b). Experimental treatment was effective for establishing the diagnosis of AIP.

DISCUSSION AND CONCLUSION

With the aging of our population and changes in lifestyle, the prevalence of diabetes has increased from 0.67% in 1980 to 10.4% in 2013, transitioning from a rare disease to an epidemic. Diabetes is divided into the following four categories based on etiological evidence: T1DM, T2DM, special types of diabetes, and gestational diabetes. Currently, the International Diabetes Federation refers to diabetes caused by pancreatic disease as "pancreatic diabetes" and classifies it as "T3c type diabetes" (T3cD). Overall, the prevalence of T3cD was once low, accounting for only 0.5-1.15% of diabetic patients (Fu&Ji, 2018). In recent years, however, studies have shown that T3cDM accounts for

Tab. 1. Patient 2 laboratory tests before and after glucocorticoid treatment

Laboratory test	ALT (U/L)	AST (U/L)	GGT (U/L)	TBIL (μmol/L)	DBIL (μmol/L)	CA-199 (U/ml)
Before treatment	145.7	77.6	708.4	78.0	59.3	51.99
After 2 weeks of hormone therapy	61.0	18.0	474.0	19.0	12.5	22.7
Normal reference value	0.0~40.0	0.0~40.0	11.0~50.0	6.0~20.5	0.0~6.0	0.0~39.0

Note: ALT: alanine aminotransfease; AST:aspartate transaminase; GGT: γ-glutamyl transpeptadase; TBIL: total bilirubin; DBIL: direct bilirubin; CA-199: carbohydrateantigen19-9

approximately 5-10% of diabetes in Western countries (Cui & Andersen). According to a UK survey, there is a higher prevalence of diabetes associated with pancreatic diseases than type 1 diabetes among adult diabetes patients (Woodmansey *et al.* 2017) . The above data suggest that the health effects of T3cDM may have been underestimated for a long time.

The causes of T3cD include acute and chronic pancreatitis, pancreatectomy, pancreatic trauma, pancreatic tumors, cystic fibrosis of the pancreas, hemochromatosis, and congenital dysplasia of the pancreas. Among these causes, chronic pancreatitis accounts for 76% of T3cD cases, whereas pancreatic tumors, hemoglobinosis cystic fibrosis and pancreatectomy account for 9%, 8%, 4% and 3%, respectively (Ewald *et al.* 2012). T3cD caused by diseases such as chronic pancreatitis and pancreatic cancer is common in the middle-aged and elderly populations, people who are also at high risk for T2DM. The clinical manifestations of T3cD vary. Compared with T1DM or T2DM, hyperglycemia in T3cD is milder, and hypoglycemia is more common. Reduced ketoacidosis is often associated with exocrine dysfunction (FU&Ji, 2018). However, in practice, it is difficult to distinguish T3cD from T1DM and T2DM, and evidence of exocrine dysfunction, including diarrhea, is easily attributable to gastrointestinal reactions to metformin and other hypoglycemic drugs. In general, T3cDM is easily misclassified because of the overlap of high-risk populations, the failure to rule out a history of pancreatic diseases at the time of initial diagnosis, and the variety of clinical manifestations. A German study reported that approximately half of these patients were misdiagnosed with T1DM (6%) and T2DM (45%) (Vipperla *et al.* 2016), and a British study indicated that 87.8% of the 599 patients who developed pancreatic disease were diagnosed with T2DM (Woodmansey *et al.* 2017). Patients with abnormal glucose metabolism are more likely to be misdiagnosed than are patients with the onset of digestive system symptoms. Among the cases presented herein, patient 1 had recently developed pain in the right upper quadrant; patient 2 had recently developed obstructive jaundice, as well as impaired pancreatic exocrine function evidenced by abdominal distension and diarrhea, which was a key indicator for a diagnosis of pancreatic diabetes. Nonetheless, a careful review of the cases showed that these two patients had

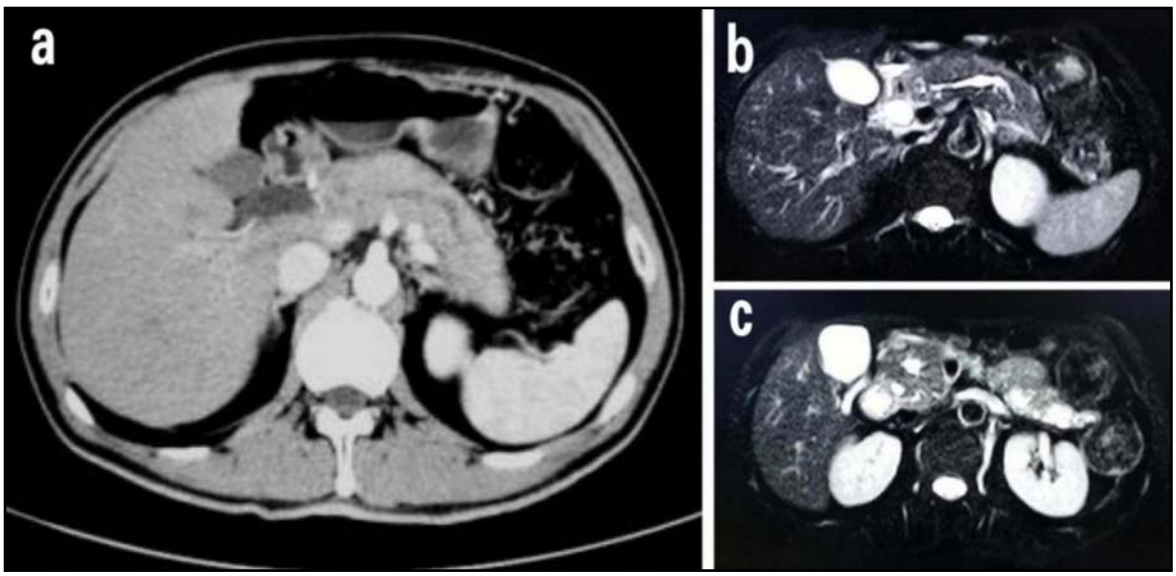

Fig. 1. Patient 1 pancreatic imaging examination. **a**, Pancreas plain scan CT: pancreatic diffuse enlargement with a sausage-like appearance and pancreatic duct dilatation. **b, c,** Pancreatic head enlargement; uneven signal, pancreatic duct dilatation, rough texture, uneven thickness, left hepatic duct, common hepatic duct and common bile duct dilatation.

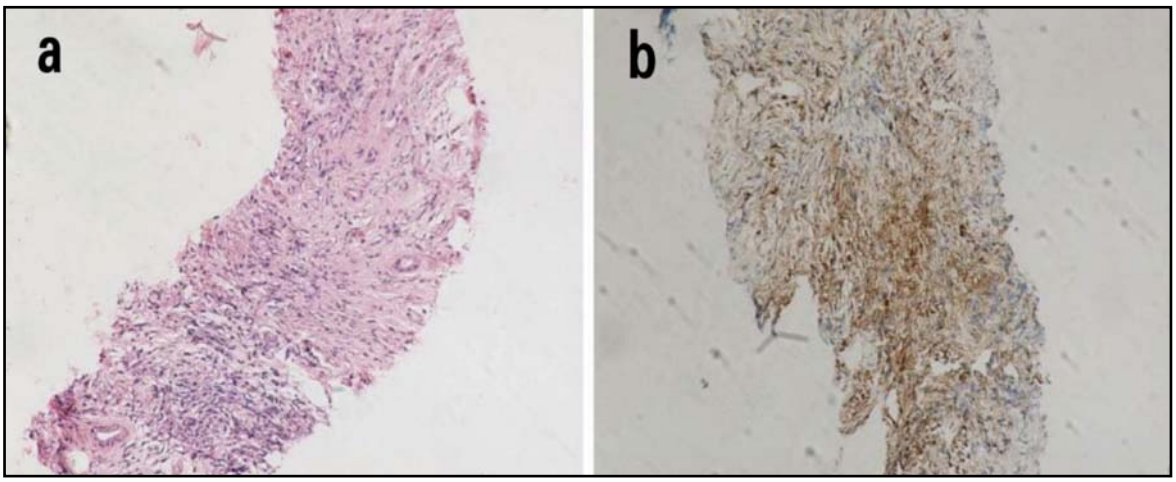

Fig. 2. Patient 1 pancreatic biopsy pathology. **a,** HE staining: pancreatic acinar atrophy, fibrous tissue hyperplasia with lymphocytes and plasma cell infiltration (100 ×). **b,** Immunohistochemistry: IgG4+ cells > 10 /HPF (100×).

still rapidly lost weight when their glycemic control improved; this finding was initially ignored, and it was not an early clue supporting the diagnosis of T2DM.

The pathophysiological mechanism underlying T3cDM includes impaired insulin secretion due to reduced insulin cell number, impaired insulin cell function, insulin insufficiency, and insulin resistance in the liver. The above mechanisms also underlie the high risk of oncogenesis, especially of pancreatic cancer, in patients with diabetes and chronic pancreatitis (Esposito *et al.* 2012; Klein *et al.* 2004). Metformin is undoubtedly the preferred oral hypoglycemic agent for T3cDM. Some patients with T3cDM exhibit insulin deficiency, which can be treated with insulin therapy. Clinical data for thiazolidinediones, α-glucosidase inhibitors, and sodium-glucose cotransporter-2 inhibitors in T3cDM are limited. Moreover, incretin-based DPP-4 inhibitors and GLP-1 receptor agonists are contraindicated in patients with pancreatitis. Overall, the misclassification of T3cDM may lead to improper selection of hypoglycemic drugs. In addition, T3cDM patients often have impaired pancreatic exocrine function, which manifests as gastrointestinal symptoms and malnutrition. If patients are misclassified, these symptoms may not be corrected, and there may be delays in treatment of the pancreatic disease.

AIP is a globally sporadic disease with a reported incidence of 8.2/1 million, a male to female ratio of 2.85:1, and an onset age >45 years old; AIP accounted for approximately 2% to 10% of the chronic pancreatitis in the period of that study(Nishimori *et al.* 2007). The diagnosis of AIP is based on imaging (pancreatic parenchymal imaging, pancreatic duct imaging), serology, extrapancreatic involvement, pathology, and diagnostic hormone therapy (Editorial Board of Chinese Journal of Pancreatology, 2012). Among these methods, imaging examinations are the most important for the diagnosis of AIP. Typical imaging findings are diffuse or localized enlargement of the pancreas with delayed enhancement. In some cases, the pancreas has a periplasmic margin, a long main pancreatic duct (>1/3 full length) and multiple stenoses, with no obvious

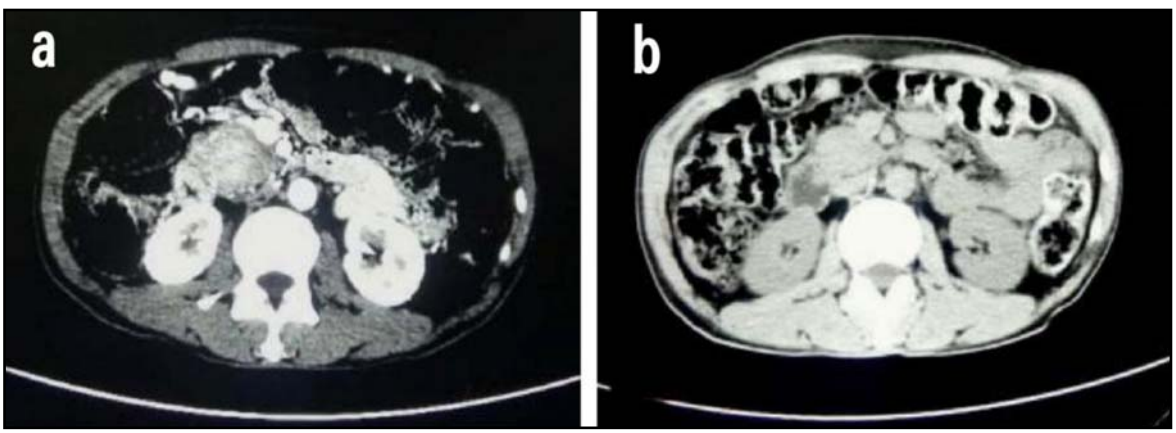

Fig. 3. Pancreatic CT before and after treatment in patient 2. **a,** Enhanced CT before treatment of the pancreas: pancreatic head uncinate mass, mild enhancement of arterial phase. **b,** Plain CT after treatment of the pancreas: the pancreatic head uncinate mass was smaller than before.

expansion at the proximal end (He&Zhang, 2018). IgG4 is considered to be a characteristic serological indicator of AIP, and up to 94% of AIP patients have elevated IgG4 levels. Hamano *et al.* used an IgG4 serum concentration of >1350 mg/L as the cutoff value for AIP diagnosis, with an accuracy, sensitivity, and specificity of 97%, 95%, and 97%, respectively (Shen *et al.* 2017). According to the diagnostic criteria issued by the 2011 IAP, AIP can be diagnosed if the patient has typical imaging signs and the combined laboratory tests are positive or the external organs of the pancreas are involved. However, Chari *et al.* reported that approximately 30% of AIP patients need to be diagnosed by pancreatic puncture, surgery or experimental sex hormone therapy (Zhou, *et al.* 2016) . Among our cases, patient 1 underwent a biopsy, and AIP was confirmed by pathology. The pathological features of AIP are as follows: plasma cells (IgG4-positive cells >10/HPF, IgG4/IgG cells >40%), fully infiltrated lymphocytes, striated fibrosis, and occlusive phlebitis (Editorial Board of Chinese Journal of Pancreatology, 2012; He&Zhang, 2018). Case 2 was diagnosed by diagnostic hormonal therapy: after 2 weeks of glucocorticoid treatment, the pancreatic mass was reduced, and laboratory indicators related to the obstructive jaundice were significantly improved.

AIP can affect the pancreas and extrapancreatic tissues, and the clinical manifestations are diverse. Obstructive jaundice, abdominal pain, and weight loss are the most common clinical manifestations. These patients are often affected by impaired pancreatic exocrine function and local compression, and impaired glucose metabolism is a characteristic of patients with impaired pancreatic endocrine. According to one survey, 42% to 78% of AIP patients have diabetes (Yuan, *et al.* 2016). A Japanese study found that 22% of these patients were initially diagnosed with diabetes (Nishimori, *et al.* 2006), likely because imaging abnormalities are often detected as the main diagnostic basis for AIP at a later stage of the disease, and islet β-cell function damage often occurs earlier. In addition, Ito *et al.* proposed that an elevated IgG4 level alone can cause pancreatic endocrine damage (Ito, *et al.* 2014) . Compared with patients with initial onset of digestive system symptoms, patients with abnormal glucose metabolism are more likely to be misdiagnosed, leading to a poor choice of hypoglycemic drugs and delays in the diagnosis and treatment of pancreatic diseases. Thus, for newly diagnosed diabetic patients, especially middle-aged and elderly men, without a family history of diabetes who lack all islet cell function, experience weight changes, and have poor glycemic control, secondary diabetes caused by AIP should be investigated by detecting globulin and plasma IgG4 levels.

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