Acute pancreatitis may be a pathogenic factor of fulminant type 1 diabetes mellitus

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To the Editor: Fulminant type 1 diabetes mellitus (FT1DM) is characterized by a rapid loss of β-cell functions, negative antibody to islet cells, ketoacidosis, and elevated pancreatic enzymes.[1] In a nationwide survey in Japan, elevated pancreatic enzymes and abdominal pain were found in 98% and 70% of patients with ketoacidosis-onset FT1DM, respectively. However, abdominal computed tomography (CT) showed no abnormalities. The increased pancreatic enzymes were related to diabetic ketoacidosis. Several Japanese scholars have reported that FT1DM appeared after acute pancreatitis (AP). So far, no such cases have been reported in China. Here, we report two cases of FT1DM following AP, review previous cases, and speculate the relationship between AP and FT1DM. Informed consents were obtained from both patients.

A 40-year-old male patient suffered from abdominal pain after jumping from a 2-meter-high platform on June 7, 2017; the following day abdominal pain worsened with fever up to 38.5°C. On June 10, CT showed pancreatic edema, obvious exudation and serum amylase was 201 U/L. He was diagnosed with AP and received therapy. On June 11, fasting blood glucose (FBG) was 4.96 mmol/L and body temperature was normal. The amylase level decreased after treatment. Two days later, the patient felt very thirsty. On June 14, the following test results were recorded: FBG, 25.69 mmol/L; HCO_3^-, 13.24 mmol/L; amylase, 872 U/L; lipase, 141 U/L; and HbA1c, 5.69%. Insulin was given to reduce the blood glucose. The patient was presented to our hospital on July 1. His body mass index (BMI) was 20.95 kg/m^2. Fasting, postprandial 1^-, and 2-h C-peptide levels were <0.01 ng/mL. Anti-glutamic acid decarboxylase antibody was positive. IgG, IgG4, antinuclear antibody spectrum, and vasculitis group were found to be negative. Pancreatic magnetic resonance imaging (MRI) and MR cholangiopancreatography were normal. He was treated with Lantus and NovoLog. Human leukocyte antigen (HLA) haplotype was DQB1*04:01-DRB1*04:05.

A 23-year-old male patient suffered from left upper abdominal pain for 3 days after overeating. Abdominal CT revealed pancreatic swelling. The laboratory data obtained in local hospital were as follows: amylase, 280 U/L; lipase, 771 U/L; and FBG, 4.6 mmol/L. The patient was diagnosed with AP and given treatment. On December 13 and 14, fingertip blood glucose fluctuated between 3.6 and 6.0 mmol/L. On December 15, it was 8.1 mmol/L at 11:00, 8.6 mmol/L at 16:00, and 22.0 mmol/L at 20:00. Hence, insulin treatment was started. The patient was admitted to our hospital after 4 days. BMI was 22.46 kg/m^2; HbA1c was 7.9%; islet autoantibodies were negative; FBG was 15.06 mmol/L; fasting and postprandial 2-h C-peptide were 0.07 and 0.11 ng/mL, respectively. Pancreatic and liver MRI were normal. HLA haplotype was DRB1*07:01-DQB1*02:02.

These two cases of FT1DM following AP are the first to be reported in China. They had elevated pancreatic enzymes, abdominal pain, and pancreatic edema, and were diagnosed with mild AP. Pancreatic exocrine functions were not measured. Hyperglycemia occurred about 6 days after AP. Fasting and postprandial 2-h C-peptide were significantly lower than normal. Severe AP can cause hyperglycemia, but rarely damage the entire islet. Hence, these patients were not considered to have pancreatogenic diabetes. According to the diagnostic criteria of FT1DM, case 1 could be definitely diagnosed. In case 2, insulin was timely given when hyperglycemia appeared, which prevented ketonuria and ketoacidosis. In view of the changes in blood glucose, HbA1c and C-peptide, case 2 was diagnosed with FT1DM.

The etiology and pathogenesis of FT1DM are not well understood, but may be related to genetic susceptibility, viral infection, autoimmunity, and pregnancy. Besides our two cases of FT1DM after AP, there were several similar cases reported in Japan. Thus, we suspect that AP is a pathogenic factor of FT1DM.

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With accumulating studies on inflammatory response during AP and the pathogenesis of FT1DM, we propose a new hypothesis about the relationship between AP and FT1DM. Pancreatic injury led to complete β-cell destruction in a patient with FT1DM and carbamazepine hypersensitivity syndrome. Hirota *et al*[2] have reported that four of nine cases with FT1DM were diagnosed with AP and hyperinsulinemic hypoglycemia appeared 1 to 3 days after initial symptoms. Later, Miyagahara *et al*[3] published a similar report and no islet was found in the pancreas biopsy. Therefore, AP caused rapid destruction of islets, leading to hyperinsulinemia-related hypoglycemia, followed by hyperglycemia. These reports led us to re-think the mechanism of AP-induced β-cell destruction.

The AP involves innate and adaptive immune responses. In a study on 117 patients with AP, the concentrations of interferon (IFN)-γ and tumor necrosis factor (TNF)-α were significantly higher than those in the control group. In AP animal models induced by bombesin, acinar cells secreted C-X-C motif chemokine 10 (CXCL10) and C-C Motif Chemokine Ligand 2 after being stimulated for 60 min. The interleukin (IL)-1 and TNF-α signaling pathways may be involved in FT1DM.[4] In patients with FT1DM caused by enterovirus infection, IFN-γ and CXCL10 are co-expressed in β-cells, and CXCL10 secreted from β-cells activates and attracts immune-active T cells and macrophages to islets, releasing inflammatory cytokines, such as IFN-γ to islets. IFN-γ can both damage β-cells and accelerate the production of CXCL10 from the remaining β-cells, further activating cell-mediated autoimmune response until β-cells are completely destroyed. Thus, the destruction of β-cells in FT1DM is the result of a vicious cycle.[5] There is a cross-immune mechanism between AP and FT1DM, hence we speculate that immune response during AP may induce the immune damage of islets, causing rapid destruction of β-cells, which develops into FT1DM [Figure 1].

Genetic susceptibility to FT1DM is related to HLA-DRB1*04:05-DQB1*04:01. In all known cases of FT1DM after AP, HLA haplotypes were different. More data are needed to identify the FT1DM susceptibility gene after AP, which will help early diagnosis and treatment to avoid serious complications. To further understand the immune course of FT1DM caused by AP, animal experiments are needed.

In conclusion, we speculate that on the basis of genetic predisposition, the immune response during AP results in immune damage and severe destruction of β-cells. Therefore, AP may be a pathogenic factor of FT1DM.

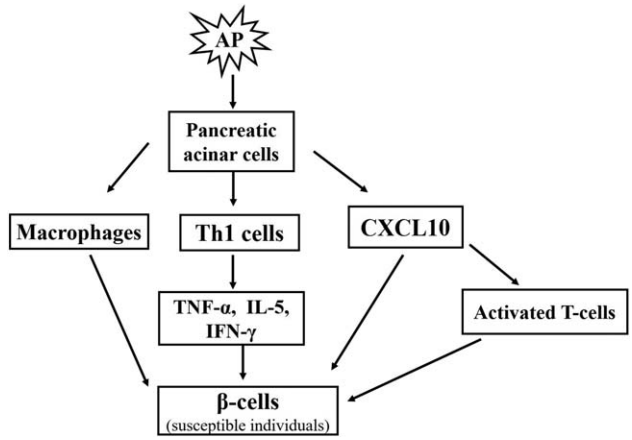

Figure 1: Tentative hypothesis of β-cell destruction in acute pancreatitis-induced fulminant type 1 diabetes. AP: Acute pancreatitis; CXCL10: C-X-C motif chemokine 10; IFN: interferon; IL: Interleukin; TNF: Tumor necrosis factor.

Conflicts of interest

None.

References

1. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies, Osaka IDDM Study Group. N Engl J Med 2000;342:301–307. doi: 10.1056/NEJM200002033420501.
2. Hirota H, Tsutsumi C, Kimata H, Watanabe D, Imbe H, Takamoto S, *et al*. A case of fulminant type 1 diabetes patient accompanied by hyperinsulinemic hypoglycemia prior to clinical diagnosis of diabetes. J Japan Diab Soc 2016;59:210–217. doi: 10.11213/tonyobyo.59.210.
3. Miyagahara T, Fujimori N, Oono T, Okamoto M, Sato N, Sonoda N, *et al*. Fulminant type 1 diabetes mellitus following acute pancreatitis and hypoglycemia with sequential imaging of the pancreas using computed tomography: a case report. Nihon Shokakibyo Gakkai Zasshi 2019;116:161–167.
4. Wang Z, Zheng C, Tan YY, Li YJ, Yang L, Huang G, *et al*. Gene expression changes in patients with fulminant type 1 diabetes. Chin Med J 2011;123:3613–3617. doi: 10.3760/cma.j.issn.0366-6999.2011.22.003.
5. Tanaka S, Nishida Y, Aida K, Maruyama T, Shimada A, Suzuki M, *et al*. Enterovirus infection, CXC chemokine ligand 10 (CXCL10), and CXCR3 circuit: a mechanism of accelerated beta-cell failure in fulminant type 1 diabetes. Diabetes 2009;58:2285–2291. doi: 10.2337/db09-0091.

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