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**Unmet needs in biomarkers for autoimmune pancreatitis diagnosis**

Wang BC *et al*. New serological biomarkers for AIP diagnosis

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**Abstract**

Autoimmune pancreatitis (AIP) is a rare chronic autoimmune disorder. The diagnosis of AIP mainly depends on histopathology, imaging and response to treatment. Serum immunoglobulin 4 (IgG4) is used only as collateral evidence in diagnostic criteria for AIP because of its moderate sensitivity. Serum IgG4 levels are normal in 15%-37% of type 1 AIP and most of type 2 AIP patients. In these patients, the indeterminate imaging and histopathology may lead to the difficulty in definitive diagnosis of AIP. Therefore, discovery of new biomarkers is important for AIP diagnosis. Here, we provide some views on the progression and challenges in identifying novel serological biomarkers in AIP diagnosis.

**Key Words:** Autoimmune pancreatitis; Immunoglobulin G4; Biomarker, Cytokine; Autoantibody

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**Core Tip:** Serum immunoglobulin 4 is currently the only biomarker and highly specific but moderately sensitive for diagnosis of autoimmune pancreatitis (AIP). Some cytokines and antibodies have been shown potential in AIP diagnosis.

**INTRODUCTION**

Autoimmune pancreatitis (AIP) is referred to as non-alcoholic destructive pancreatitis and sclerosing pancreatitis. It is a chronic pancreatitis characterized by an autoimmune inflammatory process with pancreatic swell or focal mass that responds to corticosteroid treatment. AIP was first described in 1995[1]. In 2001, elevated serum immunoglobulin 4 (IgG4) level was found as an important indicator in patients with sclerosing pancreatitis[2]. Then the International Consensus Diagnostic Criteria (ICDC) classified AIP into type 1 and type 2 in 2011[3], according to five features: Image of pancreatic parenchyma and duct, serology, other organ involvement, pancreatic histology, and response to steroid therapy. According to ICDC, more than 90% of cases are type 1 AIP, characterized by high serum IgG4 level, and IgG4-positive plasma cell infiltration in the pancreas. So, it is also known as lymphoplasmacytic sclerosing pancreatitis. Most of type 1 AIP present with the clinical signs of the systemic IgG4-related disease. Type 2 AIP is a pancreatic-specific disease, without serum IgG4 elevation, characterized by pancreatic ductal epithelium neutrophilic infiltration. So, it is also labeled as idiopathic duct-centric pancreatitis. Some of AIP patients could be diagnosed definitively, but in other patients, the clinical features including image, histopathology, IgG4 level may be not typical. Therefore, the diagnosis of AIP could not be established in all the patients using the current biomarkers[4]. Powerful new biomarkers may improve the diagnosis of AIP. Some studies have shown that some cytokines and autoantibodies could be used alone or as a panel to help diagnosing AIP.

**Diagnostic ROLE OF IG4 IN AIP**

Many studies have shown that serum IgG4 level was elevated in AIP patients. This provides the solid data for using elevation of serum IgG4 as diagnostic biomarker for AIP in clinical practice. However, the sensitivity and specificity of IgG4 varied among these studies, which may be attributed to discrepant patient population, diagnostic criteria, race/region, and year of study before and after 2011. Among these factors, cut-off point has been studied by several researchers. In a meta-analysis of 13 studies including 594 patients, the pooled sensitivity of serum IgG4 for the diagnosis of AIP was 0.72 [95% confidence interval (CI): 0.68-0.75] when cut-off value was set at 130 to 140 mg/dL, specificity was 0.93 (95%CI: 0.92-0.95), diagnostic odds ratios was 51.37 (95%CI: 23.20-113.74), and area under the curve was 0.91 (95%CI: 0.87-0.95). When cut-off value was set at two folds of upper limit of normal level (260-280 mg/dL), the specificity increased to 0.98, while the sensitivity decreased to 43%[5]. In addition, elevated serum IgG4 level at the time of glucocorticoid cessation was an independent predictor of AIP relapse (hazard ratio: 4.511)[6]. In type 2 AIP, serum IgG4 levels are usually normal[7]. These suggested that IgG4 has poor correlation with type 2 AIP. Based on these data, serum IgG4 is a useful biomarker for diagnosing tyoe 1 AIP, but its sensitivity is not high.

In the recent issue of the *World Journal of Gastroenterology*, Zhou *et al*[8] showed that elevated serum IgG4 and IgA levels were associated with a more active immune system and higher relapse rates in AIP. Their study suggested that IgG4 could be combined with other markers to evaluate the disease activity and treatment efficacy, and monitor relapse. Even if the specificity of serum IgG4 for AIP is high, slight increase of serum IgG4 could be observed in other diseases, such as pancreatic cancer, cholangiocarcinoma, primary sclerosing cholangitis[9]. Therefore, more biomarkers are needed for AIP diagnosis. The new biomarkers may be used alone or together with IgG4.

**NEW SEROLOGICAL BIOMARKERS IN AIP**

Recently, great progresses have been made in understanding the abnormality of immune networks. Different types of immune cells, including dendritic cells, monocytes, T cell subgroups, B cells, were found to be involved in the pathogenesis of AIP by producing cytokines. Serum κ, λ free light chain, interleukin (IL)-5, IL-6, IL-33, soluble IL-2 receptor, interferon (IFN)-α[10-15] were significantly changed in patients with AIP. It is worth mentioning that the serum concentrations of IFN-α and IL-33 produced by dendritic cells significantly increased in the patients with active AIP, and decreased after induction of remission. The specificities of serum levels of IFN-α and IL-33 were 91.7% and 83.3%, respectively, and the sensitivity of IFN-α and IL-33 were 85.7% each. Serum levels of IFN-α and IL-33 correlated better with disease activity than that of IgG4. This study suggests that the serum concentrations of IFN-α and IL-33 have the potential to be the biomarkers for type 1 AIP diagnosis[15]. But confirmation from more studies and patients are needed.

Multiple autoantibodies secreted by plasma cells have been found in the sera of patients with AIP, such as anti-carbonic anhydrases I (anti-CA I), anti-CA II[16], anti-lactoferrin[17], antibodies against plasminogen-binding protein[18]. These studies have shown that AIP is an autoimmune-mediated disease. But the role of these autoantibodies in the diagnosis of AIP is still undetermined. Recently, three newly identified antibodies, anti-amylase α[19], anti-laminin 511[20], and anti-prohibition[21] have shown moderate to high accuracy for AIP diagnosis in some small sample studies. Annexin A11[22] and galectin-3[23] antibodies were identified specifically in the sera of patients with AIP screened by mass spectrometry.

All these findings about autoantibodies provide the possibility for identifying the new diagnostic biomarkers for AIP. However, more studies including more patients are required to verify the sensitivity and specificity of autoantibodies as useful biomarkers for AIP.

**CONCLUSION**

Although there are accepted diagnostic criteria for AIP, many patients cannot be diagnosed definitively because their clinical features are not typical. Histopathology is an important examination for diagnosis. Serum IgG4 is the only biomarker for AIP diagnosis in clinical practice, but it is only used collaterally because of its moderate sensitivity. Therefore, discovery of new biomarkers for AIP diagnosis is highly needed. The published literatures have shown that some cytokines and autoantibodies have the potential to be developed as diagnostic biomarker for AIP.

Since AIP is a rare disease, the number of cases in published papers is limited and almost all the studies were single-center retrospective study, a collaborative group can be set up in the future to collect more AIP cases for further research. Firstly, IgG4 may be developed combined with one more biomarker or as a panel, together with imaging, histopathology and therapy response, to classify AIP more precisely. Secondly, efforts should be made to find new autoantibodies with higher sensitivity and specificity for better diagnosing and monitoring AIP.

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