Autoimmune Pancreatitis: Serology

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Introduction

Various serum markers in autoimmune pancreatitis are associated with diagnosis, disease activity and pathogenesis. This report presents results of various serum markers according to these issues.

The clinical features of autoimmune pancreatitis are summarized as:
1. Clinical findings similar to those of pancreatic cancer.
2. Preponderance in elderly males.
3. Obstructive jaundice.
4. High serum IgG4 concentration.
5. Positive for autoantibodies.
6. Association with HLA DRB1*0405-DQB1*0401 haplotype.
7. Pancreatic swelling and irregular narrowing of the main pancreatic duct.
8. Lymphoplasmacytic infiltration and fibrosis with abundant IgG4-bearing plasma cell infiltration.
11. Extra-pancreatic involvements, such as sialoadenitis, hypothyroidism, hilar lymphadenopathy, sclerosing cholangitis, tubulointerstitial nephritis and retroperitoneal fibrosis.

Among them, the most important issue is that autoimmune pancreatitis shows similar clinical findings to pancreatic cancer and therefore needs to be differentiated from pancreatic cancer. Other outstanding characteristics are high serum IgG4 concentrations. We found that patients with autoimmune pancreatitis showed a serum IgG4 concentration over 10 times higher compared with normal subjects, and found that 90% of the patients with autoimmune pancreatitis had high serum IgG4 concentrations, but patients with other conditions had no serum elevation. Accordingly, IgG4 is useful marker for the diagnosis of this disease.

Serum Markers Associated with the Diagnosis

The utility of IgG4 for the diagnosis of autoimmune pancreatitis has been evaluated worldwide. Sensitivity is variable from 73% reported by Professor Kim in Korea to 92% reported by us, Shinshu-university, Japan. The difference in sensitivity is partly due to the differences of diagnostic criteria applied by individual countries. As regard to Japanese experiences, nationwide survey by Dr. Nishimori and professor Otsuki and the Kansai Med University study by professor Okazaki showed sensitivity of 80% and 73%, which was lower than that of ours. The exact reason for this discrepancy is unclear. The specificity of IgG4 calculated from a pancreatic cancer was high for each report except for 90% reported by professor
Chari in USA. In their report, 10% of patients with pancreatic cancer showed high serum IgG4 concentration, but these values did not exceed 280 mg/dl. Sensitivity of IgG for the diagnosis of autoimmune pancreatitis was also valuable from 54% reported by Professor Kim in Korea to 75% reported by Professor Okazaki, Kansai Med University, Japan, and lower than those of IgG4. Specificity was comparable to that of IgG4 for each report except for ours, 75%. Sensitivities of various autoantibodies evaluated by Japanese nationwide survey, by Sinshu university and by Kansai Med University were compared. For disease non-specific autoantibodies, sensitivities for antinuclear antibody (ANA) and rheumatoid factor (RF) were comparable between two studies, 63%, 66% and 62% for ANA and 28%, 20% and 28% for RF. However, disease specific autoantibodies, SS-A and SS-B for Sjögren’s syndrome and anti-mitochondrial antibody for PBC, were scarcely found in sera of AIP patients.

The summary for serum markers associated with the diagnosis of AIP is following:

1. IgG4 was sensitive and specific marker, but not pathognomonic.
2. Diagnostic parameters for IgG4 were affected by diagnostic criteria and the characteristics of clinics to some extents.
4. Sensitivity for IgG was variable among different diagnostic criteria.
5. Non-specific autoantibodies, ANA and RF showed sensitivities of 60% and 20%, respectively.
6. Disease-specific autoantibodies, SS-A, AA-B (Sjoegren’s syndrome) and AMA (PBC) showed negative results for AIP.

Serum Markers Associated with the Disease Activity: Recurrence and Extra-pancreatic Involvements

The clinical course of 69 years-old woman presenting with 2 recurrences showed serum elevations of IgG4 and immune complex several months before overt appearance of recurrence, indicating that IgG4 and immune complex predicted the recurrence, or represents the disease activity sensitively. We investigated the outcome of long-term follow up of 51 patients with autoimmune pancreatitis. During long-term follow up, 21 patients (41%) showed recurrences that needed corticosteroid again. Serum immune complex levels at onset were significantly higher in recurrence group than non-recurrence group. Serum IgG4 and Soluble IL2 receptor levels showed no significant difference between two groups. ROC analysis of immune complex for recurrence showed optimal cut-off value of 10 μg/dl. If immune complex levels at onset is over 10 μg/dl, probability for recurrence is 60%.

Autoimmune pancreatitis is complicated with various extra-pancreatic involvements. Serum IgG4 level were well correlated with the number of extra-pancreatic involvements, indicating that extra-pancreatic involvements might represent active state of this disease. Among 5 extra-pancreatic involvements, lacrimal and salivary gland lesions and hilar lymph adenopathy are significantly associated with high serum levels of IgG4 and immune complex, indicating that these two lesions represents active state of this disease.

The summary for serum markers associated with the disease activity of AIP, with respect to recurrence and extra-pancreatic involvements is following:

1. Recurrence was found in over 40% of AIP patients.
2. Immune complex values at onset were significantly higher in recurrence group than non-recurrence group.
3. Immune complex value at onset over 10 (g/ml predicted the recurrence.
4. Patients with multiple extra-pancreatic involvements had higher serum IgG4 concentration.
5. Patients with lachrymal and salivary gland lesions or hilar lymph-adenopathy were found to have significantly higher IgG4 and IC levels than those without, representing the active state of this disease.

**Serum Markers Associated with the Pathogenesis of Autoimmune Pancreatitis**

Decreased serum levels of C3 and C4 were found in 35% and 37% of AIP patients at onset respectively, indicating that complement activation system is operating in the pathogenesis of this disease. Elevated serum levels of immune complex determined by C1q assay were significantly related to increased serum levels of IgG1 and decreased levels of C4, as well as to a tendency toward decreased levels of C3. Complements activation system consists of classical pathway, mannose-binding lectin (MBL) pathway and alternative pathway. Decreased level of C4 excluded the contribution of alternative pathway. We confirmed that serum MBL levels were not decreased in AIP compared with chronic pancreatitis or healthy subjects. And there were no significant differences of serum MBL value between before and after corticosteroid therapy. These results indicated that MBL pathway is not operating in the pathogenesis of AIP. Accordingly, classical pathway may be operating in the pathogenesis of AIP, and serum C3 and C4 levels may represent tissue injury of this disease.

The summary for serum markers associated with the pathogenesis is followings:
1. C3 and C4 values at onset decreased in 35% and 37% of AIP patients.
2. Immune complex values were related to disease activity.
3. Elevated serum levels of immune complex was significantly related to increased serum levels of IgG1 and decreased levels of C4, as well as to a tendency toward decreased levels of C3.
4. Mannose-binding lectin pathway is not operating in AIP.
5. Classical pathway is possibly operating in AIP and serum C3 and C3 levels may represent tissue injury of this disease.

**REFERENCES**