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Therapeutic strategy for autoimmune pancreatitis

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ABSTRACT

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune etiology. Before therapy for AIP is begun, accurate diagnosis of AIP is necessary. It is important to distinguish AIP from pancreatic cancer. Since there is currently no diagnostic serological marker for AIP, AIP should be diagnosed on the basis of a combination of abnormalities unique to AIP. The Japanese "Diagnostic Criteria for Autoimmune Pancreatitis 2006" require the characteristic imaging findings of AIP and that at least one of the laboratory criteria or histopathological criteria have to be present. Unlike in patients with usual chronic pancreatitis, corticosteroid therapy is frequently effective in resolving the morphological findings and the symptoms of AIP patients. Therefore, administration of oral steroid therapy has become standard therapy for AIP. Indications for steroid therapy for AIP are thought to include obstructive jaundice due to stenosis of the bile duct, associated extrapancreatic sclerosing lesions, and diabetes mellitus coincidental with AIP. Oral prednisolone is usually started at 30 mg/day and tapered by 5 mg every 1- 2 weeks. Serological and imaging tests are followed periodically after commencement of steroid therapy. Patients in whom complete radiological improvement is documented can stop their medication. To prevent relapses, continued maintenance therapy with prednisolone 2.5 - 5 mg/day is sometimes required. Patients who relapse should be re-treated with high-dose steroid therapy. A poor response to steroid therapy should raise the possibility of pancreatic cancer and the need for further examination, including laparotomy.

Key words: autoimmune pancreatitis, diagnostic criteria, steroid therapy, IgG4

INTRODUCTION

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune etiology. Since Yoshida et al. [1] proposed AIP as a diagnostic entity in 1995, many cases of AIP have been reported in Western countries, as well as in Japan. During the past 10 years, a number of new clinicopathological aspects of AIP have been clarified, and AIP is now considered to be a discrete entity worldwide.

Clinically, AIP is characterized by: a preponderance of elderly males, jaundice as a frequent initial symptom, an association with diabetes mellitus (DM) and various extrapancreatic lesions. Serologically, AIP patients have elevated serum IgG or IgG4 levels. On radiological examination, enlargement of the pancreas and irregular narrowing of the main pancreatic duct are frequently seen. On histopathology, AIP patients have dense infiltration of lymphocytes and IgG4-positive plasma cells, as well as fibrosis in the pancreas and various organs [1-4].

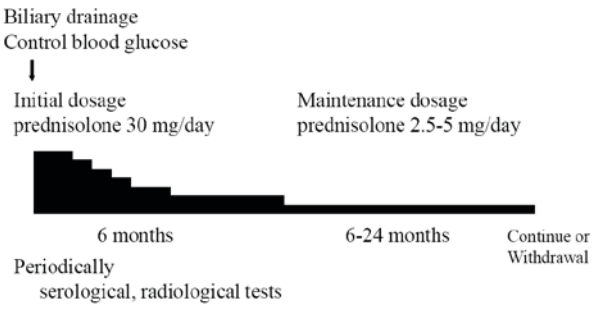
Unlike in patients with usual chronic pancreatitis, corticosteroid therapy is frequently effective in resolving the morphological findings and the symptoms in AIP patients; thus, many AIP patients are treated with corticosteroids [1-7]. Here we describe the therapeutic strategy for AIP.

REVIEW

Accurate Diagnosis of AIP and Diagnostic Criteria

Before starting therapy for AIP, accurate diagnosis of AIP is necessary. It is important to distinguish AIP from pancreatic cancer [8]. In North America, about 2.5% of pancreatoduodenectomies are done in AIP cases that have

Figure 1. **Schematic illustration of steroid therapy for autoimmune pancreatitis.**



been incorrectly diagnosed as pancreatic cancer [9]; between 21% and 23% of pancreatoduodenectomies performed for benign conditions are done for AIP [9,10]. Since there is currently no diagnostic serological marker for AIP. AIP should be diagnosed on the basis of the presence of a combination of abnormalities unique to AIP.

At present, there are 3 major sets of diagnostic criteria for AIP in Japan [11], Korea [12], and the USA [13]. In 2002, the Japan Pancreas Society established the "Diagnostic Criteria for Autoimmune Pancreatitis" [14], which were revised in 2006 [11]. The revised Japanese criteria [11] require that the characteristic imaging findings of AIP to be present, and that at least one of the laboratory criteria or histopathological criteria be be present (*Tab. 1*). The Japanese criteria are based on the minimum consensus features of AIP in order to minimize the risk of misdiagnosing malignancy. The Korean criteria [12], in addition to the Japanese criteria, include the response to steroid therapy and the presence of extrapancreatic lesions. Using the Mayo Clinic criteria [13], AIP can be diagnosed solely on the basis of diagnostic pancreatic histology, by the presence of both the imaging criteria and serum IgG4 level elevation, or by response to steroid therapy with elevated serum IgG4 levels and/or other organ involvement. When response to steroid therapy is added to the criteria, the diagnostic sensitivity is increased. Korean investigators recommend a diagnostic trial of steroid therapy in cases that do not fulfill the Japanese criteria [12]. Since relief of narrowing of the pancreatic duct with steroid administration can be seen as early as 2 weeks after steroid therapy in AIP cases and dose not occur in pancreatic cancer cases, the Korean investigators advocate a short trial of steroid therapy to differentiate AIP from pancreatic cancer [12]. We also agree that a trial of steroid therapy can be used to assist in making the diagnosis when it is used appropriately. However, since generalist physicians who are not pancreatologists use the criteria, it is possible that facile use of steroid trials may result in delaying pancreatic cancer surgery, which could lead to the cancer progression in some cases.

Therapy for AIP

Although resolution of the inflammatory process may occur spontaneously without steroid therapy in some AIP patients, oral steroid therapy has become the standard therapy for AIP, as the fibroinflammatory process in AIP responds well to such a therapy. However, the effects of steroid therapy on the natural history of AIP are not known.

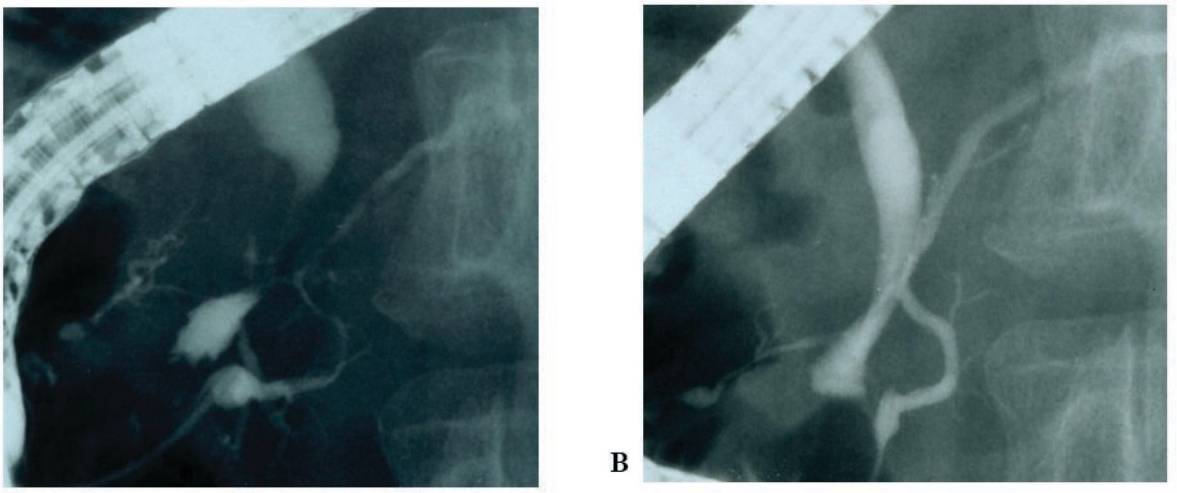
The major clinical symptom of AIP is obstructive jaundice due to stenosis of the bile duct associated with enlargement of the pancreas. Jaundice is managed initially by a biliary stent, and stent removal is possible within 4 - 6 weeks after starting steroid therapy in the majority of patients. Steroid therapy is also effective for the clinical manifestations of the extrapancreatic lesions of AIP, such as retroperitoneal fibrosis, interstitial pneumonia, and tubulointerstitial nephritis. Since DM seen in the acute presentation sometimes improves with steroid therapy, DM coincidental with AIP might be an indication for steroid therapy [1,5-7].

Before steroid therapy is started, endoscopic or percutaneous transhepatic biliary drainage must be done in cases with obstructive jaundice, and glucose levels must be controlled in cases with DM. There is no consensus on the regimen of steroid therapy, including the steroid dose or duration of therapy. Oral prednisolone is usually started at 30 - 40 mg/day for 2 - 4 weeks, and it is tapered by 5 mg every 1 - 2 weeks. Recently, Kamisawa et al. [15] recommended an initial dose of 30 mg/day, as there was no relationship between the degree of morphological improvement and the initial dose (30 mg/day and 40 mg/day). Serological and imaging tests are followed periodically after the start of steroid therapy (*Fig. 1*). Pancreatic size usually normalizes within a few weeks, and stenosis of the bile duct resolves over 1 - 2 months (*Fig. 2*). Pancreatic exocrine and endocrine functions improve after steroid therapy in half of the patients. Patients in whom complete radiological improvement is documented can stop their medication, though continued maintenance therapy with prednisolone 2.5 - 5 mg/day is sometimes required to prevent

Table 1. **Clinical diagnostic criteria for AIP (2006) [11].**

(Proposed by the Research Committee of Intractable Diseases of the Pancreas supported by the Japanese Ministry of Health, Labour, and Welfare, and Japan Pancreas Society)
1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). 2. High serum γ-globulin, IgG or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor. 3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.
Diagnosis of AIP is established when criterion 1, together with criterion 2 and/or 3, are fulfilled. However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers.

Figure 2. **ERCP (endoscopic retrograde cholangiopancreatography) of a patient with autoimmune pancreatitis before (A) and after (B) steroid therapy. Stenosis of the pancreatic duct and bile duct markedly improved.**



relapses (*Fig. 1*). However, since AIP patients are typically elderly and are at high risk of developing steroid-related complications, such as osteoporosis, diabetes and cataract, one should try to stop the medication in cases with good improvement.

Some AIP patients relapse during maintenance therapy or after stopping steroid therapy. The reported recurrence rate of AIP ranges from 6% - 26% [16,17]. AIP patients who relapse should be re-treated with high-dose steroid therapy. A poor response to steroid therapy should raise the possibility of pancreatic cancer and the need for further examination, including laparotomy.

Prognosis

The long-term prognosis of AIP is not well known. Since the pancreatic exocrine and endocrine functions, as well as the morphological findings, are reversible after steroid therapy, the prognosis of AIP seems better than that for alcoholic chronic pancreatitis, which is usually followed by exocrine and endocrine pancreatic insufficiency with disease progression. However, some patients with recurrent attacks of AIP develop pancreatic stones [16,17].

CONCLUSIONS

Since the fibroinflammatory process of AIP responds well to steroid therapy, AIP should be considered in the differential diagnosis to avoid unnecessary surgery. Administration of oral steroid has become standard therapy for AIP. The indications for steroid therapy for AIP are obstructive jaundice due to stenosis of the bile duct, associated extrapancreatic sclerosing lesions, and diabetes mellitus coincidental with AIP. To prevent relapses, continued maintenance therapy with low dose prednisolone is sometimes required.

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