Table 5 Pancreatic function during the course of the study

	Non-stone-forming patients[a]	Stone-forming patients[a]	*P* value[b]	Intraductal stone-forming patients ($n = 9$)[a]	*P* value[c]
Amylase					
At diagnosis	86 (22–478)	94 (17–431)	0.678	102 (62–323)	0.490
5 years later	85 (45–160)	80 (42–136)	0.497	92 (46–134)	0.569
8 years later	83 (59–130)	75 (37–128)	0.230	75 (48–98)	0.313
HbA1c					
At diagnosis	5.7 (4.1–11.2)	5.7 (4.5–9.5)	0.536	6.0 (4.5–9.5)	0.549
5 years later	5.8 (5.1–10.4)	6.0 (4.6–10.2)	0.366	6.0 (5.4–10.2)	0.289
8 years later	5.8 (5.1–9.8)	6.0 (5.1–10.3)	0.504	6.8 (5.1–10.3)	0.293

[a] Values are expressed as median (range)

[b] Non-stone-forming patients versus stone-forming patients

[c] Non-stone-forming patients versus intraductal stone-forming patients

may present symptoms resembling those of ordinary chronic pancreatitis. Indeed, elevation of serum IgG4 was found in 7% of ordinary chronic pancreatitis in one study, which may have in fact represented chronic stage AIP [6]. Similarly to alcoholic pancreatitis in which recurrent attacks facilitate pancreatic stone formation, stone formation in AIP is preferentially seen in relapsed cases [5].

For de novo stone cases, the median and range of the study period between diagnosis of AIP and stone formation were 57 and 8–138 months, respectively. However, since we had no prospective protocol for CT testing, the duration of pancreatic stone formation may have been affected by the timing of CT tests.

Risk factors for pancreatic stone formation

Pancreatic stone formation implies the progression of pancreatic tissue damage. Accordingly, identification of the direct risk factors of stone formation is expected to disclose the mechanism of tissue injury in order to develop treatments that suppress this progressive damage. We postulated two mechanisms for pancreatic stone formation in AIP in this study, namely severe tissue injury attributed to the specific inflammatory process of AIP and pancreatic juice stasis due to pancreatic duct narrowing, and sought to clarify the risk factors responsible for stone development.

Correlation between pancreatic stone formation and clinical and laboratory features associated with AIP-specific inflammation

There were no significant differences in observation period, age, gender, alcohol consumption, or corticosteroid treatment between the stone-forming group and the non-stone-forming group, nor were there any notable changes in serum amylase concentration at diagnosis. Therefore, acute attacks seemed not to contribute to stone formation.

In a highly active stage of AIP, serum concentrations of various markers vary in parallel with disease activity; serum IgG, IgG4, sIL2-R, and CIC increase at relapse and decrease after corticosteroid therapy, while serum C3 and C4 show reciprocal changes [19]. To determine whether the specific inflammatory process of AIP was associated with pancreatic stone formation, we investigated the correlation between stone formation and published activity markers, but found no significant differences between the two groups. However, although we could not confirm a correlation between the intensity of the inflammatory process in AIP and pancreatic stone formation, we could not completely exclude a relationship since we did not check the values of these markers throughout the patients' clinical course. In addition, serum IgG4 concentration remained slightly elevated in 60% of patients in a clinically inactive state after corticosteroid therapy, which suggested that active inflammatory processes may have persisted even when the patients were in apparent remission [20]. On the other hand, it was reported that the histology of characteristic inflammatory changes in AIP normalized after corticosteroid therapy [21, 22], and so it appears unlikely that the inflammatory process in AIP progresses to an advanced stage of severe necrosis and fibrosis like the one found in ordinary chronic pancreatitis, which also induces pancreatic stone formation.

Correlations between pancreatic stone formation and pancreatic swelling and pancreatic duct narrowing

Univariate analysis disclosed that the factors of pancreatic head swelling and narrowing of both Wirsung's and Santorini's ducts were significantly associated with pancreatic stone formation, and multivariate analysis confirmed the latter as a significant independent risk factor for pancreatic stone formation in AIP. Severe inflammation in the pancreatic head region results in swelling and Wirsung and Santorini duct narrowing, and therefore these two findings may be considered to represent the same pathophysiological feature. Diffuse irregular narrowing is a typical duct finding in AIP [4], but some cases showed duct stenosis in an area other than the head region [16]. With progression of the disease, restricted duct stenosis may

progress to diffuse lesions [15, 16]. Residual pancreatic head swelling and residual narrowing of both Wirsung's and Santorini's ducts after corticosteroid therapy were also more frequently found in stone-forming patients compared to non-stone-forming patients in our cohort, strengthening the notion that Wirsung and Santorini duct narrowing in the pancreatic head region caused pancreatic juice stasis in the pancreas and eventual stone formation. In the stone-forming group, 4 patients showed duct narrowing in the body and tail region, but 2 of them showed parenchymal pancreatic stones in the downstream pancreatic region. Accordingly, some stone formation may be due to factors other than pancreatic juice stasis.

There is a lack of consensus as to what causative factors lead to chronic pancreatitis. Hypotheses include the oxidative stress theory, toxic-metabolic theory, stone and duct obstruction theory, necrosis-fibrosis theory, primary duct hypothesis, and sentinel acute pancreatitis event hypothesis [23, 24]. With respect to pancreatic stone formation, the stone and duct obstruction theory postulates that alcohol modulates exocrine function to increase the lithogenicity of pancreatic juice, leading to the formation of protein plugs and stones in the duct. This concept presupposes that alcohol must primarily modulate the properties of pancreatic fluid to promote stone formation [25]. On the other hand, partial outflow obstruction of the pancreatic duct was also proved to induce stone formation. This condition was found in cases with Vater ampulla carcinoma and pancreatic mucin-producing adenocarcinoma [now recognized as intraductal papillary-mucinous carcinoma (IPMC)] [26, 27], and was used in experimental dog models to demonstrate that incomplete ligation of the main pancreatic duct resulted in the formation of calculi [13, 14]. The present study showed that many AIP patients with stone formation had Wirsung and Santorini duct narrowing, which supported the condition of incomplete ligation of the main pancreatic duct seen in the dog model.

Correlation between pancreatic stone formation and pancreatic function during the course of the study

In comparisons among non-stone-forming patients, stone-forming patients, and intraductal stone-forming patients at diagnosis and 5 and 8 years afterwards, both serum amylase and HbA1c values tended to be at abnormal levels in intraductal stone-forming patients compared with non-stone-forming patients, but not significantly. We believe that further observation may disclose a significant deterioration of pancreatic function in stone-forming patients despite the notion that stone-forming AIP might have a different pathophysiology from that of ordinary chronic pancreatitis.

Prevention and management of pancreatic stone formation

Our findings imply that prophylactic measures for reduction of pancreatic head swelling and duct narrowing would prevent increased or de novo stone formation. For patients presenting with narrowing of both Wirsung's and Santorini's ducts, intensive therapy that includes corticosteroids may be needed from an early stage, even when clinical symptoms, such as obstructive jaundice or abdominal pain, have not yet manifested. Furthermore, it is advisable to check for residual changes in pancreatic head swelling and Wirsung and Santorini duct narrowing after corticosteroid therapy.

Limitation of the present study

At our institute, CT has been done by MDCT since 2003, which results in improved images. Accordingly, pancreatic stone detection was likely biased by CT imaging as scans were obtained using different CT protocols during the course of this study.

In conclusion, the main risk factor for pancreatic stone formation in AIP was narrowing of both Wirsung's and Santorini's ducts at diagnosis, which most presumably led to pancreatic juice stasis in the pancreas and stone development.

Acknowledgments This work was supported partially by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan, and in part by Grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (23591012). We thank Trevor Ralph for his English editorial assistance.

Conflict of interest None of the authors have any conflicts of interest associated with this study.

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Autoimmune Pancreatitis and Diagnostic Criteria

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Abstract: Autoimmune pancreatitis is a unique form of chronic pancreatitis with autoimmune phenomena, including hypergammaglobulinemia, lymphoplasmacytic infiltration, and responsiveness to corticosteroid therapy. Autoimmune pancreatitis tends to affect elderly males and it presents with pancreatic swelling and irregular narrowing of the pancreatic duct. The symptoms of autoimmune pancreatitis mimic the clinical features of pancreatic cancer; thus, it is important to differentiate between the two conditions. Autoimmune pancreatitis is also characterized by high serum IgG4 concentrations and infiltration of IgG4-bearing plasma cells into the pancreatic tissue. Although these are considered serological and histological hallmarks of autoimmune pancreatitis, the role of IgG4 in the pathogenesis of the disease remains unclear. Furthermore, many cases are complicated by extra-pancreatic manifestations with pathological findings similar to those observed in the pancreatic lesions; these extra-pancreatic manifestations tend to respond favorably to corticosteroid therapy. Autoimmune pancreatitis is now regarded as a member of a new class of IgG4-related disease. Due to inconsistencies in the diagnostic criteria for autoimmune pancreatitis, there is a need for an international consensus on this disease.

Keywords: Autoimmune pancreatitis, IgG4, IgG4-related disease.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis [1] characterized by high serum IgG4 concentrations [2] and infiltration of large numbers of IgG4 bearing plasma cells into pancreatic tissue [3]. AIP is associated with hypergammaglobulinemia, histological evidence of lymphoplasmacytic inflammation (i.e., lymphoplasmacytic sclerosing pancreatitis [LPSP]), and positive responsive to glucocorticoid treatment, features suggesting that an autoimmune mechanism is involved in its pathogenesis [1, 4-7]. Most patients are elderly males who exhibit clinical features such as obstructive jaundice, pancreatic swelling, and irregular narrowing of the pancreatic ducts [8], all of which mimic the features indicative of pancreatic cancer [4-6]. Thus, during diagnostic workup, it is important to differentiate AIP from pancreatic cancer and biliary malignancy [9]. AIP may also be complicated by a variety of extra-pancreatic lesions [10-12], which have pathological characteristics similar to those of the pancreatic lesions in AIP, including lymphoplasmacytic infiltration, infiltration of large numbers of IgG4-bearing plasma cells, storiform fibrosis, and obstructive phlebitis; together, these lesions are indicative of a comprehensive pathological condition known as IgG4-related disease [3, 13-15]. Recently, AIP was recognized as a member of a new class of IgG4-related disease.

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A second type of AIP has also been described, based pathologically on granulocyte infiltration into the pancreatic duct epithelium [16]. These pathological findings have been termed idiopathic duct-centric chronic pancreatitis (IDCP) [17] or AIP with granulocytic epithelial lesions (AIP with GEL) [18]. Although these forms of AIP seem to be prevalent in Europe [18, 19], their clinical features remain obscure [16]. Accordingly, this article will focus on the LPSP form of AIP [7].

EPIDEMIOLOGY

AIP is a rare disease. A nationwide survey in Japan in 2002 showed a prevalence of 0.82/100,000 inhabitants, corresponding roughly to 2% of patients with chronic pancreatitis [20, 21]. Due to the formulation of diagnostic criteria in 2002, resulting in more consistent recognition of this disease, the number of patients with AIP in Japan has increased [22]. This disease primarily affects elderly males [1, 5, 6]. The 2002 nationwide survey in Japan showed that the male: female ratio of AIP patients was 2.85:1, and that the age of disease onset was over 45 years in 95% of patients [20]. In accordance with this survey, we found that 83% of patients with AIP were males, and the mean age of onset was 62.2 years [6, 23].

CLINICAL FINDINGS

Obstructive jaundice is a major symptom at AIP onset, observed in 60~70% of patients [1, 5, 6, 8, 23]. This is mainly due to stenosis in the lower bile duct caused by swelling of the pancreatic head, though concentric bile duct

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wall thickening may also contribute to the stenosis [24, 25]. Obstructive jaundice responds well to corticosteroid therapy and sometimes subsides spontaneously. In contrast to patients with ordinary chronic pancreatitis (e.g., the alcoholic type), patients with AIP rarely complain of severe abdominal pain [1, 5, 6, 8]. Diabetes mellitus (DM), primarily type II, is observed in about half of these patients, and glucose intolerance is sometimes ameliorated by corticosteroid therapy [26-28]. However, older age is associated with higher rates of new development or exacerbation of diabetes mellitus [26]. Diarrhea or steatorrhea due to severe exocrine dysfunction is rare, but exocrine function is somewhat reduced, as determined by the bentiromide and secretin tests [28]; however, function may be restored by corticosteroid therapy [29].

AIP is sometimes complicated by a variety of extra-pancreatic involvements [10-12, 30], including lachrymal and salivary gland lesions [31], respiratory lesions [32-34], sclerosing cholangitis [7, 35, 36], and retroperitoneal fibrosis [3]. These complications are associated, respectively, with lachrymal or salivary gland swelling; cough, shortness of breath, or dyspnea, and lumbago due to hydronephrosis. Further details are provided below, in the section on 'Extra-pancreatic lesions'.

LABORATORY TESTS

Blood Chemistry

In 70~80% of patients, blood chemistry tests have shown abnormal findings related to obstructive jaundice, including elevated serum concentrations of bilirubin, biliary enzymes, and transaminase [6, 23]. Pancreatic enzymes were mildly or moderately elevated in 60% of patients [6]. The tumor-associated carbohydrate antigen, CA19-9, was elevated in 50% of patients, probably due to cholestasis rather than to a malignant mechanism [6, 23].

Immunological Tests

Gamma-globulin, IgG, and IgE were found to be elevated in 60%, 70%, and 33% of AIP patients, respectively [6, 23], with significant elevations of IgG4 observed in 90% of patients [2, 6, 23]. Interestingly, decreased IgA and IgM concentrations were observed in patients with increased IgG4 [37]. Positivity for anti-nuclear antibody and rheumatoid factor was observed in 40% and 30% of patients, respectively; with positivity for other antibodies, including anti-thyroglobulin and anti-thyroid peroxidase antibodies, observed in 10~20% of patients [6, 23]. Anti-SS-A/Ro, anti-SS-B/La, and anti-mitochondrial antibodies specific to Sjogren's syndrome or primary biliary cirrhosis (PBC) are rarely observed [6, 23]. Taken together, these findings suggest that patients with AIP tend to produce various autoantibodies that are not disease-specific.

Complement

Serum concentrations of complement proteins C3 and C4 were found to be reduced in 36% of patients, suggesting that the complement activation system may contribute to the pathogenesis of AIP [38]. Reduced complement and IgG1, but not IgG4, concentrations have been closely associated with high serum immune complex (IC) concentrations [38]. The complement activation system consists of classical, alternative, and mannose-binding lectin (MBL) pathways. Reduced C4 concentrations suggest that the classical, not the alternative, pathway is involved in the pathogenesis of AIP; the contribution of the MBL pathway has not yet been determined [38]. Although overproduction of as yet undetermined IgG1 autoantibodies and immune complexes in patients with AIP may activate the classical pathway, complement deposits have never been detected in pancreatic lesions of AIP. Nevertheless, tubulointerstitial nephritis found in AIP is sometimes accompanied by hypocomplementemia [39, 40] and C3 deposits in tubular basement membranes [39].

Pancreatic Function

High HbA1c levels indicative of reduced endocrine function have been observed in 50~70% of patients with AIP [6, 26]. Although corticosteroid therapy has been shown to have a beneficial effect on the clinical course of DM in approximately 50% of patients with AIP [26, 27], corticosteroid therapy also had a negative effect in some, particularly older, patients [26]. Bentiromide tests have indicated that 66% of patients with AIP have reduced exocrine function [6]. Moreover, secretin tests have shown that 8% of AIP patients have 1-factor abnormalities, indicating reductions in volume, and 42% have 2-factor abnormalities, indicating reductions in volume and amylase output. These results suggested that duct cells possessing functional bicarbonate secretion may have been intact [28]. Another study, however, found evidence of decreased bicarbonate secretion by ductal cells, a decrease that was closely associated with the aberrant localization of cystic fibrosis transmembrane conductance regulator (CFTR) in these cells [29]. Histologically, AIP has been associated with lymphoplasmacytic cell infiltration into tissue surrounding the pancreatic ducts, but basement membranes were intact. Corticosteroid therapy can result in regeneration of acinar cells, restoring the secretion of digestive enzymes [29].

IMAGE FINDINGS (REFER TO DR. FUJINAGA'S REVIEW)

US, EUS and IDUS

Abdominal ultrasonography (US) of patients with AIP typically shows a characteristic sonolucent swelling of the pancreas (diffuse enlarged low-echo pancreas with a scattered high echo spot), giving it a so-called "sausage-like" appearance (Fig. 1) [4]. Usually, the main pancreatic duct (MPD) is not visible, but dilatation of the common bile duct is frequently observed. Bile duct dilatation is likely due to stenosis of the lower bile duct caused by pancreatic head swelling and/or inflammatory thickening of the bile duct wall [1, 24]. Endoscopic US (EUS) typically shows a relatively diffuse homogeneous hypo-echoic pattern and linear or reticular hyper-echoic inclusions [41]. EUS and intraductal US (IDUS) imaging show concentric wall thickening of the distal common bile duct [24]. This wall thickening may extend from the extra-hepatic to the intra-hepatic bile duct system, even when cholangiography shows

normal findings. Furthermore, thickening of the gallbladder wall usually occurs [42].

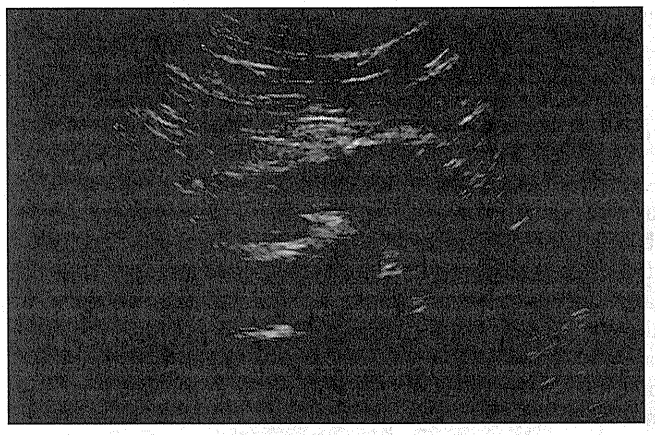

Fig. (1). Abdominal ultrasonography (US) of a patient with autoimmune pancreatitis. Sonolucent swelling is observed in the body and tail of the pancreas.

CT

Similar to US, abdominal computed tomography (CT) of patients with AIP typically shows a diffuse or focal enlargement of the pancreas [1, 4, 43, 44]. Contrast-enhanced CT has shown delayed homogeneous enhancement in pancreatic lesions, representing widespread loss of the parenchyma and severe fibrosis [1, 43]. A characteristic finding of contrast-enhanced CT is a capsule-like, low-density rim surrounding the pancreas, which is prominent at the body and tail regions and is indicative of severe fibrotic changes [43]. The presence of a capsule-like rim is highly indicative of AIP. Another characteristic feature is a straight margin with a sharp outline and an absence of the pancreatic cleft; however, aged pancreases generally show lobulated margins [44].

MRI

Magnetic resonance imaging (MRI) also typically shows a diffuse or focal enlargement of the pancreas, a delayed enhancement, and/or a capsule-like rim [43, 44]. Fat-suppressed T1-weighted images of patients with AIP show reduced signal intensity in the pancreas compared with the liver [43]; in contrast, the signal intensity of a healthy pancreas is higher than that of the liver. T2-weighted MR images generally show high signal intensity [43, 44], reflecting severe lymphoplasmacytic infiltration. T2-weighted MR images with MR cholangiopancreatography (MRCP) sometimes show the MPD clearly penetrating through the lesion mass (duct penetrating sign), a finding useful for differentiating between AIP and pancreatic cancer [45]. Dynamic T2-weighted MR images sometimes show a capsule-like rim [43, 44]. Although MRCP may reveal a diffuse narrowing of the MPD [44], current MRI resolution makes it difficult to evaluate MPD findings accurately, and MRCP is not recommended for diagnosing AIP in Japan [5, 9].

ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) typically shows a characteristic irregular narrowing with 1) a narrow caliber, 2) wall irregularity, and 3) diffuse or local distribution (Fig. **2**) [1, 4, 46-50]. In a typical case, the narrowing extends over one third of the entire pancreatic duct, with diffuse change observed in over half of these patients. Imaging in patients with focal AIP typically shows a characteristic change in the MPD over a restricted area, a finding similar to those in pancreatic cancer, thus requiring differentiation [49]. Even when the MPD change is restricted, the absence of upstream dilatation and an interrupted distribution may be useful for differentiating AIP from pancreatic cancer [46]. During follow-up, restricted changes can become diffuse changes [47]. Most patients also exhibit stenosis in the lower bile duct, which can be caused by pancreatic head swelling and/or inflammatory thickening of the bile duct wall [1, 24, 51]. Bile duct stenosis sometimes extends into the extra- or intra-bile duct systems [36, 48, 51]; in these patients, it is necessary to differentiate between AIP and primary sclerosing cholangitis [48, 51-53] or cholangiocarcinoma [53].

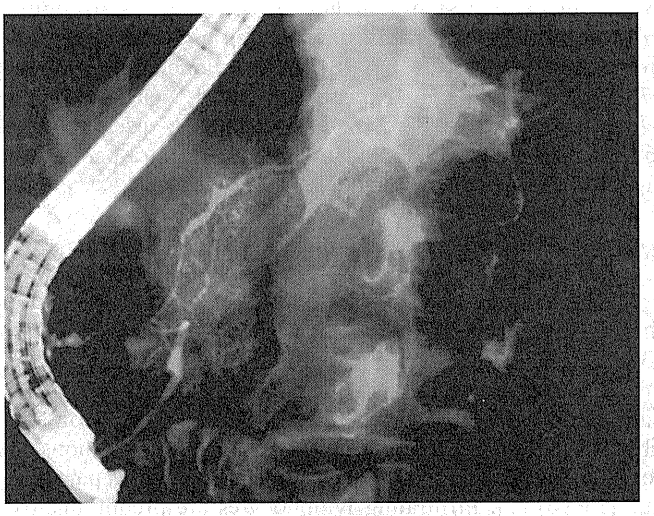

Fig. (2). ERP in a patient with autoimmune pancreatitis, showing diffuse irregular narrowing of the main pancreatic duct.

Gallium Scintigraphy and FDG-PET

Gallium scintigraphy [30, 33, 54-56] and positron emission tomography with a F-18 2-fluoro-2-deoxy-D-glucose tracer (FDG-PET) [57-71] are imaging methods useful for detecting both AIP and extra-pancreatic lesions. Since AIP is characterized by severe lymphocytic inflammation and since gallium-67 (Ga-67) accumulates in lymphoid cells, Ga-67 scintigraphy is a useful tool in examining patients with AIP. Before corticosteroid treatment, marked Ga-67 accumulation was observed in 67% of the pancreatic lesions in AIP patients, whereas, after 4 weeks of corticosteroid therapy, all patients were negative for Ga-67 [33]. Patients with Ga-67 positive images had significantly higher serum IgG4 concentrations than those with Ga-67 negative images, indicating that pancreatic lesions that accumulated Ga-67 were highly active [33]. Increased uptake of Ga-67 has also been observed in a variety of extra-pancreatic lesions [30], including lachrymal and salivary glands [30], hilar and mediastinal lymph nodes [33, 54, 56], retroperitoneal fibrosis [30], and renal lesions [55].

Although FDG uptake is commonly regarded as a diagnostic hallmark of pancreatic cancer, intense FDG uptake has also been observed in the pancreatic lesions of patients with AIP [57-60, 62-71]. To differentiate between AIP and pancreatic cancer, it is important to note that accumulation patterns characterized by nodular shapes is significantly more frequent in pancreatic cancer, whereas patterns of longitudinal or diffuse shape are usually indicative of AIP [67, 69]. Furthermore, heterogeneous accumulation is observed in almost all patients with AIP, whereas homogeneous accumulation is characteristic of pancreatic cancer [67]. Solitary localization in the pancreas is significantly more frequent in pancreatic cancer, whereas multiple localization suggests the presence of AIP [66, 67]. In addition, reduced FDG uptake after a short course of steroid treatment may distinguish AIP from pancreatic cancer [71], although Japanese diagnostic criteria discourages facile therapeutic diagnosis based on steroid administration [9]. FDG-PET also can detect a variety of extra-pancreatic lesions, including sclerosing sialadenitis [62, 67-70], hilar and mediastinal lymph nodes [67], sclerosing cholangitis [61, 62, 67, 70], retroperitoneal fibrosis [62, 67, 70], interstitial nephritis [62, 64, 69], prostate hypertrophy [63, 67, 70], and inflammatory pseudotumor [65]. Concomitant FDG uptake by these extra-pancreatic organs may support the diagnosis of AIP [67, 69].

PATHOLOGICAL FINDINGS

Gross examination of the involved pancreas typically shows a glistening white, firm or hard, enlarged mass [7, 72, 73]. The lesion may involve the whole pancreas, or be limited to one portion of the pancreas, most often the head, but also the body or tail. Lymphoplasmacytic infiltration and fibrosis are characteristic features of pancreatic lesions, a condition known as lymphoplasmacytic sclerosing pancreatitis (LPSP) [7]. Infiltrating lymphocytes are predominantly T cells, and plasma cells characteristically bear IgG4 [3, 73-75], a diagnostic hallmark of AIP. Pancreatic infiltration of IgG4-bearing plasma cells, however, may also be observed in other conditions, including pancreatic cancer and chronic pancreatitis [75, 76]. The inflammatory changes that accompany cell infiltration are most prominent around the pancreatic duct, usually resulting in stenosis or obstruction of the duct [77]. Severe fibrosis typically displays a loose texture with stromal edema [78] or a storiform arrangement. Another characteristic feature is obliterating phlebitis, consisting of marked cell infiltration into the venous wall and venous thrombosis [7, 17, 77]. Similar histological features have also been observed in extra-pancreatic lesions, including those in the salivary glands [31] and retroperitoneal regions [3]. The diagnostic criteria proposed by researchers from Japan [9], Korea [79-81], and the Mayo Clinic [75, 82] include LPSP as a typical histological feature of AIP. In contrast, researchers in Europe and the United States regard the infiltration of granulocytes into the duct epithelium, known as "idiopathic duct-centric chronic pancreatitis" (IDCP) [17] or AIP with GEL [18], as a histological feature of AIP. In Europe, the clinical features of AIP differ from those of LPSP, with the former characterized by frequent severe abdominal pain in younger patients and no gender bias, a close association with inflammatory bowel disease, and a low frequency of serum IgG4 elevation [19, 83]. These findings suggest that LPSP has distinct clinical features from IDCP and AIP with GEL, making it a distinct disease [16, 21].

DIFFERENTIAL DIAGNOSIS

Pancreatic Cancer

The clinical features of AIP mimic those of pancreatic cancer, including a preponderance in older individuals, obstructive jaundice, and a swelling or mass-forming lesion of the pancreas [1, 4-6, 23]. Pathological analysis of resected pancreatic specimens from individuals who underwent surgery for pancreatic cancer revealed that 2-3% of these patients had LPSP [84, 85]. Because AIP responds favorably to corticosteroid treatment, differentiation between the two conditions is mandatory.

Among the clinical findings differentiating these two conditions are abdominal pain, body weight loss, obstructive jaundice, and extra-pancreatic lesions [86]. Severe and persistent abdominal pain that may require narcotics is frequently present in the advanced stages of pancreatic cancer; in contrast, abdominal pain is mild in AIP [1, 5, 6]. Body weight loss is common in pancreatic cancer, but rare in AIP. Jaundice is progressive in pancreatic cancer, but fluctuates or may subside spontaneously in AIP [1, 5, 6, 21, 23]. AIP is often accompanied by a variety of extra-pancreatic lesions, including sialadenitis [31], thyroiditis [87], hilar or mediastinal lymphadenopathy [33], sclerosing cholangitis [36], and retroperitoneal fibrosis [3]; in contrast, extra-pancreatic lesions observed in patients with pancreatic cancer were found to be limited to lower bile duct stenosis, metastatic lesions, and direct invasion. Furthermore, the presentation of extra-pancreatic lesions is considered diagnostic for AIP [11, 88].

Among various serum markers, IgG4 has the highest sensitivity, specificity, and accuracy in differentiating between AIP and pancreatic cancer [2], though elevated serum IgG4 may also be observed in some patients with pancreatic cancer [89]. Accordingly, serum IgG4 elevation provides a useful tool for differentiation, but it cannot rule out the possibility of pancreatic cancer.

Various imaging methods are useful for differentiating between AIP and pancreatic cancer. Abdominal US, EUS, or T2-weighted MR images showing evidence of duct penetration indicates the presence of a benign pancreatic mass, including AIP [45]. CT or MRI showing a capsule-like rim is also considered a diagnostic hallmark of AIP [43]. FDG-PET showing diffuse, multiple, and heterogeneous uptake is indicative of AIP, whereas solitary, homogeneous uptake indicates pancreatic cancer [67]. Decreased FDG uptake after a course of steroid treatment can be useful for discriminating between AIP and pancreatic cancer [71].

Although AIP has several pathological characteristics, it is associated with inflammatory changes that are sometimes observed in pancreatic cancer [86]. Infiltration into pancreatic tissue of large numbers of IgG4-bearing plasma cells is a diagnostic hallmark of AIP [3], but has also been observed in patients with pancreatic cancer [75]. In addition, the synchronous occurrence of AIP and pancreatic cancer

has been reported, highlighting the importance of carefully evaluating patients with AIP to rule out an underlying neoplasm [7, 90, 91].

IDCP or AIP with GEL

In parallel with the new classification of AIP in Japan based on a pathological background of LPSP [1, 4, 5, 7, 50, 92-95], many reports from Western countries have described a pancreatitis that may have been caused by autoimmunity [35, 96-98]. At the American Pancreatic Association meetings in 2002, descriptions of AIP by American, Japanese, and Italian researchers were discussed [83]. As described above, in the section on Pathological findings, the Italian and Japanese descriptions of AIP were quite different [19, 83]. Furthermore, researchers at the Mayo Clinic in the USA presented pathological findings of IDCP as another type of AIP [17, 83], with a European group later presenting similar pathological findings as AIP with GEL [18]. The clinical features of AIP described by the Italian group may partly reflect the pathological background of IDCP or AIP with GEL [16, 19, 83], which may explain the distinct differences in AIP observed in Italy and Japan. The Japanese, Korean, HISORt, and Asian diagnostic criteria defined AIP on a pathological background of LPSP [9, 16, 79, 99, 100], whereas the European criteria defined AIP as including two types of pathologies, LPSP and IDCP/AIP with GEL [16].

IDCP is characterized by ductal epithelial granulocytic infiltration, which frequently results in the destruction of duct epithelium. Due to inflammatory involvement, the duct lumens appear tortuous and irregular and are sometimes obliterated. These characteristic ductal lesions are also called granulocyte epithelial lesions (GEL) [18]. These findings are not present in LPSP. Similarly, typical findings of LPSP, including obliterative phlebitis and infiltration of numerous IgG4 bearing plasma cells, are uncommon in IDCP. Thus, it has been proposed that the IDCP/AIP with GEL pathological subtype be called type 2 AIP, and the LPSP subtype be called type 1 AIP [16, 101]. The clinical features of type 2 AIP are unclear, but include the following: on average, patients are a decade or more younger than patients with type 1 AIP, there is no gender bias, no association with systemic involvement, no elevation of serum IgG4, no or minimal tissue infiltration of IgG4 bearing plasma cells, and 30% of patients show an association with inflammatory bowel disease [16].

Ordinary Chronic Pancreatitis

In general, it is not difficult to differentiate between AIP and ordinary chronic pancreatitis, including alcoholic chronic pancreatitis. The latter condition is characterized by irregular dilatation of the MPD with severe abdominal pain, impaired exocrine and endocrine functions, and pancreatic stone formation over the long-term. In contrast, AIP is characterized by irregular narrowing of the MPD with mild or no pain, mild or moderate exocrine or endocrine dysfunctions that is sometimes ameliorated after corticosteroid therapy, and no pancreatic stone formation [1, 4-6]. Other useful findings indicative of AIP include high serum IgG4 concentrations [2], CT or MRI detection of a capsule-like, low density rim in pancreatic lesions [43], and infiltration into pancreatic tissue of numerous IgG4 bearing plasma cells [3]. However, pancreatic stone formation is sometimes observed in the chronic stages of AIP [102], indicating that AIP may either transform into or represent an early stage of ordinary chronic pancreatitis [23, 102].

TREATMENT

The first report on successful corticosteroid therapy of a patient with suspected AIP was published in 1978; this patient, who had Sjoegren's syndrome, showed disappearance of an abdominal mass after corticosteroid treatment [103]. Thereafter, many reports have shown that a favorable response to corticosteroids was a characteristic feature of AIP [1, 4, 5]. An extensive survey of AIP treatments was recently conducted by the Research Committee of Intractable Pancreatic Diseases in Japan. Their report, called "Consensus for a Treatment of Autoimmune Pancreatitis", was presented as shown in Table **1** [104]. Patients treated with corticosteroids showed good results, with a high complete remission rate and a low recurrence rate compared with patients who received non-corticosteroid therapy, indicating that steroid treatment should be a standard therapy for patients with AIP [104, 105]. Most patients with obstructive jaundice, diffuse enlargement of the pancreas, associated extra-pancreatic involvement, and abdominal pain are good candidates for steroid therapy [105], though spontaneous remission has been observed in patients with low activity. However, there is no established method for predicting spontaneous remission.

Patients receiving corticosteroid therapy may also require biliary drainage to control obstructive jaundice and control of blood glucose to improve impaired glucose tolerance. In general, patients are started on 30~40mg, or 0.6mg/kg, per day of prednisolone for 2~4 weeks with careful assessment of clinical findings, and laboratory and imaging results [86, 104, 105]. Drastic amelioration of the clinical features of AIP are usually observed within 2 weeks [71], with clinical remission usually observed within 4 weeks. Thereafter, the dosage is reduced by 5 mg/day every 2 weeks over 2-3 months to 2.5~7.5mg per day, which is maintained for 6 months to 3 years [86, 104, 105], because most recurrences are observed within 3 years of treatment [21, 86, 104, 105]. Maintenance therapy may be stopped after 6 months, however, for patients with low disease activity, including those with low serum IgG4 concentrations or no systemic lesions. In contrast, some patients with high activity may continue maintenance therapy for 3 years.

Although most patients show amelioration of endocrine function after corticosteroid treatment [27, 104], others show no change or even deterioration [26, 104-106]. Increased age is associated with increased rates of newly developed or exacerbated diabetes mellitus [26]. Exocrine function is generally ameliorated or shows no deterioration after corticosteroid therapy [29, 104, 106], indicating that dysfunctions of the exocrine and endocrine systems of the pancreas are, to some extent, reversible by steroid therapy. Pancreatic tissue obtained by needle biopsy after corticosteroid therapy showed marked histological improvements, including amelioration of fibrosis, reduced

Table 1. Consensus on the Treatment for Patients with AIP in Japan[a]

1.	Administration of an oral steroid should be a standard therapy for AIP
2.	Consider performing biliary drainage for patients with jaundice
3.	Consider controlling blood glucose concentrations in patients with diabetes mellitus
4.	For patients with jaundice or bile-duct stricture, or cases in which the clinical manifestations do not improve (e.g., abdominal pain), consider administration of an oral steroid. However, for patients that have not been diagnosed with AIP, steroid therapy should be used with extreme caution. In addition, when a course of steroid therapy does not have the desired result, perform a re-evaluation, taking into consideration pancreatic carcinoma
5.	Start the oral administration of a steroid with an initial dose of 30–40 mg per day
6.	Maintain the initial dose of steroid for 2–4 weeks, while carefully monitoring the patient's clinical manifestations, laboratory data, and imaging findings. Then, gradually reduce the amount of steroid to a maintenance dose over a period of 2–3 months
7.	In principle, continue steroid maintenance treatment (2.5–5 mg per day) after remission
8.	The length of time that maintenance treatment should be continued is not yet clear, but it can probably be stopped after a predetermined period (about 6–12 months), as long as an improvement in the clinical manifestations can be observed. In addition, the patient should be followed-up to monitor for recurrences
9.	In order to evaluate the effectiveness of steroid therapy, in addition to follow-up observations for recurrence, use repeated biochemical examinations of blood findings, including serum γ-globulin, IgG, and IgG4, repeat imaging findings, and check for clinical manifestations, including jaundice and abdominal discomfort

[a]Reference [104].

infiltration of inflammatory lymphocytes, and a substantial increase in the number of pancreatic acinar cells [29, 107].

Other therapies have been attempted for patients with AIP, particularly those with highly active disease. Steroid pulse therapy has been shown effective in patients intractable to standard corticosteroid therapy and in patients with conditions that may need future surgical treatment and require a prompt steroid response [108]. Immunosuppressive therapy with azathioprine or 6-mercaptopurine has also been tested in patients with recurrent AIP [109-113], though azathioprine may induce acute pancreatitis [114]. Rituximab treatment of a patient with AIP and IgG4-associated cholangitis refractory to steroids and 6-mercaptopurine resulted in an improvement of biliary stricture and the removal of a biliary stent [115]. Although azathioprine or rituximab may be effective in patients with refractory or recurrent AIP, future improvements in corticosteroid treatment regimens may provide an effective alternative.

PROGNOSIS

Because lymphoplasmacytic inflammation of the pancreatic parenchyma represents an acute stage of AIP, it likely does not persist for long periods of time. The features of chronic stage disease may therefore differ from those generally recognized [1, 4, 5, 50]. Long-term follow-up of patients with AIP showed that 41% experienced AIP recurrence and 18% showed pancreatic stone formation, findings previously considered uncommon in AIP [1]. Pancreatic stone formation was significantly more frequent in patients with than without AIP recurrence, suggesting an association between stone formation and recurrence and that some forms of AIP may transform into ordinary chronic pancreatitis after several recurrences [102]. Other reports have also shown a close association between pancreatic stone formation and atrophy of the parenchyma [116]. The exact mechanisms that underlie pancreatic stone formation in AIP are obscure, but pancreatic stones are regarded as resulting from incomplete obstruction of the main pancreatic duct system due to irregular narrowing and stasis of pancreatic juices. In addition, recurrent attacks may intensify an incomplete obstruction of the duct system and facilitate pancreatic juice stasis. In contrast, we found that 7% of patients with ordinary chronic pancreatitis had high serum IgG4 concentrations [23]. Because high serum IgG4 concentration is specifically found in AIP [2] and persists even after remission in over 60% of patients [117], ordinary chronic pancreatitis may include an advanced stage of AIP with high serum IgG4 concentrations. That is, some forms of AIP may constitute an early stage of ordinary chronic pancreatitis, such as alcoholic chronic pancreatitis [23]. In agreement with our results, a Korean study reported that 12% of patients with ordinary chronic pancreatitis had elevated serum IgG4 [118].

Various serum markers and genetic, including circulating immune complex (CIC) [119] and polymorphisms in the human leukocyte antigen (HLA) [120] and cytotoxic T lymphocyte antigen 4 (CTLA4) genes [121], have been reported to predict the recurrence of AIP. A Japanese report showed that patients with recurrent AIP frequently had high serum IgG concentrations, diffuse pancreatic swelling, and lower bile duct stenosis, with logistic regression analysis showing that diffuse pancreatic swelling was a predictor of recurrence [122]. Early detection of recurrences with these markers may facilitate prompt treatment and prevent disease progression.

AIP is generally found in elderly people with suppressed immunosurveillance systems who may therefore be susceptible to various malignant diseases. Many reports have found that various malignancies were accompanied by AIP [106, 116, 123-128]. The lymphoid hyperplasia in AIP or IgG4-related disease may provide a substrate for the emergence of lymphoma, and a close association between IgG4-related disease and non-Hodgkin lymphoma has been reported [123, 125-127]. Most patients showed evidence of extranodal involvement, including of the ocular adnexa, liver, adrenal glands, kidneys and lungs [125]. Although it is unclear whether these patients had lymphoma complicating IgG4-related disease or de novo IgG4+ MALT lymphoma, B-cell lymphoma can arise on a background of IgG4-related chronic inflammation, and IgG4-producing cells can be transformed to IgG4-producing marginal zone B-cell lymphoma [126, 127]. Pancreatic cancer has also been reported to be complicated with AIP, mainly by researchers in Japan [90, 91, 122, 129-131]. Some of these patients had

pancreatic cancer simultaneous with AIP, whereas others developed pancreatic cancer several years after the diagnosis of AIP. Many of these pancreatic cancers were located in the body and tail of the pancreas, suggesting that this may be a characteristic of pancreatic cancer associated with AIP (Tanaka S *et al.*, Suizo 2007; 22: 663-71 in Japanese). Pancreatic malignancies may be evoked by the combination of an immunosuppressed state with a chronic inflammatory process similar to ordinary chronic pancreatitis [132]. K-ras mutations have been reported in significant numbers of AIP tissues [133]. Because we had no age-matched controls, we could not conclude that AIP represents a significantly higher risk for malignant diseases. However, a careful follow-up with tumor markers is mandatory.

CHARACTERISTIC IMMUNOLOGICAL FEATURES

Efficacy of IgG4

IgG4 is a minor subclass of IgG, comprising only 4~7% of total IgG, which is elevated only under restricted conditions, including various forms of atopy [134], parasitic infestations [135], and pemphigus vulgaris and pemphigus foliaceus [136]. However, high serum concentrations of IgG4 were observed in 90% of patients with AIP [2] but rarely in other conditions, including pancreatic cancer, chronic pancreatitis, and other autoimmune diseases [2]. In differentiating between AIP and pancreatic cancer, IgG4 showed a sensitivity of 90%, a specificity of 98%, and an accuracy of 95% [2]. After corticosteroid therapy, serum IgG4 content and IgG4 to IgG ratio decreased significantly, suggesting that IgG4 levels reflect the activity of AIP [2]. Sequential serum IgG4 measurements in patients with multiple AIP recurrences demonstrated that IgG4 may be elevated several months before a clinical recurrence, suggesting that IgG4 may be a sensitive marker for predicting recurrence [23]. Accordingly, IgG4 is considered the most reliable serum marker for a diagnosis of AIP [2, 23]. At present, elevated IgG4 is included in various diagnostic criteria for AIP [9, 79, 82, 100]. Furthermore, infiltration of IgG4-bearing plasma cells, a characteristic finding in patients with AIP, has been recognized as a histological hallmark for diagnosing AIP and other IgG4-related diseases [3, 15].

The role of IgG4 in the pathogenesis of AIP remains unclear; it may be beneficial or harmful. In contrast to pemphigus, where IgG4 recognition of skin autoantigens (desmogleins) is at the origin of the disease process [136], there is little evidence showing that IgG4 autoantibodies play a direct role in the pathogenesis of AIP. IgG4 of patients with AIP has been reported to react with duct cells from a healthy pancreas [137]. Recent studies have shown that IgG4 has two outstanding characteristics: Fab-arm exchange [138] and rheumatoid factor-like activity [139], properties that may confer on IgG4 activities that defend against disease progression. For example, Fab arm exchange results in bi-specific antigen binding, which interferes with the formation of IgG4-associated immune complexes [138]. In addition, *via* Fc-Fc interactions, IgG4 binds to other IgG4 and to conformationally altered IgG1 [139, 140]; this rheumatoid factor-like activity may promote the formation of large circulating immune complexes that are easily eliminated from the circulation.

Other Autoantibodies

Several studies have showed that carbonic anhydrase II (CA II) and lactoferrin may be the candidate target antigens for pathogenic autoantibodies in AIP [141]. For example, neonatally thymectomized BALB/c mice immunized with CA II or lactoferrin showed evidence of discrete inflammatory changes in pancreatic tissue; moreover, transfer of whole, CD4+, or CD8+ spleen cells from these mice into nude mice caused the appearance of these inflammatory changes in the latter [142]. Furthermore, the *Helicobactor pylori* derived HLA DRB1 0405 molecule, with a peptide structure mimicking that of CA II, was found to be closely associated with AIP, suggesting that infection with *H. pylori* may trigger an autoimmune response leading to AIP [143, 144]. Other candidate target antigens include pancreatic secretory trypsin inhibitor (PSTI) [145], amylase alpha-2A [146], HSP 10 [147], and the plasminogen-binding protein (PBP) peptide of *Helicobacter pylori* [148]. However, it is unclear whether these autoantibodies belong to the IgG4 subclass and are involved in both systemic and pancreatic lesions.

HLA and Immunogenetic Findings

Common autoimmune diseases are multifactorial; thus, pathogenesis involves a complex interplay between multiple genetic and environmental factors. Several genes have been found to contribute to autoimmune diseases, including HLA complex genes [144, 149, 150], the Fc receptor-like 3 (FCRL3) gene [151], and the CTLA4 gene [121]. The proteins encoded by these genes may play key roles in antigen presentation, B cell immunity, and T cell recognition/activation.

We reported an association between HLA alleles and susceptibility to AIP in the Japanese population. Indeed, the frequency of the DRB1*0405-DQB1*0401 haplotype was significantly higher in patients with AIP than in controls, suggesting that the DRB1*0405 and/or DQB1*0401 alleles play a functional role in autoantigen presentation and, therefore, autoimmunity [150]. These findings also suggests the involvement of other non-HLA alleles that are in linkage disequilibrium with these polymorphic HLA genes [144]. Genes that confer susceptibility or resistance to a significant number of autoimmune diseases are considered to be located elsewhere in the major histocompatibility complex (MHC); i.e., within non-HLA genes. In our study of genes widely associated with the MHC, we mapped AIP susceptibility to two regions: the HLA-DRB1 to -DQB1 region in the centromeric part of the MHC and the telomeric MHC, near C3-2-11, between HLA-E and HLA-A in the class I region [149]. The neighboring C3-2-11 region also contains the 121 kb centromerically located ATP-binding cassette sub-family F (ABCF1) gene, which is regulated by TNF-α, a major cytokine in inflammatory and auto-immune reactions. Thus, ABCF1 may also be a susceptibility gene for AIP [149]. Although AIP responds well to corticosteroid therapy, relapse is not uncommon during maintenance therapy or after the cessation of corticosteroids. Although another study

found that DQβ1 mutations with substitutions in an aspartic acid at residue 57 were significantly associated with AIP relapses [120], this finding could not be confirmed [152].

Polymorphisms in Fc receptor-like genes (FCRLs) have been associated with various autoimmune diseases in Japanese populations [153]. These polymorphisms alter the binding affinity of nuclear factor κB and regulate FCRL3 expression. An analysis of genotype distribution frequencies of FCRL3-110 polymorphisms revealed a significant association between the -110A/A genotype and AIP [151]. In patients with AIP, serum IgG4 concentrations were significantly positively correlated with the number of susceptibility alleles [151].

One characteristic pathological feature of AIP is lymphoplasmacytic infiltration, including CD4+ and CD8+ T lymphocytes, into the pancreatic parenchyma and other involved organs. Thus, factors that regulate T-cell function may also influence the development of AIP. The CTLA4 (or CD152) gene product is an inhibitory receptor expressed on the cell surface of activated memory T cells and CD4+ CD25+ regulatory T cells that acts largely as a negative regulator of T-cell responses [154]. CTLA4 +49A/G single nucleotide polymorphisms (SNPs) have been associated with susceptibility to autoimmune diseases. We found that the +6230 G/G genotype was significantly higher in Japanese patients with than without AIP, and that the +49A/A and +6230A/A genotypes were associated with an enhanced risk of AIP relapse [121]. The CTLA-4 49A polymorphism and -318C/+49A/CT60G haplotype have also been associated with AIP in a Chinese population [155].

Toll-like receptor-4 (TLR-4) is an important mediator in both innate and adaptive immunity, and polymorphisms in the TLR4 gene have been linked to several autoimmune diseases. However, an analysis of allelic frequencies in patients with AIP revealed no statistical associations between TLR4 polymorphisms and either AIP susceptibility or relapse [156].

EXTRA-PANCREATIC LESIONS

A variety of extra-pancreatic involvements have been associated with AIP [10-12, 30]. Similar to pancreatic lesions, these extra-pancreatic lesions may exhibit IgG4-positive plasma cell infiltration [3] and show a favorable response to corticosteroid therapy [10-12], similarities suggesting a common background associated with IgG4. However, it is not certain that all of these reported extra-pancreatic lesions are closely associated with or share the same background as pancreatic lesions. Pathological studies have confirmed that pancreatic lesions are closely associated with lachrymal and salivary gland lesions, respiratory lesions, sclerosing cholangitis, renal lesions, retroperitoneal fibrosis, and prostate hypertrophy. Because an extra-pancreatic lesion can be erroneously diagnosed as an inherent disease of the corresponding organ, the identification of the AIP-related characteristics of each extra-pancreatic lesion may provide a means to distinguish the true underlying disease.

Hypophysitis

Hypophysitis has been reported to be associated with AIP [14, 157]. Patients with AIP have presented with compressive optic neuropathy, panhypopituitarism, pituitary hypothyroidism, adrenocortical insufficiency, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). MRI analysis revealed pituitary gland and pituitary stalk swelling that produced a high signal on T1-weighted images and early enhancement on dynamic studies; all of these findings disappeared after corticosteroid treatment [157].

Lachrymal and Salivary Gland Lesions

Symmetrical lachrymal and salivary gland lesions have been observed in 14~39% of patients with AIP, making it important to differentiate AIP from Sjögren's syndrome [31, 103, 158, 159]. Compared with Sjögren's syndrome, AIP was associated with milder exocrine dysfunction of lachrymal and salivary gland lesions, and patients with AIP were negative for anti SS-A/Ro and SS-B/La autoantibodies [158] and a preponderance of submandibular gland lesions [30].

Hypothyroidism

Hypothyroidism, indicated by high TSH (27%), low T4 (15%), and positive anti-thyroid peroxidase (TPO) autoantibody (37%), has been reported as a complication in patients with AIP [87]. Serum IgG4 concentrations were similar in hypothyroid and euthyroid patients, suggesting that the hypothyroid state or thyroiditis represents a burnout after thyroid injury. Patients with Hashimoto's thyroiditis could be classified based on immunostaining of IgG4 into patients with IgG4 thyroiditis (IgG4-related thyroiditis, rich in IgG4-positive plasma cells) and non-IgG4 thyroiditis (non-IgG4-related thyroiditis, poor in IgG4-positive plasma cells) [160]. Hypothyroidism associated with AIP may be included in IgG4 thyroiditis.

Respiratory Lesions

A variety of respiratory lesions are associated with AIP, including interstitial pneumonia [30, 32, 34, 161-163], inflammatory pseudotumor [30, 164], and hilar or mediastinal lymphadenopathy [30, 33]. Interstitial pneumonia has been observed in 8~13% of patients with AIP, presenting as dry cough, high serum KL-6 concentrations, and appearance on CT of a ground glass appearance in the middle and lower lung fields and honeycombing in the lower lung field [162]. Inflammatory pseudotumor, corresponding to plasma cell granuloma [164, 165], is frequently misdiagnosed as a lung tumor. CT, Gallium scintigraphy, and FDG-PET revealed hilar and mediastinal lymphadenopathy in 60~70% of patients with AIP [30, 33, 67]. AIP-related central airway stenosis and hilar lymphadenopathy should be differentiated from sarcoidosis [33, 163], and the absence of angiotensin-converting enzyme (ACE) may help differentiate between these conditions.

Gastric Ulcers

Gastric ulcers may be a complication of AIP. These ulcers typically have a linear presentation, with the long axis perpendicular to the incisura on the lesser curvature of the stomach, and they occur independently of NSAID medication or *Helicobacter pylori* infection [166, 167].

Numerous IgG4-bearing plasma cells infiltrate these gastric lesions [166].

Main Duodenal Papilla Lesions

Swelling of the main duodenal papilla is observed in 40~65% of patients with AIP, and these lesions respond to corticosteroid therapy [168, 169]. Similar to pancreatic lesions, significant numbers of IgG4-positive plasma cells have been detected in this lesion [169], suggesting that assays of these tissues may provide an alternative to pancreatic tissue biopsy.

Sclerosing Cholangitis

Sclerosing cholangitis has been observed in 60~70% of patients with AIP [7, 35, 36, 51, 52, 170-172] and should be differentiated from primary sclerosing cholangitis (PSC) and biliary malignancies [51, 52, 173, 174]. PSC is usually observed in young and middle-aged patients and may accompany inflammatory bowel disease [51]. Its characteristics on cholangiography include a band-like stricture, beaded or pruned tree appearance, and diverticulum-like outpouching [48, 51, 52]. In contrast, cholangiography of sclerosing cholangitis associated with AIP showed evidence of lower bile duct stenosis and relatively long strictures from the hilar to intrahepatic biliary systems with simple distal dilatation [48, 51, 52].

Hepatic Lesions

Hepatic lesions associated with AIP display a variety of histological changes, including portal inflammation, interface hepatitis, large bile-duct obstructive features, portal sclerosis, lobular hepatitis, and canalicular cholestasis; these are collectively designated IgG4 hepatopathy [175]. Some of these lesions mimic those observed in autoimmune hepatitis (AIH), with similar clinical presentation; thus, some patients with AIP that display these symptoms may be misdiagnosed with AIH [176].

Renal Lesions

Most renal lesions affect the uriniferous tubules, with few being glomerular. These patients present with tubulointerstitial nephritis indicative of hypocomplementemia, and deposits of immune complexes and C3 in tubular basement membranes [39, 76, 177-181]. Renal cortical lesions show decreased enhancement and appear as small peripheral cortical nodules, round or wedge-shaped lesions, or with diffuse patchy involvement [30, 182, 183].

Retroperitoneal Fibrosis

Retroperitoneal fibrosis, observed in about 10-20% of patients with AIP, may affect the urinary system [3, 184-188] or accompany periaortitis or aortic aneurysma [189]. Patients with renal lesions sometimes complain of lumbago or back pain due to hydronephrosis, which may result in renal atrophy and renal failure with elevated serum BUN and creatinine concentrations [3, 186, 187]. Aortic lesions consist of dense soft tissue masses along the abdominal aorta [30, 184, 187]. Thickening of the aortic wall or aneurysms are sometimes observed, giving rise to the concept of IgG4-related periaortitis [189].

Prostatitis

Prostatitis that responds well to corticosteroid therapy is another complication of AIP [63, 190, 191]. Patients with prostatitis complain of pollakiuria, dysuria, and nocturia, and display a symmetrical, non-tender, swollen prostate. Imaging has shown severe inflammatory lesions, mainly in the central and transition zones [191].

Thrombocytopenic Purpura

AIP-related thrombocytopenic purpura has been reported [157, 192, 193]. Patients complain of petechia, and blood tests show thrombocytopenia, positive platelet associated IgG (PA IgG), and hypocomplementemia. Platelet counts recover promptly after corticosteroid therapy.

DIAGNOSTIC CRITERIA

Diagnostic Criteria in Japan

AIP was first described in 1992 as an unusual type of chronic pancreatitis with diffuse irregular narrowing of the entire main pancreatic duct on ERCP [8]. The entity AIP was proposed in 1995 by the same researchers who proposed the concept of chronic pancreatitis caused by an autoimmune abnormality; AIP was characterized by 11 clinical features (Table **2**) [1]. Thereafter, many patients were diagnosed with AIP based on these clinical features, providing new information for the development of AIP diagnostic criteria in Japan and other countries. For example, imaging showing irregular narrowing of the MPD and pancreatic swelling were cardinal features of AIP, and these were adopted as diagnostic criteria in Japan. Histopathologically, however, AIP showed massive infiltration of lymphoplasmacytes with storiform fibrosis and obliterating phlebitis, findings consistent with lymphoplasmacytic sclerosing pancreatitis (LPSP), which was proposed in 1991 as being associated with AIP [7].

In 2002, the Japan Pancreas Society (JPS) became the first in the world to propose diagnostic criteria for AIP [83, 194]. The original criteria were updated in 2006 (Table **3**) [9]. The original criteria required that the irregular narrowing of the MPD cover more than one third of the length of the entire pancreas, a criterion intended to strictly differentiate between AIP and pancreatic cancer. Furthermore, the original criteria did not include elevated serum IgG4. Although many patients had been diagnosed with AIP based on these original criteria, the latter were criticized since; 1) many patients with AIP were excluded because the extent of MPD narrowing was less than one-third the length of the entire pancreas, and 2) elevated IgG4 was not included as a useful serum marker [2, 83, 195]. Therefore, the Research Committee of Intractable Pancreatic Diseases (RCIPD), provided by the Ministry of Health, Labor, and Welfare of Japan, and the JPS issued revised clinical diagnostic criteria for AIP in 2006 (Table **3**) [9]. These revised criteria deleted the extent of MPD involvement and introduced elevated serum IgG4 levels as a serological criterion.

Table 2. Characteristic Features of Autoimmune Pancreatitis[a]

1. Increased serum γ-globulin or IgG levels.
2. Presence of autoantibodies.
3. Diffuse enlargement of the pancreas.
4. Diffuse irregular narrowing of the main pancreatic duct on ERP.
5. Fibrotic change with lymphocyte infiltration observed with histopathology.
6. No symptoms or only mild symptoms, usually without acute attacks of pancreatitis.
7. Common bile duct in the pancreas is constricted with dilation of the upstream bile duct, and cholestatic liver dysfunction and hyperbilirubinemia.
8. No pancreatic calcification.
9. No pancreatic cysts.
10. Occasional association with other autoimmune diseases.
11. Effectiveness of steroid therapy.

[a]Reference [1].

Diagnostic Criteria of Other Countries and Asian Criteria

The concept of AIP has been widely recognized in Asian [196] and Western [83, 197, 198] countries. Several other diagnostic criteria for AIP have been proposed by researchers from Korea [79], Japan and Korea [100], the US [99], and Italy [19]. Most of the differences among these criteria are due to differences in the methods first used to detect the disease, consisting primarily of imaging findings in Japan [8, 43, 50] and pathological findings in Western countries [17, 18, 199]. In addition, there were differences in pathological backgrounds, with LPSP being predominant in Japan, Korea [7], and the US [99], while LPSP+IDCP/AIP with GEL was prevalent in European countries [17, 18]. Moreover, the recognition of extra-pancreatic involvement

Table 3. Japanese Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006[a]

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas detected in imaging studies, including abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI).
2. High serum γ-globulin, IgG, or IgG4, or the presence of autoantibodies, including 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 autoimmune pancreatitis is established when criterion 1, together with criterion 2 and/or 3, are fulfilled. However, it is necessary to exclude malignant diseases, particularly pancreatic or biliary cancers.

[a]Reference [9].

Table 4. Korean Diagnostic Criteria for AIP[a]

Criterion I. Imaging (both required)
Imaging (US, CT, MRI) of pancreatic parenchyma
Diffusely/segmentally/focally enlarged gland, occasionally with a mass and/or hypoattenuated rim
Imaging (ERCP or MRCP) of pancreaticobiliary ducts
Diffuse/segmental/focal pancreatic ductal narrowing, often with stenosis of the bile duct
Criterion II. Serology (one required)
Elevated level of serum IgG or IgG4
Detection of autoantibodies
Criterion III. Histopathology of pancreatic/extrapancreatic lesions (one required)
Lymphoplasmacytic infiltration and fibrosis, often with obliterative phlebitis
Presence of abundant [10 cells/HPF] IgG4-positive plasma cells
Criterion IV. Response to steroids
Resolution/marked improvement of pancreatic/extrapancreatic lesions with steroid therapy
Diagnosis of AIP is made when criterion I and at least one other criterion are satisfied
Definite diagnosis (one required)
1. Criterion I together with any other criterion (II to IV)
Before establishing the preoperative diagnosis of AIP, a thorough work-up should be performed to exclude pancreatobiliary malignancies
When it is still uncertain whether pancreatic cancer is present, short-interval imaging (CT and ERCP/MRCP) at 2 weeks after the initiation of steroid therapy must be used to confirm whether there is resolution/marked improvement of the main pancreatic duct stricture
2. A full spectrum of changes in lymphoplasmacytic sclerosing pancreatitis and abundant IgG4-positive cell infiltrations identified in pancreatic resection specimens
Probable diagnosis
Unexplained pancreatic disease without pancreatic enlargement, but associated with other organ involvement or elevated serum IgG4 levels

[a]Reference [79].

changed the concept of AIP to a systemic disease [3, 7, 13, 15]; thus, extra-pancreatic lesions were considered characteristic findings of this disease and were incorporated into some diagnostic criteria [19, 99].

Korean criteria for AIP, modified from the Japanese criteria, were proposed in 2006 [79, 80] and modified by the Korean Society of Pancreatobiliary Diseases in 2007 [21, 80] (Table **4**). Although the Korean diagnostic criteria emphasize the use of imaging methods, the Korean criteria include response to steroid. This type of diagnostic test is prohibited in Japan due to the possibility for delays in diagnosis and treatment for patients later found to have pancreatic or biliary malignancies. Other items have also been incorporated into the Korean criteria, together with recent advances in AIP studies. These include 1) the use of magnetic resonance cholangiopancreatography (MRCP) as an alternative to ERCP, 2) omission of high serum γ-globulin concentration, 3) inclusion of abundant IgG4-positive plasma cells in pancreatic or extra-pancreatic lesions, and 4) inclusion of histopathologic evaluation of extra-pancreatic lesions and response to steroids.

Due to differences among these criteria, it became difficult after 2007 to compare data in studies from different countries and to elucidate the general characteristics of AIP. Thus, the RCIPD and the Korean Society of Pancreatobiliary Diseases held three Japan-Korea symposia on AIP to reach a consensus [100, 200, 201] and establish Asian criteria for the diagnosis of AIP (Table **5**). The major points in this consensus were: 1) MRCP could not replace ERCP in diagnosing AIP because the imaging resolution of MRCP is too low; 2) γ-globulin concentration is not necessary as a serological criterion because its sensitivity is lower than that of IgG and IgG4; 3) AIP should be diagnosed on the basis of pancreatic, not extra-pancreatic, lesions; 4) LPSP, when confirmed by surgical resection of specimens, can establish the diagnosis of AIP; 5) histological criteria based on pancreatic biopsy specimens can include findings of lymphoplasmacytic infiltration in fibrosis together with abundant IgG4-positive cell infiltration; and 6) response to steroid therapy may be diagnostic. The diagnosis of AIP should be based on satisfaction of criterion I and one of the other two criteria, or when histology shows the presence of lymphoplasmacytic sclerosing pancreatitis in the resected pancreas. The criteria recommend that a diagnostic trial of steroid therapy be performed by expert pancreatologists only in patients who fulfill criterion I and show negative results in a diagnostic work-up for pancreatobiliary cancer.

In 2006, a group from the Mayo clinic proposed diagnostic criteria for AIP known as the HISORt criteria, which consisted of 5 items, including histology, pancreatic imaging, serology, other organ involvement, and response to steroid therapy (Table **6**) [88, 99]. According to these criteria, AIP diagnosis is established when (a) a review of histology shows a full spectrum of LPSP changes or immunostaining shows abundant IgG4-positive cells; (b) imaging shows a diffusely enlarged pancreas and diffusely irregular narrowing of the MPD, and serology shows elevated IgG4 levels; or (c) the patient has elevated IgG4 and/or extra-pancreatic manifestations, with the latter resolving with steroid therapy. The HISORt criteria focus on histological findings, but, in practice, it is difficult to obtain a specimen large enough to assess the full spectrum of LPSP changes. Like the Korean criteria, the HISORt criteria recommend a diagnostic trial of steroid therapy. Of note, the HISORt criteria cover a diverse spectrum of disease conditions, from acute to post-acute stages, including pancreatic atrophy and calcification [99, 102]. A revised version of the HISORt criteria included IDCP or AIP with GEL as type 2 AIP, with LPSP defined as type 1 AIP [202, 203].

Authorized European criteria for AIP have not been established, although Italian diagnostic criteria have been proposed (Table **7**) [19]. These combine the clinical features of LPSP and IDCP/AIP with GEL. AIP is diagnosed following surgery by assessment of resected pancreatic specimens, including periductal lymphoplasmacytic infiltration, and fibrosis that includes granulocytic epithelial lesions (GEL) [18]. In non-operated patients, AIP is diagnosed based on at least three of the criteria reported in Table **7**. In contrast to other criteria, the Italian criteria stress the close association between AIP and inflammatory bowel diseases [19].

Comparison of Diagnostic Criteria and Towards the Construction of an International Consensus

A comparison of the diagnostic criteria for AIP is shown in Table **8**. Several differences are apparent.

Table 5. Asian Diagnostic Criteria for Autoimmune Pancreatitis

Criterion I. Imaging (Both Required)
1. Imaging of pancreatic parenchyma: Diffuse/segmental/focal enlargement of the gland, occasionally with a mass and/or hypoattenuated rim
2. Imaging of pancreaticobiliary ducts: Diffuse/segmental/focal pancreatic ductal narrowing, often with stenosis of the bile duct
Criterion II. Serology (One Required)
1. High levels of serum IgG or IgG4
2. Detection of autoantibodies
Criterion III. Histopathology of Pancreatic Biopsy Lesions
Lymphoplasmacytic infiltration with fibrosis and abundant IgG4-positive cell infiltrations
AIP should be diagnosed when criterion I and one of the other two criteria are satisfied or when the histology shows lymphoplasmacytic sclerosing pancreatitis in the resected pancreas
Optional criterion: Response to steroid therapy
Diagnostic trials of steroid therapy should be conducted carefully by pancreatologists and only in patients that fulfill criterion I and have negative results in a work-up for pancreatobiliary cancer

Proposed by the Research Committee of Intractable Pancreatic Diseases, provided by the Ministry of Health, Labor, and Welfare of Japan and the Korean Society of Pancreatobiliary Diseases [100].

Table 6. HISORt Diagnostic Criteria for Autoimmune Pancreatitis[a]

Category	Criteria
A. Histology	1. Diagnostic (any one)
	(a) Pancreatic histology showing lymphoplasmacytic sclerosing pancreatitis (LPSP)
	(b) Lymphoplasmacytic infiltrate with abundant (>10cells/HPF) IgG4-positive cells in the pancreas
	2. Supportive (any one)
	(a) Lymphoplasmacytic infiltrate with abundant (>10cells/HPF) IgG4-positive cells in an extrapancreatic organ
	(b) Lymphoplasmacytic infiltrate with fibrosis in the pancreas
B. Imaging	Typical imaging features
	1. CT/MRI: diffusely enlarged gland with delayed (rim) enhancement
	2. ERCP: diffusely irregular, attenuated main pancreatic duct
	Atypical imaging features
	Pancreatitis, focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy, pancreatic calcification
C. Serology	Elevated serum IgG4 levels
D. Other organ involvement	Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
E. Response to Diagnosis	Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
	1. Group A: diagnostic histology alone
	2. Group B: typical imaging features and elevated serum IgG4
	3. Group C: unexplained pancreatic disease with serology or other organ involvement and response to steroid therapy

MRI, magnetic resonance imaging.
[a]Reference [88, 89].

Table 7. Italian Diagnostic Criteria for AIP[a]

Suggestive radiological features (CT or MR)
• Diffuse or focal involvement of the pancreas
• Delayed enhancement in the involved parenchyma
• No dilation of the main pancreatic duct in diffuse form
• No extra-pancreatic or vascular involvement
Association with autoimmune diseases
Ulcerative colitis, Crohn's disease, Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, retroperitoneal fibrosis, autoimmune thyroiditis, tubulointerstitial nephritis, uveitis, and Mikulicz's disease
Consistent cytological or histological features
• Periductal lymphoplasmacytic infiltration
• Presence of granulocytic epithelial lesions
• Negative for epithelial atypia
Response to steroid therapy
• Clinical: resolution of symptoms/signs of AIP
• Radiological (CT or MRI): disappearance/significant reduction in the size of the involved pancreas, normalization of the main pancreatic duct

[a]Reference [193].

First, these criteria define at least two distinct histological types of AIP, LPSP and IDCP/AIP with GEL. The Japanese, Korean, original HISORt, and Asian criteria are based on LPSP, whereas the Italian criteria are based on a mixture of LPSP and IDCP/AIP with GEL. There are also differences in clinical stages. The Japanese, Korean, and Asian criteria refer to an acute stage of LPSP, whereas the HISORt criteria refer to both acute and post-acute or chronic stages of LPSP. Accordingly, the term AIP likely refers to more than one distinct disease or clinical stage [16, 99]. To reach an international consensus, we should clearly define the type of AIP identified by the diagnostic criteria.

Second, the Japanese, Korean, and Asian criteria stress imaging findings, while the HISORt and Italian criteria stress pathological findings. In practice, it is difficult to obtain specimens from AIP tissues large enough for full pathological assessment; moreover, pathological analyses may be available only for surgical specimens. Therefore, it seems appropriate to regard imaging findings and serology as most important for diagnostic criteria. There are no controversies in the clinical utility of IgG4 [2, 89, 118]. Because the diagnostic use of ERCP has been recently restricted, it is necessary to confirm useful findings by non-invasive imaging methods, including US, CT, and MRI. A capsule-like low-density rim apparent on CT or MRI is a specific indication of AIP and some criteria have adopted this indication, although its sensitivity is not high [43].

Other criteria, but not the Japanese criteria, include response to corticosteroid therapy. The major reason the Japanese criteria exclude response to steroid is that treatment

Table 8. Comparison of Diagnostic Criteria for AIP

	Japanese Criteria (Revised in 2006)	Korean Criteria	Asian Consensus Criteria	Mayo Clinic HISORTs Criteria	Italian Criteria
Disease type	LPSP Acute stage	LPSP Acute stage	LPSP Acute stage	LPSP Acute and post-acute stage	LPSP/AIP with GEL Acute and Post-acute stage
I. Image findings	Mandatory ERCP irregular narrowing CT, MRI swelling	Mandatory ERCP/MRCP irregular narrowing CT, MRI swelling	Mandatory ERCP irregular narrowing CT, MRI swelling	Not mandatory Typical : irregular narrowing swelling Atypical: pancreatitis focal mass focal duct stricture atrophy calcification	Not mandatory
II. Serology	γ-globulin IgG, IgG4 autoantibodies	IgG, IgG4 autoantibodies	IgG, IgG4 autoantibodies	IgG4	Not included
III. Histology	LPSP	LPSP IgG4 positive plasma cell infiltration	LPSP IgG4 positive plasma cell infiltration	LPSP IgG4 positive plasma cell infiltration	Periductal lymphocyte infiltration GEL
IV. Extra-pancreatic lesions	Not included	IgG4 positive plasma cell infiltration steroid response	Not included	IgG4 positive plasma cell infiltration steroid response	IBD Autoimmune diseases
V. Steroid response	Not included	Included	Option	Included	Included
Diagnosis	I+II I+III	I+II I+III I+IV I+V	I+II I+III	Group A: III Group B: I+II Group C: I (atypical) +II or IV +V	Operation: III Non-operation: Any 3 of I, III, IV, and V

may delay the diagnosis and treatment of potential pancreatic or biliary malignancies. However, the Asian criteria have adopted the steroid trial as an option that should be applied carefully and only by pancreatologists familiar with AIP [100]. Prompt assessment is crucial for its clinical use. In the clinical setting of suspected AIP, there is a continuous need for differentiation from pancreatic cancer due to atypical imaging for AIP. Thus, "a 2-week steroid trial and subsequent assessment of its response" may be helpful in confirming the diagnosis of AIP without negative consequences for patients with resectable pancreatic cancer [204]. Steroid pulse therapy may contribute to the prompt assessment of a diagnostic trial [108]. In addition, FDG-PET may also prove effective for evaluating response to steroid therapy within one week [70, 71]. However, a steroid trial should be performed carefully and only by pancreatologists.

Unlike the Japanese and Asian criteria, other criteria include the presence of extra-pancreatic lesions. A variety of extra-pancreatic lesions may complicate AIP, and they may exhibit pathological characteristics similar to those observed in AIP tissues, including abundant IgG4-positive plasma cell infiltration [3, 10, 11]. The recognition of these extra-pancreatic lesions and their response to steroid may be useful for the diagnosis of AIP. However, it is necessary to define the extent of extra-pancreatic lesions before including them with the diagnostic criteria, because it is difficult to perform a whole body check for each patient. The response to corticosteroid therapy is markedly different for each extra-pancreatic lesion, so the targets of a steroid trial should be strictly defined. In addition, the incorporation of extra-pancreatic lesions into the diagnostic criteria of AIP is controversial, because in principle, the diagnosis of AIP should be based on findings from the pancreatic lesion [100].

ACKNOWLEDGEMENTS

This study was supported by a grant-in-aid for Intractable Diseases, the Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, and in part by Grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (20590805).

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