After washing in distilled water, the slides for GCP-2 and IL-8 were incubated for 30 min with secondary antibodies at a 1:100 dilution using biotinylated rabbit anti-goat IgG (Vector Laboratories, Burlingame, CA). After washing in distilled water, the slides were incubated for 30 min with avidin–biotin–peroxidase complex (Vectastain ABC Kit, Vector Laboratories). Finally, antibody binding was detected using 3,3'-diaminobenzidine (DAB) (Dojindo, Kumamoto, Japan). Sections were counterstained with hematoxylin. Negative controls were evaluated by replacing the primary antibody with similarly diluted non-immunized IgG. In the interlobular pancreatic ducts, 10 of the 12 IDCP cases had GELs, whereas none of the patients with LPSP had any GELs. In the intralobular pancreatic ducts, 9 of the 12 IDCP cases and one of the 10 LPSP cases had GELs.

We counted neutrophils and infiltrated cells around the inter- and intralobular pancreatic ducts in the three different inflammatory areas where neutrophils most infiltrated per high power field (hpf) (×400). The numbers of neutrophils and the ratio of neutrophils to infiltrated cells in the three different fields were averaged and compared with ACP, LPSP and IDCP respectively. These methods were performed according to our previous reports [37–40].

Thus, the evaluation was conducted using anti-GCP-2 and anti-IL-8 antibody. The expression of GCP-2 and IL-8 in the inter- and intralobular pancreatic duct epithelia was examined in three different active inflammatory areas. The cell staining intensity is scored as negative (0), weak (1), moderate (2) and strong (3) (Fig. 1). These methods were performed according to the previous reports [41,42].

Statistical analysis

For all studies, data are expressed as median and interquartile range. Differences were analyzed using the Mann–Whitney U-test if the Kruskal–Wallis test led to significant results. In their tests, p-values of <0.05 were considered statistically significant.

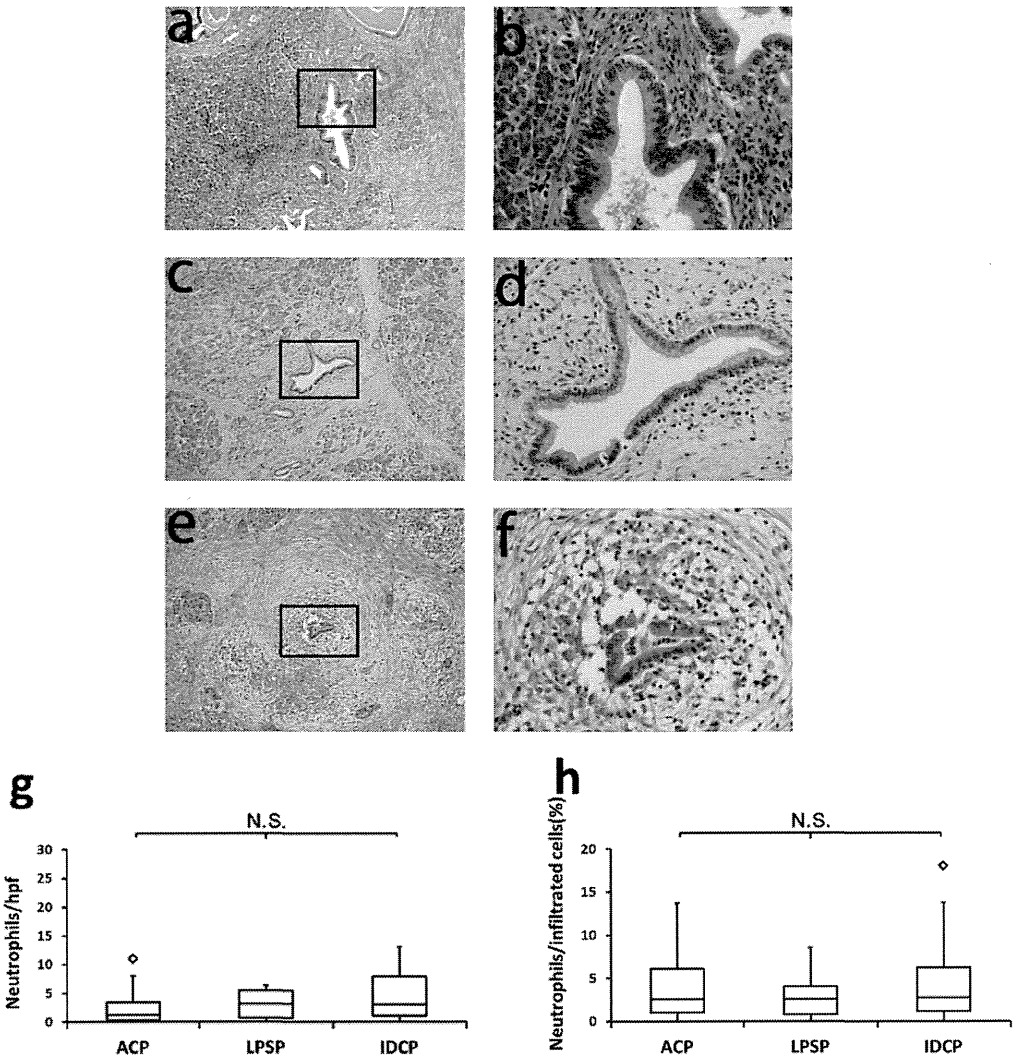

Fig. 3. Histological findings of the intralobular pancreatic ducts (H&E) and comparison of the neutrophils infiltration around the intralobular pancreatic ducts. Infiltrated cells were seen around the intralobular pancreatic ducts in ACP (a, ×100), LPSP (c, ×100) and IDCP (e, ×100). There was no significant difference in the number of neutrophils around the intralobular pancreatic ducts among ACP (b, ×400), LPSP (d, ×400) and IDCP (f, ×400). Abundant infiltration of granulocytes around and into pancreatic duct with destruction of epithelia was seen in IDCP (f, ×400). (g). There was no significant difference in the median number of neutrophils around the intralobular pancreatic ducts among ACP (1.16; IQR: 0.33–3.41), LPSP (3.16; IQR: 0.74–5.50), and IDCP (3.00; IQR: 1.08–7.91). (h). There was no significant difference in the median ratio of neutrophils to infiltrated cells around the intralobular pancreatic ducts among ACP (2.55; IQR: 1.02–6.14), LPSP (2.54; IQR: 0.78–4.05) and IDCP (2.76; IQR: 1.18–6.22).

Result

Comparison of the number of neutrophils and the ratio of neutrophils to infiltrated cells around the interlobular pancreatic ducts among ACP, LPSP and IDCP

The median number of neutrophils around the interlobular pancreatic ducts was significantly higher in IDCP (15.16; interquartile range [IQR]: 9.74–18.41; Fig. 2f) than in ACP (2.66; IQR: 1.33–4.33; Fig. 2b) ($P < 0.05$; Fig. 2g) and LPSP (3.16; IQR: 2.74–4.57; Fig. 2d) ($P < 0.01$; Fig. 2g). The median ratio of neutrophils to infiltrated cells around the interlobular pancreatic ducts was significantly higher in IDCP (8.29; IQR: 6.59–9.85; Fig. 2f) than in LPSP (2.28; IQR: 1.81–3.89; Fig. 2d) ($P < 0.05$; Fig. 2h).

Comparison of the number of neutrophils and the ratio of neutrophils to infiltrated cells around the intralobular pancreatic ducts among ACP, LPSP and IDCP

There was no significant difference in the median number of neutrophils around the intralobular pancreatic ducts among ACP (1.16; IQR: 0.33–3.41; Fig. 3b), LPSP (3.16; IQR: 0.74–5.50; Fig. 3d) and IDCP (3.00; IQR: 1.08–7.91; Fig. 3f, g). There was no significant difference in the median ratio of neutrophils to infiltrated cells

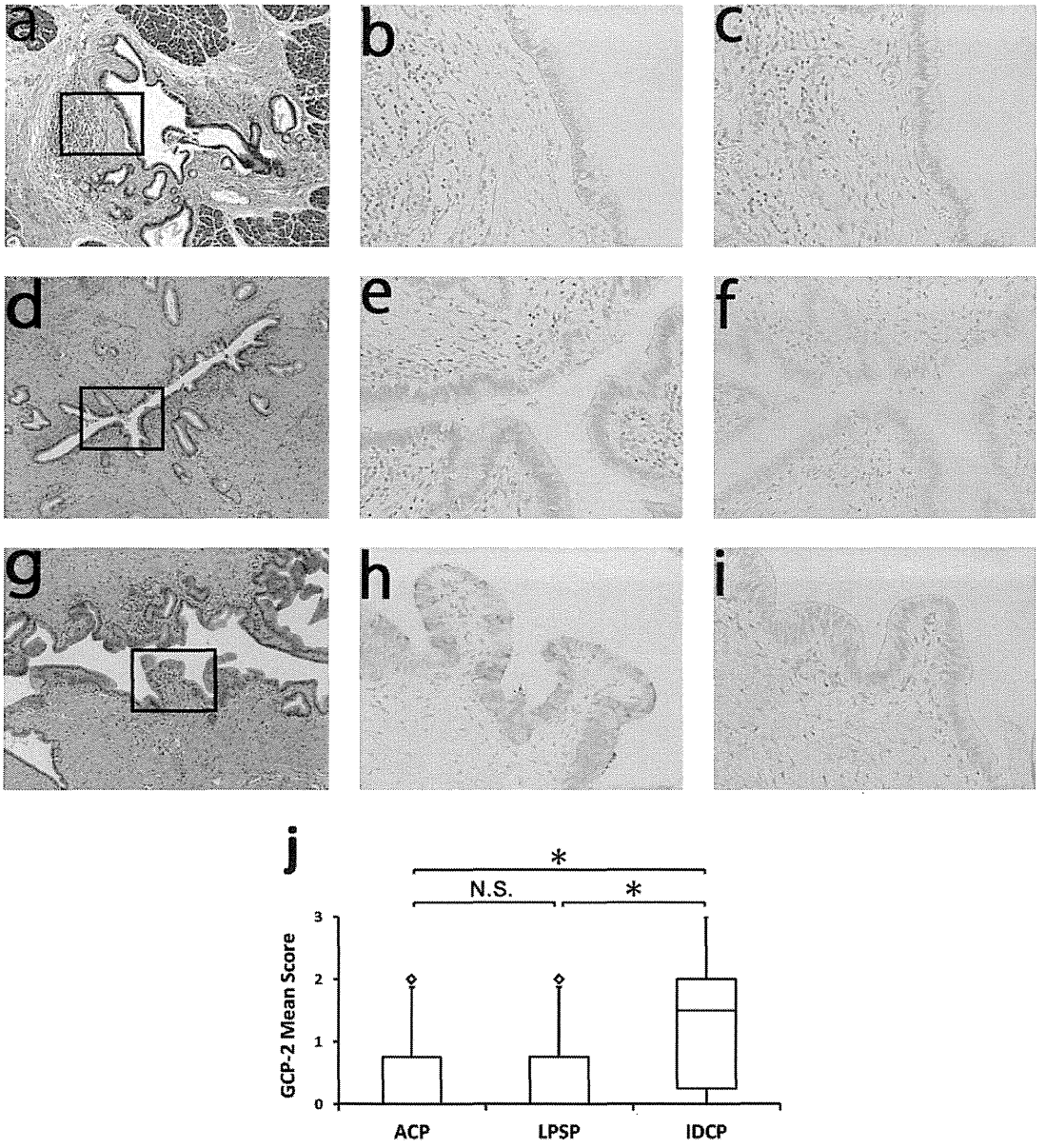

Fig. 4. Immunohistochemical findings of the interlobular pancreatic duct epithelia stained in reaction to anti-GCP-2 antibody and comparison of the score of staining intensity. (a). The interlobular pancreatic duct epithelia in ACP (H&E, ×100). (b). The interlobular pancreatic duct epithelia were not stained in ACP (anti-GCP-2 antibody staining, ×400, score = 0). (c). Negative control in ACP (×400). (d). The interlobular pancreatic duct epithelia in LPSP (H&E, ×100). (e). The interlobular pancreatic duct epithelia were weakly stained in LPSP (anti-GCP-2 antibody staining, ×400, score = 1). (f). Negative control in LPSP (×400). (g). The interlobular pancreatic duct epithelia in IDCP (H&E, ×100). (h). The interlobular pancreatic duct epithelia were strongly stained in IDCP (anti-GCP-2 antibody staining, ×400, score = 3). (i). Negative control in IDCP (×400). (j). The median score of GCP-2 in the interlobular pancreatic duct epithelia was significantly higher in IDCP (1.5; IQR: 0.25–2) than in ACP (0; IQR: 0–0.75) ($P < 0.05$) and LPSP (0; IQR: 0–0.75) ($P < 0.05$). *$p < 0.05$.

around the intralobular pancreatic ducts among ACP (2.55; IQR: 1.02–6.14; Fig. 3b), LPSP (2.54; IQR: 0.78–4.05; Fig. 3d) and IDCP (2.76; IQR: 1.18–6.22; Fig. 3f, h).

CXCR1 was expressed on the neutrophils in both LPSP and IDCP while there was no CXCR2 expression in either LPSP or IDCP

There was no significant difference in the median ratio of CXCR1-positive neutrophils to neutrophils around the interlobular pancreatic ducts among ACP (3.73; IQR: 0–8), LPSP (5.13; IQR: 0.81–9.06) and IDCP (3.66; IQR: 0.62–5.96).

There was no significant difference in the median ratio of CXCR1-positive neutrophils to neutrophils around the intralobular pancreatic ducts among ACP (0; IQR: 0–3.57), LPSP (0; IQR: 0–0.67) and IDCP (1.65; IQR: 0.25–4.62).

CXCR2 was not expressed on the neutrophils around the inter- and intralobular pancreatic ducts in ACP, LPSP and IDCP.

Comparison of the score of GCP-2 and IL-8 in the interlobular pancreatic ducts epithelia among ACP, LPSP and IDCP

The interlobular pancreatic duct epithelia were stained in reaction to anti-GCP-2 and anti-IL-8 antibody. The median score of GCP-2 in the interlobular pancreatic duct epithelia was significantly higher in IDCP (1.5; IQR: 0.25–2; Fig. 4h) than in ACP (0; IQR: 0–0.75; Fig. 4b) ($P < 0.05$; Fig. 4j) and LPSP (0; IQR: 0–0.75; Fig. 4e)

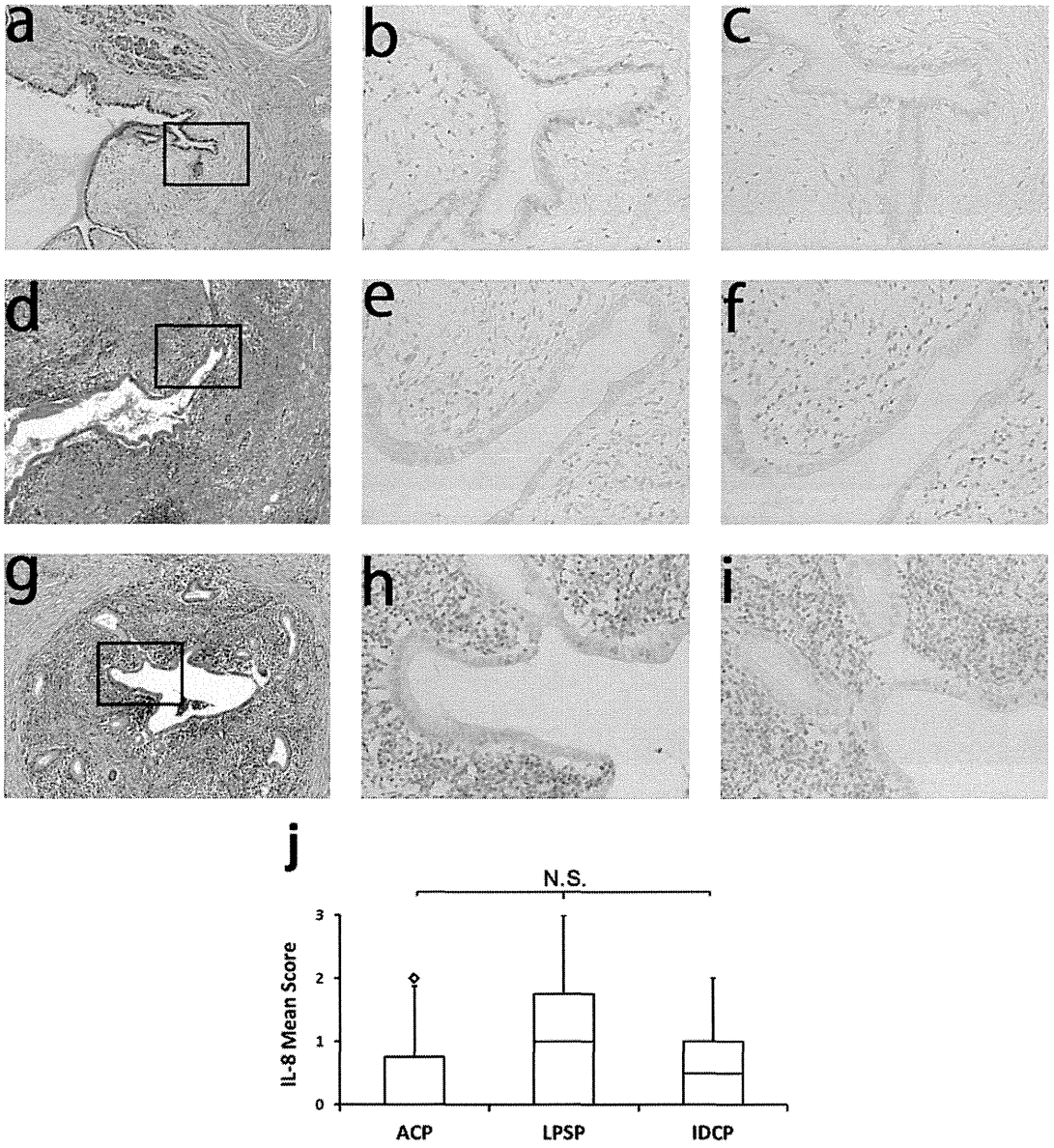

Fig. 5. Immunohistochemical findings of the interlobular pancreatic duct epithelia stained in reaction to anti-IL-8 antibody and comparison of the score of staining intensity. (a). The interlobular pancreatic duct epithelia in ACP (H&E, ×100). (b). The interlobular pancreatic duct epithelia were not stained in ACP (anti-IL-8 antibody staining, ×400, score = 0). (c). Negative control in ACP (×400). (d). The interlobular pancreatic duct epithelia in LPSP (H&E, ×100). (e). The interlobular pancreatic duct epithelia were weakly stained in LPSP (anti-IL-8 antibody staining, ×400, score = 1). (f). Negative control in LPSP (×400). (g). The interlobular pancreatic duct epithelia in IDCP (H&E, ×100). (h). The interlobular pancreatic duct epithelia were weakly stained in IDCP (anti-IL-8 antibody staining, ×400, score = 1). (i). Negative control in IDCP (×400). (j). There were no significant difference in the median score of IL-8 in the interlobular pancreatic duct epithelia among ACP (0; IQR: 0–0.75), LPSP (1; IQR: 0–1.75), and IDCP (0.5; IQR: 0–1).

($P < 0.05$; Fig. 4j). There was no significant difference in the median score of IL-8 in the interlobular pancreatic duct epithelia among ACP (0; IQR: 0–0.75; Fig. 5b), LPSP (1; IQR: 0–1.75; Fig. 5e) and IDCP (0.5; IQR: 0–1; Fig. 5h, j).

Comparison of the score of GCP-2 and IL-8 in the intralobular pancreatic ducts epithelia among ACP, LPSP and IDCP

The intralobular pancreatic duct epithelia were stained in reaction to anti-GCP-2 and anti-IL-8 antibody. There was no significant difference in the median score of GCP-2 in the intralobular pancreatic duct epithelia among ACP (0; IQR: 0–0.75; Fig. 6b), LPSP (0; IQR: 0–1; Fig. 6e) and IDCP (0; IQR: 0–1; Fig. 6h, j). The median score of IL-8 in the intralobular pancreatic duct epithelia was significantly lower in ACP (0; IQR: 0–0.75; Fig. 7b) than in LPSP (1; IQR: 0.25–1.75; Fig. 7e) ($P < 0.05$; Fig. 7j) and IDCP (1.5; IQR: 1–2.75; Fig. 7h) ($P < 0.01$; Fig. 7j).

Discussion

In this study, which is focused on differences in neutrophil infiltration around the pancreatic ducts in LPSP and IDCP, the degree of neutrophil infiltration around the interlobular pancreatic duct was significantly higher in IDCP than in LPSP (Fig. 2g).

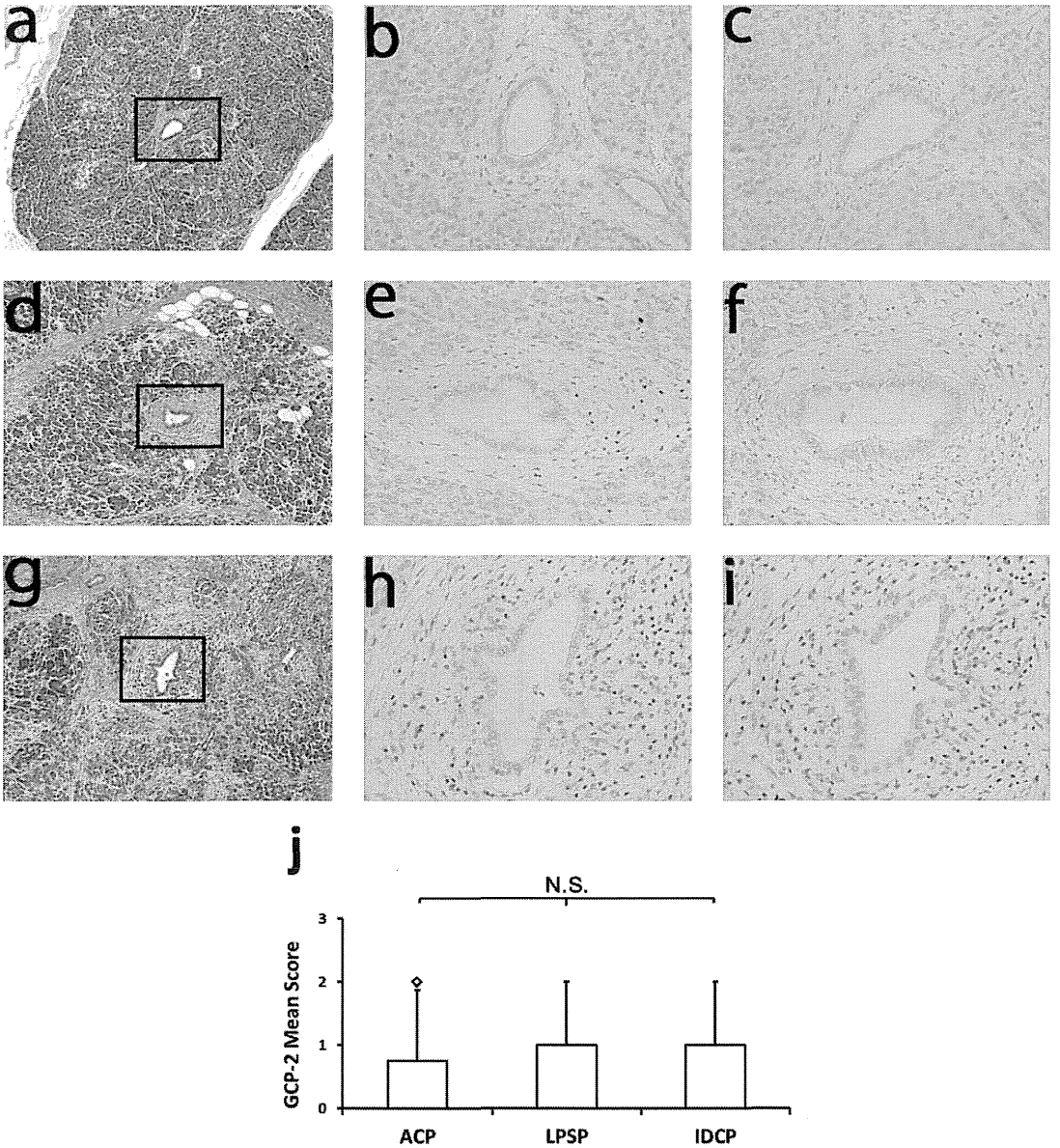

Fig. 6. Immunohistochemical findings of the intralobular pancreatic duct epithelia stained in reaction to anti-GCP-2 antibody and comparison of the score of staining intensity. (a). The intralobular pancreatic duct epithelia in ACP (H&E, ×100). (b). The intralobular pancreatic duct epithelia were not stained in ACP (anti-GCP-2 antibody staining, ×400, score = 0). (c). Negative control in ACP (×400). (d). The intralobular pancreatic duct epithelia in LPSP (H&E, ×100). (e). The intralobular pancreatic duct epithelia were not stained in LPSP (anti-GCP-2 antibody staining, ×400, score = 0). (f). Negative control in LPSP (×400). (g). The intralobular pancreatic duct epithelia in IDCP (H&E, ×100). (h). The intralobular pancreatic duct epithelia were not stained in IDCP (anti-GCP-2 antibody staining, ×400, score = 0). (i). Negative control in IDCP (×400). (j). There was no significant difference in the median score of GCP-2 in the intralobular pancreatic duct epithelia among ACP (0; IQR: 0–0.75), LPSP (0; IQR: 0–1) and IDCP (0; IQR: 0–1).

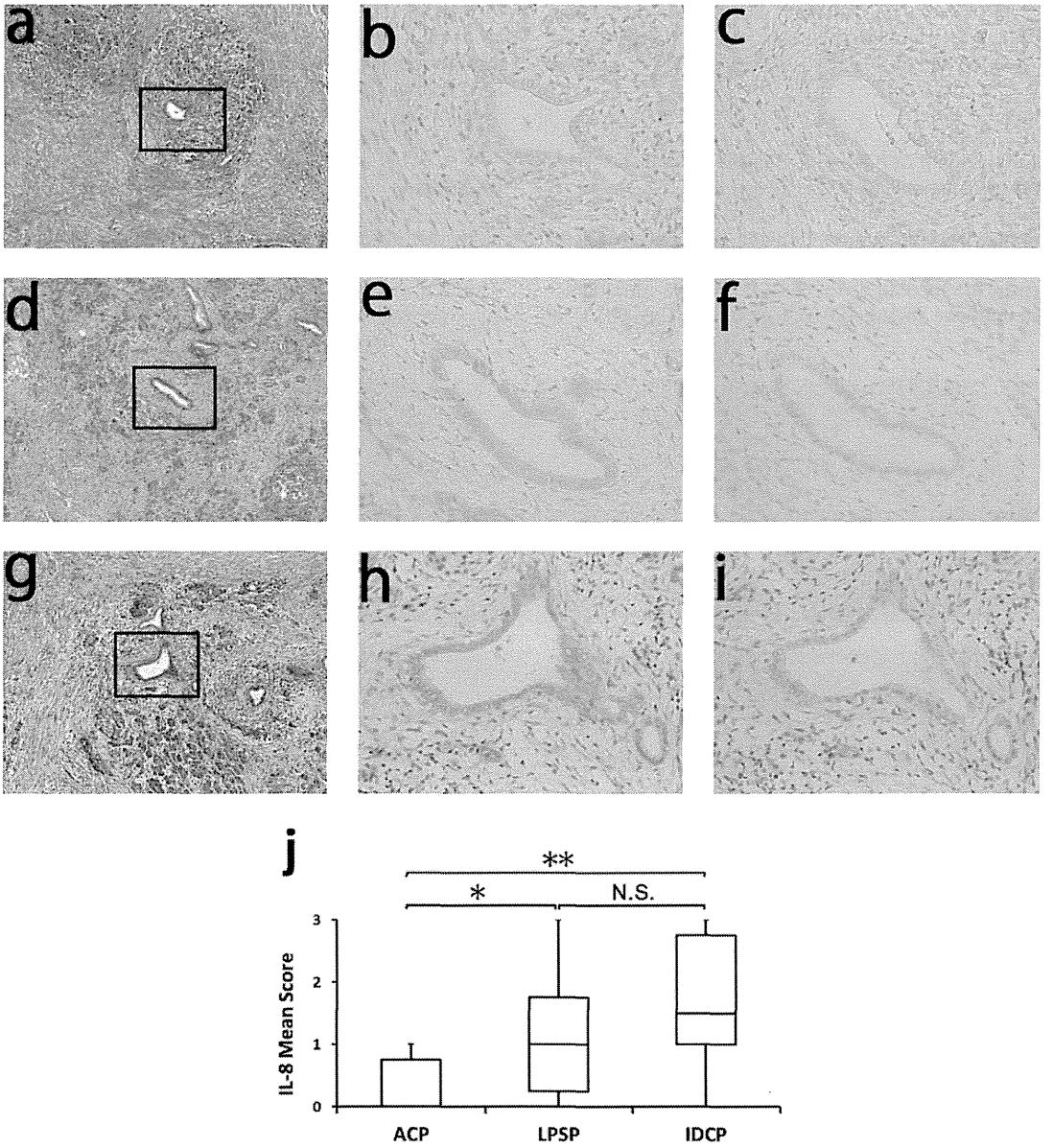

Fig. 7. Immunohistochemical findings of the intralobular pancreatic duct epithelia stained in reaction to anti-IL-8 antibody and comparison of the score of staining intensity. (a). The intralobular pancreatic duct epithelia in ACP (H&E, ×100). (b). The intralobular pancreatic duct epithelia were not stained in ACP (anti-IL-8 antibody staining, ×400, score = 0). (c). Negative control in ACP (×400). (d). The intralobular pancreatic duct epithelia in LPSP (H&E, ×100). (e). The intralobular pancreatic duct epithelia were moderately stained in LPSP (anti-IL-8 antibody staining, ×400, score = 2). (f). Negative control in LPSP (×400). (g). The intralobular pancreatic duct epithelia in IDCP (H&E, ×100). (h). The intralobular pancreatic duct epithelia were moderately stained in IDCP (anti-IL-8 antibody staining, ×400, score = 2). (i). Negative control in IDCP (×400). (j). The median score of IL-8 in the intralobular pancreatic duct epithelia was significantly lower in ACP (0; IQR: 0–0.75) than in LPSP (1; IQR: 0.25–1.75) ($P < 0.05$) and IDCP (1.5; IQR: 1–2.75) ($P < 0.01$). *$p < 0.05$, **$p < 0.01$.

Conversely, no significant differences were observed in the neutrophil infiltration around the intralobular pancreatic ducts (Fig. 3g). Based on these findings, we assumed that neutrophils infiltration around the interlobular pancreatic ducts is more important than around the intralobular pancreatic ducts for the differentiation between LPSP and IDCP, as previously reported [43]. Meanwhile, no significant difference in neutrophil infiltration around either inter- or intralobular pancreatic ducts was observed between the Italian and Japanese patients with IDCP, and there were no apparent differences in the histopathological features of IDCP between the Italian and Japanese patients (data not shown).

In the present immunohistochemical study, CXCR1 was expressed on the neutrophils in both LPSP and IDCP while there was no CXCR2 expression in either LPSP or IDCP. In view of the lack of CXCR2 expression on the neutrophils, this study focused on GCP-2 and IL-8. These two chemokines are the only $ELR^{+}CXC$ chemokines that chemoattract and activate neutrophils by binding to both CXCR1 and CXCR2, whereas the other $ELR^{+}CXC$ chemokines signal only through CXCR2 [16,17].

We noted significant differences in the number of neutrophils around the interlobular pancreatic duct and the score of GCP-2 in the interlobular pancreatic duct epithelia between LPSP and IDCP (Figs. 2g and 4j). GCP-2 and IL-8 were expressed in the pancreatic duct epithelia in both IDCP and LPSP. In general, GCP-2 and IL-8 are potent activators and chemoattractant for neutrophils. Van Damme J et al. [44] reported that GCP-2 complements the activity of IL-8 as neutrophil chemoattractant and activator. Meanwhile, there were no significant differences in the score of IL-8 in the interlobular pancreatic duct epithelia between LPSP and IDCP (Fig. 5j). Therefore, our findings suggest that a significantly increased infiltration of neutrophils around the interlobular pancreatic duct in IDCP may depend on secretion of GCP-2 from the pancreatic duct epithelia. Furthermore, GCP-2 may play a key role in neutrophil infiltration around the interlobular pancreatic duct in IDCP. Additionally, there were no significant differences in the score of GCP-2 in the intralobular pancreatic duct epithelia between LPSP and IDCP (Fig. 6j), so there was no significant difference in the number of neutrophils around the intralobular pancreatic duct (Fig. 3g). Therefore, our data may also suggest different characteristics between inter- and intralobular pancreatic duct.

Chemokines are secreted by various tissue cells such as fibroblasts, inflammatory cells, epithelial cells, and vascular endothelial cells, and are involved in the pathogenesis of a variety of acute and chronic inflammatory diseases via neutrophil, monocyte and other cell migration [45]. In general, it has been recognized that GCP-2 is produced by osteosarcoma cells [46]. On the other hand, IL-8 is secreted by inflammatory cells such as monocytes, neutrophils and T-cells [47]. Additionally, there are some reports that GCP-2 and IL-8 are secreted from epithelia [44,48–50]. Our findings suggest that GCP-2 and IL-8 are secreted from the pancreatic duct epithelia and these chemokines are involved in the migration of neutrophils around the pancreatic ducts in both LPSP and IDCP.

Moreover, there were no significant differences in the ratio of CXCR1-positive neutrophils to neutrophils between LPSP and IDCP (data not shown). Thus, our data suggest the difference in neutrophil infiltration around the pancreatic ducts between LPSP and IDCP may be due to abnormal interlobular ductal characteristics of ICDP, but not be due to leukocytes.

Alternate techniques may be required for these studies. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has widely been adopted and is an important modality for the diagnosis of pancreatic diseases. However, it is difficult to evaluate the interlobular pancreatic ducts with the small samples that can be obtained by EUS-FNA. The present study confirmed that there is no significant difference in neutrophil infiltration around the intralobular pancreatic ducts and that GELs may even be presented in the intralobular pancreatic ducts in LPSP. Furthermore there is also a report that IgG4–positive plasma cell infiltration may be found in IDCP [51]. Thus, clinicians should be careful making a differential diagnosis of LPSP and IDCP based on the number of neutrophils and IgG-4 positive plasma cells as well as the presence or absence of GELs with a small biopsied sample obtained by EUS-FNA.

In conclusion, this study identified GCP-2 and IL-8 expression in the pancreatic duct epithelia. Significantly increased neutrophil infiltration around the interlobular pancreatic duct in IDCP may depend on secretion of GCP-2.

Acknowledgments

This study was partially supported by (1) Grant-in-Aid for Scientific Research (C) of the Ministry of Culture and Science of Japan (23591017, 24591020), (2) Grant-in-Aid for "Research for Intractable Diseases" Program from the Ministry of Labor and Welfare of Japan, and (3) Grants-in-Aid from CREST Japan Science and Technology Agency, (4) NEXT-Supported Program for Strategic Research Foundation at Private Universities.

The authors thank Dr. A-H. Kwon, Department of Surgery, Kansai Medical University, for his support with this work.

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J Gastroenterol (2015) 50:805–815
DOI 10.1007/s00535-014-1012-5

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Autoimmune pancreatitis complicated with inflammatory bowel disease and comparative study of type 1 and type 2 autoimmune pancreatitis

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Received: 1 September 2014 / Accepted: 27 October 2014 / Published online: 16 November 2014

Abstract
Background Two types of autoimmune pancreatitis (AIP) have been reported, lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric chronic pancreatitis (IDCP), which are now recognized as type 1 and type 2 AIP, respectively. Since the clinical features of type 2 AIP have not been fully elucidated and this condition is frequently accompanied by inflammatory bowel disease (IBD), we performed a nationwide survey of patients with AIP complicated with IBD to precisely characterize this disease entity.

Methods We collected 138 cases of pancreatitis with complicating IBD from affiliated institutes specializing in AIP or IBD, and comparative study between the IDCP groups and type 1 AIP was performed.
Results Histological examination revealed 15 AIP cases to be IDCP of institutional diagnosis, among which 11 cases were upgraded to IDCP of central diagnosis by an expert pathologist. The IDCP group exhibited younger onset age, no gender bias, frequent abdominal pain, and normal IgG4 value, similar to those of type 2 AIP reported previously. We also witnessed a lower prevalence of jaundice in type 2 AIP than in type 1 AIP that corresponded to imaging findings of less frequent pancreatic head swelling and scarce bile duct stenosis.
Conclusions A characteristic feature of type 2 AIP compared with type 1 AIP is a low frequency of obstructive jaundice that is related to rare lower bile duct stricture due to lower prevalence of pancreatic head swelling. Contrary to type 1 AIP, lower bile duct stricture in this condition has no apparent relation to sclerosing cholangitis.

Keywords Autoimmune pancreatitis (AIP) · Lymphoplasmacytic sclerosing pancreatitis (LPSP) · Idiopathic duct-centric chronic pancreatitis (IDCP) · Granulocytic epithelial lesion (GEL) · Inflammatory bowel disease (IBD) · Ulcerative colitis (UC) · Crohn's disease

Members of the study group are listed in Appendix.

Electronic supplementary material The online version of this article (doi:10.1007/s00535-014-1012-5) contains supplementary material, which is available to authorized users.

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Introduction

Autoimmune pancreatitis (AIP) is a specific type of pancreatitis whose pathogenesis has been implicated with autoimmune mechanisms [1]. In 1992, Toki et al. described the characteristic pancreatic duct findings of this condition, which they termed chronic pancreatitis with diffuse

irregular narrowing of the main pancreatic duct [2]. Later, in 1995, Yoshida et al. proposed the concept of AIP based on apparent autoimmune phenomena [3]. In 2001 and 2002, Hamano et al. reported on the characteristic clinical findings of high serum IgG4 concentration and abundant IgG4-bearing plasma cell infiltration in the affected organ in AIP, which became useful serological and pathological hallmarks for AIP diagnosis [4, 5]. This type of AIP was reported mainly from Japan and Korea and became characterized by (1) elderly male preponderance, (2) similar imaging findings to pancreatic cancer, and (3) a close association with IgG4. AIP with pathological lymphoplasmacytic infiltration and fibrosis was referred to as lymphoplasmacytic sclerosing pancreatitis (LPSP) [6]. The inflammatory process of LPSP encroached on pancreatic and peripancreatic tissues, resulting in various degrees of parenchymal damage.

Elsewhere, another type of pancreatic lesion was being reported mainly from Europe and the USA as showing pathological neutrophil infiltration in the pancreatic duct epithelium that was referred to idiopathic duct-centric chronic pancreatitis (IDCP) [7], or AIP with granulocytic epithelial lesion (GEL) [8]. This type of lesion was proposed to be included in the AIP spectrum by several groups. However, the clinical features of IDCP/AIP with GEL differed considerably from those of LPSP, showing (1) young and middle age preponderance, (2) no gender bias, (3) complicating inflammatory bowel disease (IBD), and (4) no correlation with IgG4 [9, 10]. In the International Consensus Diagnostic Criteria (ICDC) for AIP established in 2011, AIP became classified as type 1 and type 2 based on the pathological subtypes of LPSP and IDCP/AIP with GEL, respectively. IDCP/AIP with GEL has since been widely accepted as a distinct type of AIP [11]. Similar imaging criteria are used for both type 1 and 2 AIP diagnosis in the ICDC [11]. Although imaging findings are indeed considered to resemble each other for the two conditions [12, 13], there have been few studies on the precise differences in clinical features between type 1 and type 2 AIP [12–16]. Especially in Japan, there is a scarcity of reports on type 2 AIP [14, 15, 17–20] and the clinical characteristics of this type of AIP have not been fully elucidated.

The Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour, and Welfare of Japan (Chairman: Tooru Shimosegawa) conducted a national survey on type 2 AIP from July 2009 to March 2011 and preliminarily identified the clinical features of this condition, which included complicating IBD. However, both AIP and pancreatic diseases complicated with IBD have been reported to exhibit similar clinical features as type 2 AIP: Okano et al. described a case of pseudotumorous pancreatitis associated with ulcerative colitis (UC) that featured obstruction of the main pancreatic duct [21]. Toda et al. reported that among 79 patients with UC, five presented with magnetic resonance cholangiopancreatography (MRCP) finding of diffuse irregular narrowing as seen in AIP, whereas their serum IgG4 concentration was found to be within the normal range [22]. Nve et al. reported on the clinical outcome of a 25-year-old man with idiopathic fibrosing pancreatitis associated with UC who showed obstructive jaundice and diffuse enlargement of the pancreas [23], and Oishi et al. disclosed that irregular narrowing of the main pancreatic duct was found in 13 % of Crohn's disease cases with abnormal pancreatic imaging findings [17]. Ueki et al. reported that all seven cases of AIP complicated with IBD were classified as type 2 [20]. There have been few reports in which full pathological examination of type 2 AIP was done. As there are many patients with IBD in Japan, we hypothesized that a survey of AIP complicated with IBD would enable effective identification and investigation of type 2 AIP. Accordingly, we performed a collaborative study with The Research Committee for Intractable Pancreatic Disease (Chairman: Tooru Shimosegawa) and The Research Committee for Intractable Inflammatory Bowel Disease (Chairman: Mamoru Watanabe), both of which are supported by the Ministry of Health, Labour, and Welfare of Japan. While the former organization specializes in AIP, the latter focuses primarily on IBD. The present study sought to clarify the clinical features of type 2 AIP and compare them with those of type 1 AIP.

Materials and methods

Patients

Pancreatitis complicated with IBD

We collected cases of pancreatitis complicated with IBD, which included UC and Crohn's disease, from affiliated institutes. The pancreatic diseases assessed in this study were AIP, acute pancreatitis, and chronic pancreatitis that had been diagnosed and treated after 1995 when the concept of AIP had first been proposed. AIP was classified into two groups: IDCP of institutional diagnosis and that of central diagnosis. IDCP of institutional diagnosis corresponded to IDCP that was determined at individual institutes based on the ICDC for AIP 2011 with pathological examination of pancreatic tissue [18]. Among the cases with IDCP of institutional diagnosis, IDCP of central diagnosis was then established by careful examination of tissue slides by an expert pathologist (KN) who had proposed the concept of IDCP in 2003.

Type 1 AIP

For further analysis of IDCP complicated with IBD, 84 patients with type 1 AIP were selected as controls from a cohort recruited at Shinshu University and Kansai Medical School between 1992 and 2013, in which the diagnosis was based on the ICDC for AIP 2011 [11] and the Japanese Clinical Diagnostic Criteria for AIP 2011 [24], ten cases were available for pathological diagnosis and no cases were complicated with IBD.

Methods

Patient surveys

In a preliminary survey, we first asked member institutes about cases of acute pancreatitis, chronic pancreatitis, or AIP that were complicated with UC or Crohn's disease and had been confirmed by CT and MRI between 1995 and 2011. In a follow-up questionnaire, we then asked institutes that responded to the first survey to provide the detailed clinical features of each case. The completed reports were sent to the centers for clinical analysis at Shinshu University and Kansai Medical School.

Analysis of clinical features

We analyzed the collected patient data to elucidate the precise clinical features of pancreatitis complicated with IBD. To clarify IDCP in comparison with type 1 AIP, AIP with complicating IBD was further subdivided into IDCP of institutional diagnosis and that of central diagnosis, as described above.

Analysis of imaging findings collected from patients with IDCP of central diagnosis

We obtained CT, MRI, and ERCP images from institutes reporting cases with IDCP of central diagnosis and examined them for characteristic imaging findings.

Pathological analysis

When available, tissue slides were gathered for central pathological examination at Kurashiki Central Hospital. Tissue specimens with IDCP of institutional diagnosis were also obtained for review. The diagnosis of type 2 AIP was based on established ICDC histological criteria.

Statistical analysis

The Chi-squared test or Fisher's exact test were adopted for comparisons of categorical variables. The Mann–Whitney *U* test was used for comparisons of continuous variables. A p value of <0.05 was considered to be statistically significant. Statistical analyses were performed using StatFlex 6.0 software (Artech Co., Ltd., Osaka, Japan).

Ethics

Inquiries, patient data, and tissue slides for analysis were all handled anonymously. This study was approved by the respective ethics committees of each participating institute.

Results

Overall preliminary survey results

We initially sent inquiries to 132 institutes about the type and number of cases of pancreatitis with IBD they had encountered and received replies from 85 institutes (64 %). Based on the first survey, we sent a second questionnaire concerning detailed clinical features to 43 institutes and received the case data of 138 patients with pancreatitis complicated with IBD from 36 institutes (81 %).

The patient diagram flow chart for 138 patients complicated with IBD is shown in Fig. 1. The clinical characteristics of our 138 patients demonstrated a male/female ratio of 83/55 and mean disease onset age of 36.7 ± 17.2 years (Supplementary Table S1). IBD complications consisted of 90 cases of UC and 48 cases of Crohn's disease. Fifty-eight patients were clinically diagnosed as having acute pancreatitis, 28 as having chronic pancreatitis, and 52 as having AIP. The 52 cases of AIP consisted of seven confirmed cases based on the Japanese

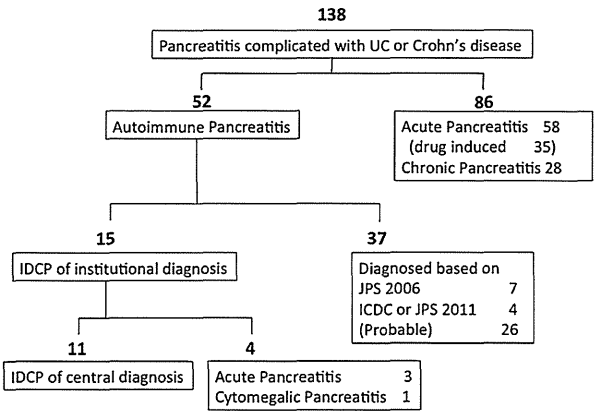

Fig. 1 The patient diagram flow chart for 138 patients complicated with IBD, IDCP: idiopathic duct-centric chronic pancreatitis, JPS 2006: Japanese Clinical Diagnostic Criteria of AIP 2006, ICDC: International Consensus Diagnostic Criteria, JPS 2011: Japanese Clinical Diagnostic Criteria for AIP 2011

Clinical Diagnostic Criteria of AIP 2006, and 19 confirmed and 26 probable cases based on the ICDC or the Japanese Clinical Diagnostic Criteria for AIP 2011. Histological examination was possible for 28 AIP cases and revealed 15 to be IDCP of institutional diagnosis, of which 11 were IDCP of central diagnosis. Among the 58 cases of acute pancreatitis, 35 were closely associated with immunosuppressive drugs used for IBD, such as mesalazine and azathioprine. Although patients with IDCP may have been included in the acute pancreatitis or chronic pancreatitis groups, a shortage of tissue samples made pathological examination and confirmed diagnosis of IDCP difficult. Accordingly, acute pancreatitis and chronic pancreatitis complicated with IBD were not analyzed in the present study.

Central pathological review

Tissue samples from 28 patients were obtained and reviewed by an expert pathologist. Two samples were from a pancreas resection and 26 were from a biopsy. In total, two (one each from a resected tissue and biopsy) and nine (all from a biopsy) cases fulfilled the level 1 and level 2 criteria for type 2 AIP, respectively. These 11 cases comprised the IDCP of central diagnosis group in this study. Cases with level 1 histological findings displayed neutrophilic infiltration in the duct epithelium (GEL) (Fig. 2a), while those meeting the level 2 criteria exhibited neutrophilic infiltration within lobules. Although numerous ductules were formed and infiltrated by neutrophils within lobules in the latter cases, we did not regard this finding to be GEL since these small ducts were considered to be acinar-ductular metaplasia rather than genuine intralobular ducts (Fig. 2b).

Four cases in the IDCP of institutional diagnosis group were excluded from the IDCP of central diagnosis group during central pathological review. Three of these cases displayed histological features of acute pancreatitis, such as acinar cell disappearance, edema, and/or fibroblastic proliferation, but neutrophilic infiltration was minimal. Although we considered that these findings may not have necessarily excluded a diagnosis of IDCP, the cases also did not meet the ICDC level 2 criteria for IDCP. The remaining excluded case showed marked destruction of the pancreas. As a cytomegalic inclusion body was identified, we concluded that this patient had cytomegalic pancreatitis (Fig. 1). None of the cases that underwent histological examination were diagnostic for type 1 AIP.

Analysis of AIP complicated with IBD

Overall analysis

Overall analysis of 52 patients with AIP revealed a male preponderance and median age of disease onset of 35 years (Supplementary Table S2). AIP was preferentially complicated with UC over Crohn's disease. Clinical features at presentation were jaundice in several cases consistent with slight elevation of transaminase and biliary enzymes. Diarrhea was present in 22 patients. Abdominal pain was noted in 29 patients, who also showed high serum amylase concentration. Although serum immunoglobulin concentrations were generally normal, seven patients had high serum IgG4, indicating that various conditions, such as type 1 AIP, may have been included in this group. Many patients exhibited pancreatic swelling and pancreatic duct narrowing, but few displayed lower bile duct stenosis, which likely accounted for the low prevalence of jaundice. Half of the patients had received corticosteroid therapy apart from the immunosuppressive drugs mesalazine and azathioprine.

Analysis of the clinical features of IDCP and type 1 AIP

Among the 52 patients with AIP, the IDCP group was established via pathological examination of pancreatic

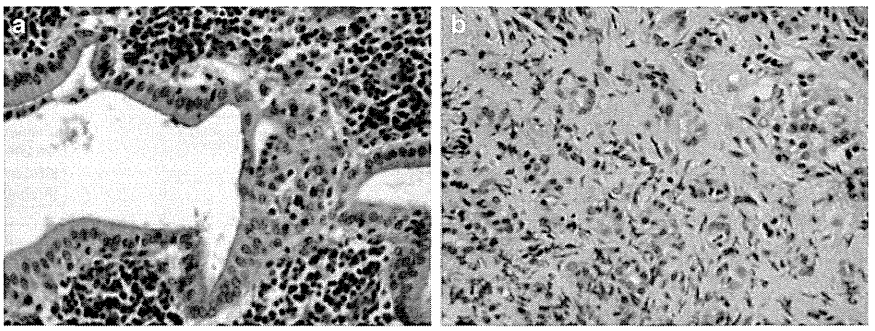

Fig. 2 Histological findings. **a** Level 1 histology of the ICDC for AIP 2011 with neutrophilic infiltration within the duct lumen and epithelium, which is termed GEL, in a resected tissue sample. **b** Level 2 histology with neutrophilic infiltration in the lobules. Small ductules corresponding to acinar-ductular metaplasia are infiltrated by neutrophils, which are not regarded as GEL in this study

Table 1 Comparison of clinical features and symptoms between idiopathic duct-centric chronic pancreatitis (IDCP) and type 1 autoimmune pancreatitis (AIP)

	IDCP				Type 1 AIP
	Institutional diagnosis		Central diagnosis		
	$n = 15$	p	$n = 11$	p	$n = 84$
Clinical feature					
Sex (male/female)	7/8	0.0289	5/6	0.0649	64/20
Age at onset (years)	31 (17–84)	0.0001	29 (17–84)	0.0001	65 (38–84)
UC[a]/Crohn's disease (+/+)	11/4		8/3		
Symptom (+/−)					
Abdominal pain	9/6	0.6043	7/4	0.5457	41/43
Abdominal tenderness	7/8	0.0055	5/6	0.0181	11/73
Backache	3/11	0.3911	2/8	0.611	10/74
Jaundice	0/15	0.0059	0/11	0.0156	31/53
Weight loss	3/11	1	3/7	0.6809	16/68
Fever	1/14	1	1/10	0.3939	3/81
Diarrhea	4/11	0.0055	4/7	0.0014	2/82
Constipation	0/15	1	0/11	1	0/84

[a] Ulcerative colitis

tissues and its clinical features were compared with those of type 1 AIP.

Gender and age

The IDCP groups of institutional diagnosis and central diagnosis consisted of 15 and 11 patients, respectively, and had an approximately equal male-to-female ratio (Table 1). This was markedly different from type 1 AIP, for which a male preponderance was seen. IDCP manifested at a significantly younger age of disease onset (approximately 30 years) than did type 1 AIP (65 years). Similarly to clinically diagnosed AIP, complicating UC was roughly three times more frequent than Crohn's disease in the IDCP groups.

Symptoms

No patients presented with jaundice in the IDCP groups, which was significantly different from type 1 AIP (Table 1). Although there were no remarkable differences in the prevalence of abdominal pain between the IDCP groups and type 1 AIP, abdominal tenderness was significantly more prevalent in IDCP. Diarrhea was predictably more frequent in the IDCP groups compared with type 1 AIP due to IBD complications.

Blood tests

In accordance with the absence of jaundice in the IDCP groups, serum concentrations of total bilirubin, biliary enzymes, and transaminase were significantly lower than those in type 1 AIP, except for that of total bilirubin in IDCP of central diagnosis (Table 2). The serum concentration of amylase in the IDCP groups was significantly higher than that in type 1 AIP.

Blood immunology tests

The serum concentrations of IgG and IgG4 in the IDCP groups were significantly lower than those in type 1 AIP, whereas the concentration of IgM in the IDCP groups was significantly higher (Table 2).

Imaging tests

The prevalences of pancreatic swelling and duct narrowing in the IDCP groups were significantly lower than those in type 1 AIP (Table 3). A lower prevalence of pancreatic head swelling in the IDCP groups was evident as compared with type 1 AIP. In accordance with the absence of jaundice, the prevalence of lower bile duct stenosis was significantly lower in the IDCP groups.

Treatment and recurrence

Prednisolone treatment was given to approximately half of IDCP group patients, which was significantly less frequent than in type 1 AIP (Table 4). Other immunosuppressant drugs were also used for patients in the IDCP groups, but their effects on pancreatic manifestations were unclear. There were no significant differences in the prevalence of recurrence between the IDCP and type 1 AIP groups.

Other organ involvement

The complication of other organ involvement, such as Mikulicz's disease, chronic thyroiditis, sclerosing cholangitis, and retroperitoneal fibrosis, which represent the predominant members of IgG4-related disease, tended to be less frequent in the IDCP groups, with significant differences noted for Mikulicz's disease and sclerosing cholangitis (Table 4).

Analysis of imaging findings collected from patients with IDCP of central diagnosis

The imaging findings of six patients with IDCP of central diagnosis were available for further analysis. Whereas pancreatic head swelling was found in three patients, lower

Table 2 Comparison of blood test results between idiopathic duct-centric chronic pancreatitis (IDCP) and type 1 autoimmune pancreatitis (AIP)

	IDCP				Type 1 AIP
	Institutional diagnosis		Central diagnosis		
	$n = 15$	p	$n = 11$	p	$n = 84$
AST	17 (8–297)	0.002	17 (8–297)	0.005	34 (4–730)
ALT	16 (7–504)	0.0037	14 (7–504)	0.0063	52 (9–833)
T-Bil	0.6 (0.2–0.9)	0.0088	0.7 (0.3–0.9)	0.052	0.8 (0.3–17.2)
ALP	226 (106–2,688)	0.0097	226 (106–2,688)	0.0166	496 (73–2,855)
γ-GTP	17 (8–934)	0.0019	17 (8–934)	0.0059	12 (8–1543)
BUN	6.0 (0.7–16.8)	0.0159	6.0 (3–16.8)	0.011	14 (6.6–58)
Creatinine	0.6 (0.4–1.1)	0.0177	0.6 (0.4–1.0)	0.0123	0.8 (0.4–7.9)
Amylase	241 (74–1541)	0.0004	241 (83–962)	0.0012	83 (17–1470)
IgG	1,271 (950–2433)	0.0002	1,255 (1,180–2,035)	0.0056	1,997 (918–5,247)
IgG4	34 (3–86)	0.0001>	24 (4–86)	0.0002	442 (18–2,696)
IgA	235 (138–637)	0.7078	235 (138–407)	0.955	245 (52–624)
IgM	112 (44–248)	0.0115	112 (44–248)	0.0313	81 (23–274)
ANA[a]	6/9	0.4835	4/7	0.4449	42/31
RF[b](+/−)	0/13	0.0612	0/9	0.1924	17/49

[a] Anti-nuclear antibody

[b] Rheumatoid factor

Table 3 Comparison of imaging findings between idiopathic duct-centric chronic pancreatitis (IDCP) and type 1 autoimmune pancreatitis (AIP)

	IDCP				Type 1 AIP
	Institutional diagnosis		Central diagnosis		
	(+/−)	p	(+/−)	p	(+/−)
Pancreatic swelling	10/5	0.0001	8/3	0.0012	84/0
	(Head/body/tail) 8/7/5		(Head/body/tail) 6/7/5		(Head/body/tail) 63/46/56
Pancreatic duct narrowing	12/3	0.0245	8/3	0.0107	81/2
	(Head/body/tail) 9/8/5		(Head/body/tail) 5/6/3		(Head/body/tail) 55/34/48
Pancreatic cyst	2/13	1	1/10	1	9/75
Pancreatic stone	0/15	0.3539	0/11	0.5901	8/76
Lower bile duct stenosis	2/13	0.0001>	1/10	0.0001>	64/20

bile duct stenosis was seen in only one patient who showed no jaundice but serum elevation of biliary enzymes and transaminase (Supplementary Table S3, figure S4 and S5), as reported previously [18]. Intra-ductal ultrasonography (IDUS) results from this patient revealed no bile duct wall thickening at either strictured or normal portions in cholangiography findings (Fig. 3), indicating no complication of sclerosing cholangitis.

Discussion

AIP complicated with IBD

The present study aimed to clarify the clinical features of type 2 AIP (IDCP/AIP with GEL) in Japan by analyzing pancreatic diseases complicated with IBD, among which type 2 AIP is preferentially found. We collected patient records for cases of acute pancreatitis, chronic pancreatitis, and AIP. Although type 2 AIP may also exhibit acute or chronic pancreatitis, the present analysis focused on the AIP group only because histological examination of acute and chronic pancreatitis proved difficult. Pancreatic diseases that are complicated with IBD consist mainly of acute pancreatitis and less frequently of chronic pancreatitis and AIP [17, 25]. Similarly to the present study, previous reports have shown that the main cause of acute pancreatitis was immunosuppressive drugs in addition to duodenal lesions from Crohn's disease and other idiopathic etiologies [17, 25]. The prevalence of AIP in pancreatic diseases complicated with IBD is reportedly low, as indicated in Oishi's report that irregular narrowing of the

Table 4 Comparison of treatment, relapse, and extra-pancreatic lesions between idiopathic duct-centric chronic pancreatitis (IDCP) and type 1 autoimmune pancreatitis (AIP)

	IDCP				Type 1 AIP
	Institutional diagnosis		Central diagnosis		
	(+/−)	*p*	(+/−)	*p*	(+/−)
Treatment					
Prednisolone	7/8	0.0029	5/6	0.0073	71/13
Azathioprine	2/11	0.0168	2/8	0.0103	0/84
Biliary drainage	1/14	0.0607	0/11	0.0302	28/56
Pancreatic resection	1/14	0.3925	1/10	0.3116	2/82
Relapse	2/12	0.7276	2/8	1	19/65
Extra-pancreatic lesion					
Mikulicz's disease	0/14	0.0022	0/10	0.0040	40/44
Chronic thyroiditis	0/14	0.2041	0/10	0.3474	13/71
Sclerosing cholangitis	1/14	0.0001>	1/10	0.0001>	63/21
Retroperitoneal fibrosis	0/14	0.2041	0/10	0.3474	18/66
Inflammatory pseudotumor	0/14	1	0/10	1	1/83
Prostatitis	0/14	0.1183	0/10	0.2097	15/69
Asthma	0/14	0.3488	0/10	0.3758	10/74
Polyarthritis	1/12	0.134	1/8	0.0968	0/84
Erythema nodosa	0/13	1	0/9	1	0/84

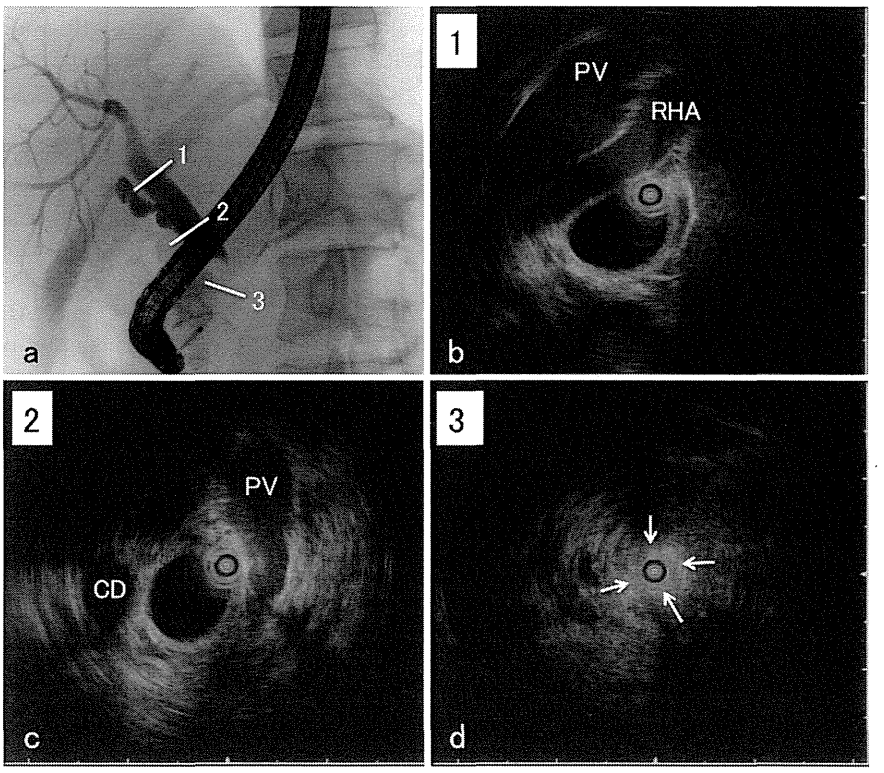

Fig. 3 IDUS findings of case 2 in supplementary Table S3 for IDCP of central diagnosis showing lower bile duct stenosis. **a** Cholangiography showing the position of IDUS, **b** IDUS finding for position 1, **c** IDUS finding for position 2, **d** IDUS finding for position 3. *PV* portal vein, *RHA* right hepatic artery, *CD* cystic duct. *Arrows* indicate strictured bile duct lumen and IDUS

pancreatic duct was found by ERCP in only two of 16 patients with abnormal pancreatic imaging among 255 cases of Crohn's disease [17]. Ueki et al. also reported that type 2 AIP was found in 5 (0.5 %) of 961 patients with UC and 2 (0.3 %) of 790 patients with Crohn's disease [20]. However, in collaboration with specialized organizations, we were able to collect a more substantial number of subjects with AIP complicated with IBD for analysis, though our analysis cannot make clear the prevalence of type 2 AIP in IBD cases because of collection bias mainly due to enrolled institutes that specialized in AIP or IBD.

Although AIP with complicating IBD demonstrated several clinical features of type 2 AIP, it was apparent that this group contained a variety of conditions that indicated probable AIP in half of the cases; indeed, a male preponderance and seven patients with high serum IgG4 concentration suggested that type 1 AIP was also included in this group. Thus, AIP complicated with IBD may be thought to include mainly type 2 AIP and to a lesser extent other conditions, including type 1 AIP. Park et al. reported that among six AIP patients with UC, four were diagnosed as having IDCP and two showed serum elevation of IgG and IgG4 [26]. Here, histological examination was possible for 28 cases of AIP complicated with IBD, which revealed 15 cases with IDCP of institutional diagnosis and ultimately 11 cases with IDCP of central diagnosis. A total of four cases (26.7 %) were excluded from the IDCP of central diagnosis group, reflecting the difficulty of histological IDCP diagnosis in general practice. Ikeura et al. reported on a case of type 1 AIP with histologically proven LPSP and prominent neutrophilic infiltration in the acinar lobules and epithelium of interlobular ducts, i.e., LPSP with GEL [19]. Therefore, we could not exclude the possibility that some cases of type 2 AIP were included with those having a biopsy diagnosis of simple acute pancreatitis due to sampling error or an atypical histological feature dependent on inflammatory stage because IDCP of institutional diagnosis and that of central diagnosis showed virtually identical clinical features.

It was mentioned that type 2 AIP was quite rare in the Japanese population [24], though correct incidence for it remains unclear because of diagnostic difficulty due to poor histological confirmation described above. In an international survey of 1,064 patients with AIP, type 2 AIP consisted of 86 patients (8 %) and the proportion of patients diagnosed with type 2 AIP was lower in Asian countries (3.7 %) compared with European (12.9 %) and North American (13.7 %) countries [27]. In Korean experience, however, type 2 AIP in all histologically confirmed AIP cases may not be as rare as originally thought, with an estimated prevalence rate of 28.8 % (15/52) [12]. These reports imply that the incidence of type 2 AIP in Japanese population seems to be more than expected previously, if extensive survey with detailed histological confirmation is done.

Characteristic clinical features of type 2 AIP and type 1 AIP

To clarify the characteristic features of type 2 AIP in Japan, this comparative study of clinical features between an IDCP group (composed of IDCP of institutional diagnosis and that of central diagnosis) and type 1 AIP was performed. The characteristics of type 2 AIP have been reported mainly from Europe and the USA to be different from those of type 1 AIP, including a younger onset age of 30–40 years, no gender bias, frequent symptoms of abdominal pain, and no relation to IgG4 [9, 10, 12, 28, 29]. The present study uncovered comparable results in that the IDCP group showed an onset age of 30–35 years, no gender bias, frequent abdominal pain with high serum amylase concentration, and no serum elevation of IgG4. Treatment with prednisolone was performed in half of the IDCP patients and achieved a favorable result. Immunosuppressive drugs for IBD had also been given to some patients, but their effect on pancreatic lesions was unclear. IDCP has been reported to have an excellent response to corticosteroids and no or few relapses during follow-up [12, 20, 27, 28]. Accordingly, we noted no significant difference in the frequency of relapse between the IDCP and type 1 AIP groups.

Low prevalence of jaundice in the IDCP group

The present study revealed that a characteristic feature of type 2 AIP was a low prevalence of jaundice compared with type 1 AIP that was closely associated with a decreased frequency of pancreatic head swelling and lower bile duct stenosis. Previous studies have similarly reported infrequent jaundice in type 2 AIP [12, 20, 27, 28]. They also reported imaging findings of type 2 AIP identical to those of type 1 AIP [12], but we wonder if this is truly the case since a difference in the frequency of obstructive jaundice should theoretically correspond to associated imaging findings, such as the decreased pancreatic head swelling and lower bile duct stenosis that were evident in this study.

Two mechanisms have been proposed to underlie the lower bile duct stenosis frequently encountered in type 1 AIP: compression stricture caused by pancreatic head swelling [30] and luminal stricture caused by bile duct thickening due to IgG4-related sclerosing cholangitis [31]. The IDCP group exhibited less frequent pancreatic head swelling that resulted in infrequent compression stricture of the bile duct and a correspondingly low frequency of jaundice. In addition, analysis of the CT, MRI, and ERCP images from six patients with IDCP of central diagnosis

revealed pancreatic head swelling in three patients (50 %), whereas pancreatic head swelling was found in 75 % of our patients with type 1 AIP. Analysis of IDUS images from one IDCP patient with lower bile duct stenosis showed no bile duct wall thickening at the portions of either strictured or non-strictured cholangiography findings, which indicated an absence of sclerosing cholangitis [31]. Accordingly, the major reason for a low frequency of jaundice in type 2 AIP is regarded to be a lower frequency of pancreatic head swelling and a corresponding decrease in the incidence of compression stricture of the lower bile duct, and bile duct wall thickening due to sclerosing cholangitis likely does not contribute to its formation.

In conclusion, we evaluated the clinical characteristics of type 2 AIP by analyzing pancreatic diseases complicated with IBD and uncovered several results that were similar to previous reports from Europe and the USA. We also revealed that a characteristic feature of type 2 AIP was a significantly lower frequency of obstructive jaundice compared with type 1 AIP that was related to rare lower bile duct stricture and a relatively lower prevalence of pancreatic head swelling. Furthermore, the lower bile duct stricture found in type 2 AIP has no apparent relation to intraluminal stricture due to bile duct wall thickening or sclerosing cholangitis.

Acknowledgments This work was supported partially by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan. We thank Trevor Ralph for his English editorial assistance.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

Study Group for Pancreatitis Complicated with Inflammatory Bowel Disease organized by The Research Committee for Intractable Pancreatic Disease (Chairman: Tooru Shimosegawa) and The Research Committee for Intractable Inflammatory Bowel Disease (Chairman: Mamoru Watanabe), both of which are supported by the Ministry of Health, Labour, and Welfare of Japan.

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Digestive Endoscopy 2015; **27**: 250–258 doi: 10.1111/den.12343

Review

Endoscopic approaches for the diagnosis of autoimmune pancreatitis

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Autoimmune pancreatitis (AIP) is characterized by diffuse pancreatic enlargement and irregular narrowing of the main pancreatic duct (MPD). Immunoglobulin (Ig)G4-related sclerosing cholangitis (IgG4-SC) associated with AIP frequently appears as a bile duct stricture. Therefore, it is important to differentiate AIP and IgG4-SC from pancreatic cancer and cholangiocarcinoma or primary sclerosing cholangitis, respectively. Endoscopy plays a central role in the diagnosis of AIP and IgG4-SC because it provides imaging of the MPD and bile duct strictures as well as the ability to obtain tissue samples for histological evaluations. Diffuse irregular narrowing of MPD on endoscopic retrograde cholangiopancreatography (ERCP) is rather specific to AIP, but localized narrowing of the MPD is often difficult to differentiate from MPD stenosis caused by pancreatic cancer. A long stricture (>1/3 the length of the MPD) and lack of upstream dilatation from the stricture (<5 mm) might be key features of AIP on ERCP. Some cholangiographic features, such as segmental strictures, strictures of the lower bile duct, and long strictures with prestenotic dilatation, are more common in IgG4-SC than in cholangiocarcinoma. Endoscopic ultrasonography (EUS) reveals diffuse hypoechoic pancreatic enlargement, sometimes with hypoechoic inclusions, in patients with AIP. In addition, EUS-elastography and contrast-enhanced harmonic EUS have been developed with promising results. The usefulness of EUS-guided fine-needle aspiration has been increasingly recognized for obtaining adequate tissue samples for the histological diagnosis of AIP. Further improvement of endoscopic procedures and devices will contribute to more accurate diagnosis of AIP and IgG4-SC.

Key words: endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), EUS-guided fine-needle aspiration (EUS-FNA), immunoglobulin (Ig)G4-related disease, IgG4-related sclerosing cholangitis

INTRODUCTION

AUTOIMMUNE PANCREATITIS (AIP) has been increasingly recognized as a distinctive type of pancreatitis with a presumed autoimmune etiology. In 1995, Yoshida *et al.*[1] first proposed the concept of AIP as a disease entity. They summarized the clinical features as follows: increased serum γ-globulin or immunoglobulin (Ig) G levels and the presence of autoantibodies; diffuse and irregular narrowing of the main pancreatic duct (MPD) and enlargement of the pancreas; occasional association with stenosis of the lower bile duct and other autoimmune diseases; mild symptoms, usually without acute attacks of pancreatitis; effectiveness of steroid therapy; and histological findings of lymphoplasmacytic sclerosing pancreatitis (LPSP).[2] Thereafter, cases of AIP have been reported worldwide including from Japan, Korea, Europe and the USA. Importantly, the histopathological features of AIP other than LPSP were reported in Western countries.[3–5] This type of pancreatitis was also defined as idiopathic duct-centric chronic pancreatitis (IDCP) or granulocytic epithelial lesion (GEL), which is histologically characterized by the infiltration of neutrophils in the pancreatic duct epithelium, and associated with destruction of the pancreatic duct epithelium and the accumulation of neutrophils in the pancreatic duct.[3–5] AIP with the histological findings of either LPSP or IDCP (AIP with GEL) has been categorized as type 1 or type 2 AIP, respectively.[6,7] Patients with type 1 AIP often develop other organ involvement (OOI), such as sclerosing cholangitis and sclerosing sialoadenitis, suggesting that type 1 AIP is a systemic disorder.[8] Over the decade, several diagnostic criteria for AIP have been proposed and revised, and the endoscopic findings have been incorporated in them. In the present article, we

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Received 8 May 2014; accepted 4 August 2014.

will review the role and future perspectives of endoscopy in the diagnosis of AIP.

HISTORY OF DIAGNOSTIC CRITERIA FOR AIP

SARLES *ET AL.*[9] FIRST REPORTED a form of idiopathic chronic pancreatitis possibly caused by an autoimmune mechanism in 1961. In 1995, Yoshida *et al.*[1] proposed AIP as a new clinical entity from Japan. Thereafter, cases of AIP have been extensively reported worldwide. With the accumulation of similar cases in Japan, the Japan Pancreas Society (JPS) proposed the world's first clinical diagnostic criteria for AIP in 2002 (JPS2002).[10] The JPS2002 criteria consisted of three items: (i) specific imaging findings (a mandatory requirement); (ii) serological; and/or (iii) pathological evidence. A diagnosis of AIP is made when more than two items, including the essential imaging findings, are observed. In the criteria, the length of MPD narrowing on endoscopic retrograde pancreatography (ERP) was defined as more than one-third the length of the entire pancreas, because the differential diagnosis of AIP from pancreatic cancer was very difficult in cases of localized MPD narrowing. As a result, the 2002 criteria were diagnostic for typical diffuse-type AIP, but were unable to diagnose atypical localized/segmental-type AIP, which shows focal or segmental swelling of the pancreas and MPD narrowing in less than one-third of the entire pancreas.

The JPS2002 were revised in 2006 by the JPS and Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour and Welfare of Japan (RCIPD) (JPS2006).[11] Major revisions included elimination of the dependency on the length of MPD narrowing and the incorporation of IgG4 as a serology criterion.[12] In addition, several AIP diagnostic criteria were proposed from other countries such as Korea,[13] the USA,[14] Italy,[15] and Germany.[16] Therefore, it was necessary to create an international consensus for the diagnosis, clinicopathological understanding, and treatment of AIP. In 2012, the international consensus diagnostic criteria for AIP (ICDC) were proposed based on the opinions of experts in each country.[17] According to the ICDC, AIP has been classified into two subtypes: type 1 related with IgG4 (LPSP) and type 2 with GEL (IDCP). The ICDC used a combination of five cardinal features of AIP: (i) pancreatic imaging (parenchyma [P] and duct [D]); (ii) serology (S); (iii) OOI; (iv) histology (H); and (v) steroid responsiveness (Rt). The ICDC can be applied worldwide and contribute to avoiding the misdiagnosis of pancreatic cancer. Because these criteria might be complicated for general use and because type 2 AIP is extremely rare in Japan, the JPS and RCIPD revised the Japanese diagnostic criteria for AIP, focusing on type 1 AIP in 2011 (JPS2011).[18,19]

ROLE OF ENDOSCOPY IN THE DIAGNOSIS OF AIP

Endoscopic retrograde cholangiopancreatography

Endoscopic pancreatogram

Typical AIP exhibits diffuse irregular narrowing of the MPD with a diffusely enlarged pancreas.[1] Narrowing of the MPD is usually determined based on ERP images. Diffuse irregular MPD narrowing is rather specific to AIP (Figs 1,2), and long (>1/3 length of the MPD), or multiple strictures without marked upstream dilatation are adopted as level 1 findings in the ICDC.[17] The narrowing of the MPD is different from obstruction or stenosis, as the narrowing extends and the diameter is narrower than normal, but with some irregularities.[20] It is not easy to differentiate localized MPD narrowing from MPD stenosis as a result of pancreatic cancer (Fig. 3). ERP findings were adopted as mandatory criteria in the definitive diagnosis of focal/segmental-type AIP according to the ICDC[17] and JPS2011.[18,19] There have been several studies reporting the features of ERP findings in patients with AIP and pancreatic cancer.[21–23] Wakabayashi *et al.*[21] compared the pancreatograms of nine patients with focal-type AIP and 80 patients with pancreatic cancer. They

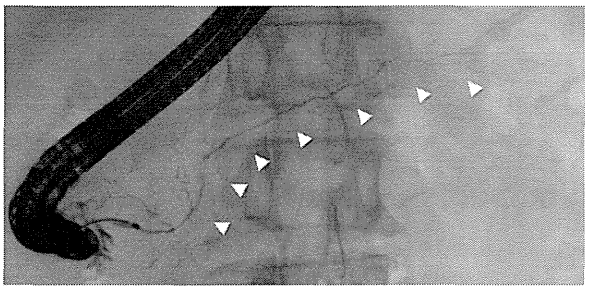

Figure 1 Endoscopic retrograde pancreatography reveals diffuse irregular narrowing of the main pancreatic duct (arrowheads).

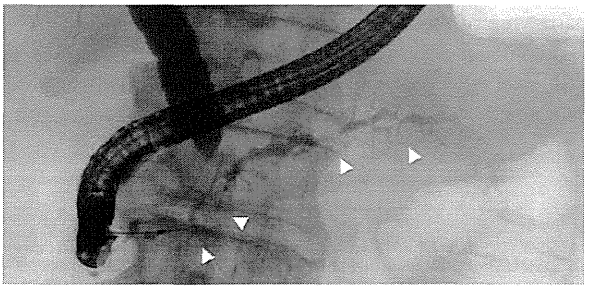

Figure 2 Endoscopic retrograde pancreatography shows skipped stenosis of the main pancreatic duct (arrowheads).