elevated serum IgG4 levels. Infiltration of many IgG4-positive plasma cells into the lacrimal and salivary glands has been detected in Mikulicz's disease. Thus, Mikulicz's disease appears to be salivary gland lesions of IgG4-related systemic disease [25,26].

7 IgG4-related retroperitoneal fibrosis

Retroperitoneal fibrosis was present simultaneously or metachronously in 7% of our AIP patients. Dense infiltration of IgG4-positive plasma cells and obliterative phlebitis were found in both the pancreas and the retroperitoneal fibrous mass. Both the retroperitoneal fibrosis and AIP resolved after steroid therapy [27,28].

8 Other IgG4-related sclerosing diseases

Some cases of inflammatory pseudotumors of the liver [29], lung [30,31], and hypophysis [31,32]; interstitial pneumonia [33,34]; tubulointerstitial nephritis [35,36]; prostatitis [37]; and aortitis [38,39] may be included in IgG4-related sclerosing disease.

9 Conclusions

IgG4-related sclerosing disease is a new clinicopathological systemic entity. It is characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs, and major clinical manifestations are apparent in the organs, in which tissues fibrosis with obliterative phlebitis is pathologically induced. As steroid therapy is effective, accurate diagnosis is necessary.

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INTERNAL MEDICINE

ORIGINAL ARTICLE

Metachronous Extrapancreatic Lesions in Autoimmune Pancreatitis

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Abstract

Objective Autoimmune pancreatitis (AIP) is frequently associated with various extrapancreatic lesions. The distribution and frequency of extrapancreatic lesions preceding or subsequent to AIP are unknown. The aim of this study was to investigate metachronous extrapancreatic lesions of AIP.

Patients and Methods Extrapancreatic lesions were examined clinically, radiologically, and histologically in 56 AIP patients.

Results Extrapancreatic lesions were associated in 25 (45%) of 56 AIP patients. Twenty-nine extrapancreatic lesions were detected synchronously with AIP in 18 patients, and 18 lesions were detected metachronously in 11 AIP patients. Fourteen patients had more than 2 extrapancreatic lesions. There was no significant difference in serum IgG4 levels between AIP patients with preceding extrapancreatic lesions and synchronous extrapancreatic lesions. Extrapancreatic lesions preceding AIP were sclerosing sialadenitis (n=8), cervical lymphadenopathy (n=4), swelling of the lacrimal glands (n=2), retroperitoneal fibrosis (n=1), and hilar lymphadenopathy (n=1). Retrospective histopathological examination confirmed that these lesions were compatible with IgG4-related sclerosing disease. Steroid therapy was not given for these initial lesions, and AIP occurred 3 to 48 months after these initial lesions. Swelling of the preceding extrapancreatic lesions persisted when AIP occurred. Extrapancreatic lesions subsequent to AIP were retroperitoneal fibrosis (n=1) and systemic lymphadenopathy (n=1), both of which occurred during follow-up of AIP without steroid therapy. All extrapancreatic lesions improved after steroid therapy.

Conclusion Swelling of salivary or lacrimal glands, lymphadenopathy, and retroperitoneal fibrosis can precede AIP. Lymphadenopathy and retroperitoneal fibrosis can occur subsequent to AIP. Recognition of these findings will aid in the correct diagnosis of AIP.

Key words: autoimmune pancreatitis, extrapancreatic lesion, sclerosing sialadenitis, retroperitoneal fibrosis, lymphadenopathy

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Introduction

Autoimmune pancreatitis (AIP), a recently described clinical entity, appears to involve autoimmune mechanisms in its pathogenesis. AIP is characterized clinically by a preponderance of elderly males, jaundice as a frequent initial symptom, and responsiveness to steroid therapy; serologically by elevation of serum IgG or IgG4 levels; radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct; and histopathologically by dense fibrosis with lymphoplasmacytic infiltration in the pancreas (1, 2). Other prominent features of this disease involve a variety of extrapancreatic complications (1, 3-5).

We found dense fibrosis with abundant infiltration of T lymphocytes and IgG4-positive plasma cells and obliterative phlebitis in extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing

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sialadenitis, and retroperitoneal fibrosis. Furthermore, we also found dense infiltration of IgG4-positive plasma cells and T lymphocytes in various organs of AIP patients, such as the periportal area of the liver, gastric mucosa, colonic mucosa, dermis, lymph nodes, and bone marrow (5-7). Therefore, we proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease" (5, 6). It is a systemic disease characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs. Clinical manifestations are apparent in organs such as the pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, and others where tissue fibrosis with obliterative phlebitis is present on pathology.

Although several papers have dealt with the extrapancreatic lesions of AIP, few studies have focused on the metachronous extrapancreatic lesions of AIP (8). It is important to study patterns of onset of each extrapancreatic lesion. Therefore, we retrospectively examined the clinical features of extrapancreatic lesions preceeding or subsequent to AIP.

Patients and Methods

We treated 56 AIP patients (45 males and 11 females; mean (± SD) age, 62.8 (± 13.3) years) in Tokyo Metropolitan Komagome Hospital. They were diagnosed as having AIP according to the Asian Diagnostic Criteria for AIP (9): pancreatic enlargement on computed tomography (CT) and ultrasonography (US) (n=56), irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP) (n=56), elevated serum IgG (n=36) and IgG4 (n=43), presence of autoantibodies (n=22), histological findings of lymphoplasmacytic sclerosing pancreatitis (n=17), and steroid responsiveness (n=39). Six patients underwent pancreatoduodenectomy, one patient underwent distal pancreatectomy, and four patients underwent choledochojejunostomy with pancreatic biopsy due to suspicion of pancreatic cancer.

The medical records of these 56 patients were reviewed to identify metachronous and synchronous extrapancreatic lesions. Extrapancreatic lesions of AIP were defined as lesions that were frequently associated with AIP and had IgG4-related histological findings similar to those of the pancreas of AIP, such as sclerosing cholangitis, sclerosing cholecystitis, sclerosing sialadenitis, sclerosing dacryoadenitis, retroperitoneal fibrosis, inflammatory pseudotumor and lymphadenopathy (3, 5). Extrapancreatic lesions first identified at the diagnosis of AIP were defined as synchronous, and those identified before or after the diagnosis were defined as metachronous. Bile duct lesions were examined by ERCP. The presence of lacrimal and salivary gland lesions was determined by physical examination and CT. The presence of other extrapancreatic lesions was determined by CT. Although stenosis of the lower bile duct was detected in 40 patients, we did not regard segmental stenosis of the intrapancreatic bile duct as an extrapancreatic lesion because it could be influenced by pancreatic enlargement. Swelling of the peripancreatic lymph nodes was observed in almost half of the AIP patients who underwent laparotomy (3). However, to exclude reactive lymphadenopathy, we did not regard them as extrapancreatic lesions. We regarded only distant lymphadenopathy including cervical and hilar lymphadenopathy as extrapancreatic lesions. We excluded 1 sclerosing cholangitis of the intrahepatic bile duct that recurred at the same site during steroid tapering from the subsequent extrapancreatic lesions.

Embedded sections of 5 resected and 6 biopsied extrapancreatic lesions preceding or subsequent to AIP were obtained and immunostained with anti-IgG4 antibody (The Binding Site, Birmingham, UK) using the avidin-biotin-peroxidase complex (ABC) method (6, 7).

Statistical analysis was performed using chi-squared analysis or Mann-Whitney's U test. P values of less than 0.05 were considered statistically significant.

Results

Forty-six extrapancreatic lesions were present in 25 (45%) of 56 AIP patients. Among them, fourteen patients had more than 2 extrapancreatic lesions including synchronous and metachronous lesions. Twenty-nine extrapancreatic lesions, such as sclerosing cholangitis of the intrahepatic bile duct (n=4), sclerosing cholecystitis (n=14), swelling of bilateral salivary glands (n=5), retroperitoneal mass (n=2), inflammatory pseudotumor of the lung (n=1) and cervical lymphadenopathy (n=3), were detected synchronously with AIP in 18 patients. And eighteen lesions were detected metachronously in 11 AIP patients (Table 1).

There was no significant difference in age of diagnosis, gender, and serum IgG4 levels between AIP patients with preceding extrapancreatic lesions and those with synchronous extrapancreatic lesions (Table 2).

Extrapancreatic lesions preceding AIP were swelling of bilateral salivary glands (n=8), cervical lymphadenopathy (n=4), swelling of bilateral lacrimal glands (n=2), retroperitoneal mass (n=1), and hilar lymphadenopathy (n=1). Eight swollen salivary gland lesions, 1 swollen lymph node lesion, and 1 retroperitoneal mass lesion were resected or biopsied on suspicion of salivary gland tumor, malignant lymphoma, and urethral tumor, respectively. Histopathological findings of the salivary glands and the retroperitoneal mass, which were retrospectively examined, were sclerosing sialadenitis and retroperitoneal fibrosis that consisted of dense fibrosis with abundant infiltration of T lymphocytes and IgG4-positive plasma cells and obliterative phlebitis. Retrospective examination of a biopsied cervical lymph node (Case 5) revealed abundant infiltration of IgG4-positive plasma cells. No steroid therapy was performed for these initial lesions, and AIP occurred 3 to 48 months after these initial lesions. Swelling of the preceding extrapancreatic lesions persisted when AIP occurred. Steroid therapy was performed for AIP in 7 patients, in all of whom the preceding extrapancreatic lesions also improved. In Case 8, distal pancreatectomy was

Table 1. Extrapancreatic Lesions in Patients with Autoimmune Pancreatitis

	Preceding	Synchronous	Subsequent	Total
Sclerosing cholangitis of the intrahepatic bile duct	0	4	0	4
Sclerosing cholecystitis	0	14	0	14
Sclerosing sialadenitis	8	5	0	13
Swelling of lacrimal glands	2	0	0	2
Retroperitoneal fibrosis	1	2	1	4
Inflammatory pseudotumor of the lung	0	1	0	1
Distant lymphadenopathy	5	3	1	9

Table 2. Comparison of Parameters between Autoimmune Pancreatitis Patients with Synchronous and Preceding Extrapancreatic Lesions

	Patients with synchronous extrapancreatic lesions	Patients with preceding extrapancreatic lesions	p value
Age at diagnosis (years)	67.7±4.9	64.4±8.9	NS
Male/Female	12/2	6/1	NS
Serum IgG4 (mg/dL)	521.16±392.9	536.8±330.7	NS*

NS, not significant

performed for a mass in the pancreatic tail, and the histological diagnosis was AIP. Steroid therapy was given after resection, and the swelling of the salivary and lacrimal glands improved (Table 3).

Extrapancreatic lesions occurred subsequent to AIP in 2 of 17 patients followed up without steroid therapy. One was retroperitoneal fibrosis occurring 12 months after a by-pass operation for AIP (Case 10), and the other was systemic lymphadenopathy occurring 36 months after pancreatoduodenectomy for AIP (Case 11). In the latter case abundant infiltration of IgG4-positive plasma cells was detected in the biopsied cervical swollen lymph node. Retroperitoneal fibrosis and systemic lymphadenopathy improved after steroid therapy (Table 4).

Discussion

AIP patients frequently have significantly elevated serum IgG4 levels and various extrapancreatic lesions. Based on histological and immunohistochemical examinations of various organs of AIP patients, we proposed a novel clinicopathological entity, an "IgG4-related sclerosing disease" (5, 6). It is a systemic disease, and AIP appears to be a pancreatic lesion reflecting an IgG4-related sclerosing disease. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected (5).

From this point of view, both AIP and the extrapancreatic lesions of AIP may occur randomly. However, in this study, some patterns were recognized in the synchronous and metachronous extrapancreatic lesions of AIP. Sclerosing cholangitis and sclerosing cholecystitis occurred synchronously with AIP. Swelling of bilateral salivary glands was present in 13 AIP patients. Cervical lymphadenopathy was also present in 7 of these patients, as was swelling of bilateral lacrimal glands in 2. Swelling of bilateral salivary glands preceded AIP in 8 patients. They were followed up without steroid therapy, and AIP occurred 3 to 48 months later. Retrospective immunohistochemical examination revealed that the swollen salivary glands were compatible with IgG4-related sclerosing sialadenitis.

Lymphadenopathy in the cervical or hilar lymph nodes, as well as the peripancreatic lymph nodes, is sometimes found in AIP patients. Dense infiltration of IgG4-positive plasma cells was detected in swollen lymph nodes. Cervical lymphadenopathy occurred with swelling of the salivary glands preceding AIP in 4 patients, and malignant lymphoma was suspected. In case 1, sarcoidosis was suspected because the chest X-ray showed bilateral hilar lymphadenopathy 4 years before AIP occurred. Hamano et al also reported 3 AIP patients who were initially diagnosed as having sarcoidosis based on bilateral hilar lymphadenopathy on chest X-ray (8). In case 11, systemic lymphadenopathy appeared 3 years after surgery for AIP. All lymphadenopathy disappeared after steroid therapy. Cheuk et al (10) reported that 2 of 6 cases of unexplained lymphadenopathy associated with elevated serum IgG4/IgG levels and/or increased IgG4-positive plasma cells in the lymph nodes developed IgG4-related sclerosing disease (sclerosing cholangitis, and scle-

Table 3. Extrapancreatic Lesions Preceding Autoimmune Pancreatitis

Case	Preceding extrapancreatic lesions	Initial diagnosis	Initial treatment (duration)	Extrapancreatic lesions when AIP occurred	Treatment for AIP	Outcome
1	Swelling of salivary glands Hilar lymphadenopathy	Sialadenitis* s/o sarcoidosis	Follow-up (48 months)	Swelling Swelling	Steroid	Improved Improved
2	Swelling of salivary glands Cervical lymphadenopathy	Sialadenitis* Lymphadenopathy	Follow-up (18 months)	Swelling Swelling	Steroid	Improved Improved
3	Swelling of salivary glands	Sialadenitis**	Follow-up (12 months)	Swelling	Steroid	Improved
4	Swelling of salivary glands Cervical lymphadenopathy	Sialadenitis* Lymphadenopathy	Follow-up (12 months)	Swelling Swelling	Follow-up	Swelling Swelling
5	Swelling of salivary glands Swelling of lacrimal glands Cervical lymphadenopathy	Sialadenitis* Lymphadenopathy**	Follow-up (10 months)	Swelling Swelling Swelling	Steroid	Improved Improved improved
6	Swelling of salivary glands Cervical lymphadenopathy	Sialadenitis** Lymphadenopathy	Follow-up (8 months)	Swelling	Steroid	Improve d
7	Swelling of salivary glands	Sialadenitis**	Follow-up (6 months)	Swelling	Steroid	Improved
8	Swelling of salivary glands Swelling of lacrimal glands	Sialadenitis **	Follow-up (3 months)	Swelling Swelling	Resection	Improved with steroid
9	Retroperitoneal mass	Retroperitoneal fibrosis*	Resection (10 months)	Urinary stent	Steroid	Improved

First diagnosis of extrapancreatic lesions was histologically confirmed by resection* or biopsy**. s/o, suspicious of; AIP, autoimmune pancreatitis

Table 4. Extrapancreatic Lesions Subsequent to Autoimmune Pancreatitis

Case	Subsequent extrapancreatic lesion	Treatment for AIP	Period from AIP to extrapancreatic lesion	Treatment for extrapancreatic lesion	Outcome
10	Retroperitoneal fibrosis	By-pass operation	12 months	Steroid	Improved
11	Systemic lymphadenopathy**	Resection	36 months	Steroid	Improved

AIP, autoimmune pancreatitis; **, IgG4-related lymphadenopathy was histologically confirmed by biopsy retrospectively.

rosing sialadenitis and dacryoadenitis, respectively), and suggested that these cases may represent the lymphadenopathic form of this systemic disease.

Retroperitoneal fibrosis was present in 4 AIP patients [preceding (n=1), synchronous (n=2), and subsequent (n=1)]. A preceding retroperitoneal mass was resected due to suspicion of a urethral tumor, and retrospective histological examination revealed that it was retroperitoneal fibrosis with abundant infiltration of IgG4-positive plasma cells. Hamano et al reported 3 cases in which retroperitoneal fibrosis preceded AIP and 3 cases in which retroperitoneal fibrosis occurred subsequent to AIP (8).

All extrapancreatic lesions of AIP showed similar histopathological findings or good responsiveness to steroid therapy. They appear to be clinically involved organs in IgG4-related sclerosing disease. However, in our study, the extrapancreatic lesions preceding AIP were sclerosing sialadenitis, swelling of the lacrimal glands, lymphadenopathy, and retroperitoneal fibrosis, while those subsequent to AIP were lymphadenopathy and retroperitoneal fibrosis. It is unclear why the onset period of each lesion was different in IgG4-related systemic disease. AIP occurs most frequently with obstructive jaundice due to associated sclerosing cholangitis (1-5). Compared with AIP, swelling of the salivary or lacrimal glands can be easily noticed even without symptoms. AIP might exist subclinically when preceding salivary or lacrimal gland lesions were diagnosed.

Most of these preceding lesions were resected or biopsied on suspicion of malignant tumors. We should recognize that these lesions are manifestations of IgG4-related sclerosing disease. We should follow them up, being aware of the possibility of AIP. Some AIP cases are still difficult to differentiate from pancreatic cancer, but recognition of a past history of suspicion of salivary gland tumor, malignant lymphoma, sarcoidosis, or urethral tumor will further support the diagnosis of AIP.

In conclusion, swelling of the salivary or lacrimal glands, lymphadenopathy, and retroperitoneal fibrosis can precede AIP. Lymphadenopathy and retroperitoneal fibrosis can occur subsequent to AIP. Recognition of these findings will aid in the correct diagnosis of AIP.

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INTERNAL MEDICINE

EDITORIAL

Idiopathic Duct-Centric Pancreatitis (IDCP)

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Key words: autoimmune pancreatitis, IDCP, LPSP

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Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis originally proposed by Japanese investigators. Its histopathological finding are characterized by dense infiltration of T lymphocytes and IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis in the pancreas; this is called lymphoplasmacytic sclerosing pancreatitis (LPSP) (1). It is characterized clinically by elderly male preponderance and responsiveness to steroid therapy, radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct, and serologically by elevation of serum IgG4 levels (2, 3). Because AIP is frequently associated with various sclerosing extrapancreatic lesions with the same peculiar histological findings as those in the pancreas, AIP is currently considered to represent a pancreatic lesion of IgG4-related systemic disease (3).

Based upon retrospective, histological examination of the resected pancreases of patients with mass-forming chronic pancreatitis, American and European pathologists have described another unique histological pattern in AIP, which they have termed idiopathic duct-centric pancreatitis (IDCP) in 2003 (4) or AIP with granulocyte epithelial lesion (GEL) in 2004 (5). Neutrophilic infiltration in the epithelium of the pancreatic ducts is a characteristic feature of IDCP, which is not detected in LPSP. Infiltration of IgG4-positive plasma cells and obliterative phlebitis are uncommon in IDCP (4-6). The necessity for histological examination to diagnose IDCP makes the diagnosis difficult. From the early reports, IDCP patients are younger than LPSP patients (average age 48.1 years vs. 63.4 years), may not have a male preponderance (male : female ratio 5:7), and are more likely to have acute pancreatitis and ulcerative colitis (4). Recently, Sah et al (7) compared the clinical records of 78 LPSP patients and 19 IDCP patients and noted that IDCP patients were younger than LPSP patients (62±14 vs. 48±19 years); IDCP patients were less likely to show elevation of serum IgG4 levels [1/6 (17%) vs. 47/59 (80%)] and sclerosing extrapancreatic lesions (0% vs. 60%). Acute pancreatitis and association with inflammatory bowel disease were detected in 6 (32%) and 3 (16%) IDCP patients, respectively. IDCP tended to have focal enlargement of the pancreas (diffuse enlargement vs. focal enlargement: IDCP, 16% vs. 84%; LPSP, 40% vs. 60%), and surgery was more common in IDCP patients (68% vs. 32%), reflecting the difficulty in making the diagnosis. On follow-up, none of the IDCP patients experienced disease relapse, while 47% of LPSP patients relapsed requiring treatment. The prevalence of IDCP is different throughout the world. Although 20-40% of AIP cases are IDCP in the United States and Europe, most AIP cases are LPSP, and IDCP is quite rare in Japan and Korea (4-8). LPSP and IDCP have become two distinct subtypes of AIP, and it is proposed that LPSP be called type 1 AIP and IDCP type 2 AIP (6-8).

In this issue of Internal Medicine, Kusuda et al (9) report a 65-year-old woman who was histologically proven to have IDCP. The patient had no symptoms, but only serum amylase elevation. She had no other organ involvement. From the radiological findings of moderate swelling of the pancreatic body and tail without a capsule-like rim and disruption of the main pancreatic duct, distal pancreatectomy was performed, since pancreatic cancer could not be ruled out. The histology of the resected pancreas was fibrosis with neutrophilic infiltration and numerous microabscesses that were compatible with IDCP. Although this may be the first case of IDCP evaluated clinicopathologically in Japan, the clinical profile of the patient was not typical for IDCP as reported in the literature. It is unknown whether or not radiological features can be used to distinguish between LPSP and IDCP. The epithelium of the pancreatic duct of LPSP is well preserved, and long narrowing of the main pancreatic duct induced by periductal cellular infiltration is a characteristic pancreatographic feature of LPSP patients. Obstruction of the main pancreatic duct on ERP is reported to occur in only 6% (1/17) of LPSP patients (10). The pancreatogram of this patient showed abrupt ending of the main pancreatic duct. Neutrophilic infiltration within the lumen and epithelium of the pancreatic duct in IDCP suggests obstruction of

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the main pancreatic duct on ERP. Although further pancreatographic studies are necessary, the pancreatogram may be useful to distinguish between LPSP and IDCP.

Although the clinical features of IDCP differ substantially from those of LPSP in age, sex, symptoms, associated diseases, serology, and disease relapse, the biggest clinical problem in diagnosing both diseases is accurately distinguishing them from pancreatic cancer. However, the diagnosis of IDCP is currently much more difficult, because it requires histological examination of an adequate pancreatic specimen. IDCP can be suspected in subjects with pancreatic enlargement with enhancement who are seronegative and have ulcerative colitis or acute pancreatitis, but no sclerosing extrapancreatic lesions frequently associated with LPSP. Greater awareness of IDCP and identification of the serological markers and radiological features of IDCP are needed.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

K-ras mutation in the major duodenal papilla and gastric and colonic mucosa in patients with autoimmune pancreatitis

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Abstract
Background Pancreatic cancer occurs in some patients with autoimmune pancreatitis (AIP). Significant K-ras mutations are frequently detected in the pancreas of AIP patients. AIP may be a pancreatic lesion of IgG4-related systemic disease. Gastric and colonic cancer can occur during the follow up of AIP patients. We examined K-ras mutations in the major duodenal papilla and gastric and colonic mucosa of AIP patients.
Methods K-ras analysis and/or immunohistochemical study was performed on the tissues of the major duodenal papilla ($n = 8$), gastric mucosa ($n = 5$), colonic mucosa ($n = 3$), pancreas ($n = 5$), common bile duct ($n = 5$), and gallbladder ($n = 4$) of 12 AIP patients.
Results Significant K-ras mutations were detected in the major duodenal papilla of 4 of 8 cases [GAT ($n = 4$)], in the gastric mucosa of 2 of 4 cases [AGT ($n = 2$)], and in the colonic mucosa of 2 of 3 cases [GAT ($n = 2$)]. Significant K-ras mutations were detected in the pancreas of all 5 cases [GAT ($n = 5$), in the common bile duct of 4 cases (GAT ($n = 2$), TGT ($n = 1$), and GCT/TGT ($n = 1$)], and in the gallbladder epithelium of 3 cases [GAT ($n = 1$), GCT ($n = 1$), and GTT ($n = 1$)]. K-ras mutations were detected in the organs associated with IgG4-related fibroinflammation with abundant infiltration of T lymphocytes and forkhead box P3-positive cells.
Conclusions Significant K-ras mutations were frequently detected in the major duodenal papilla and gastric and colonic mucosa of AIP patients. AIP patients may have risk factors for gastric and colonic cancer, but the mechanisms of K-ras mutation and its clinical implications are not clear.

Keywords Autoimmune pancreatitis · K-ras · IgG4 · Foxp3

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Introduction

Autoimmune pancreatitis (AIP) is a type of pancreatitis with presumed autoimmune etiology. AIP is characterized radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct, serologically by the elevation of serum IgG4 levels, histopathologically by fibrosis with dense infiltration of T lymphocytes and IgG4-positive plasma cells in the peripancreatic and interlobular areas of the pancreas, and clinically by a preponderance of elderly males and good responsiveness to steroid therapy. However, AIP cases may be difficult to differentiate from pancreatic cancer, and some AIP patients in whom pancreatic cancer is suspected undergo unnecessary laparotomy or pancreatic resection [1, 2].

AIP responds well to steroid therapy and appears to be reversible, unlike ordinary chronic pancreatitis [3]. However,

several reports of AIP associated with pancreatic cancer occurring simultaneously or during follow up have recently been described [2, 4–8]. To assess the relationship between AIP and pancreatic cancer, we previously demonstrated high K-ras mutation levels in the pancreas of 8 patients, in the common bile duct of 5 AIP patients, and in the gallbladder epithelium of 4 AIP patients [9]. We also reported that K-ras mutations were detected in the fibroinflammatory pancreas, bile duct, and gallbladder with abundant infiltrating IgG4-positive plasma cells and forkhead box P3 (Foxp3)-positive cells of AIP patients with elevated serum IgG4 levels [9].

AIP is frequently associated with various extrapancreatic lesions. We have found dense infiltrations of IgG4-positive plasma cells and CD4- or CD8-positive T lymphocytes, as well as fibrosis, in extrapancreatic lesions, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis. Furthermore, abundant infiltration of IgG4-positive plasma cells was detected in various organs, such as the liver, stomach, major duodenal papilla, colon, dermis, lymph node, and bone marrow of AIP patients. Both the pancreatic and extrapancreatic lesions of AIP respond well to steroid therapy. Therefore, we have proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease", and suggested that AIP is a pancreatic lesion of this systemic disease [10–12]. From the standpoint of the systemic disease, we investigated K-ras mutations in the major duodenal papilla and gastric and colonic mucosa of AIP patients.

Materials and methods

Study patients and study materials

Between 1989 and 2009, 63 patients were diagnosed as having AIP, based on the Asian diagnostic criteria for AIP [13]. They were followed up for 3.8 ± 2.3 years (mean ± SD). With respect to associated malignancies, pulmonary cancer occurred in 2 patients (9 years after onset of AIP and simultaneously with AIP, respectively); esophageal cancer occurred 1 year after onset of AIP, and prostatic cancer occurred 1 year after AIP.

K-ras analysis and/or immunohistochemical study was performed on the tissues of the major duodenal papilla ($n = 8$), gastric mucosa ($n = 5$), and colonic mucosa ($n = 3$) of 12 AIP patients (9 males and 3 females; age range, 25–79 years; average age, 59.1 ± 18.5 years). One patient had a history of heavy drinking and smoking and 2 had a history of heavy smoking. Nine patients showed diffuse enlargement of the pancreas, and 3 patients showed segmental enlargement of the pancreatic head. Five patients underwent pancreatoduodenectomy on suspicion of pancreatic cancer, and the histopathological findings of the resected pancreas were compatible with lymphoplasmacytic sclerosing pancreatitis. The other 7 patients received steroid therapy and responded well. As to the long-term outcome, 9 patients have been followed up until now, 1 patient was lost to follow up 3 years after the operation, and 2 patients died, of pulmonary cancer and pneumonia, respectively (Table 1).

The study materials consisted of 5 stomachs, and 4 major duodenal papillae obtained from pancreatoduodenectomies, 4 endoscopically biopsied major duodenal papillae, and 3 endoscopically biopsied colonic mucosa [rectum ($n = 2$) and sigmoid colon ($n = 1$)] specimens. Endoscopically, the major duodenal papilla was swollen in 1 case (Case 6), and a biopsy was performed prospectively for examining the infiltration of IgG4-positive plasma cells. Biopsy specimens were taken from an area of colitis in the sigmoid colon of Case 11, from a reddish area in the rectum of Case 10, and from a tiny polypoid lesion in the rectum of Case 12. The duration between the clinical onset

Table 1 Clinical and radiological findings in 12 patients with autoimmune pancreatitis

Case	Age (years)	Sex	Type	Therapy	Long-term outcome
1	65	m	Segmental (H)	Pancreatoduodenectomy	Currently alive 9 years after the operation
2	71	m	Segmental (H)	Pancreatoduodenectomy	Died of pneumonia 1 year after the operation
3	65	f	Diffuse	Pancreatoduodenectomy	Currently alive 13 years after the operation
4	69	m	Diffuse	Pancreatoduodenectomy	Died of pulmonary cancer 10 years after the operation
5	79	m	Diffuse	Pancreatoduodenectomy	Lost to follow up 3 years after the operation
6	66	f	Diffuse	Steroid therapy	Currently alive 2 years after the diagnosis
7	76	m	Diffuse	Steroid therapy	Currently alive 4 years after the diagnosis
8	66	m	Diffuse	Steroid therapy	Currently alive 2 years after the diagnosis
9	64	m	Segmental (H)	Steroid therapy	Currently alive 3 years after the diagnosis
10	26	m	Diffuse	Steroid therapy	Currently alive 2 years after the diagnosis
11	25	m	Diffuse	Steroid therapy	Currently alive 1 year after the diagnosis
12	37	f	Diffuse	Steroid therapy	Currently alive 10 years after the diagnosis

H Head

of AIP and the tissue sampling was within 1.5 months in all cases. The 5 pancreases, common bile ducts, and gallbladders obtained from pancreatoduodenectomies were also examined; all of these specimens were the subject of a previous report [9].

The surgical, biopsied, and autopsied tissues were fixed in 10% neutral buffered formalin. Each 1-cm-wide tissue section was examined. Tissue blocks were routinely processed and embedded in paraffin. Serial sections were cut at a thickness of 3 μm. All sections were stained with hematoxylin and eosin (H&E) and examined immunohistochemically.

All subjects provided their written informed consent. This study was approved by the relevant institutional review boards.

Immunohistochemical study

Immunohistochemistry was performed on an average of 2 representative sections from each case, using antibodies against IgG4 (The Binding Site, Birmingham, UK), CD4 T-cell subset (Novocastra, Newcastle, UK), CD8 T-cell subset (Nichirei Bio Science, Tokyo, Japan), and Foxp3 (clone 22509; Abcam, Oxford, UK). All sections were stained by the avidin–biotin horseradish peroxidase method (Vectastain Elite ABC kit; Vector, Burlingame, CA, USA). The additional staining procedures used have all been previously reported [10, 11, 14]. The degrees of infiltrating IgG4-positive plasma cells and Foxp3 were classified as (3+) [more than 30/high power field (HPF)], (2+) (10–30/HPF), (1+) (5–10/HPF), (+/−), (1–4/HPF), and (−) (0/HPF) [11].

K-ras mutation analysis

Paraffin blocks were prepared for DNA extraction. Two lesions from the gastric mucosa, major duodenal papilla, pancreatic duct epithelium, common bile duct epithelium, and gallbladder mucosal epithelium of pancreatoduodenectomy specimens, and biopsy specimens taken endoscopically from the major duodenal papilla and colonic mucosa were used for DNA extraction. The target lesions were microdissected, using a 20-G needle, by comparing an H&E-stained section in the same position. DNA was extracted from paraffin-embedded tissue using a QIAamp DNA FFPE Tissue Kit (QIAGEN, Hilden, Germany). DNA was extracted from the pancreatic juice using a QIAamp DNA Mini Kit (QIAGEN). Mutation of K-ras codon 12 was analyzed and results were compared by enriched polymerase chain reaction-enzyme linked mini-sequence assay (PCR-ELMA) [9, 15].

K-ras was amplified by PCR and then detected and quantitated using a microtiter plate reader (MULTISKAN JX; ThermoFisher Scientific, Yokohama, Japan). The results of the semiquantitative analysis were scored as (3+), (2+), (1+), (+/−), and (−) according to the percentage of mutant ras gene. In general, (3+), (2+), (1+), (+/−), and (−) represented approximately more than 20%, 2%–20%, 0.2%–2%, less than 0.2%, and none (not detected) of the mutant, respectively, according to the manufacturer [9, 15].

Results

Histopathological and immunohistochemical findings

Histopathologically, marked lymphoplasmacytic infiltration with mild to moderate fibrosis was detected in the major duodenal papilla, but there were no atypical changes in the epithelium of the major duodenal papilla (Fig. 1a). Most infiltrated lymphocytes were CD4- or CD8-positive T lymphocytes. Infiltration of IgG4-positive plasma cells in the major duodenal papilla was abundant (3+ or 2+) in 4 cases (Fig. 1b) and mild (1+) in 4 cases. Infiltration of Foxp3-positive cells in the major duodenal papilla was abundant (2+) in 2 cases, mild (1+) in 3 cases, and few (+/−) in 3 cases.

Histologically, marked lymphoplasmacytic infiltration was detected in the gastric mucosa in 2 cases (Cases 1 and 3), but there were no atypical changes in the epithelium of the gastric mucosa. Infiltration of IgG4-positive plasma cells in the gastric mucosa of the antrum was abundant (2+) in 2 cases (Fig. 1c), and few (+/−) in 2 cases. Infiltration of Foxp3-positive cells in the gastric mucosa was mild (1+) in 1 case, and few (+/−) in 3 cases.

Histologically, marked lymphoplasmacytic and neutrophilic infiltration was detected in the colonic mucosa in 1 case (Case 11), but there were no atypical changes in the epithelium of the colonic mucosa. Infiltration of IgG4-positive plasma cells in the colonic mucosa was abundant (2+) in 2 cases (Fig. 1d) and none (−) in 1 case. Infiltration of Foxp3-positive cells in the colonic mucosa was abundant (2+) in 1 case (Fig. 1e), mild (1+) in 1 case, and none (−) in 1 case.

Marked lymphoplasmacytic infiltration, periductal and interlobular fibrosis, and obliterative phlebitis in the pancreas, and transmural fibrosis with marked lymphoplasmacytic infiltration in the common bile duct were detected in the tissues from all AIP cases. Transmural fibrosis with lymphoplasmacytic infiltration was detected in the gallbladder wall of 4 cases (Cases 1–4). There were no atypical changes in the epithelium of the pancreatic and biliary ducts and gallbladder. Abundant infiltration of IgG4-positive plasma cells (2+ or 3+) in the pancreas, bile duct, and gallbladder was detected in all cases. Abundant (2+) and mild (1+) infiltration of Foxp3-positive cells in the

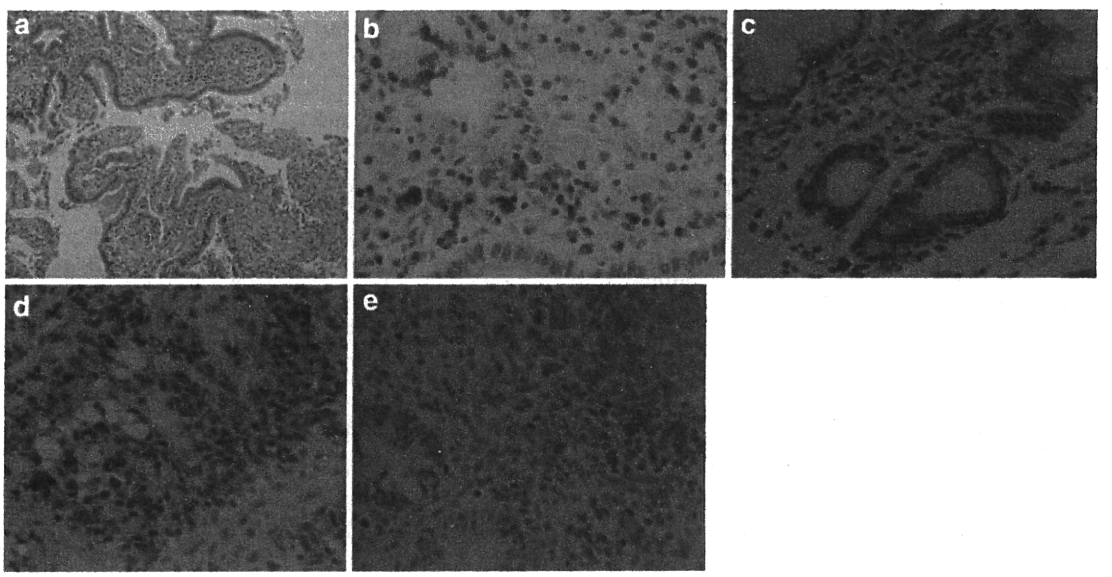

Fig. 1 Histopathological and immunohistochemical findings in the major duodenal papilla and gastric and colonic mucosa of patients with autoimmune pancreatitis. **a** Marked lymphoplasmacytic infiltration with mild fibrosis was detected in the major duodenal papilla (Case 1). **b** Abundant infiltration of IgG4-positive plasma cells detected in the major duodenal papilla (Case 1). **c** Abundant infiltration of IgG4-positive plasma cells detected in the gastric mucosa (Case 3). Abundant infiltration of **d** IgG4-positive plasma cells and **e** forkhead box P3 (Foxp3)-positive cells detected in the colonic mucosa (Case 11)

pancreas, bile duct, and gallbladder was detected in 60 and 40%, 40 and 60%, and 0 and 40%, respectively (Table 2).

K-ras mutation

Significant K-ras mutations (3+) were detected in the major duodenal papilla of 4 of 8 cases [GAT ($n = 4$)] (Fig. 2a). Significant K-ras mutations (3+) were detected in the gastric mucosa of 2 of 4 cases [AGT ($n = 2$)] (Fig. 2b). Significant K-ras mutations (2+) were detected in the colonic mucosa of 2 of 3 cases [GAT ($n = 2$)] (Fig. 2c).

Significant K-ras mutations (3+) were detected in the pancreas of all 5 cases [GAT ($n = 5$)]. Significant K-ras mutations (3+) were detected in the common bile duct of 4 cases [GAT ($n = 2$), TGT ($n = 1$), and GCT/TGT ($n = 1$)]. Significant K-ras mutations (3 +or 2+) were detected in the gallbladder epithelium of 3 cases [GAT ($n = 1$), GCT ($n = 1$), and GTT ($n = 1$)].

Abundant or mild infiltration of IgG4-positive plasma cells and Foxp3-positive cells was also detected in the major duodenal papilla and gastric and colonic mucosa of all cases with significant K-ras mutations (Table 2).

In comparisons of the distribution of K-ras mutation and the density of IgG4-positive or Foxp3-positive cells in the major duodenal papilla with those in the stomach of the same patient (Cases 1, 3, and 4), significant K-ras mutation of different mutant types with abundant infiltration of IgG4-positive plasma cells and mild or few Foxp3-positive cells was detected in both the major duodenal papilla and stomach in Case 3. However, in Cases 1 and 4, the distribution of K-ras mutation and the densities of IgG4-positive plasma cells and Foxp3-positive cells were different in the major duodenal papilla and stomach.

Discussion

K-ras mutation is believed to occur at a relatively early stage during the multistep carcinogenesis process. K-ras mutations were detected in more than 95% of pancreatic cancers [16] and in 27% of hyperplastic pancreatic duct epithelium in chronic pancreatitis [17]. Furthermore, as the cumulative risk of pancreatic cancer in subjects with chronic pancreatitis was reported to be 1.8% after 10 years and 4.0% after 20 years, chronic pancreatitis is considered to be a risk factor for the development of pancreatic cancer [18].

Several reports of AIP associated with pancreatic cancer occurring simultaneously or during follow up have recently been described [2, 4–8]. We have demonstrated that significant K-ras mutations occurred frequently in the pancreas, common bile duct, and gallbladder with fibroinflammation with abundant infiltrating IgG4-positive plasma cells and Foxp3-positive cells in AIP patients, although the mechanism of the K-ras mutation was unclear [9].

Table 2 Serum IgG4 levels, distribution of IgG4- and Foxp3-positive cells, and K-ras mutations in the pancreas, common bile duct, gallbladder, major duodenal papilla, stomach, and colon of 12 patients with autoimmune pancreatitis

	Serum IgG4 (mg/dl)	Pancreas	Common bile duct	Gallbladder	Duodenal papilla	Stomach	Colon
1	505	K-ras: 3+ (GAT) IgG4+: 3+ Foxp3+: 2+	K-ras: 3+ (TGT) IgG4+: 3+ Foxp3+: 1+	K-ras: 2+ (GAT) IgG4+: 3+ Foxp3+: +/−	K-ras: 3+ (GAT) IgG4: 2+ Foxp3: 2+	K-ras: +/− (CGT) IgG4+: 2+ Foxp3+: +/−	NE
2	550	K-ras: 3+ (GAT) IgG4+: 3+ Foxp3+: 2+	K-ras: 3+ (GAT) IgG4+: 3+ Foxp3+: 1+	K-ras: 3+ (GTT) IgG4+: 3+ Foxp3+: 1+	NE	K-ras: +/− (GTT) IgG4+: +/− Foxp3+: +/−	NE
3	1240	K-ras: 3+ (GAT) IgG4+ : 3+ Foxp3+: 2+	K-ras: 3+ (GCT/TGT) IgG4+: 3+ Foxp3+: 2+	K-ras: 3+ (GCT) IgG4+: 3+ Foxp3+: 1+	K-ras: 3+ (GAT) IgG4+: 3+ Foxp3+: 1+	K-ras: 3+ (AGT) IgG4+: 2+ Foxp3+: 1+	NE
4	150	K-ras: 3+ (GAT) IgG4+: 3+ Foxp3+: 1+	K-ras: 3+ (GAT) IgG4+: 3+ Foxp3+: 2+	NA IgG4+: 2+ Foxp3+: −	K-ras: +/− (AGT) IgG4+: 2+ Foxp3+: 1+	K-ras: 3+ (AGT) IgG4+: +/− Foxp3+: +/−	NE
5	43	K-ras: 3+ (GAT) IgG4+ : 3+ Foxp3+: 1+	NA IgG4+: 2+ Foxp3+: 1+	+/− (GAT) IgG4+: 2+ Foxp3+: −	K-ras: 3+ (GAT) IgG4+: 1+ Foxp3+: 1+	NA IgG4+: − Foxp3+: −	NE
6	1230	NE	NE	NE	K-ras: 3+ (GAT) IgG4+: 2+ Foxp3+: 2+	NE	NE
7	1160	NE	NE	NE	K-ras: − IgG4+: 1+ Foxp3+: +/−	NE	NE
8	395	NE	NE	NE	K-ras: − IgG4+: 1+ Foxp3+: +/−	NE	NE
9	867	NE	NE	NE	K-ras: − IgG4+: 1+ Foxp3+: +/−	NE	NE
10	647	NE	NE	NE	NE	NE	K-ras: 2+ (GAT) IgG4+: 2+ Foxp3+: 1+
11	45	NE	NE	NE	NE	NE	K-ras: 2+ (GAT) IgG4+: 2+ Foxp3+: 2+
12	11	NE	NE	NE	NE	NE	K-ras: +/− (AGT) IgG4+: − Foxp3+: −

NE Not examined, *NA* not amplified, *Foxp3* forkhead box P3

Because dense infiltration of IgG4-positive plasma cells and CD4- or CD8-positive T lymphocytes, as well as fibrosis, was detected in extrapancreatic lesions, and abundant infiltration of IgG4-positive plasma cells was also detected in various other organs in AIP patients, we have proposed a new clinicopathological entity, an "IgG4-related sclerosing disease", and suggested that AIP is a pancreatic lesion of this systemic disease [10–12]. This concept led us to investigate K-ras mutation in the major duodenal papilla, and in the gastric and colonic mucosa of AIP patients.

In the present study, significant K-ras mutations were detected in the major duodenal papilla of 4 (3 resected and 1 biopsied cases) of 8 AIP cases. All major duodenal papillae with significant K-ras mutations were associated with abundant or mild infiltration of IgG4-positive plasma cells and Foxp3-positive cells. The mutant type of ras gene was GAT in all 4 cases, which was quite similar to the

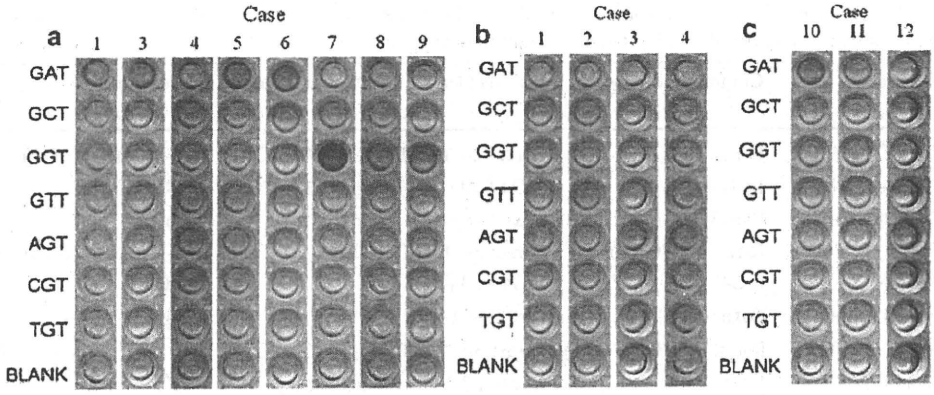

Fig. 2 Actual images of microwells in semiquantitative analysis of mutant K-ras gene by polymerase chain reaction-enzyme linked minisequence assay (PCR-ELMA) in **a** the major duodenal papilla (Cases 1, 3–9), **b** the gastric mucosa (Cases 1–4), and **c** the colonic mucosa (Cases 10–12). Hybridization was performed using both wild-type (GGT) and 6 kinds of mutant specific probes (GAT, GCT, GTT, AGT, CGT, and TGT) that were immobilized to the microtiter plate well. The type and semiquantitation of the K-ras gene were identified as mutant type (3+) or (2+), when the signal was observed exclusively in the mutant specific probe well

K-ras mutation type in the pancreas. It was reported that K-ras mutation was detected in about 40% of cancers of the major duodenal papilla, and the mutations were mainly GAT or GTT [19, 20]. However, because histological examination of the resected pancreas showed inflammation of the major duodenal papilla followed by inflammation of the pancreatic head in AIP cases, it seems that the K-ras mutation in the major duodenal papilla might be the consequence of K-ras mutation in the pancreas.

Significant K-ras mutations were detected in the gastric mucosa of 2 of 4 resected cases in the present study, and the mutation type was AGT in the 2 cases. Lee et al. [21] reported that K-ras mutations were detected in 7.9% of gastric cancers, and the mutation type was AGT in 78% of them. Gong et al. [22] reported that the AGT transition was important for the progression of gastric mucosal cells to a more advanced premalignant stage. Watari et al. [23] reported that K-ras mutations in chronic gastritis with GAT and TGT types disappeared after *Helicobacter pylori* eradication, but AGT remained in most cases after treatment, and mutations with AGT were considered more likely to be advantageous in K-ras gene alterations.

Significant K-ras mutations were detected in the colonic mucosa of 2 of 3 biopsied cases in the present study, and the mutation type was GAT in the 2 cases. One specimen was taken from an area of colitis in the sigmoid colon, and the other was taken from a reddish area in the rectum. It has been reported that K-ras mutations were detected in 32%–44% of colonic cancers, and the mutant types were mainly GAT and GTT [24, 25].

In the present AIP patients, high levels of significant K-ras mutation were frequently detected in the major duodenal papilla, gastric mucosa, and colonic mucosa, associated with abundant infiltration of IgG4-positive plasma cells, T lymphocytes, and Foxp3-positive cells, similar to the findings in the pancreas, bile duct, and gallbladder. K-ras mutation types in the major duodenal papilla, gastric mucosa, and colonic mucosa were similar to those in cancers of each organ. It has been reported that gastric cancer and colonic cancer developed simultaneously or during the follow up of AIP [26, 27]. In AIP patients, the major duodenal papilla, gastric mucosa, and colonic mucosa, as well as the pancreas, bile duct, and gallbladder, may be the sites of a premalignant lesion. However, the mechanism of K-ras mutation in the various organs of AIP patients is still unclear. The epithelia of these organs did not show any atypical changes, although there was a report of a stepwise increase in K-ras mutation that correlated with the grade of dysplasia in pancreatic intraepithelial neoplasia (PanIN) [28]. Foxp3-positive regulatory T cells, producing interleukin 10 and transforming growth factor β, which was followed by IgG4 class switching and fibroplasias, were increasingly detected in the pancreas and the biliary tract of AIP patients [1, 29]. It has been reported that Foxp3-positive regulatory T cells were increased locally in pancreatic cancer [30], and Foxp3-positive regulatory T cells and inflammation played an essential and important role in K-ras-mediated lung tumorigenesis in mice [31]. Brembeck et al. [32] showed dramatic lymphocytic infiltration around the periductal area in transgenic mice fused to mutant K-ras and suggested that these lymphocyte infiltrations might act as an adaptive immune response to activated ras-mediated signaling. Watari et al. [23] reported that, because K-ras mutations sometimes occurred in gastric intestinal metaplasia with *H. pylori* infection, but some mutations disappeared after *H. pylori* eradication, early events in K-ras mutations in gastric intestinal metaplasia were unstable in some cases and may have been related to the lymphocyte infiltration caused by *H. pylori* infection.

AIP appears to be a pancreatic lesion of an IgG4-related systemic disease. AIP is usually diagnosed in the active stage, but IgG4-related fibroinflammation may have persisted subclinically in various organs for a long time. In AIP patients, K-ras mutation may occur in the organs showing persistent IgG4-related fibroinflammation with abundant infiltration of T lymphocytes and Foxp3-positive cells.

The present study is the first to have demonstrated frequent and significant K-ras mutations in the major duodenal papilla and gastric and colonic mucosa of AIP patients, but the number of cases and the number of samples in which K-ras mutation was investigated were small. However, we believe that the data presented here, as a pilot study, are very interesting and will generate interest to extend the studies. Further investigations are thus required using a larger series of samples with a longer-term follow up to determine the possible role of K-ras mutation as a precancerous lesion in AIP patients. Furthermore, investigations of K-ras mutation in other organs in AIP patients and changes in K-ras mutation after steroid therapy should also be informative.

In conclusion, in AIP patients, significant K-ras mutations were frequently detected in the major duodenal papilla, and in the gastric and colonic mucosa, as well as in pancreatobiliary regions associated with IgG4-related fibroinflammation with abundant infiltration of T lymphocytes and Foxp3-positive cells. AIP patients may have risk factors for gastric and colonic cancer, but the mechanism of K-ras mutation and its clinical implications are not clear.

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Two Clinicopathologic Subtypes of Autoimmune Pancreatitis: LPSP and IDCP

See "Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis," by Sah RP, Chari ST, Pannala R, et al, on page 140.

Autoimmune pancreatitis (AIP) is a rare disease that has emerged recently as a peculiar type of pancreatitis with a presumed autoimmune etiology. Sarles et al[1] first reported a form of idiopathic chronic pancreatitis suspected to be induced by an autoimmune mechanism in 1961. In 1991, Kawaguchi et al[2] reported 2 cases of an unusual inflammatory disease involving the pancreas and biliary tract that were resected on suspicion of pancreatic cancer, and described the histology as lymphoplasmacytic sclerosing pancreatitis (LPSP) based on the peculiar histologic findings. In 1995, Yoshida et al[3] first proposed the concept of AIP, and summarized the clinical features as follows: increased serum γ-globulin or immunoglobulin (Ig)G levels and presence of autoantibodies; diffuse irregular narrowing of the main pancreatic duct 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 histologic finding of LPSP.[3] In 2001, serum IgG4 levels were found to be frequently elevated in AIP patients.[4] Because AIP is frequently associated with various sclerosing extrapancreatic lesions with the same peculiar histologic findings as in the pancreas, AIP is currently considered to represent a pancreatic lesion of IgG4-related systemic disease.[5-7]

Using retrospective, histologic examination of pancreases resected on suspicion of pancreatic cancer from patients with mass-forming chronic pancreatitis, American and European pathologists have described another unique histologic pattern, described as idiopathic duct-centric pancreatitis (IDCP)[8] or AIP with granulocytic epithelial lesion.[9] LPSP and IDCP share some represen-