

[CASE REPORT]

Autoimmune Pancreatitis with Gastric Cancer: Some IgG4-related Diseases May Be Paraneoplastic Syndrome

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Abstract:

A 70-year-old man was referred to our department for the treatment of early gastric cancer. Contrast-enhanced computed tomography (CT) incidentally showed diffuse enlargement of the pancreas with a capsule-like rim, and blood tests showed elevated serum IgG4 levels, leading to a diagnosis of autoimmune pancreatitis (AIP). Endoscopic treatment for gastric cancer was performed, and pathological findings showed adenocarcinoma with abundant IgG4-positive plasma cell infiltration. Thereafter, the serum IgG4 levels normalized, and the findings of AIP disappeared on CT without steroid treatment. These findings suggest that the gastric cancer activated an IgG4-related immune response, resulting in the development of AIP.

Key words: autoimmune pancreatitis, early gastric cancer, paraneoplastic syndrome

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Introduction

Autoimmune pancreatitis (AIP) is a peculiar pancreatitis that often develops in obstructive jaundice and sometimes forms a pancreatic mass. It is categorized into types 1 and 2 (1, 2). Type 1 AIP is now regarded as a pancreatic manifestation of systemic immunoglobulin 4-related disease (IgG4-RD) (3). The typical histological findings are lymphocyte and IgG4-positive plasma cell infiltration, fibrosis and obliterative phlebitis in the pancreas (4). Although the pathogenesis of AIP remains unknown, various environmental and immunological factors are thought to be involved in the onset (5). Various types of cancer are reportedly complicated in AIP or/and IgG4-RD (6-8), and some AIP or/and IgG4-RD may develop as paraneoplastic syndromes. However, there are no prospective studies that support this hypothesis (9).

We herein report a case of AIP achieving long-term maintenance of remission without steroid treatment after curative endoscopic resection of a coexisting early gastric cancer

with IgG4-positive plasma cell infiltration. This case may confirm the concept that some cases of AIP develop as paraneoplastic syndrome.

Case Report

A 70-year-old man who underwent esophagogastroduodenoscopy for epigastralgia and a depressed lesion at the lesser curvature of the gastric body was identified. An endoscopic biopsy revealed a well differentiated adenocarcinoma, and the patient was referred to our department for treatment. He had a history of having undergone *Helicobacter pylori* eradication therapy three years before, with no other notable medical or family history of diseases. There were no abnormalities on a physical examination. Although contrast-enhanced computed tomography (CT) showed no enlarged lymph nodes or distant metastases, diffuse enlargement of the pancreas and a capsule-like rim that appeared as a band-like area around the whole pancreas were incidentally detected (Fig. 1).

Laboratory data showed no elevation of hepatobiliary en-

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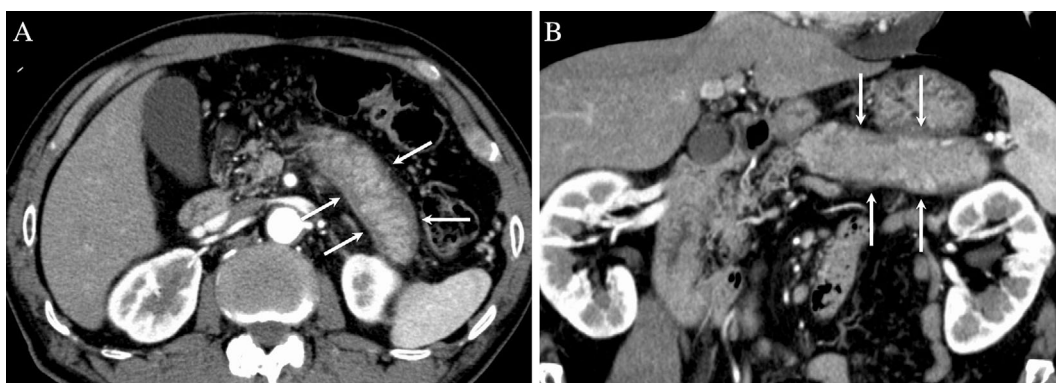


Figure 1. Abdominal arterial phase-enhanced computed tomography (CT) performed at the time of the visit to our department. The axial image (A) and coronal image (B) showing enlargement of the pancreas with a capsule-like low-density rim (arrows).

Table. Laboratory Data at the Onset of Autoimmune Pancreatitis.

Peripheral blood		Amylase	41 U/L
WBC	7,400 / μ L	Lipase	20 U/L
Eosinophil	0.5 %	BUN	19 mg/dL
Basophil	0.5 %	Creatinine	0.82 mg/dL
Lymphocyte	18.4 %	Glucose	108 mg/dL
Monocyte	5.4 %	HbA1c (NGSP)	5.4 %
Neutrophil	75.2 %		
RBC	516 \times 10 ⁴ / μ L	Serology	
Hemoglobin	15.9 g/dL	CRP	0.04 mg/dL
Platelet	17.9 \times 10 ⁴ / μ L	IgG	1,939 mg/dL
		IgG4	239 mg/dL
Biochemistry		Tumor markers	
Total protein	7.3 g/dL	CEA	1.2 ng/mL
Albumin	4.1 g/dL	CA19-9	<0.6 U/mL
Total bilirubin	0.5 mg/dL		
AST	23 U/L		
ALT	23 U/L		
LDH	169 U/L		
ALP	209 U/L		
GGT	16 U/L		

WBC: white blood cell, RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic dehydrogenase, ALP: alkaline phosphatase, GGT: γ -glutamyl transpeptidase, BUN: blood urea nitrogen, HbA1c: hemoglobin A1c, CRP: C-reactive protein, IgG: immunoglobulin G, IgG4: immunoglobulin G4, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

zymes, pancreatic enzymes or tumor markers. The serum IgG4 level was high (239 mg/dL). The laboratory data on admission are summarized in Table. Endoscopic ultrasonography (EUS) showed hypoechoic swelling of the whole pancreas without thickening of the extrahepatic bile duct. On magnetic resonance cholangiopancreatography (MRCP), the main pancreatic duct was stenotic and partially obscured, and there was no stenosis of the common bile duct (Fig. 2). In addition, contrast-enhanced CT showed no obvious swelling of the lacrimal, parotid or submandibular glands and no pulmonary or renal lesions or retroperitoneal fibrosis. We therefore diagnosed the patient with AIP according to the International Consensus Diagnostic Criteria

(ICDC) (10), including typical imaging findings, diffuse pancreatic enlargement with delayed enhancement of the parenchyma with a capsule-like rim and increased serum levels of IgG4. EUS-guided fine needle aspiration was not performed because contrast-enhanced CT showed typical features of AIP, with no findings suggesting pancreatic cancer.

We performed endoscopic submucosal dissection of the gastric cancer, as we determined that there was no evidence of submucosal invasion on endoscopic findings (Fig. 3). The postoperative pathological diagnosis was early gastric cancer (type 0-IIa+IIc), 80 mm, tub1, pT1a (M), Ly0, V0, pHM0, pVM0 according to the 15th edition of Japanese Classification of Gastric Carcinoma (11) (Fig. 4A, B). Therefore,

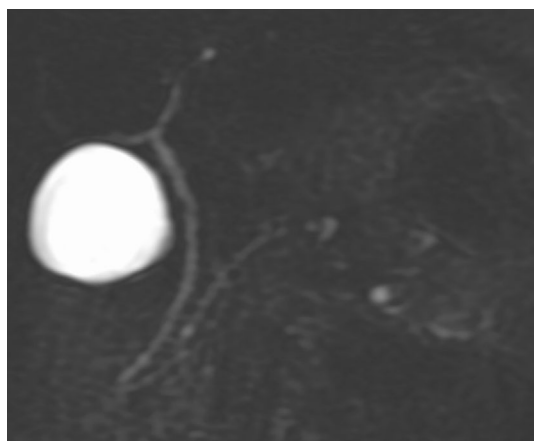


Figure 2. Magnetic resonance cholangiopancreatography (MRCP) showing stenosis of the main pancreatic duct with partial obscuration.

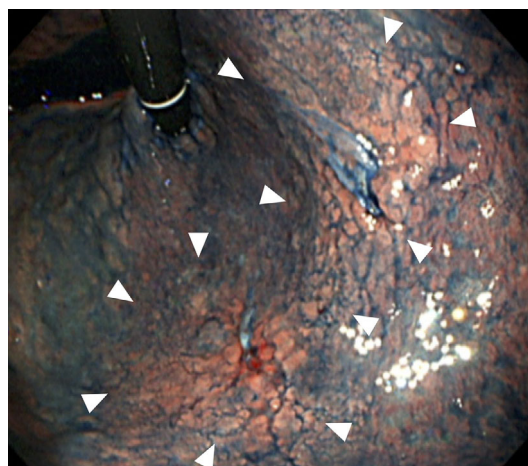


Figure 3. Esophagogastroduodenoscopy performed in our department showing a flat, depressed lesion at the lesser curvature of the gastric body (arrows).

curative resection was achieved. In addition, the cancer lesion showed the infiltration of plasma cells, with marked infiltration of IgG4-positive plasma cells on immunostaining (Fig. 4C, D).

Regarding the treatment of AIP, since there were no symptoms, such as obstructive jaundice or abdominal pain, pancreatic enzymes were normal, and there was no new-onset of diabetes mellitus nor any extra-pancreatic manifestations on imaging, we did not perform steroid treatment. Ten months after the endoscopic treatment, the serum IgG4 levels normalized and were maintained at normal levels for the next 30 months (Fig. 5). One year after the endoscopic treatment, diffuse enlargement of the pancreas with a capsule-like rim had disappeared on CT, and there has been no relapse to date (Fig. 6).

Discussion

Several reports have shown that various cancers are complicated by AIP or/and IgG4-RD, such as pancreatic cancer (12), lung cancer (13), gastric cancer (9), lymphoma (14) and thyroid cancer (15). It has also been suggested that AIP or/and IgG4-RD might have developed as a paraneoplastic syndrome in some cases (9). We herein report a case of AIP wherein long-term maintenance of remission was achieved without steroid treatment after curative endoscopic resection of the coexisting early gastric cancer with IgG4-positive plasma cell infiltration. This case may confirm the concept that some AIP should be categorized as a paraneoplastic syndrome.

Long-term chronic inflammation is well known to play an important role in carcinogenesis. The best examples of inflammation-associated cancer are *Helicobacter pylori*-associated gastric cancer, ulcerative colitis-associated colon cancer, and viral hepatitis-associated hepatocellular carcinoma (16). AIP is also a chronic inflammatory disease regarded as a pancreatic lesion of IgG4-RD characterized by the enlargement in systemic organs due to abundant IgG4-

positive plasma cell infiltrations (2). Kamisawa et al. analyzed *K-ras* mutations in the pancreatobiliary tissues of AIP patients and showed that a high rate of *K-ras* mutations were observed in the epithelium of pancreatic ducts, bile ducts and gallbladder, suggesting that AIP may be a risk factor of pancreatobiliary cancer (17). In contrast to these previous findings, however, Shiokawa et al. and Yamamoto et al. showed no occurrence of pancreatic cancer in AIP and/or IgG4-RD patients during 3.1 and 3.3 years of follow-up, respectively (9, 18). Furthermore, they showed that cancers are observed in the extra-target organs of IgG4-RD rather than target organs (9, 18). In cases of carcinogenesis associated with chronic inflammation, the risk of carcinogenesis increases in proportion to the activity and duration of the autoimmune diseases (16). In AIP patients, by contrast, the occurrence of malignancies at or within 1 year after the diagnosis of AIP is significantly higher than in subsequent years (9). Another feature of AIP patients with concomitant cancer with IgG4-positive cell infiltration was that curative treatment of coexisting cancers has prevented the relapse of AIP during or after steroid treatment (9).

The above findings are similar to the relationship between dermatomyositis (DM) and cancer. DM is well known to be a paraneoplastic syndrome. In DM patients, the standardized incidence ratio of cancer development is 7.7 (19). In many cases of DM associated with cancers, the cancer was diagnosed within one year after the diagnosis of DM, and the activity of DM was alleviated after the successful treatment of the cancer (20, 21). In our case, AIP may have developed as a paraneoplastic process because early gastric cancer was recognized at the time of the diagnosis of AIP, and normalization of serum IgG4 levels and improvement of diffuse pancreatic enlargement occurred after curative endoscopic resection of cancer without steroid treatment.

Here, the question arises as to whether or not the occurrence of gastric cancer in the present case is associated with chronic inflammation related to IgG4-RD. In other words,

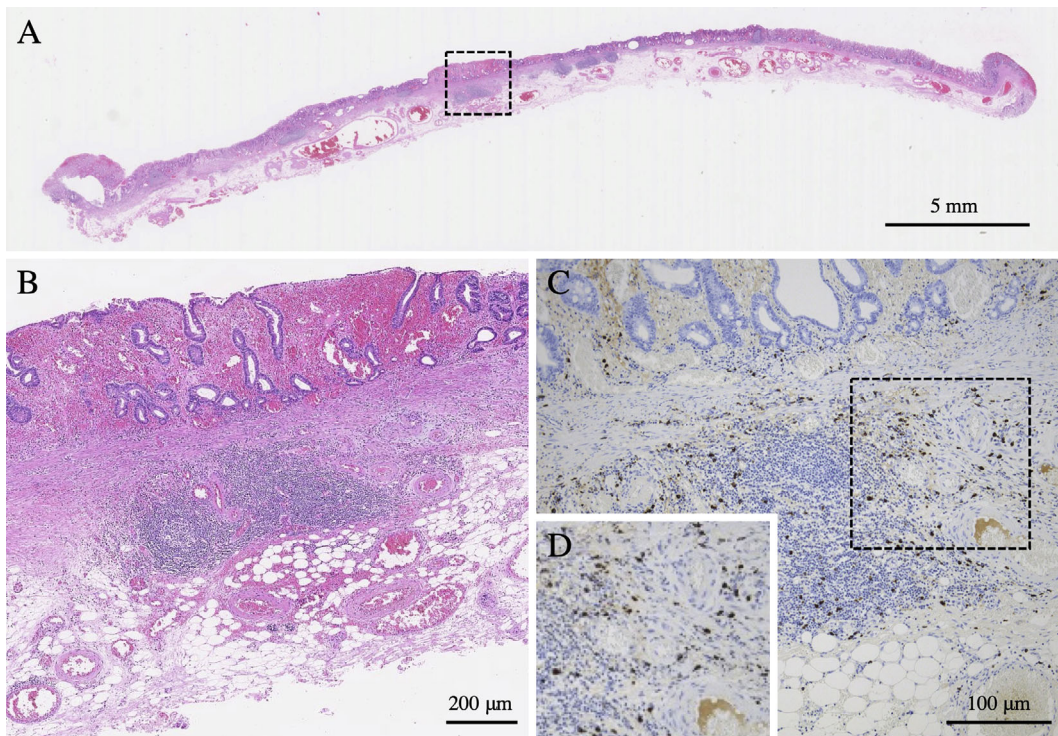


Figure 4. A histological examination of the resected specimen by endoscopic submucosal dissection showing a well-differentiated adenocarcinoma. (A) Loupe image of the gastric lesion stained with Hematoxylin and Eosin staining (Scale bar=5 mm). (B) Higher magnification of the boxed area shown in (A) (Scale bar=200 μ m). (C) Immunohistochemical staining for IgG4 with the boxed area shown enlarged in (D) showing >30 IgG4-positive plasma cells per high-power field (Scale bar=100 μ m).

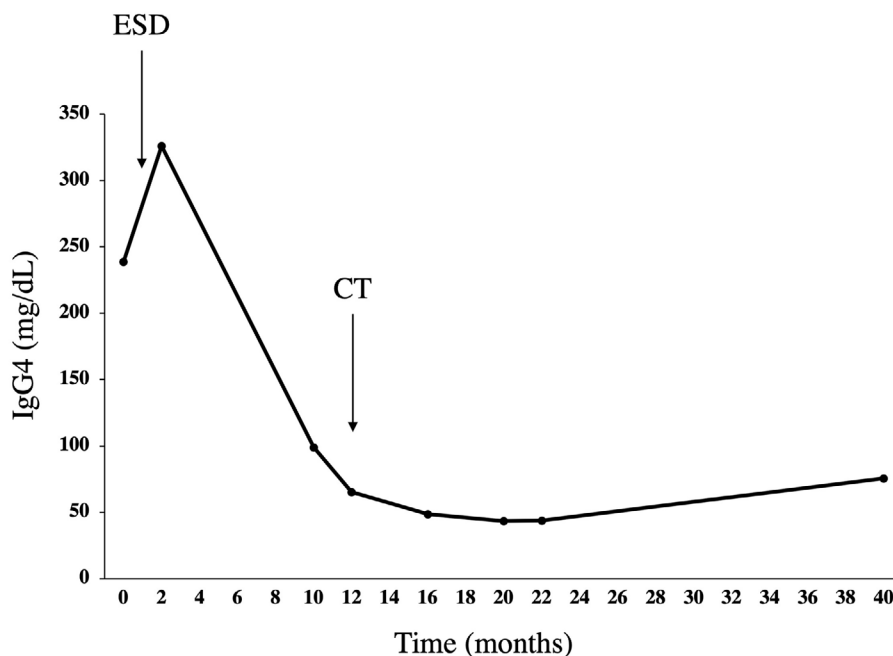


Figure 5. Serum IgG4 levels over three years. At 10 months after endoscopic submucosal dissection (ESD) for early gastric cancer, the serum IgG4 levels normalized and have remained normal since then. One year after ESD, computed tomography (CT) was performed.

one wonders whether or not the stomach was the target organ of IgG4-RD in the present case. It has been reported that 33-47% of AIP patients have IgG4-positive plasma cell

infiltration in the gastric mucosa (22). To diagnose IgG4-related gastric lesion, the infiltration of numerous IgG4-positive plasma cells in the deep mucosal intrinsic layer is



Figure 6. Arterial phase-enhanced computed tomography (CT) performed one year after endoscopic submucosal dissection (ESD) showing the disappearance of pancreatic enlargement and a capsule-like low-density rim.

an important pathological feature, and storiform fibrosis and obliterative phlebitis are also occasionally seen (23). The consensus statement on the pathology of IgG4-RD lists the following histological features as criteria for recognizing a new organ as an IgG4-RD: (A) dense lymphoplasmacytic infiltrate, (B) fibrosis, usually storiform in character and (C) obliterative phlebitis (24). The cases reported in the literature as IgG4-related gastrointestinal lesions were divided into two types: those with marked wall thickness in the esophagus and stomach due to dense fibrosis with abundant infiltration of IgG4-positive plasma cells and fibrosis, and those with IgG4-related pseudotumor in the stomach and colon showing polypoid or mass-like lesions (25). In our case, there were no findings of mucosal thickening or mass-like lesion, and histologically, IgG4 positive plasma cell infiltration was found only in the cancerous area, not accompanied by storiform fibrosis or obliterative phlebitis. Based on these findings, we concluded that the gastric cancer activated an IgG4-related immune response, not IgG4-related gastric lesion. In fact, IgG4-positive plasma cell infiltration has been reported in several malignant tissues, such as extrahepatic cholangiocarcinoma, pancreatic cancer and gastric cancer without AIP (25-27). In an examination of 131 patients with gastric cancer without AIP, the median number of IgG4-positive plasma cells that had infiltrated the gastric cancer tissue was 8.6 per high-power field (HPF) in the early stage and 16.5/HPF in the advanced stage (25). In contrast, in the present case, abundant infiltration of IgG4-positive plasma cells (>30/HPF) was seen in the cancer tissue. Consistent with our case, in Shiokawa's study, the frequency of the patients with abundant IgG4-positive plasma cells around gastric cancer was significantly higher in AIP patients than in non-AIP patients (9).

In the present case, the serum IgG4 levels increased from 239 mg/dL to 326 mg/dL 1 month after ESD. According to a report comparing serum IgG4 levels before and after surgery for gastric cancer, including in the early stage, the serum IgG4 levels were significantly higher one month after surgery than before surgery (25). The underlying mechanism

is unknown, but gastric cancer may have attracted IgG4-positive plasma cells from the peripheral blood to the site of the cancer (25).

There are some cases of spontaneous AIP remission without steroid treatment. In a multicenter study, spontaneous remission was achieved in 54 of 97 patients (55.7%) who were followed without steroid treatment (28). Kubota et al. reported that 13 out of 20 patients (65%) with AIP showed spontaneous remission without steroid treatment, and those predictors were localized AIP and no elevated serum IgG4 levels (29). Although we cannot deny the possibility of spontaneous remission in our case, it is noteworthy that the patient achieved remission despite the absence of the above predictors. However, relapse was more common in AIP patients without steroid treatment than in those with steroid treatment (42% vs. 24%) (30). In our case, steroid treatment was not administered because the patient did not have symptoms such as obstructive jaundice, abdominal pain or back pain and lacked extra-pancreatic manifestations on imaging; however, close observation will be essential in the future.

We encountered a case of AIP remission achieved by curative endoscopic resection alone for gastric cancer with IgG4-positive cell infiltration. This case is valuable in demonstrating that some AIP cases may develop as paraneoplastic syndromes.

The authors state that they have no Conflict of Interest (COI).

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