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Case Report

A Rare Case of Diffuse Large B-cell Lymphoma in a Patient with IgG4-Related Autoimmune Pancreatitis

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A 61-year-old Japanese man with IgG4-related autoimmune pancreatitis was referred to our hospital because of perspiration during food intake. Abdominal computed tomography (CT) with contrast media revealed multiple mesenteric lymphadenopathies. An open surgical abdominal biopsy and subsequent histopathological analysis revealed abnormally large lymphoid cells that were negative for CD3, CD5, and c-myc and positive for CD20 and bcl-2, leading to a diagnosis of diffuse large B-cell lymphoma. Here, we discuss the risk of malignancies, particularly malignant lymphoma in patients with IgG4-related disease. The importance of pathological analysis to reach the appropriate diagnosis in such cases should be emphasized.

Key words: IgG4-related disease, autoimmune pancreatitis, immunophenotyping, diffuse large B-cell lymphoma

IgG4-related disease (IgG4-RD) is a clinical entity established within the last decade. It is characterized by tumor-like lesions, fibrosis, and lymphoplasmacytic infiltration to virtually every organ, including the pancreas, salivary glands, kidneys, breasts, and aorta [1-3]. Elevated serum concentrations of IgG4 and glucocorticoid responsiveness have been considered important for proper diagnosis [4]. Though the pathogenesis of IgG4-RD is still poorly understood [5], an association between IgG4-RD and malignant tumors has been suggested [6, 7]. Herein, we describe a rare complication of diffuse large B-cell lymphoma (DLBCL) in a patient with IgG4-related autoimmune pancreatitis.

Case Report

A 61-year-old Japanese man with IgG4-related autoimmune pancreatitis (AIP) was referred to our hospital because of perspiration upon food intake. The perspiration was noted immediately during food intake and had been progressively getting worse. He had been diagnosed with AIP 3 years earlier. His serum IgG at his first visit to his primary doctor was 2,288 mg/dL, serum IgG4 549.0 mg/dL, and CRP 0.11 mg/dL. Abdominal CT at his first visit with his primary doctor revealed enlargement of the pancreatic head and narrowing of the main pancreatic duct and proximal bile duct. Endoscopic retrograde cholangiopancreatography (ERCP) confirmed the finding noted on the CT. After the initiation of steroid therapy, the bile duct narrowing improved. These findings led to a

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possible diagnosis of AIP. Subsequently, he had no fever, chills, or night sweats, but after 3 months he reported 10 kg weight loss. He had a history of diabetes mellitus and a gastric resection due to advanced gastric cancer.

A blood test on the day of admission revealed increased levels of serum IgG4 (596 mg/dl; reference range 4.8–105.0 mg/dl) and soluble interleukin-2 receptor (sIL-2R; 704 U/ml; reference range 122–496 U/ml). Test results are shown in Table 1. A second abdominal CT with contrast media after admission revealed focal pancreatic enlargement and dilatation of the main pancreatic duct (Fig. 1A), multiple mesenteric lymphadenopathies (Fig. 1B), and no hepatic lesions (Fig. 1C). In addition, 18F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) revealed diffuse involvement of the para-aortic and mesenteric lymph nodes (Fig. 1E). To further investigate the cause of the lymphadenopathy, an open surgical abdominal biopsy for the mesenteric lymph nodes was performed. During the surgery, a tumor-like lesion in the ileum was incidentally found and subsequently resected for pathological analysis (Fig. 2A). Flow cytometry of the mesenteric lymph node revealed an abnormal population of CD10-positive and CD20-positive lymphocytes. Histopathological analysis revealed diffuse proliferation of large atypical lymphoid cells and effacement of the normal lymph node architecture (Fig. 2B). Immunostaining showed that those lymphoid cells were negative for CD3, CD5, and c-myc and positive for CD10, CD20, and bcl-2 (Fig. 2C–E). Accordingly, a diagnosis of DLBCL was made. Contrast-enhanced CT of the liver performed 3 weeks after admission showed multiple hepatic lesions, suggesting a need for emergent treatment (Fig. 1D). Bone marrow aspiration and biopsy revealed no lymphoma infiltration. Consequently, the patient was diagnosed with DLBCL involving the ileum and liver. The clinical stage was considered stage IV. He was subsequently treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). After 2 courses of this treatment, substantial reductions in hepatic lesions and lymphadenopathies were noted.

Table 1 Laboratory data

Variable	Reference range	On admission	On discharge
Blood			
Hematocrit (%)	40.7–50.1	38.4	24.7
Hemoglobin (%)	13.7–16.8	12.7	8.1
White-cell count (/mm^3)	3,300–8,600	5,920	4,300
Platelet (/mm^3)	158–348×10^3	211×10^3	152×10^3
Sodium (mEq/L)	138–145	134	139
Potassium (mEq/L)	3.6–4.8	4.2	3.7
Chloride (mEq/L)	101–108	101	106
Calcium (mg/dL)	8.8–10.1	7.8	8.0
Magnesium (mg/dL)	2.0–2.5	1.8	1.8
HbA1c (%)	4.9–6.0	7.1	5.7
LDH (U/L)	124–222	298	149
Soluble IL2-R (U/mL)	122–496	704	1,268
IgG4 (mg/dL)	4.8–105	596	178
IgG (mg/dL)	861–1,747	2,483.6	1,129.1
IgA (mg/dL)	93–393	476.8	265.1
IgM (mg/dL)	33–183	119.8	55.9

Discussion

IgG4-RD frequently involves the lymph nodes, and tumefactive lesions typically characterize the disease. These lesions sometimes mimic malignancies, posing a diagnostic challenge [8, 9]. With regard to tumorigenesis, the increased risk of development of malignant tumors in patients with IgG4-RD has been controversial [7, 10, 11]. Hirano *et al.* reported that the risk of malignant tumors in patients with IgG4-RD is similar to that of the general population [10]. On the contrary, a Japanese retrospective study revealed a 383.0 standardized incidence ratio (SIR) for malignancies in patients with IgG4-RD, which is strikingly higher than that of the general population [7]. Malignancies that have been reported as complications include non-Hodgkin lymphoma, including extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type (MALT lymphoma), as well as non-lymphoid tumors such as breast, colorectal, lung, renal, and prostate carcinoma [7]. According to Takahashi *et al.*, in IgG4-RD the SIR for malignant lymphoma is 16.0-fold higher than in the general population [12]. They examined 111 IgG4-related autoim-

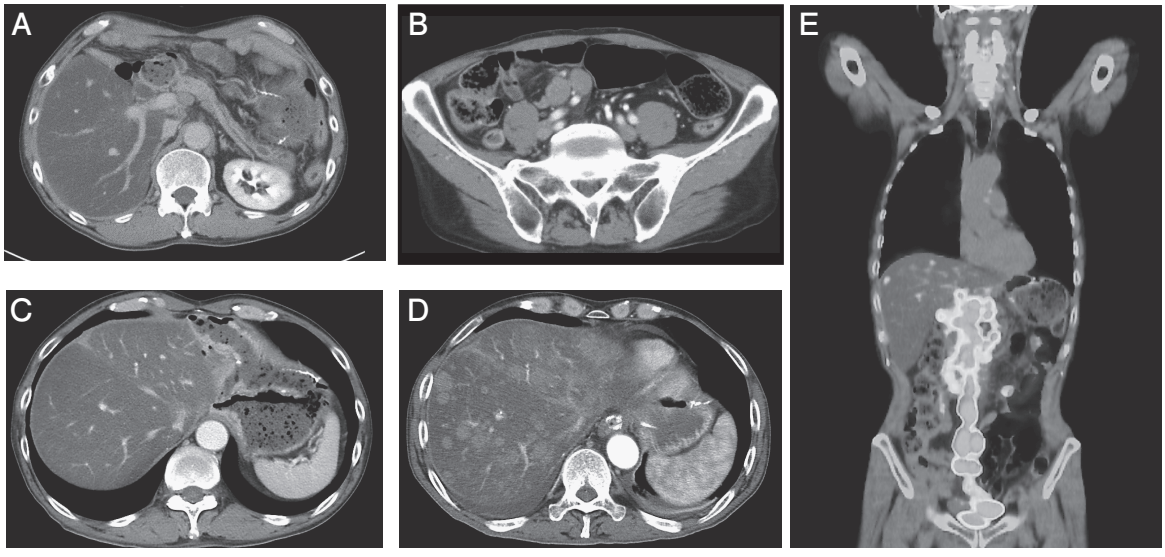

Fig. 1 Radiological findings of IgG4-related pancreatitis and malignant lymphoma. Contrast-enhanced abdominal computed tomography (CT) upon admission revealed focal pancreatic enlargement and dilatation of the main pancreatic duct (**A**). There were multiple mesenteric lymphadenopathies (**B**). No hepatic space-occupying lesions (SOL) were observed at the time (**C**). Contrast-enhanced CT of the liver performed 3 weeks after admission showed multiple hepatic lesions, suggesting rapid progression of the disease (**D**). 18F-fludeoxyglucose positron emission tomography/CT revealed diffuse involvement of para-aortic and mesenteric lymph nodes (**E**).

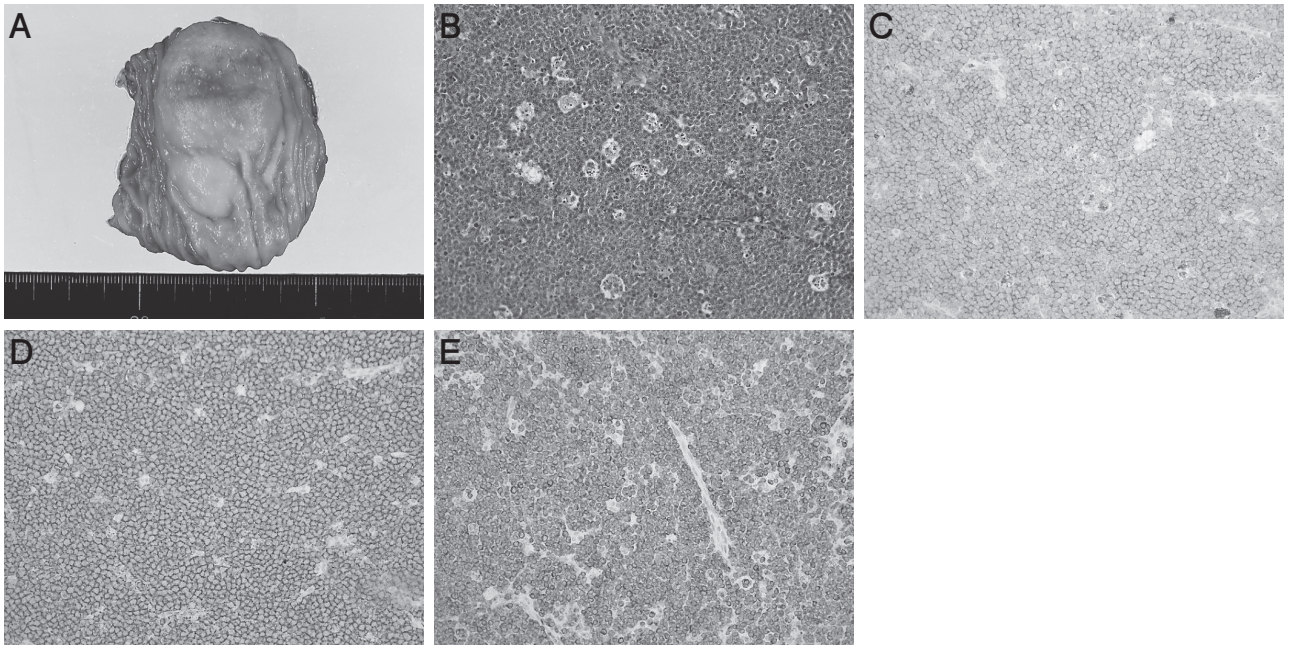

Fig. 2 Pathological findings of mesenteric lymph nodes. A tumefactive lesion in the ileum was incidentally found during an open surgical biopsy of the mesenteric lymph nodes (**A**). The mass was resected for pathological analysis, revealing diffuse proliferation of large atypical lymphoid cells exhibiting effacement of the normal lymph node architecture (**B**). Immunopathological staining showed that those lymphoid cells were negative for CD3, CD5, and c-myc and positive for CD10 (**C**), CD20 (**D**), and bcl-2 (**E**). These immunopathological findings led to the final diagnosis of DLBCL.

mune pancreatitis patients, of whom 3 developed non-Hodgkin lymphoma with extranodal involvement during the follow-up period. Development of anaplastic large cell lymphoma in a patient with IgG4-RD autoimmune pancreatitis, cholecystitis, and a history of DLBCL has also been reported [13]. Other reports suggest that IgG4-producing lymphoma, marginal zone B-cell lymphoma, and mantle cell lymphoma may develop [14, 15]. MALT lymphoma is a common subtype of non-Hodgkin lymphoma that can be complicated with IgG4-RD [14, 16]. To date, however, only a few reports have described the development of malignant lymphoma in a patient with IgG4-RD. Characteristics of previous cases as well as the present one are summarized in Table 2. Our patient, who had IgG4-related autoimmune pancreatitis without any other extraglandular involvement, developed DLBCL during the follow-up period for IgG4-related autoimmune pancreatitis, which is a rare complication. Thus, the differentiation of IgG4-RD and malignant lymphoma is of clinical importance, as there is a reported possibility of the development of malignant lymphoma based on IgG4-RD. Chronic inflammation is a known predisposing factor for the development of malignant lymphoma [17, 18]. Based on previous case reports, we speculate that chronic inflammation due to IgG4-RD predisposes patients to develop malignant lymphoma. As increased secretion of Th2 cytokines such as interleukin-4, 5, 10, and 13, which activate B-cells [19], is implicated in the pathogenesis of IgG4-RD, the predominance of B-cell lymphoma as a secondary development to IgG4-RD is plausible.

In the present case, the patient visited our hospital because of progressive perspiration; this unusual complaint may have several possible causes, such as dumping syndrome due to his history of gastric resection or malignant lymphoma. Perspiration itself is suggestive of a B symptom of malignant lymphoma, but the relationship between food intake and perspiration is unclear. However, since the abdominal CT at the time of admission revealed multiple mesenteric lymphadenopathies, a complication of malignant lymphoma was highly suspected. An immediate open abdominal biopsy and the following pathological analysis were the most crucial steps in determining a definitive diagnosis and treatment plan. Currently, biopsy is strongly recommended as the most important diagnostic procedure [4]. We performed IgG and IgG4 immunostaining for the mesenteric lymph nodes (Fig. 3A-B). Since the IgG/IgG4 ratio was less than 40% in the lesion, DLBCL was thought to be the mainstay of the patient's clinical condition. However, as IgG4-positive cells were recognized in the lesion, it is still probable that IgG4-RD is related to the tumorigenesis of DLBCL. Since only a few cases have been reported regarding the pathophysiology of DLBCL in patients with IgG4-RD, it will be essential to accumulate more cases for further analysis.

In conclusion, even though there is no current consensus regarding the risk of malignancies in patients with IgG4-RD as described above, our case emphasizes the importance of pathological evaluation

Table 2 Features of malignant lymphoma in patients with IgG4-RD

Case No.	Author	Age/Sex	Primary IgG4-RD	Type of ML	Characteristics
1	Takahashi [12]	65/F	AIP	BCL (liver)	BCL developed 4 years after the diagnosis of AIP
2	Takahashi [12]	72/M	AIP	DLBCL (adrenal)	DLBCL developed 5 years after the diagnosis of AIP
3	Takahashi [12]	69/M	Chronic parotitis	DLBCL (kidney)	DLBCL developed 3 years after the diagnosis of chronic parotitis
4	Ishida [13]	61/M	AIP, IgG4-related cholecystitis	DLBCL	IgG4-RDs occurred 5 years after DLBCL. ALCL was found a year after the diagnosis of IgG4-RDs
6	Mulay [15]	65/F	Dacryoadenitis	EMZL	Concurrent IgG4-related dacryoadenitis and EMZL, presenting with bilateral upper eyelid swelling
7	This case	61/M	AIP	DLBCL	DLBCL developed 4 years after the diagnosis of AIP, presenting with progressive perspiration

IgG4-RD, IgG4-related disease; ML, malignant lymphoma; AIP, autoimmune pancreatitis; BCL, B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma; EMZL, extranodal marginal zone B-cell lymphoma.

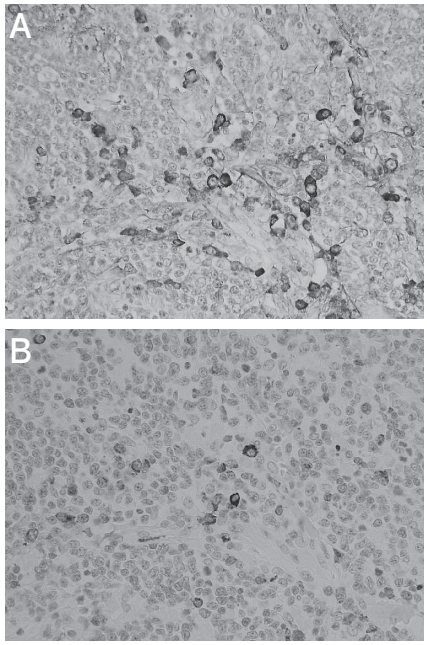

Fig. 3 IgG/IgG4 immunostaining of mesenteric lymph nodes. Immunostaining for IgG and IgG4 was performed on mesenteric lymph nodes. Numerous cells were positive for IgG immunostaining (**A**). Although the IgG/IgG4 ratio was less than 40%, a considerable proportion of cells were still positive for IgG4 (**B**).

to correctly detect malignant lymphoma in IgG4-RD patients, in addition to thorough history-taking and laboratory examinations.

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