A Case of Mikulicz’s Disease Complicated by Malignant Lymphoma: A Postmortem Histopathological Finding

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Abstract

A 66-year-old Japanese man with an 11-year history of Mikulicz’s disease (MD) received continuous corticosteroid administration. At age 58, a left renal pelvic mass was identified and diagnosed as an IgG4-related inflammatory pseudotumor. The patient underwent an operation to remove the tumor. Subsequently, he contracted repeated pulmonary infections and eventually died of severe gastrointestinal bleeding. Autopsy revealed systemic lymph node swelling and infiltration in some organs, and diffuse large B-cell lymphoma (DLBCL) was diagnosed. These findings suggest that an IgG4-related disease can be causally related to the development of malignant lymphoma through the occurrence of mucosa-associated lymphoid tissue lymphoma.

Key words: IgG4-related disease, Mikulicz’s disease, malignant lymphoma


Introduction

Although Mikulicz’s disease (MD) was originally defined as painless symmetrical swelling of the lachrymal, parotid, and submandibular glands (1), the underlying conditions in this disease were shown to be heterogeneous (2). Among them Sjögren’s syndrome (SS) has been considered to be the most common cause of MD due to the histopathological similarity of the two disorders (3). However, recent immunohistochemical studies have revealed a characteristic feature that distinguishes MD from SS: prominent infiltration of IgG4-positive plasma cells into the lachrymal and salivary glands is pathognomonic for the former disease, which indicates that MD is a phenotype of IgG4-related disease (4). These studies have also shown elevated serum levels of IgG4 in patients with MD.

IgG4-related disease has been recently proposed as a corticosteroid-responsive multisystem fibroinflammatory disorder with various designations, such as IgG4 related autoimmune disease (5), IgG4-related plasmacytic disease (6) and IgG4 positive multi-organ lymphoproliferative syndrome (7), and is characterized by high serum levels of IgG 4 (8) and abundant IgG4-bearing lymphoproliferative infiltrate (9). However, the precise pathogenesis and natural course of this disease remain unclear. In this report, we describe the autopsy findings of a man who was initially diagnosed with Mikulicz type of primary SS but was later confirmed to be suffering from IgG4-related MD that was finally complicated by malignant lymphoma.

Case Report

The patient had been experiencing nasal obstruction, swelling of the salivary glands (Fig. 1A), and diplopia caused by markedly enlarged lachrymal glands for 2 years and had been treated with prednisolone (15 mg/day). At the age of 55 years, gallium scintigram revealed strong uptake on the nasal mucosa, enlarged lachrymal and submandibular glands. He was diagnosed as having primary SS on the basis

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of positive results in Schirmer’s test and biopsy findings showing severe lymphoplasmacytic infiltration in the lower lip, including the salivary glands. There was no evidence of mucosa-associated lymphoid tissue (MALT) lymphoma features. Further, CT showed swelling of the whole pancreas (Fig. 2A) and increased wall thickness in the common bile duct and the gall bladder. Magnetic resonance cholangiopancreatography showed segmental narrowing of the main pancreatic duct and marked stenosis of the common bile duct (Fig. 2B). Laboratory examinations showed normal results in the hepatic and renal function tests, and the serum amylase level was 48 IU/L. The patient had polyclonal gammapathy with elevated levels of serum IgG (4,873 mg/dL, normal: 875-1,593 mg/dL) and IgE (900 IU/mL, normal: <500 IU/mL); his blood chemistry was positive for anti-SS-A antibody but other auto-antibodies including anti-SS-B, anti-nuclear and anti-DNA ones were negative. The C-reactive protein (CRP) level in his serum was 0.1 mg/dL.

High-dose corticosteroid therapy was started; this included steroid pulse therapy with an initial dose of methylprednisolone 1 g/day 3 times, which was then tapered from prednisolone 60 mg/day to 20 mg/day during the following year. All of his symptoms gradually improved, and he continued taking prednisolone 10 mg/day and azathioprine 25 mg/day.

A screening CT examination at the age of 58 years showed left hydropnephrosis, which was later shown to be caused by a small tumor located in the lower pole of the left renal pelvis. He underwent insertion of a stent for this ureter stenosis at another hospital, but the tumor slowly enlarged (Fig. 3). He was, therefore, referred to us at the age of 61 years. Laboratory examinations revealed high serum levels of IgG4 (462 mg/dL, normal: 4.8-105 mg/dL) with a normal concentration of serum total IgG (835 mg/dL); the lower lip biopsy, including the salivary glands, was, therefore, re-examined, showing severe lymphoplasmacytic infiltration, fibrosis (Fig. 1B), and presence of numerous IgG4-positive plasma cells. IgG staining results could not be obtained because we did not use IgG staining for diagnoses at that time. Since the IgG4/plasma cell ratio was greater than 0.5, the patient was diagnosed with IgG4-related MD. CT revealed no changes in the size of the enlarged lachrymal and salivary glands, or of the pancreas, and a positive shadow of left renal pelvic tumor was not seen on either gallium scintigraphy or FDG positron emission tomography.
Then he underwent needle biopsy of the left pelvic tumor. In the histological analysis, the biopsy specimen showed a nodular growth pattern with cellular nodules surrounded by collagen bands. The cellular areas contained a mixed population of lymphocytes, plasma cells, and eosinophils (Fig. 4). Although a number of plasma cells were IgG4-positive, IgG staining was not performed due to quite old case. The IgG/plasma cell ratio was measured instead of the IgG4/IgG ratio, and the IgG4/plasma cell ratio was greater than 0.5; these findings and the laboratory data were consistent with the diagnosis of an IgG4-related inflammatory pseudotumor resembling the histologic findings and laboratory data of AIP. No atypical cells were seen within this nodule. In situ hybridization analysis (Ventana; INFORM EBER) of the nodule showed that the cells were negative for Epstein-Barr virus (EBV)-encoded RNA. PCR analysis showed the absence of clonal immunoglobulin gene rearrangements. After this diagnosis, the patient’s prednisolone dose was increased to 30 mg/day. However, the tumor showed further enlargement, and the patient experienced fever and back pain. Laboratory data revealed eosinophilia (2,562/μL) and elevated serum levels of CRP (3.38 mg/dL) and soluble IL-2 receptor antibody (25,190 U/mL, normal: <466 U/mL), but the renal function and the serum amylase level were normal. At the age of 63 years, the patient underwent left nephrectomy, which included resection of a tumor: the tumor had a diameter of 13 cm, and the histopathological examinations showed a large mass with persistent fibrous tissue, numerous foamy macrophages, and scattered CD3 or CD20 positive inflammatory cell infiltration. IgG4-positive cells were not seen. These findings indicated that steroid therapy caused a dramatic decrease in the number of IgG4 positive-plasma cells in the pelvic IgG4-related inflammatory pseudotumor. After the operation, the patient continued to receive treatment with prednisolone (10 mg/day). He subsequently contracted repeated pulmonary bacterial and fungal infections due to immunodeficiency; his IgG serum level at 64 years of age was 205 mg/dL, and cytomegalovirus (CMV) antigenemia was frequently found. He eventually died of severe gastrointestinal bleeding at the age of 66 years.

**Autopsy findings**

Autopsy was performed about 3 hours after death. There was a large volume (1,000 mL) of bloody peritoneal fluid. Numerous swollen nodules detected on CT images before death were found in the abdominal cavity, including the mesentery, para-aortic lymph nodes, and peripancreatic lymph nodes (Fig. 5). Numerous swollen nodules were also observed in the chest cavity, including the pulmonary hilar lymph nodes (Fig. 6A). The stomach wall was thick, and multifocal bleeding ulcers were seen. The cut surface of the stomach showed a grayish white solid tumor. The ileum wall was also thick, and a number of deep ulcers were also observed. Although, the pancreas was not firm, it was slightly swollen. Both lungs (500: 400 g) had diffuse alveolar damage and their cut surfaces showed extensive bleeding and the presence of a number of nodules with a size of approximately 5 mm. In the histological analysis, the nodules were composed of a proliferation of large-sized atypical lymphoid cells with hyperchromatic enlarged nuclei and conspicuous prominent nucleoli, which were arranged in a...
monotonous and diffuse infiltrative growth pattern (Fig. 6B). Plasmacytic differentiation was observed in some parts of the nodules. However, although many organs, especially the stomach, salivary glands, and gastrointestinal tract, were investigated in detail, we found no evidence of MALT lymphoma features, such as lymphoepithelial lesions or centrocyte-like cells. In the immunohistochemical analysis, the proliferative abnormal cells were positive for CD20 (L26, DAKO) (Fig. 6C) and focally positive for CD138 (MI15, DAKO), CD30 (Ber-H2, DAKO), CD5 (DAKO), cyclineD1 (DAKO) and CD15 (MMA, Becton Dickinson, Mountain View, CA); further, they were positive for EBV-encoded RNA in in situ hybridization. In the PCR analysis of the nodules, a single band representing rearrangement of the heavy chain gene was detected in the PCR products. These findings suggested that atypical lymphoid cells were monoclonal. Chromosome analysis and FISH studies were not performed. On the basis of the pathological findings and rearrangement of the heavy chain gene, we had no choice but to diagnose the patient with diffuse large B-cell lymphoma (DLBCL), possibly originating from MALT lymphoma. DLBCL was also observed in stomach, ileum, pancreas, and lung nodules. In the case of the ileum and lung nodules, immunohistochemical analysis of the capillary endothelium revealed CMV infection. The stomach ulcers showed severe bleeding caused by vascular rupture. Because the areas surrounding the ulcer lesions of the stomach were occupied by necrotic lymphoid cells, lymphoma was thought to be the most likely cause of stomach ulcer bleeding and vascular rupture and the primary cause of death.

Although the pancreas had thick interlobular fibrosis, there were no findings suggestive of IgG4-related disease, such as AIP, retroperitoneal fibrosis, and sclerosing cholangitis.

Discussion

Here, we have reported an autopsy case of MD complicated by malignant lymphoma. MD has been recognized worldwide since Yamamoto et al reported that MD is a phenotype of IgG4-related diseases (4). The present case was initially diagnosed as SS. However, prolonged swelling of the lachrymal and salivary glands, high serum IgG4 levels, and the presence of numerous IgG4-positive plasma cells in the salivary gland portion of the biopsy specimen proved that the patient in fact had MD. We analyzed the IgG4/plasma cell ratio in place of the IgG4/IgG ratio. Esposito et al (10) reported that the IgG4/plasma cell ratio could also be used as a tool to detect IgG4-related diseases. In IgG4-related diseases, the IgG4/plasma cell ratio will be greater than 0.3; thus, our results were consistent with those observed in cases of IgG4-related diseases. IgG4-related diseases often present with involvement and disorders of multiple organs, and include AIP, retroperitoneal fibrosis, tubulointerstitial nephritis, autoimmune hypophysitis, Riedel's
thyroiditis, and MD, all of which show IgG4-positive plasma cell involvement in their pathogenesis (6, 11). In the present case, the pelvic tumor that was initially diagnosed as an IgG4-related inflammatory pseudotumor may have been a manifestation of retroperitoneal fibrosis; thus, the present case was consistent with an IgG4-related disease showing involvement of multiple organs.

Although a few reports have described IgG4-related disease with malignant lymphoma arising from the salivary glands and ocular adnexa, including the lacrimal gland (12-14), malignant lymphoma associated with MD is a rare finding. To our knowledge, such lymphomas have not been reported to occur during follow-up in patients with MD. In patients with IgG4-related diseases, malignant lymphoma may sometimes arise in organs different from those affected by IgG4-related diseases (12). Although the lymphoma cells in the present case were observed in extranodal regions such as the stomach, small intestine, and so on, DLBCL may also arise from lymph nodes, since the swelling of numerous systemic lymph nodes was observed in this patient. Among the cases of IgG4-related diseases occurring with malignant lymphoma on the salivary glands and ocular adnexa, most show MALT lymphoma (13, 14). However, at other organ sites, IgG4-related diseases occurring with malignant lymphoma may develop into other subtypes, including DLBCL (12). In fact, MALT lymphoma seems to transform into DLBCL (15); thus, in cases of DLBCL associated with IgG4-related diseases, a history of MALT lymphoma may exist, or histology suggestive of MALT lymphoma may be present. Although the present patient may have had MALT lymphoma in the stomach or other organs, his clinical history did not suggest the presence of MALT lymphoma, and postmortem findings showed only DLBCL, not MALT lymphoma. Recently, Kato et al reported that chronic inflammation and B-cell lymphomas are causally related (16). Systematic assessments of the relationship between the risk for lymphoma subtypes and autoimmune chronic inflammatory disorders have been conducted (17), and it has been suggested that a history of IgG4-related disease may be a predisposing condition in the development of lymphoma. In particular, MALT lymphoma may be correlated with IgG4-related diseases. The resulting complications may have been responsible for the pathogenesis of the lymphoproliferative disorder in this case.

MD is now recognized as a new disease entity among the various clinical manifestations of IgG4-related diseases. Thus, it is important to distinguish MD from SS, since these conditions may require different therapeutic approaches (6). The present report has described a patient with IgG4-related MD likely complicated by malignant lymphoma, and the pathogenetic relationship of both disorders is still not completely understood.

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

**References**