Marginal Zone Lymphoma and Lung Adenocarcinoma with an EGFR Exon 19 E746-S752del Mutation in a Patient with IgG4-related Disease

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Abstract:
A 68-year-old man presented with a solid mass at the left renal pelvis and ureter with multiple systemic lymphadenopathies and a mass with a cavity in the right lower lobe of the lung. While a transbronchial lung biopsy revealed no malignancy, a biopsy of the renal pelvis showed marginal zone lymphoma with polyclonal IgG4-positive cells. The serum IgG4 level and presence of a bilateral orbital mass suggested Mikulicz disease. The lesions shrank following the administration of steroids. A rebiopsy confirmed lung adenocarcinoma, and its background showed IgG4-positive cells a year later. IgG4-related diseases require careful follow-up because they can be complicated by malignancy.

Key words: EGFR, IgG4-related disease, marginal zone lymphoma, osimertinib

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Introduction
IgG4-related disease (IgG4-RD) was first reported in Japan following the discovery of a high serum IgG4 concentration in autoimmune pancreatitis (1). IgG4-RD is generally characterized by systemic organ development and has been reported to be associated with marginal zone lymphoma (MZL) and malignancy (2). However, there are few reports on the association of IgG4-related diseases with primary lung cancer.

We herein report the first case of lung adenocarcinoma with an EGFR exon 19 E746-S752del mutation and MZL in a patient with IgG4-RD.

Case Report
A 68-year-old man with a history of chronic obstructive pulmonary disease was transferred to our hospital because of trauma. Computed tomography (CT) revealed a solid mass in the left renal pelvis and ureter. Multiple lymphadenopathy was also observed in the para-aortic region and bilateral pelvis, and a mass with a cavity was also found in the right lower lobe of the lung (Fig. 1).

The patient’s IgG4 level was above 1,500 mg/dL, with an elevated serum soluble interleukin-2 receptor level (2,108 U/mL) (Fig. 2). Notably, a CT-guided biopsy of the mass in the left renal pelvis resulted in the diagnosis of MZL. Dense infiltration and proliferation of medium-sized atypical lymphoid cells was also observed. Immunostaining showed atypical lymphoid cells of CD20 (+), CD3 (−), BCL2 (+),...
Figure 1. Computed tomography (CT) findings of the chest showing a mass with a cavity in the right lower lobe of the lung (A). Abdominal CT also showed a solid tumor at the left renal pelvis and ureter, along with multiple systemic lymphadenopathy (B). The uptake of FDG during PET-CT showed the same lesions as B (C, D).

Figure 2. Clinical course and duration of steroid therapy and its temporary efficacy against IgG4-related disease (IgG4-RD). Serum IgG4 and interleukin-2 receptor levels remarkably improved during the administration of steroids and increased after the discontinuation of steroids, along with gradual enlargement in the tumor mass in the right lower lobe of the lung.

CD10 (−), and cyclin D1 (−) with a low Ki-67 labeling index. In addition, the background of IgG4-positive cells lacked light chain restriction; this suggested IgG4-RD in a background of MZL (Fig. 3).
Flow cytometry confirmed that CD20-positive cells exhibited definite light chain restriction, supporting the development of MZL (Fig. 4). Notably, ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT) revealed a high accumulation of FDG (maximum standardized uptake value: 8.64) mainly in the lung tumor (Fig. 1). Bronchoscopy was performed to test for lung cancer; however, no malignancy was detected. Both the hepatic and renal functions as well as the thyroid function were also normal, confirming there was no autoimmune disease. No typical physical findings suggesting connective tissue disease were observed, and the antinuclear antibody test was negative. IgG4-RD was diagnosed based on localized masses in multiple organs and high IgG4 (over 135 mg/dL) as well as pathological findings of marked infiltration of lymphocytes and plasma cells, an IgG4/IgG-positive cell ratio of ≥40% and IgG4-positive plasma cells exceeding 10/high-power fields (HPFs). Hence, a final diagnosis of MZL with IgG4-RD
was established (3).

Nearly a month later, the patient felt dizzy and was hospitalized. Masses were observed in both orbits by magnetic resonance imaging (MRI), consistent with Mikulicz disease (Fig. 5). Steroid therapy (1 mg/kg/day) was started, and gradual shrinkage of the renal lesions was observed, allowing the steroid dosage to be tapered. The patient was continued on maintenance steroid therapy (5 mg/day) for 26 months after starting the steroid therapy. However, the lung tumor gradually enlarged after having remained almost the same size for one year (Fig. 2), although the renal lesion remained small. Bronchoscopy of the lung mass was performed again to exclude the possibility of lung cancer, and a diagnosis of non-small-cell lung cancer was finally reached.
IgG4-RD is a disease concept that has been proposed in recent years and is characterized by the onset of systemic disease. It has been reported that 10.4% of patients with IgG4-RD develop lung and colon cancer as well as malignant lymphomas, with an incidence rate that is approximately 3.5 times higher than that in the general population (5).

MZLs are low-grade B-cell lymphomas, a diverse group of indolent lymphomas that comprises three subtypes: nodal MZL, splenic MZL, and mucosa-associated lymphoid tissue (MALT) (6). Notably, the gastrointestinal tract accounts for 50% of all cases of organs developing MALT, of which 85% are related to the stomach, while the remaining are related to the lungs, salivary glands, eye appendages, and skin. However, most of the reported MALT lymphoma cases with IgG4-RD have been reported to occur in individuals of Asian ethnicity and in the orbits. Lymphomas occurring with an IgG4-RD background are more uncommon and varied in terms of location and type in Western populations than in Asian populations (7). Ohno et al. (8) revealed that the expression of various cytokine mRNAs of IgG4-RD and IgG4 (+) MZL exhibited statistically the same pattern and suggested that IgG4 (+) MZL might develop malignant lymphoma against the background of IgG4-RD. Some researchers have suggested that a tissue biopsy and IgG4 immunostaining are required in all cases, as IgG4-positive MALT lymphoma may develop from preexisting IgG4-positive chronic inflammatory lesions (9). Importantly, when a diagnosis of IgG4-RD is established, the lesion should be assessed to determine whether or not it exhibits an MZL component.

Various reports (2, 5) have shown that the incidence of malignant tumors is significantly higher in patients with IgG4-RD than in those without IgG4-RD, highlighting the notion that high-activity markers of IgG4-positive cell infiltration may be a risk factor for the development of malignancy (5). As lung cancer is difficult to distinguish from IgG4-RD nodule shadows, surgical resection is often performed to confirm the diagnosis (10). In a retrospective study by Fujimoto et al. on surgeries performed for lung cancer, IgG4-positive cell infiltration (>20/HPF) was observed in 35 out of 294 cases (12%) while examining surgical tissue containing non-small-cell lung cancer. The authors thus suggested that squamous cell carcinoma and high-grade adenocarcinoma were more likely to be accompanied by intratumoral IgG4+ plasma cells than other lung cancer subtypes (11). In our case, we did not perform surgical resection because the patient refused. However, the uptake of FDG during PET-CT was increased at the time of the second bronchoscopy, suggesting the possibility of a malignant tumor according to previous reports (12). We therefore decided to perform a rebiopsy using bronchoscopy, which revealed lung cancer with an EGFR mutation, and the patient was appropriately treated.

Two hypotheses are currently available regarding the relationship between cancer and IgG4-RD. The first hypothesis that the IgG4 response develops as a paraneoplastic response, improving the prognosis of non-small-cell lung cancer (13). IgG4 antibodies triggered in the presence of tumor
cells participate in local inflammation and may represent one regulatory mechanism by which tumors evade immune attacks (14). The pathophysiology of IgG4-RD is thought to be due to the altered interaction between the innate and adaptive immune systems, characterized by T-helper cell type 2 cytokine production, increased IgG4 production, and increased regulatory T-cell production (15). The other hypothesis states that cancer also occurs during the continuous inflammation caused by IgG4-RD, like MZL. Some previous reports have indicated that chronic inflammation triggers cellular events that can promote malignant transformation of cells and carcinogenesis (16, 17).

In this case, as Mikulicz disease and the tumor in the renal pelvis secondary to IgG4-RD were independent of the small lung tumor observed (Figs. 1, 5), it was strongly suspected that this MZL arose from IgG4-RD. Furthermore, the pathological review suggested that EGFR-mutation lung adenocarcinoma had developed as a result of the inflammation caused by IgG4-RD. Although the correlation between IgG4-RD and EGFR gene mutations is still unclear, Fujimoto et al. described a potential relationship between IgG4-RD and EGFR mutations (11).

In conclusion, we herein report the first case of marginal zone B-cell lymphoma and lung adenocarcinoma with an EGFR exon 19 E746-S752del mutation in a patient with IgG4-RD with a clear pathology of IgG4 cell infiltration in the background. MZL associated with IgG4-RD as well as EGFR mutation-positive lung cancers are common in Asians, suggesting some common genetic factors in their tumor immune response. Although the basic mechanism underlying how these diseases manage to simultaneously coexist remains unclear, in clinical settings, it is important to observe systemic tumors carefully and continuously rule out malignancies when IgG4-RD is diagnosed.

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

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References


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