IgG4-Related Disease and Malignancy

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Key words: autoimmune pancreatitis, cancer, IgG4, Mikulicz’s disease

(DOI: 10.2169/internalmedicine.51.6782)

Mikulicz’s disease (MD) has been included within the diagnosis of primary Sjögren’s syndrome (SS), but it represents a unique condition involving the enlargement of the lacrimal and salivary glands and characterized by few autoimmune reaction (1). Glucocorticoid treatment is effective for the clinical improvement of this disease (2). Now it is considered that MD is quite a different disease from primary SS (1), and a type of IgG4-related disease (IgG4-RD) (3). IgG4-RD is characterized by a swelling of the affected organs along with elevated levels of serum IgG4, and abundant infiltration of IgG4-bearing plasma cells and fibrosis. IgG4-RD is a new concept of systemic and chronic inflammation (3), and usually includes MD, autoimmune pancreatitis (AIP) (4), and IgG4-related tubulointerstitial nephritis (5). IgG4-RD is an important disease for clinical physicians to discriminate from cancers and other rheumatic diseases.

On the other hand, recent focus has been on the relationship between IgG4-RD and malignancies. IgG4-RD with pancreatic cancer has often been reported in cases of AIP (6, 7). It is known that positron emission tomography (PET) is very useful for systemic evaluation in IgG4-RD (8, 9). Whenever we make a diagnosis of IgG4-RD, we consult PET images. In some instances, we are presented with cases involving abnormal accumulation at the lesion sites outside of the involved organs; this is known as organic dysfunction of IgG4-RD. Upon further examination, we often find that the lesion is cancer. In such instances, PET is very useful for detecting cancer. Our previous study (SMART database: Sapporo Medical University and Related institutes database for investigation and best treatments of IgG4-related disease) demonstrated that malignancies occurred in 10.4% of IgG4-RD cases. Using the database of national cancer registries in the monitoring of cancer incidence in Japan (2005) (10), the standardized incident ratio (SIR) for cancers in male patients with IgG4-RD was 331.1, and in female patients with IgG4-RD, 471.6. The total was 383.0. It was approximately 3.5 times higher than the incidence of cancer in the general population (11).

Malignancies as complications of IgG4-RD are divided into lymphoma and non-lymphoid tumors. Lymphoma includes mucosa-associated lymphoid tissue (MALT) lymphoma and non-Hodgkin lymphoma. Lymphoma can present as a background of chronic inflammation. In SS, antigenic activation of B cells, together with oncogenic events, including p53 inactivation and bcl-2 activation, may play important roles in B cell monoclonal proliferation and malignant transformation (12). It is reported that the SIR for lymphoma in patients with SS was higher, 8.7 to 48.1 (13-15). It is suggested that this rate for lymphoma in MD is also high as well as in SS.

In this issue of Internal Medicine, Uehara et al (16) report a 66-year-old man, who suffered from IgG4-RD, and performed autopsy. The patient had been followed as MD and IgG4-related pseudo-inflammatory tumor in the pelvis, but autopsy disclosed the coexistence of diffuse large B cell lymphoma. It could not be considered that lymphoma was complicated at the diagnosis of IgG4-RD. It is suggested that an activated B cell caused malignant transformation in the background of chronic inflammation. Therefore, it is critical to recognize the risk of lymphoma in MD as well as SS.

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

References


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Received for publication October 21, 2011; Accepted for publication November 9, 2011
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