Clinical Practice in Immunoglobulin G4-Related Disease

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Immunoglobulin G4-related disease is a chronic inflammatory disease that has gained much attention in the last decade [1]. In this issue of *IMAJ*, Sthoeger and colleagues [2] describe IgG4 and IgG4-RD, and we report our experience dealing with IgG4-RD in clinical practice.

Typical IgG4-RDs include IgG4-related Mikulicz disease and type 1 autoimmune pancreatitis. IgG4-related tubulointerstitial nephritis, pulmonary involvement, prostatitis, and retroperitoneal fibrosis can also arise as complications. In our database, the Sapporo Medical University and Related Institutes Database for Investigation and Best Treatments of IgG4-RD (SMART), autoimmune pancreatitis was seen in 18% of IgG4-related Mikulicz disease cases at the first visit. Autoimmune pancreatitis is an important gastroenterological complication of Mikulicz disease. IgG4-related tubulointerstitial nephritis was encountered in 16% of IgG4-related cases of Mikulicz disease. The frequencies of pulmonary involvement, prostatitis, and retroperitoneal fibrosis were 6%, 2% and 22%, respectively [3]. On the other hand, when we observed patients with type 1 autoimmune pancreatitis, Mikulicz disease was seen in 14%–38%. The frequencies of IgG4-related tubulointerstitial nephritis, pulmonary lesions, prostatitis, and retroperitoneal fibrosis were 1%, 1%, 3%, and 7%, respectively [4]. Furthermore, with regard to IgG4-related tubulointerstitial nephritis, Mikulicz disease and autoimmune pancreatitis were seen in 83% and 39%, respectively [5]. These represent high frequencies. An epidemiological study in Japan identified Mikulicz disease as the most frequent IgG4-RD [6]. Such findings suggest that Mikulicz disease and autoimmune pancreatitis are representative diseases for IgG4-RD.

Patients with IgG4-related Mikulicz disease are usually referred by ophthalmologists and otolaryngologists. The diagnosis is based on clinical, serological and pathological findings [3]. We always check for enlargement of the lacrimal and submandibular and/or parotid glands on computed tomography or echocardiography and perform a biopsy to exclude other conditions such as lymphoma or sarcoidosis. In particular, lymphoma is ruled out by histological and genetic examinations. We recently encountered cases of mucosa-associated lymphoid tissue lymphoma proved by biopsy, presenting with bilateral swelling of the lacrimal and submandibular glands. If possible, biopsy of the lacrimal or salivary gland involvements should be performed.

On the other hand, patients with autoimmune pancreatitis usually present initially to gastroenterologists. The diagnostic criteria for autoimmune pancreatitis differ between countries [7-9]. The important thing to recognize, however, is that there are two types [10]. Type 1 autoimmune pancreatitis, i.e., IgG4-related pancreatitis, accounts for the majority of cases in Asia, whereas type 2 predominates in Europe and is associated with neutrophils and presentation without elevated serum levels of IgG4. It is recognized that they are quite different disorders. Type 1 is the pathogenesis presenting with a Th2-dominant reaction [11], similar to Mikulicz disease [12]. The class-switch to IgG4 is considered to be led by Th2 cytokines and interleukin-10 [11]. The present discussion focuses on type 1 autoimmune pancreatitis.

Differentiation from pancreatic cancer is crucial in the diagnosis of autoimmune pancreatitis. Diagnosis is not difficult when contrast-enhanced CT reveals diffuse enlargement of the pancreas with a capsule-like rim. In cases presenting with focal pancreatic swelling, we perform endoscopic retrograde cholangiopancreatography to evaluate stricture of the main pancreatic duct and common bile duct and to differentiate it from pancreatic cancer.

After reaching a definitive diagnosis of Mikulicz disease and autoimmune pancreatitis, we perform a systemic examination to check for the presence of other complications. In addition to contrast-enhanced CT, gadolinium scintigraphy or fluorodeoxyglucose positron emission tomography is usually performed. These modalities cannot directly differentiate IgG4-RDs from cancers, but they can reveal the severe inflammation present in IgG4-RD and are useful for the systemic evaluation in Mikulicz disease and autoimmune pancreatitis. When gadolinium scintigraphy or FDG-PET reveals the abnormal accumulation in atypical sites, as described in only a few case reports, cancer should be suspected. In the SMART database, malignancies

IgG4 = immunoglobulin G4
IgG4-RD = immunoglobulin G4-related disease

FDG-PET = fluorodeoxyglucose positron emission tomography

occurred in 10.4% of patients within 3 years after the diagnosis of IgG4-RD [13]. These malignancies involved both lymphoma and solid carcinoma. We also pay attention to malignancies as complications in the diagnosis of IgG4-RD. On the other hand, we sometimes encounter non-IgG4-RD cases presenting with infiltration of IgG4-bearing plasmacytes in non-cancerous tissues around a carcinoma. This phenomenon has been observed in pancreatic cancer, colon cancer and hepatic cell carcinoma. Infiltration of IgG4-positive plasma cells is considered characteristic of but not specific to IgG4-RD. IgG4 also appears to be associated with tumor immunity.

Almost all cases of Mikulicz disease or type 1 autoimmune pancreatitis present with elevated serum levels of IgG4, but we often diagnose IgG4-RD without measuring serum IgG4. From our data, 73.5% of Mikulicz disease cases show hypergammaglobulinemia and elevated serum levels of IgE. Hypocomplementemia and elevated levels of circulating immune complexes are sometimes also seen. The former is observed in about 25% of patients, and the latter in around 50% [3]. Eosinophilia is sometimes observed. These findings all contribute to the diagnosis.

Elevated serum levels of IgG4 are also considered characteristic of but not specific to IgG4-RD. Most patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) [14] and some patients with rheumatoid arthritis and systemic sclerosis [15] show elevated serum levels of IgG4. The phenomenon also appears to occur under specific Th2-dominant conditions.

Finally, we need appropriate treatments for IgG4-RD. Glucocorticoids are currently prescribed for the induction of remission due to the short-term clinical efficacy of this approach [16]. The initial dose of prednisolone is 0.6–0.8 mg/kg/day and we gradually decrease the dose, usually to around 5–10 mg/day. However, some patients experience relapses. According to the SMART database, about 20–30% of cases present with relapse after reduction of their steroid dose. Interestingly, relapse patterns are not always the same as the clinical form at the first visit [17]. This simply means that IgG4-RD needs to be addressed as a systemic condition. Rituximab reportedly shows efficacy as a treatment for cases with relapse of IgG4-RD [18]. Our analysis showed amelioration of steroid dependency with every 6 months of rituximab administration [19].

IgG4-RD is a new disease concept, and many aspects of pathogenesis, diagnosis and treatment remain unclear. When dealing with IgG4-RD in clinical practice, we should examine physical and histological findings carefully to diagnose correctly.

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It is better to ask some of the questions than to know all the answers

James Thurber (1894-1961), American author, cartoonist and celebrated wit