Immunoglobulin G4-related Disease with Features of Mikulicz's Disease and Autoimmune Pancreatitis Which Firstly Presented as Asymptomatic Lymphadenopathy: A Case Report

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To the Editor: Mikulicz's disease (MD), also known as benign lymphoepithelial lesion, refers to idiopathic, bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands. The complications of MD include autoimmune pancreatitis, retroperitoneal fibrosis, tubulointerstitial nephritis, autoimmune hypophysitis, and Riedel's thyroiditis, all of which show elevated serum immunoglobulin G4 (IgG4) levels and prominent infiltration of IgG4-positive plasmacytes. Members of two Japanese research teams from the Ministry of Health, Labor and Welfare agreed, at their second meeting in Kanazawa in 2010, to use the term "IgG4-related disease (IgG4-RD)" to identify this clinical disease entity. IgG4-RD mainly affects middle-aged to elderly men. It often involves one or multiple organs. As its clinical symptoms are relatively mild, the condition usually comes to clinical attention as a result of organ swelling or damage.[1] Asymptomatic IgG4-related lymphadenopathy is common, and sometimes can be the initial or only manifestation.[2] Comprehensive clinical diagnostic criteria (CCD criteria) for IgG4-RD were introduced by Japan in 2012.[3] Here, we report a typical case of IgG4-RD, who was mis-diagnosed 5 years ago.

An 82-year-old man was admitted to our hospital on April 16, 2012 because of anorexia, anergy, emaciation, and painless lumps in postaurem. Five years ago, he found a painless lump (about 2.3 cm × 1.2 cm) both in his left and right postaurem and the left one was surgically excised after 1 year. Reactive lymphadenopathy was diagnosed at that time. However, the lump again began to appear. His medical history included primary hypertension. Upon admission, physical examination revealed bilateral cervical lymph node swelling and prominent submandibular gland enlargement. No fever was observed. Chest auscultation revealed normal lung and heart sounds, and no abnormalities were evident in the abdomen.

Laboratory findings were as follows: Serum concentrations of the IgG subclass: IgG1 765 mg/dl (normally <1080 mg/dl); IgG2 801 mg/dl (normally <931 mg/dl); IgG3 63.7 mg/dl (normally <121 mg/dl); IgG4 1320 mg/dl (normally <108 mg/dl). The patient was tested weakly positive for rheumatoid factor (25.4 IU/ml). Test results for antinuclear antibody (ANA), myeloperoxidase antineutrophil cytoplasmic antibody (ANCA), and proteinase three ANCA were all negative. Blood counts, biochemical tests, tumor markers, and thyroid function were almost within the normal range. Urinary protein and urinary occult blood were both negative. Blood sugar monitoring showed an almost normal level.

Ultrasonography showed multiple nodes in the thyroid gland and lymph node swelling in both parotid regions. Abdominal magnetic resonance imaging (MRI) scans showed changes in appearance and signals in the tail of the pancreas, consisted with manifestations of autoimmune pancreatitis. Gastroscopy revealed chronic superficial atrophic gastritis. Nasendoscopy showed nasal mucosal swelling. Subsequent positron emission tomography and computed tomography (PET-CT) scan images showed abnormal 18-fluorodeoxyglucose (FDG) uptake in the bilateral submandibular glands and parotid glands. The maximum standardized uptake value (SUV) of the submandibular glands was 11.16 and of the parotid glands was 10.86. Swelling of the mediastinal lymph node also could be seen, with a maximum diameter of the flow path of about 1.66 cm and a maximum SUV of about 5.21. The tail of the pancreas was mildly swollen. Diffuse radioactive uptake of the tail of the pancreas was increased, and the maximum SUV was about 4.48. Delayed scan radioactive uptake still showed an increase, with a maximum SUV of about 5.06 [Figure 1].

These clinical, laboratory, and imaging findings indicated the possibility of IgG4-RD involving the lymph nodes, submandibular glands, and pancreas, according to the comprehensive diagnostic criteria for IgG4-RD.[4] A right submandibular gland biopsy was performed in May 2012 for confirmation. The pathological report stated that the salivary glands were atrophic and cirrhotic, and fibrous tissues and myofibroblasts were proliferating. Interstitial tissues were infiltrated with large numbers of lymphocytes and plasmacytes. Immunostaining indicated diffuse infiltration of IgG4 (+) plasma cells. The ratio of IgG4/IgG positive cells was >50% and there were >10 IgG4-positive plasma cells per high power field (HPF) [Figure 2].

Considering the advanced age of the patient, we gave him 8 mg methylprednisolone daily. Clinical symptoms showed rapid improvement and the blood sugar was almost in the normal range.

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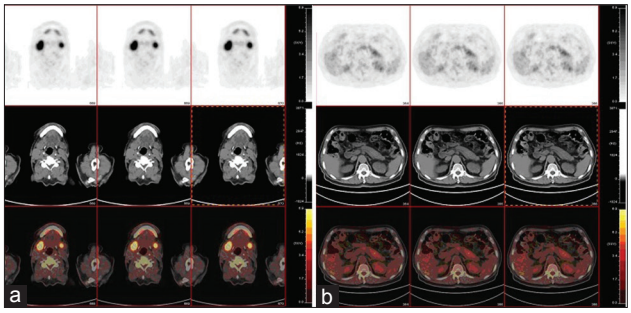

Figure 1: Positron emission tomography and computed tomography (PET-CT) images. (a) Abnormal 18-fluorodeoxyglucose uptake in bilateral submandibular glands and parotid glands. The maximum standardized uptake value (SUV) of the submandibular glands was 11.16, and of the parotid glands was 10.86; (b) The tail of the pancreas was mildly swollen. The maximum SUV was about 4.48, and about 5.06 after a delayed scan.

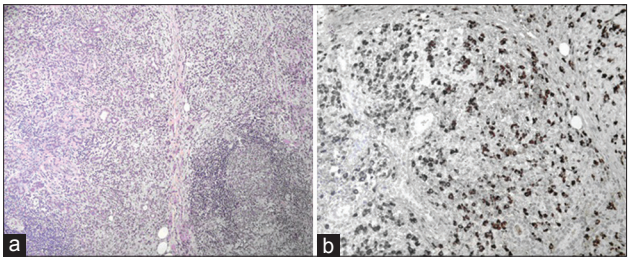

Figure 2: Biopsy specimen of right submandibular gland. (a) Salivary glands are atrophic and cirrhotic, and fibrous tissues and myofibroblasts are proliferating. Interstitial tissues are infiltrated with large numbers of lymphocytes and plasmacytes (H and E, ×100); (b) Immunostaining indicating diffuse infiltration of immunoglobulin G4 (IgG4) (+) plasma cells. The ratio of IgG4/IgG positive cells was >50% and there were >10 IgG4-positive plasma cells/high power field (IgG4 immunostaining, Original magnification, ×200).

At 6 weeks after treatment initiation, there was a marked reduction in the size of masses. Cervical lymph node and submandibular gland cannot be touched. Abdominal MRI scans showed almost normal pancreas. The serum concentration of IgG4 had decreased from 1320 to 130 mg/dl. At 2 months after treatment initiation, we began to gradually taper the methylprednisolone dose, reducing to 4 mg/day at 6 months after medication. The patient is now in a stable condition. The blood sugar was in the normal range.

In our case, the patient became aware of lymphadenectasis in his postaurem 5 years ago. However, at that time, as awareness of IgG4-RD was low and diagnostic criteria had not been published, the patient did not receive further examination, and the case was mis-diagnosed. He didn't receive suitable treatments, and the illness re-emerged. Five years later, the patient presented with anorexia, anergy, and emaciation. These can be the symptoms of many diseases, such as diabetes, lymphoma, and malignancy. Blood sugar after admission immediately helped us to exclude the possibility of diabetes. On a physical examination, the patient exhibited prominent asymptomatic lymphadenopathy. As a result, the possibility of lymphoma and malignancy should be taken into consideration. Under such a condition, PET/CT as a new noninvasive operative inspection method can provide us with a powerful tool to make the differential diagnosis. In addition, it is also very useful for systemic evaluation of IgG4-RD. In this case, a PET-CT examination showed abnormal 18-FDG uptake in mediastinal lymph nodes, submandibular glands, and pancreas. No evidence of lymphoma or malignancy was observed. Laboratory examination showed elevated serum IgG4. Histopathologic examination showed lymphocyte and plasmacyte infiltration and fibrosis in salivary glands. Immunohistochemistry demonstrated that the ratio of IgG4/IgG positive cells was >50% and there were >10 IgG4-positive plasma cells/HPF. Other serological analyses (such as tumor markers, aminotransferases, creatinine, antibody ANA, anti-SS-A, anti-SS-B, and ANCA) were all in the normal range. According to the CCD criteria, we diagnosed IgG4-RD.

Treatment guidelines for IgG4-RD have not been developed. Corticosteroid therapy has been regarded as an effective treatment. Himi *et al.*,[4] initiated treatment with prednisolone at 30–40 mg/day against MD without encountering organ failure, and suggested that it is necessary to continue administering at 5–10 mg/day or to combine it with an immunosuppressant. Taking into account the advanced age of our patient, we decreased the dose of corticosteroid, and he was successfully treated. However, the optimal initial doses of steroids, tapering procedures, and maintenance doses are still controversial. Further investigation is necessary to establish the most effective therapy. Besides, malignancies can be complications in the diagnosis or subsequent follow-up of IgG4-RD patients. We should be cognizant of the possible existence of malignancies during follow-up care.

To summarize, IgG4-RD is a novel clinical disease entity with multi-organ involvement, and the clinical manifestation can be variable. It is important that asymptomatic IgG4-related lymphadenopathy is common, and sometimes can be the initial or only manifested. When we meet a patient with lymphadenopathy, IgG4-RD should be taken into consideration. PET-CT, the examination of serum IgG4 and histopathologic examination are very useful for diagnosis. Here, we have described a typical case of IgG4-RD, previously mis-diagnosed. This time he was successfully treated.

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