Introduction

Immunoglobulin G4-related disease (IgG4RD) is a chronic inflammatory condition characterized by tissue infiltration with lymphocytes and IgG4-secreting plasma cells, as well as varying degrees of fibrosis. We report a case of a 70-year-old man with a rapid-growing cervical mass for several months. Computed tomography and positron emission tomography showed a huge, ill-defined mass involving left thyroid lobe and encasing the common carotid artery, which was clinically and radiologically suspicious for anaplastic thyroid carcinoma. Ultrasonography-guided core needle biopsy was performed and histopathology examination revealed to be consistent with IgG4RD, and the IgG4/IgG ratio was 0.6. After oral corticosteroid was administered, the mass was dramatically resolved. Because IgG4RD often presents as a single localized and infiltrated mass lesion, it can be confused and misdiagnosed as a malignancy. Thus, clinicians should consider IgG4RD as a differential diagnosis in a rapid-growing neck mass to prevent unnecessary and excessive treatments. (J Clinical Otolaryngol 2018;29:301-306)

KEY WORDS: Immunoglobulin G4-related disease · Anaplastic thyroid carcinoma · Inflammatory tumor · Neck mass.
benign prostatic hypertrophy, and cerebral infarction, complained of a rapidly growing, huge left anterolateral cervical mass for 2 months. At first presentation, the clinical impression was anaplastic thyroid carcinoma with cervical lymph node involvement.

The computed tomography (CT) showed the huge, ill-defined neck mass encasing the left common carotid artery and invading the left thyroid gland and the adjacent cervical structures (Fig. 1A, B, C). The positron emission tomography (PET) revealed a hypermetabolic mass in the left neck (level II to V) and increased fluorodeoxyglucose uptake in the left thyroid gland (Fig. 1D). Laboratory tests were performed at presentation showed an upper-normal range of leukocytosis (9870/µL) with normal percentage of neutrophil (57.6%), elevated C-reactive protein level (5.83 mg/dL), and elevated erythrocyte sedimentation rate (56.0 mm/h). The serum IgG4 level was not assessed at initial presentation. Ultrasonography-guided core needle biopsy (CNB) was performed for definite pathological confirmation.

Histopathologic examination showed that the lesion had lymphoplasmacytic infiltration and storiform pattern of fibrosis with no evidence of obliterative phlebitis, the IgG4/IgG positive cell ratio of 60%, and the IgG4 positive cell count of 68 per high power field (HPF) (Fig. 2). Additional serum IgG subclass laboratory test was done after biopsy report. Total serum IgG level was 939 mg/dL, and serum IgG4 level was 84.2 mg/dL.

On the basis of these findings, it was finally diagnosed as IgG4RD. After 2 months of oral corticosteroid treatment, histopathologic examination and CT were performed to evaluate the treatment response. It showed remarkable decrease in lymphoplasmacytic infiltration and a dramatic reduction in the size of the

Fig. 1. Computed tomography (CT) and positron emission tomography (PET) images acquired at first visit. A: CT axial view, at the hyoid greater horn level. B: CT axial view, at the thyroid cartilage level. C: CT coronal view. D: PET-CT axial view, at the thyroid cartilage level. Radiologic studies showed ill-defined left neck mass encasing the left common carotid artery and involving the left thyroid gland and the adjacent cervical structures.
Fig. 2. Histopathologic findings obtained by ultrasonography-guided core needle biopsy. A: Hematoxylin and eosin (H&E) staining (100×), storiform pattern of fibrosis with plasma cells. B: H&E staining (400×), lymphoplasmacytic infiltration. C: Immunostaining of IgG (brown color). D: Immunostaining of IgG4 (brown color); IgG4/IgG ratio was 60%.

Fig. 3. Computed tomography (CT) images and histopathologic findings after 2 months of oral corticosteroid treatment. A: CT axial view, at the hyoid greater horn level. B: CT axial view, at the thyroid cartilage level. CT axial views showed a dramatic reduction in the size of the left neck mass with no tracheal deviation. C: Histopathologic findings of the left neck mass. Hematoxylin and eosin (H&E) staining (100×) showed remarkable decrease of lymphocyte infiltration.
mass (Fig. 3). There has been no evidence of recurrence for 6 months.

**Discussion**

IgG4RD is a novel clinical entity, first proposed in relation to autoimmune pancreatitis by Japanese investigators in 20016. Since then, this condition has been identified in almost every organ system with many clinical manifestations. The head and neck region is the second most common site of presentation of IgG4RD, which most often presents as a mass lesion. According to a systematic review of IgG4RD presentation in the head and neck, the most common site of presentation was the orbit (n = 384, 52.6%) among the 730 presentations of systemic and head and neck manifestations. Relatively, the thyroid gland was a rare involvement site and manifested as Riedel’s thyroiditis (n = 31, 4.2%). Thyroid involvement has been postulated as a variant of thyroiditis. For example, Riedel’s thyroiditis has been immunohistochemically proven to be a part of the IgG4RD spectrum, and fibrosing variant of Hashimoto’s thyroiditis is also a part of the IgG4RD spectrum. Moreover, several case reports have also documented thyroid papillary carcinoma with IgG4+ plasma cells and fibrosis.

Laboratory or radiologic tests to diagnose IgG4RD accurately are currently unavailable. Serum IgG4 elevation showed poor specificity (60%) and low positive predictive value (34%) because it could increase in non-IgG4 related condition-malignancies or immune-mediated conditions, such as Sjogren syndrome, Mikulicz’s disease, granulomatosis with polyangiitis, Churg-Strauss syndrome, and sarcoidosis. Moreover, imaging studies are not critical for a diagnosis of IgG4RD. Thus, confirmatory biopsy is mandatory to exclude various conditions mentioned above and accurately diagnose IgG4RD. Especially in soft tissue mass with a suspicion of autoimmune disease, CNB was preferred modality because it can obtain tissue specimen with more preserved architecture. Although histopathologic examination alone is not a comprehensive clinical criterion, it is a gold standard for the diagnosis of IgG4RD. The team of the Research Program for Intractable Disease, Ministry of Health, Labor and Welfare in Japan has proposed the criteria for the diagnosis of IgG4RD in 2011. They called it as “comprehensive diagnostic criteria” to cover various organ involving cases, not organ specific. It contains three major criteria of clinical, laboratory and histopathologic features: (1) clinical features like characteristic diffuse/localized swelling or masses in single or multiple organs, (2) laboratory data with elevated serum IgG4 concentrations (≥ 135 mg/dL), (3) histopathologic features like marked lymphoplasmacytic infiltration and fibrosis, infiltration of IgG4 positive plasma cells (the ratio of IgG4/IgG-positive cells > 40% and IgG4-positive cells/HPF > 10). According to the criteria, it can be categorized as “definite IgG4RD” (with all the criteria satisfied), “probable IgG4RD” (with the clinical and histopathologic satisfied), and “possible IgG4RD” (with the clinical and laboratory criteria satisfied). However, it is important to differentiate from other similar diseases (e.g. malignant tumors, Sjogren’s syndrome, Churg-Strauss syndrome and Castleman’s disease).

Deshpande et al. suggested the international consensus statement on the pathology of IgG4RD. They suggested three criteria for conclusive diagnosis on the basis of characteristic quantitative and qualitative histopathologic findings in biopsy specimens obtained from affected tissues. According to the statement, IgG4/IgG-positive cell ratio of > 40% is mandatory for the diagnosis of IgG4RD. Three characteristic histopathologic features for IgG4RD were suggested: (1) a dense lymphoplasmacytic infiltrate, (2) storiform pattern of fibrosis, and (3) obliterative phlebitis. And the tissue-specific threshold of the number of IgG4-positive cells/HPF were established by expert consensus. According to the algorithm, IgG4RD was categorized as the two groups: “highly suggestive” of IgG4RD (with two or more major histopathologic features) and “probable” IgG4RD (with just one histopathologic feature). In this case, the patient complained of a rapidly grow-
ing left cervical mass for several months. CT and PET revealed the huge, ill-defined mass encasing the common carotid artery and invading the left thyroid, as well as multiple metastatic lymph nodes and salivary glands. Although there are many reports about IgG4RD with thyroiditis,\textsuperscript{4,17} the patients had no history for hypoor hyper-thyroidism, and diffuse thyroid enlargement. Laboratory data showed elevated ESR and CRP level, normal range of white blood cell count, and serum IgG4 of 84.2 mg/dL with total serum IgG of 939 mg/dL. Histopathologic examination revealed lymphoplasma- cytic infiltration and storiform pattern of fibrosis with no evidence of obliterative phlebitis. And, IgG4+/IgG+ cell ratio was 60% in biopsy and the number of IgG4-positive plasma cell count/HPF was 68. These findings satisfied the clinical and histopathological features of Japan’s criteria, thus it could be diagnosed as “probable” IgG4RD.\textsuperscript{14,15} Also, according to the international consensus, two characteristic findings met with the histopathologic criteria, and the IgG4+/IgG ratio was greater than 40% (60%). The number of IgG4-positive cell count/HPF was not sufficient to diagnose highly suggestive of IgG4RD. However, the specific threshold of thyroid tissue is not established. Considering the cut-off value for the biopsies of various organs is \( > 10 \) or \( > 20 \), the cell number of 68 is not low in this case. Comprehensively, it could be diagnosed as probable IgG4RD according to the international criteria.

On the basis of the above findings, it was clinically diagnosed as IgG4RD and we decided the steroid treatment for the patient. After 2 months of an oral corticosteroid treatment, histopathologic examination and CT was done to evaluate the treatment response. It showed remarkable decrease in lymphoplasmacytic infiltration and a dramatic reduction in the size of the mass. Even if he had rare clinical feature (thyroid invaded unilateral cervical mass), histopathologic findings are suitable for IgG4RD, and it showed good response to corticosteroid treatment. Thus, confirmatory biopsy is mandatory to exclude various conditions and accurately diagnose IgG4RD.

The differential diagnosis of a cervical mass is broad and includes both benign and malignant processes. The treatments for cervical mass are in the broad spectrum- medical, interventional, surgical, or sometimes observational strategies. Therefore, the failure of accurate diagnosis can lead unnecessary and invasive treatment or disease progression because IgG4RD is an autoimmune disease and responds to corticosteroids.\textsuperscript{4,17} Therefore, clinicians should consider IgG4RD as a differential diagnosis for mass lesions mimicking head and neck malignancies.

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