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WILEY
Clinical Utility of $^{18}$F-Fluorodeoxyglucose/Positron Emission Tomography in Diagnosis of Immunoglobulin G4–Related Sclerosing Sialadenitis

Kenichi Takano, MD, PhD; Ryoto Yajima, MD; Ryuta Kamekura, MD, PhD; Motohisa Yamamoto, MD, PhD; Hiroki Takahashi, MD, PhD; Naoya Yama, MD, PhD; Masamitsu Hatakenaka, MD, PhD; Tetsuo Himi, MD, PhD

**Objectives/Hypothesis:** The aim of this study was to evaluate the utility of $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for accurately diagnosing immunoglobulin G4-related sclerosing sialadenitis (IgG4-SS).

**Study Design:** Retrospective cohort study.

**Methods:** We reviewed the records of 64 patients with IgG4-SS (35 male and 29 female patients) and 10 patients with clinically suspected IgG4-SS. Pathological diagnoses of patients clinically suspected with IgG4-SS included four cases of malignant lymphoma, one case of multilocular Castleman disease, one case of Sjögren’s syndrome, and four cases of sialadenitis. All patients underwent submandibular gland (SMG) biopsies and baseline FDG-PET/CT evaluation. Clinical, serological, pathological, and PET/CT findings were analyzed. We also investigated maximum standardized uptake values (SUVmax) in the salivary glands of 15 patients with malignant disease of the salivary glands during the same period.

**Results:** Increased FDG uptake in the SMG and parotid gland was found in 63 (98%) and 23 (35%) patients with IgG4-SS, respectively. FDG uptake of the bilateral SMG and unilateral SMG was recorded in 57 patients (89%) and six patients (9%), respectively. Mean SUVmax in patients with malignant disease of the salivary glands was significantly higher than that in patients with IgG4-SS ($P = 0.035$). We defined a positive test for IgG4-SS diagnosis as high SMG FDG uptake and serum IgG4 level $\geq 135$ mg/dL, resulting in a sensitivity, specificity, and accuracy of 96.9%, 90.0%, and 86.4%, respectively.

**Conclusions:** FDG-PET/CT findings in combination with serological and clinical findings may have the capacity to diagnose IgG4-SS and lead to less-invasive biopsy procedures.

**Key Words:** Immunoglobulin G4–related disease, immunoglobulin G4–related sclerosing sialadenitis, $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography, diagnosis.

**Level of Evidence:** 4.

**Laryngoscope, 128:1120–1125, 2018**

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic immune-mediated disease characterized by elevated serum immunoglobulin G4 (IgG4) levels, dense lymphoplasmacytic infiltration, and fibrosis of the affected organs.1–4 IgG4-RD, which is more common than previously suspected, can affect various organs, but the pathogenesis remains unclear. IgG4-RD involving the head and neck is a common manifestation of this disease, affecting the salivary glands, lacrimal glands, sinonasal region, thyroid, pituitary gland, dura mater, and lymph nodes.1 In particular, IgG4-related sclerosing sialadenitis (IgG4-SS), which represents an enlargement of the salivary gland, is one of the most common lesions of IgG4-RD.1–4 Although the submandibular gland (SMG) is most frequently affected, the parotid gland (PG), sublingual gland, and labial salivary gland (LSG) may also be involved.5 Küttners’s tumor, which was first described as chronic sclerosing sialadenitis by Küttnier in 1896, is now known to be a type of disorder in IgG4-RD.1,6 The histopathological hallmark of IgG4-RD includes lymphoplasmacytic tissue infiltration with abundant IgG4-positive plasma cells, fibrosis, obliterator phlebitis, and dacyrooadenitis.7

Clinically, treatment by corticosteroids has led to rapid improvements in glandular swelling and increased gland secretion3,4; however, approximately 50% of IgG4-RD relapse patients present with lesions in other organ systems.8 To determine appropriate treatment for this disease, it is important to provide differential diagnosis in clinically suspected patients, identify affected organs, and evaluate disease activity. However, clinical diagnosis
of IgG4-RD is generally difficult due to variable clinical symptoms and mimicking malignancies. Furthermore, IgG4-RD confirmation and definitive diagnosis is highly dependent on tissue biopsy of the affected organ. In the field of otorhinolaryngology, SMG biopsies are generally performed in potential IgG4-SS cases. However, an SMG biopsy under general anesthesia may be too invasive, and not all suspected patients with IgG4-SS are able to undergo an SMG biopsy. Therefore, establishment of noninvasive IgG4-SS diagnosis techniques are required in the clinical field.

Recent studies have demonstrated that FDG-PET/CT may be a useful tool for differentiating IgG4-RD from other diseases in clinically suspected patients. Because tissue infiltration by inflammatory cells and lymphocytes is associated with an increased uptake of FDG in patients with IgG4-RD, the characteristic pattern of FDG-PET/CT imaging is helpful in the diagnosis of IgG4-RD. A recent study showed that FDG-PET/CT may be a useful tool for differentiating IgG4-RD from other diseases in clinically suspected patients. However, the extent to which FDG-PET/CT can diagnose IgG4-SS in suspected patients with collated clinical and pathological findings has not been previously studied. Therefore, in the present study, we investigated the utility and ability of FDG-PET/CT in the clinical diagnosis of IgG4-SS. Our results may increase the diagnostic precision of IgG4-SS and help avoid unnecessary invasive biopsies.

MATERIALS AND METHODS

We examined 64 patients with IgG4-SS (35 male and 29 female patients) and 10 patients with clinically suspected IgG4-SS (five cases of malignant disease and one of multicentric Castleman disease [MCD]). Pathological diagnoses of patients clinically suspected with IgG4-SS included four cases of malignant lymphoma, one case of MCD, one case of Sjögren’s syndrome, and four cases of salivary adenitis. All patients underwent SMG biopsies, and had previously consulted doctors at Sapporo Medical University, Japan and its related facilities between March 2011 and March 2017. Thirty-three cases underwent both SMG and LSG biopsies at the same time for clinical and pathological diagnosis. Formalin-fixed paraffin-embedded blocks of these tissues were analyzed. Written consent to use the information from these cases was obtained from the patients in accordance with the Declaration of Helsinki. This study proceeded under the approval of our institutional review board.

IgG4-SS was diagnosed according to the Japanese Society for Sjögren’s Syndrome, 2008, and the 2011 comprehensive diagnostic criteria for IgG4-RD. In addition, our institutional pathologists provide diagnoses according to the 2012 Consensus Statement for Clinical Pathologists. Briefly, IgG4-SS was diagnosed as follows: 1) symmetrical swelling of at least two pairs of SMGs, lachrymal glands, or PGs for at least 3 months; 2) serum IgG4 levels of >135 mg/dL; 3) >40% of plasma cells being IgG4-positive cells with >10 cells/high powered field of biopsy sample; and 4) two of the following histopathological features: dense lymphoplasmacytic infiltration, fibrosis (arranged at least focally in a storiform pattern), and obliterative phlebitis.

We also investigated FDG standardized uptake value (SUV) in the salivary glands of 15 patients with malignant disease of the salivary glands who underwent FDG-PET/CT examination (seven male and eight female patients, mean age 59.1 ± 9.8 years ± standard deviation) during the same period. Their pathological diagnosis included follicular lymphoma (n = 3), salivary duct carcinoma (n = 3), diffuse large B-cell lymphoma (n = 2), adenoid cystic carcinoma (n = 2), adenocarcinoma (n = 1), myoepithelial carcinoma (n = 1), carcinoma ex pleomorphic adenoma (n = 1), and large cell carcinoma (n = 1).

All samples were biopsied before therapy. Serum immunoglobulin G (IgG) and IgG4 levels were measured and determined at the Department of Laboratory Diagnosis, Sapporo Medical University. All patients in this study underwent whole-body FDG-PET/CT at Sapporo Medical University before treatment, and the data were retrospectively acquired from their medical records. All PET/CT studies were performed using a single PET/CT scanner (Discovery ST Elite; GE Healthcare, Tokyo, Japan) with a 700-mm field of view and a 3.3-mm slice thickness. After a minimum of 6 hours of fasting, hyperglycemia was ruled out by measuring blood glucose levels (<200 mg/dL). Imaging was performed 60 minutes after the intravenous injection of 5 MBq/kg of FDG (FDGscan, Universal Giken; Nihon Mediphysics, Tokyo, Japan). The patients were scanned between the skull vertex and midthigh with the arms down. The emission scan lasted for 2 to 4 minutes for each bed position. All PET data were reconstructed with and without CT-based attenuation correction. Three experienced nuclear medicine physicians, without knowledge of the patients’ serum IgG4 levels or medical history, performed the visual analysis of PET/CT characteristics and patterns. The SUV of FDG uptake in tissue was computed as follows: SUV = PET activity/(injected dose/body weight), where the FDG concentration is expressed in mg/mL. The SUVmax was measured by manually placing a circle around regions of interest on transaxial tomographic PET images. Uptake of FDG was assessed visually and semiquantitatively based on the maximum SUVmax of each region of interest. Visual analysis of FDG uptake was also conducted, with high FDG uptake defined as higher uptake than the surrounding tissue in salivary glands, and as higher than liver uptake in other organs. To obtain reproducibility and reliability, three experienced nuclear medicine physicians performed visual analysis in a blinded fashion, and the results were compared among the physicians. Each area of interest was evaluated by each physician. In cases of divergent interpretations, consensus was reached by discussion.

The Mann-Whitney U test was used to determine differences between the two groups. The data are expressed as the mean ± standard deviation. A P value of <.05 was considered statistically significant.

RESULTS

Patient Characteristics and FDG-PET/CT Findings in Patients With IgG4-SS

Patient baseline characteristics and FDG-PET/CT findings of patients with IgG4-SS are shown in Table I. The mean age of patients with IgG4-SS was 63.1 ± 10.5 years (range, 27–81 years). Serological analysis of patients with IgG4-SS showed that the mean total IgG level was 2124.2 ± 1120.2 mg/dL and the mean IgG4 level was 11121.
629.6 ± 541.1 mg/dL (the mean IgG4/IgG ratio was 25.3% ± 10.1%). Hypergammaglobulinemia (IgG/C21 = 1800 mg/dL) was detected in 38 patients (59.4%). The mean total IgE (IU/mL) and peripheral blood eosinophils were 315.8 ± 440.2 IU/mL and 3.6% ± 2.9%, respectively. The mean serum interleukin 2 receptor (sIL-2R) was 674.2 ± 370.8 IU/mL. Extra salivary gland diseases in patients with IgG4-SS included autoimmune pancreatitis (n = 16, 25%), tubulointerstitial nephritis (n = 8, 13%), sclerosing cholangitis (n = 2, 3%), retroperitoneal fibrosis (n = 10, 16%), autoimmune hypophysitis (n = 1, 2%), bronchitis (n = 4, 6%), and interstitial pneumonia (n = 3, 5%). Multiple organ lesions were observed in 38 of 64 patients (59.4%).

The mean serum IgG4 levels of groups showing FDG uptake of bilateral and unilateral SMG was 675.3 ± 556.1 mg/dL (26.5% ± 10.5%) and 244.8 ± 76.7 mg/dL (14.2% ± 3.9%), respectively. The FDG uptake pattern of the SMG was more often diffuse (n = 54, 84%) than focal (n = 9, 14%). Increased FDG uptake of the PG was found in 23 patients (35%), and the mean SMG SUVmax and mean serum IgG4 level was 3.6 ± 1.3 and 969.2 ± 753 mg/dL (32.1% ± 11.4%), respectively. The PET/CT also showed high FDG uptake in the following other organs: lacrimal glands (n = 29, 45%), pancreas (n = 10, 16%), lymph nodes of hilum (n = 21, 33%), and sublingual salivary glands (n = 20, 31%). Typical FDG-PET/CT images of a patient with IgG4-SS are shown in Figure 1A and B.

**FDG-PET/CT Findings in Patients With Suspected IgG4-SS**

Clinical characteristics of patients with clinically suspected IgG4-SS in the study period are shown in Table II. Pathological diagnosis included diffuse large B-cell lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, IgG4-producing marginal zone diffuse large B-cell lymphoma, and MCD. The patients who were clinically suspected to have IgG4-SS underwent SMG biopsy, FDG-PET/CT, and serological examinations. Although unilateral FDG uptake of SMG was found in patients 1 and 2, bilateral FDG uptake of the SMG and PG was found in patients 3 and 4. These four patients had malignant lymphoma. Although three of the four patients with lymphoma did not show a high serum IgG4 levels (<135 mg/dL), one patient with IgG4-producing marginal zone diffuse large B-cell lymphoma...
had high serum IgG and IgG4 concentrations (3,172 mg/dL and 1,220 mg/dL, respectively). On the other hand, a patient with MCD (patient 5) showed a high serum IgG4 level, but increased FDG uptake in the salivary glands was not recorded. A high sIL-2R level was found in all five patients.

Comparison of FDG Uptake Between IgG4-SS and Malignant Diseases

To investigate whether SUVmax of FDG uptake in SMG of patients with IgG4-SS is a useful value for differential diagnosis from other malignant diseases of the salivary glands, we compared lesion SUVmax between IgG4-SS and malignant diseases. Although the mean SUVmax of SMG in patients with IgG4-SS was 5.9 ± 2.1, the mean lesion SUVmax in patients with malignant diseases of the salivary glands was 8.7 ± 5.2. As shown in Figure 2, patients with malignant disease had a significantly higher SUVmax than patients with IgG4-SS (P = .035). Typical PET/CT images of malignant diseases of the salivary glands are shown in Figure 1C and D.

Accuracy of Diagnostic Tests Using a Combination of IgG4 Levels and FDG-PET/CT Findings

In the diagnosis of IgG4-SS, we defined a positive test as high FDG uptake of the SMG and serum IgG4 level >135 mg/dL and calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (Table III). The number of patients testing positive with IgG4-SS and non–IgG4-SS was 62 (83.8%) and one (1.4%), respectively. The number of patients testing negatively with IgG4-SS and non–IgG4-SS was two (2.7%) and nine (12.2%), respectively. The results of the calculated sensitivity, specificity, PPV, NPV, and accuracy were 96.9%, 90.0%, 98.4%, 81.8%, and 86.4%, respectively.
**TABLE III.**

Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of the Combination of FDG Positron Emission Tomography/Computed Tomography and Serum IgG4 Level.

<table>
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<tr>
<th></th>
<th>IgG4-SS, No. (%)</th>
<th>Non-IgG4-SS, No. (%)</th>
<th>Total</th>
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<tr>
<td><strong>Test positive</strong></td>
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<tr>
<td>Test positive</td>
<td>62 (83.8%)</td>
<td>1 (1.4%)</td>
<td>63 (85.1%)</td>
</tr>
<tr>
<td>Test negative</td>
<td>2 (2.7%)</td>
<td>9 (12.2%)</td>
<td>11 (14.9%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>64 (86.5%)</td>
<td>10 (13.5%)</td>
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<tr>
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<td>90.0%</td>
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<tr>
<td>Specificity</td>
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FDG = \(^{18}F\)-fluorodeoxyglucose; IgG4 = immunoglobulin G4; IgG4-SS = immunoglobulin G4–related sclerosing sialadenitis; SMG = submandibular gland.

**DISCUSSION**

This retrospective cohort study investigated the utility and ability of FDG-PET/CT in the clinical diagnosis of IgG4-SS. The diagnosis of IgG4-SS can be based on clinical imaging, serological, and pathological findings. The currently proposed diagnostic criteria include enlarged or hypertrophic organs, elevated serum IgG4 levels, and pathological findings. Clinically, typical IgG4-SS disease is found in middle-aged and elderly people, and gender differences are nearly equivalent with persistent swelling (>3 months) of the SMG or PG.

Most patients with IgG4-RD exhibit elevated serum IgG4 levels; however, it is known that this parameter is neither sufficiently sensitive nor specific for diagnosis. Overall, 3% to 30% of patients with IgG4-RD show normal serum IgG4 concentrations, particularly those with a single organ affected. The sensitivity/specificity/PPV/NPV/accuracy of serum IgG4 levels alone for the diagnosis of IgG4-SS in the present study was 96.9%, 70.0%, 95.4%, 77.8%, and 93.2%, respectively. These values, except sensitivity, are inferior compared to those calculated by combining IgG4 levels and FDG-PET/CT findings. Elevated serum IgG4 levels have also been associated with various other disorders, including atopic dermatitis, pemphigus, asthma, and MCD. Therefore, serum IgG4 levels may be useful for screening, but cannot be used as the sole diagnostic marker. Most patients with IgG4-RD can often be identified based on high serum IgG4 concentrations, and can then be diagnosed in combination with other diagnostic components such as imaging and histological examination.

The most important disease in differential diagnoses for IgG4-RD is malignant disease, especially malignant lymphoma. Tumor tissue shows high FDG uptake due to overexpression of glucose transport proteins and certain key enzymes. Tissue affected by infection, autoimmune disease, or granulomatous disease also shows an increased uptake of FDG due to activated granulocytes, lymphocytes, and macrophages, all requiring a high glucose turnover. Our results showed that the mean SUVmax of SMG in IgG4-SS was significantly lower than that of malignant lesions in salivary glands. However, lesion SUVmax in both IgG4-SS and malignant diseases varied widely; therefore, it is difficult to distinguish IgG4-SS from malignant diseases of salivary glands using SUV alone. A previous study showed that tissue IgG4-positive cell count did not show a significant correlation with SUVmax, supporting the notion that FDG uptake by immune cells is not a key component of lesion SUVmax in IgG4-SS. Taken together, although mild to moderate lesion FDG uptake may not be conclusive, it may nonetheless be helpful for differentiating IgG4-SS from other malignant diseases, which have higher uptake levels. On the other hand,
MCD, which is also important in the differential diagnosis for IgG4-SS, is able to distinguish IgG4-SS by FDG-PET/CT. Although MCD often mimics IgG4-SS due to high serum IgG4 levels and clinical findings, FDG uptake of bilateral SMG is normally not found, as in the present case. One of the PET/CT interpretation pitfalls is that symmetrical diffuse uptake of FDG can be seen in normal salivary glands. Although this finding is similar to those seen in patients with IgG4-SS, serum IgG4 levels and physical findings are helpful in the differential diagnosis.

To differentiate IgG4-SS from other mimicking diseases, especially a malignancy, tissue biopsy is finally needed. FDG-PET/CT can help the selection of an adequate biopsy site because it reflects glucose metabolism and reveals the disease activity of lesions associated with IgG4-RD. In the present study, all patients underwent biopsy from SMG based on FDG-PET/CT findings, which reveals the disease activity of lesions associated with other diseases, especially a malignancy, tissue biopsy is finally needed. Although this finding is similar to those seen in patients with IgG4-SS, serum IgG4 levels and physical findings are helpful in the differential diagnosis.

Therefore, FDG-PET/CT plays a crucial role in determining the biopsy site, leading to a reduction in the false-negative rate by providing a more accessible lesion with high accumulation. In addition, our results suggest that the combination of FDG-PET/CT, serological, and clinical findings is helpful in the diagnosis of IgG4-SS and may lead to a less-invasive biopsy procedure. Although FDG-PET/CT has not achieved its rightful place in the consensus diagnostic criteria for IgG4-RD, the present data indicate that FDG-PET/CT is a potentially useful tool in many aspects of IgG4-SS diagnosis.

Although FDG-PET/CT has been broadly used in oncology, it can also serve as a sensitive tool in evaluating organ involvement and disease distribution, and it is useful in the selection of a minimal and adequate biopsy site. Although the FDG-PET/CT is associated with the risk of radiation and biopsy is essential to obtain a definitive diagnosis and to deny malignancy, we consider that PET/CT will provide useful information, simultaneously not only determining the involvement of other organs but also determining the appropriate site for biopsy and diagnosis, even if the patient refuses biopsy.

CONCLUSION

The diagnosis of IgG4-SS remains a challenge in clinical practice. The pattern of FDG distribution on PET/CT in addition to serological and clinical findings can be helpful in the diagnosis of IgG4-SS in clinically suspected patients. Although the clinical value of PET/CT for the diagnosis of IgG4-SS remains controversial, the possibility of excessive medical testing exists. In the future, FDG-PET/CT may lead to less-invasive biopsy procedures, and the image pattern of FDG-PET/CT in patients with IgG4-SS may be updated into the consensus diagnostic criteria.

BIBLIOGRAPHY