ABSTRACT

We aimed to show the differentiation of the degree and distribution on Fluorine-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) between patients with immunoglobulin G4-related disease (IgG4-RD) and sarcoidosis, though both diseases frequently show bilateral hilar lymphadenopathy (BHL). The clinical records were retrospectively reviewed in 25 patients with IgG4-RD with BHL and 15 patients with sarcoidosis (stage I–II) diagnosed at Shinshu University Hospital. All patients underwent FDG-PET at Aizawa Hospital from January 2004 to December 2015. The FDG accumulation pattern and maximum standardized uptake value (SUVmax) of the hilar lymph nodes were compared between the two groups. The IgG4-RD group (21 men; median age 69 years) showed a significant male predominance and older age compared with the sarcoidosis group (3 men, median age 55.4 years). The IgG4-RD group showed a significantly higher incidence of FDG accumulation in the lachrymal gland, submandibular gland, pancreas, prostate and periurethral and periarterial regions compared with the sarcoidosis group. In contrast, the sarcoidosis group showed a significantly higher incidence of FDG accumulation in the supraclavicular and abdominal lymph nodes, muscle and soft tissues compared with the IgG4-RD group. Furthermore, the SUVmax of the hilar lymph nodes was significantly higher in the sarcoidosis group (median 7.20) than in the IgG4-RD group (median 4.20, p=0.002). In conclusion, significant differences were observed in the FDG accumulation patterns and SUVmax values of the hilar lymph nodes between IgG4-RD with BHL and sarcoidosis, although both diseases develop through the lymphatic routes of the lungs and are frequently associated with BHL.

Keywords: bilateral hilar lymphadenopathy (BHL), Fluorine-18 fluorodeoxyglucose-positron emission tomography (FDG-PET), Immunoglobulin G4-related disease (IgG4-RD), Sarcoidosis, maximum standardized uptake value (SUVmax)
INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a systemic disorder involving the salivary glands, pancreas, lungs and several organs.² Sarcoidosis is also a systemic disease and is characterized by noncaseous epithelioid cell granuloma involving the lungs, other various organs and lymphatic system, including the hilar lymph nodes.³,⁴ Because both IgG4-RD and sarcoidosis develop through the lymphatic routes of the lungs, chest computed tomography (CT) frequently shows lung lesions and bilateral hilar lymphadenopathy (BHL) in patients with IgG4-RD, which resembles the findings of chest CT in patients with sarcoidosis.⁵-⁷ Similarly, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) shows the accumulation of FDG in the hilar lymph nodes of several patients with IgG4-RD, which resembles the findings of FDG-PET in patients with sarcoidosis. Because many IgG4-RD and sarcoidosis patients develop minimal respiratory symptoms, it can be difficult to differentiate IgG4-RD from sarcoidosis clinically, and there are occasionally cases with the coincidental occurrence of both diseases.⁸,⁹ Furthermore, elevated IgG4 levels have been noted in patients presenting with sarcoidosis-like radiologic findings of the lung, suggesting that undiagnosed suspected sarcoidosis may include some cases of unrecognized IgG4-RD.¹⁰

Gallium-67 (67Ga) scintigraphy has been reported to be useful for the clinical differentiation between IgG4-RD and sarcoidosis.¹¹ However, the disadvantage of 67Ga scintigraphy is that it has less diagnostic accuracy in staging, evaluating disease activity, and monitoring the treatment response in patients with sarcoidosis in comparison to FDG-PET.¹² FDG-PET may have the potential to yield even more accurate information, as it has a greater resolution than 67Ga scintigraphy and was recently used to evaluate systemic lesions in patients with IgG4-RD.¹²-¹⁵ Thus far, however, the features of FDG-PET concerning the similarities and differences between IgG4-RD with BHL and sarcoidosis have not been reported.

We therefore aimed to show the differentiation of the degree and distribution on FDG-PET between the patients with IgG4-RD and sarcoidosis though the both diseases frequently showed BHL.

METHODS

Patients and diagnostic criteria

This study was performed in accordance with the recommendations of the Helsinki Declaration of 1975. The Ethics Committee of Shinshu University School of Medicine approved the collection and analysis of the clinico-radiological-pathological data (Approval Number: 3458).

We retrospectively assessed 25 patients with IgG4-RD and 15 patients with sarcoidosis. All 40 patients showed BHL on chest CT.

The records of 25 consecutive untreated IgG4-RD patients with BHL on chest CT who were diagnosed in our institution (Shinshu University School of Medicine, Matsumoto, Japan) and who received FDG-PET in a single institution (Aizawa Hospital, Matsumoto, Japan) from January 2004 to December 2015 were retrospectively analyzed. The lesions in the IgG4-RD patients were mainly located in the pancreas (n=16), lung (n=4), submandibular gland (n=4), and the periurethral region (n=1).¹⁶ Patients with pancreatic involvement were diagnosed in the department of gastroenterology according to the International Consensus Diagnostic Criteria for autoimmune pancreatitis (AIP).¹⁷ Patients without pancreatic involvement were diagnosed by excisional biopsy of the lesions, according to the comprehensive diagnostic criteria for IgG4-RD, 2011.¹⁸

Fifteen consecutive untreated patients with biopsy-proven sarcoidosis (stage I-II)⁴ who were
diagnosed in our institution, and who underwent FDG-PET at the same institution, were analyzed.

**PET**

FDG-PET scans for all the patients were performed in the single institution (Positron Imaging Center, Aizawa Hospital).\(^\text{15}\) Written informed consent was obtained from all patients. PET scans were performed with a dedicated PET/CT scanner (2004 to 2009, Advance Nxi, GE, Milwaukee, WI, USA) in two-dimensional imaging mode, or a dedicated PET/CT scanner (2010 to 2015, Discovery PET/CT 600, GE, Milwaukee, WI, USA) in three-dimensional imaging mode. Emission scans were obtained with a 2–3 min acquisition time per table position, requiring 6 or 9 table positions to cover the area from the pelvis floor to the head. After at least 4 h of fasting, 3.7–5 MBq/kg (maximum 370 MBq) of F-18 FDG was intravenously injected. A whole-body scan was performed 60 min after the injection of FDG. The presence of lymph node enlargement was defined by a short axis diameter of ≥10 mm.\(^\text{19}\)

**Data analyses**

The focal FDG accumulation was evaluated visually and the maximum standardized uptake values (SUVmax) of the hilar lymph nodes were calculated.\(^\text{15}\) FDG accumulation was assessed in the lachrymal, submandibular and parotid glands, thyroid, lung, bile duct, pancreas, liver, spleen, retroperitoneal tissue, prostate/periurethral tissue, the cervical, supraclavicular, axillary, inguinal, hilar, abdominal and intrapelvic lymph nodes, periarterial lesions, muscle/soft tissue, and perivertebral tissue. Three radiologists (A.F., S.K., and K.O.) assessed the abnormal FDG uptake independently, without knowledge of the diagnosis and clinical data. In the case of disagreement, the final decision was made after a discussion between the radiologists.

**Statistical analyses**

A chi-squared test was used to compare two possible variables such as the sex ratio and positive FDG accumulation ratio between the IgG4-RD and sarcoidosis groups. The Mann-Whitney U-test was used to compare continuous variables such as age, blood biochemical findings and SUVmax (SPSS Statistics version 22; IBM, Armonk, NY, USA). P values of <0.05 were considered to indicate statistical significance.

**RESULTS**

**Clinical characteristics and laboratory data**

The clinical characteristics of the patients between the two groups are compared in Table 1. None of the patients received corticosteroid therapy prior to the FDG-PET. The IgG4-RD patients (male, n=21; female, n=4; median age, 69 [range: 43–82] years) showed a significant male predominance (p<0.001) and were significantly older (p<0.005) in comparison to the sarcoidosis patients (male, n=3; female, n=12; median age 55.4 years [24–80] years). The serum levels of blood urea nitrogen (BUN) and lactase dehydrogenase (LDH) did not show significant differences between the two groups. The serum levels of creatinine, c-reactive protein (CRP), IgG, and soluble interleukin-2 receptor (sIL-2R) were significantly higher in the IgG4-RD patients than the sarcoidosis patients. In addition, the IgG4-RD group showed significantly higher white blood cell counts, especially with larger amount of eosinophil counts, comparing with the sarcoidosis group. In contrast, the sarcoidosis patients showed significantly higher serum levels of ACE comparing with the IgG4-RD group. We did not have the data of the serum IgG4 concentration in the sarcoidosis patients in this study.
**FDG uptake**

Figures 1–3 show the FDG-PET findings of the IgG4-RD and sarcoidosis patients. In a 79-year-old woman with a characteristic IgG4-related periurethral lesion mimicking an enlarged prostate in a man,16 FDG-PET revealed the uptake of FDG by the lachrymal glands (b), hilar lymph nodes (c), abdominal lymph nodes and a periaortic lesion (d), and a periurethral lesion (e) (Figure 1). In a 59-year-old woman with IgG4-related pancreatitis (autoimmune pancreatitis) FDG-PET revealed the uptake of FDG by the lachrymal glands (b), submandibular gland (c), hilar lymph nodes (d), and pancreas (e) (Figure 2). In a 24-year-old man with sarcoidosis, FDG-PET revealed the uptake of FDG by the supraclavicular lymph nodes (b), mediastinal lymph nodes (c), hilar lymph nodes and lung (d), and inguinal lymph nodes (e) (Figure 3).

The two diseases showed significant differences with regard to their prevalence and patterns of FDG accumulation (Table 2).

In comparison to the sarcoidosis patients, the IgG4-RD patients showed a significantly higher incidence of FDG accumulation in the lachrymal gland (9 [36.0%] vs. 0 [0%], p=0.008), submandibular gland (14 [56.0%] vs. 1 [6.7%], p=0.002), pancreas (16 [64.0%] vs. n=0 [0%], p<0.001), prostate/periurethral lesions (12 [48.0%] vs. 0 [0%], p=0.001), and periartrial lesions (7 [28.0%] vs. 0 [0%], p=0.02).

In contrast, sarcoidosis patients showed significantly a higher incidence of FDG accumulation in the supraclavicular lymph node (8 [53.3%] vs. 3 [12.0%], p=0.005), abdominal lymph node (7 [46.7%] vs. 2 [8.0%], p=0.005), and muscle/soft tissue (4 [26.6%] vs. 0 [0%], p=0.006).

Patients with both diseases showed the accumulation of FDG in the hilar lymph node;
Fig. 1 The FDG-PET findings in a patient with IgG4-related periurethral lesion. A 79-year-old woman with IgG4-related periurethral lesion showed multi-organ involvements ((a) whole-body view; (b) lachrymal glands; (c) hilar lymph nodes; (d) abdominal lymph nodes and periaortic lesion; (e) periurethral lesion). The black line on the left side of the patient is a urethral catheter.

Fig. 2 The FDG-PET findings in a patient with IgG4-related pancreatitis. A 59-year-old woman with IgG4-related pancreatitis (autoimmune pancreatitis) showed multi-organ involvements ((a) whole-body view; (b) lachrymal glands; (c) submandibular gland; (d) hilar lymph nodes; (e) pancreas).
however, the SUVmax of the hilar lymph nodes in the sarcoidosis patients (median, 7.20 [range: 1.50–20.70]) was significantly higher than that in the IgG4-RD patients (4.20 [3.30–8.10], p=0.002) (Fig. 4).

**DISCUSSION**

In this study, it was evaluated that FDG accumulation in the hilar was seen in both IgG4-RD and sarcoidosis, but the distribution of the FDG uptake in multiple organs differed significantly between IgG4-RD and sarcoidosis, despite both being multi-organ-involving diseases.

The differences in the FDG accumulation patterns between these two groups might be due to differences in the etiology and immunological status of the diseases. A recent study reported that almost half of all patients with AIP have an autoantibody against Laminin 511-E 8, namely truncated Laminin 511 (an extracellular protein), while only 1.6% of healthy controls possess the same autoantibody. The injection of human serum from patients with AIP into mice or the immunization of mice with human laminin 511-E8 induced pancreatitis similar to AIP. Thus, this autoantigen could be involved in the pathogenesis of IgG4-RD. Although the detailed mechanism underlying the pathogenesis in patients with IgG4-RD with negative autoantibody against Laminin 511-E 8 is unclear at present, lesions of IgG4-RD may occur in organs expressing antigens like Laminin 511-E8 and/or some sort of antibody. However, Eishi et al reported that sarcoidosis is caused by an excessive response to infection by Propionibacterium(P) acnes. It is considered that three conditions are essential to the development of sarcoidosis caused by P. acnes: (1) latent infection with cell wall-deficient P. acnes, (2) endogenous activation of dormant P. acnes triggered by certain environmental factors, and (3) a hypersensitive Th1 immune response towards the intracellular proliferation of P. acnes. In addition, we previously showed that the cytokine

![Fig. 3 The FDG-PET findings in sarcoidosis.](image-url)

A 24-year-old man with sarcoidosis showed multi-organ involvements ((a) whole-body view; (b) supraclavicular lymph nodes; (c) mediastinal lymph nodes; (d) hilar lymph nodes and lung; (e) inguinal lymph nodes).
PET-CT of IgG4-RD and sarcoidosis

Table 2  FDG accumulation in IgG4-related disease and sarcoidosis

| Accumulation region     | IgG4-related disease | Sarcoidosis |
|-------------------------|----------------------|-------------|
|                         | N=25 (% )            | N=15 (% )   | p value |
| Lachrymal gland         | 9 (36.0)             | 0 (0)       | 0.008   |
| Submandibular gland     | 14 (56.0)            | 1 (6.7)     | 0.002   |
| Parotid gland           | 6 (24.0)             | 1 (6.7)     | N.S.    |
| Thyroid                 | 0 (0)                | 1 (6.7)     | N.S.    |
| Lung                    | 6 (24.0)             | 4 (26.6)    | N.S.    |
| Bile duct               | 1 (4.0)              | 1 (6.7)     | N.S.    |
| Pancreas                | 16 (64.0)            | 0 (0)       | <0.001  |
| Liver                   | 2 (8.0)              | 1 (6.7)     | N.S.    |
| Spleen                  | 1 (4.0)              | 1 (6.7)     | N.S.    |
| Retropertitoneal tissue | 3 (12.0)             | 0 (0)       | N.S.    |
| Prostate/Perirethral tissue | 12 (48.0)   | 0 (0)       | 0.001   |
| Cervical lymph node     | 8 (32.0)             | 2 (13.3)    | N.S.    |
| Supraclavicular lymph node | 3 (12.0)       | 8 (53.3)    | 0.005   |
| Axillary lymph node     | 2 (8.0)              | 1 (6.7)     | N.S.    |
| Inguinal lymph node     | 0 (0)                | 2 (13.3)    | N.S.    |
| Hilar lymph node        | 25 (100)             | 15 (100)    | ~        |
| Mediastinal lymph node  | 25 (100)             | 15 (100)    | ~        |
| Abdominal lymph node    | 2 (8.0)              | 7 (46.7)    | 0.005   |
| Intrapelvic lymph node  | 4 (16.0)             | 3 (20.0)    | N.S.    |
| Periarterial tissue     | 7 (28.0)             | 0 (0)       | 0.02    |
| Muscle/soft tissue      | 0 (0)                | 4 (26.6)    | 0.006   |
| Perivertebral tissue    | 1 (4.0)              | 2 (13.3)    | N.S.    |

N.S.: Not significant

![Boxplot](image)

**Fig. 4**  The SUVmax of the hilar lymph nodes in sarcoidosis and IgG4-RD.
The boxplot shows the SUVmax of the hilar lymph nodes in sarcoidosis (median, 7.20 [range: 1.50–20.70]) were significantly higher in comparison to those in IgG4-related disease (4.20 [3.30–8.10], *p*=0.002 [Mann-Whitney U Test]). SUVmax: maximum standardized uptake value.
profiles in the BAL fluid of IgG4-RD patients with BHL were characterized by a stronger Th2 response than in patients with sarcoidosis. Recently, we also reported that the BALF levels of CC-chemokine ligand (CCL)26 that were possibly associated with an allergic immune response in IgG4-RD patients were significantly higher than those in sarcoidosis patients. Therefore, the detailed mechanisms are still unknown, the differences in the pathogeneses and immunological conditions of these two diseases might contribute to the discrepancy in the patterns of FDG accumulation.

Several reports have described the efficacy of FDG-PET in assessing the multi-organ involvement in IgG4-RD diseases. Tokue et al reported that FDG-PET was useful for detecting the lacrimal or salivary gland (LSG) involvement and the associated extra-LSG lesions in patients with IgG4-RD. A study by Zhang et al showed that FDG-PET/CT was able to detect more organ involvement in 71.4% of patients with IgG4-RD than conventional evaluations (e.g. physical examinations, ultrasonography, CT alone). In addition, Ozaki et al suggested that FDG-PET was useful not only for detecting autoimmune pancreatitis and associated extrapancreatic lesions but also for differentiating autoimmune pancreatitis from pancreatic cancer. However, there has been no comparison study of FDG-PET between IgG4-RD and sarcoidosis. To our knowledge, this is a first comparison study of FDG-PET between IgG4-RD and sarcoidosis.

Furthermore, FDG-PET appeared to have higher diagnostic accuracy in comparison to 67Ga scintigraphy for evaluating systemic lesions in patients with IgG4-RD and sarcoidosis. Ishii et al demonstrated the usefulness of Ga-67 scintigraphy for differentiating between sarcoidosis and IgG4-RD in 27 patients with sarcoidosis and 16 with IgG4-RD. They noted that the 67Ga uptake in the mediastinal and supraclavicular lymph nodes and muscles was specific to sarcoidosis, whereas the 67Ga uptake in the pancreas, lacrimal gland, and submandibular gland was significantly higher in IgG4-RD. The sample size of the present study was similar to that in the Ga-67 scintigraphy study. However, the present FDG-PET examination showed significant differences in the frequencies of FDG accumulation in the lachrymal gland, prostate/periurethral lesions, periarterial lesions, and abdominal lymph nodes between sarcoidosis and IgG4-RD, while such differences were not detected in the 67Ga scintigraphy study. The sensitivity for the differentiation of the two diseases appears to be superior with the FDG-PET technique compared with 67Ga scintigraphy. Because BHL on chest CT was a selection criterion for the present study, all patients with IgG4-RD and sarcoidosis showed the uptake of FDG at the bilateral hilar and mediastinal lymph nodes. Therefore, no significant differences were observed in terms of the uptake ratio of the hilar and mediastinal lymph nodes between the two groups in this study.

BHL is frequently detected in patients with IgG4-RD. Fujinaga et al reported that 78% of patients with autoimmune pancreatitis showed BHL on CT, and 75% the patients of IgG4-RD showed BHL on Ga-67 scintigraphy. Furthermore, Matsui et al also noted that 100% (18/18) of patients with IgG4-related respiratory disease showed BHL on CT. The 67Ga scintigraphy study by Ishii et al found that accumulation was detected in the hilar lymph nodes in 75% of IgG4-RD patients and 78% of sarcoidosis patients, and the lymph nodes of sarcoidosis patients were more intense than those of IgG4-RD patients. However, they did not perform a quantitative assessment of the hilar lymph nodes with 67Ga scintigraphy. The present study quantitatively measured the FDG accumulation in cases of BHL and showed that the SUVmax values of the hilar mediastinal lymph nodes were significantly higher in sarcoidosis patients than in IgG4-RD patients (Figure 4). To our knowledge, this is the first study using FDG-PET to assess the difference in the biological activity of the hilar lymph nodes quantitatively between IgG4-RD and sarcoidosis patients.

The histopathology of enlarged hilar lymph nodes is characterized by granuloma in sarcoidosis, while abundant IgG4-positive cell infiltration without granuloma is noted in IgG4-RD.
In sarcoidosis, inflammatory cells such as macrophages and lymphocytes express high levels of glucose transporters, specifically the glucose transporter (GLUT)-1 and GLUT-3. Active granuloma-forming lymph nodes of sarcoidosis showed an increased uptake of FDG transported through GLUT-1 and GLUT-3 in the activated lymphocytes and macrophages in the lesions. In contrast, an immunofluorescence analysis of the liver biopsy specimen in a patient with IgG4-related hepatitis indicated the clear expression of GLUT-3 in IgG4-positive cells infiltrating the lesion; however, other inflammatory cells showed almost no GLUT-3 expression. Furthermore, all inflammatory cells, including IgG4-positive cells in the case of IgG4-related hepatitis, were negative for GLUT-1. Thus, FDG could be transported GLUT-3 rather than GLUT-1 in the lesions of IgG4-RD. Because GLUT-1 and GLUT-3 both participated in the uptake of FDG in inflammatory lesions, discrepancies in the expression of glucose transporters between IgG4-RD and sarcoidosis might partly explain the difference in the FDG uptake of the hilar lymph nodes between the two diseases.

FDG-PET can have several uses in the clinical setting. IgG4-RD often mimics sarcoidosis on chest CT. Furthermore, a patient with suspected sarcoidosis showed progressive IgG4-related systemic disease over a 7-year period. Thus, FDG-PET might be useful for differentiation between IgG4-RD and sarcoidosis.

Whereas the association between sarcoidosis and malignant diseases has been well described, it remains controversial whether this association is merely a coincidence or the consequence of a common pathophysiologic mechanism. A study from Germany reported that 61 patients with malignant disease were identified in a cohort of 425 patients with sarcoidosis. On the other hand, a Japanese report showed that an active IgG4-RD state is presumed to be a strong risk factor for the development of malignancy. It was reported that, using FDG-PET/CT, pancreatic malignancies were detected prior to the initiation of steroid therapy in 3 of 53 patients with suspected autoimmune pancreatitis. Bearing in mind the FDG accumulation patterns and the SUVmax of hilar lymph nodes in this study, FDG-PET could be useful for detecting sites of abnormal accumulation, such as malignancies, prior to the administration of treatment for patients with suspected sarcoidosis or IgG4-RD. If a malignant tumor is detected, treatment for the malignancy must be given priority over therapy for sarcoidosis or IgG4-RD. FDG-PET may be especially useful in cases in which coexisting malignancy is highly suspected but biopsy is inconclusive. An accurate diagnosis is of the utmost importance, since surgical resection is the only curative treatment for common malignant tumors.

Furthermore, a prospective cohort study described that FDG-PET is a useful tool for both assessing organ involvement and monitoring the therapeutic response and guiding interventional treatment for IgG4-RD. Especially for cardiovascular lesions of IgG4-RD, the persistent uptake of FDG during corticosteroid treatment is considered to be the result of persistent active inflammation, which indicates an increased risk of future relapse. In patients with sarcoidosis, FDG-PET is reported to be useful for staging, evaluating disease activity, and monitoring the treatment response. Furthermore, in the evaluation of cardiac involvement in sarcoidosis (which was not evaluated in this study) FDG-PET is reported to have shown promising results as a complementary technique to magnetic resonance imaging, especially in the guidance of treatment.

The present study is associated with several limitations. First, it was a retrospective study with a limited number of patients, and FDG-PET was performed at a single institution. Second, we were unable to evaluate cardiac lesions as there was no appropriate method available in the study period. Third, since FDG-PET is not covered by health insurance for IgG4-RD and extracardiac sarcoidosis in Japan, it could not be routinely scheduled for all patients with IgG4-RD and sarcoidosis in our hospital. Thus, FDG-PET was performed at the discretion of several doctors.
for assorted purposes, such as excluding malignancy. Despite these limitations, the findings from our study suggest that FDG-PET may be used for the clinical differentiation of IgG4-RD with BHL and sarcoidosis.

CONCLUSION

Significant differences were observed in the FDG accumulation patterns and SUVmax values of the hilar lymph nodes between the IgG4-RD with BHL and sarcoidosis, although both diseases develop through the lymphatic routes of the lungs and are frequently associated with BHL. The differences in the pathogeneses and immunological conditions of these two diseases might contribute to the discrepancy in the accumulation of FDG.

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CONFLICT OF INTEREST

None declared.

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