

Case Study

Grade I Lymphomatoid Granulomatosis with Increased Uptake of [¹⁸F] Fluorodeoxyglucose in Positron Emission Tomography : A Case Report

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There are several reports describing [¹⁸F] fluorodeoxyglucose positron emission tomography (FDG-PET) findings in patients with lymphomatoid granulomatosis (LYG). We report a case of grade I LYG that showed increased uptake of FDG. The patient was a 63-year-old Japanese male who underwent an FDG-PET/computed tomography (CT) scan in screening for a malignant lesion. Increased uptake of FDG [maximum standard uptake value (SUV_{max}), 3.7] was observed in the right hilar region in FDG-PET and enhanced CT revealed a round, abnormal mass that also showed increased FDG uptake. The patient had no previous symptoms. A tumor biopsy was performed and the histological diagnosis was grade I LYG. Therefore, increased SUV_{max} in FDG-PET might be useful for diagnosing of LYG. [*J Clin Exp Hematopathol* 49(1) : 39-44, 2009]

Keywords: lymphomatoid granulomatosis, fluorodeoxyglucose positron emission tomography, grade, lung, surgery

INTRODUCTION

Lymphomatoid granulomatosis (LYG) is a rare disease that resembles Wegener's granulomatosis clinically and lymphoma histologically. Its characteristics include an angiocentric, angiodestructive infiltration of the lungs, nervous system and skin with a polymorphous infiltrate of lymphocytes, plasma cells, histiocytes and atypical lymphoreticular cells. Epstein-Barr virus (EBV) has been identified by polymerase chain reaction (PCR) in most cases of LYG, but the exact etiology is still unknown. The natural history is extremely variable and there is no standard treatment for LYG. In

addition, there are neither typical clinical features nor radiographic findings, including for [¹⁸F] fluorodeoxyglucose (FDG) uptake in FDG positron emission tomography (FDG-PET). Here, we describe a case of LYG of grade I that showed an increased maximum standard uptake value (SUV_{max}) in FDG-PET.

CASE REPORT

The patient was a 63-year-old Japanese male with type II diabetes mellitus who was admitted to our hospital for control of his blood sugar level. Fasting blood sugar was 193 mg/dL and HbA1c was 9.4% on admission. Other blood tests were almost within the normal range. After good control of diabetes mellitus was established, FDG-PET/computed tomography (CT) was performed in screening for a malignant lesion. The scan showed increased uptake of FDG (SUV_{max} = 3.7) in the right hilar region, and enhanced CT revealed a round, abnormal mass with high uptake of FDG. The tumor was about 20 x 15 mm in size and was located in the right pulmonary lower lobe, extremely close to a pulmonary artery. No abnormal uptake of FDG was seen elsewhere and there were no other abnormal shadows on chest CT (Figs. 1a-1d).

Tumor markers for primary lung cancer (carcinoembryonic antigen, CYFRA, squamous cell carcinoma related antigen, sialyl Lewis^x, neuron specific enolase, and pro-

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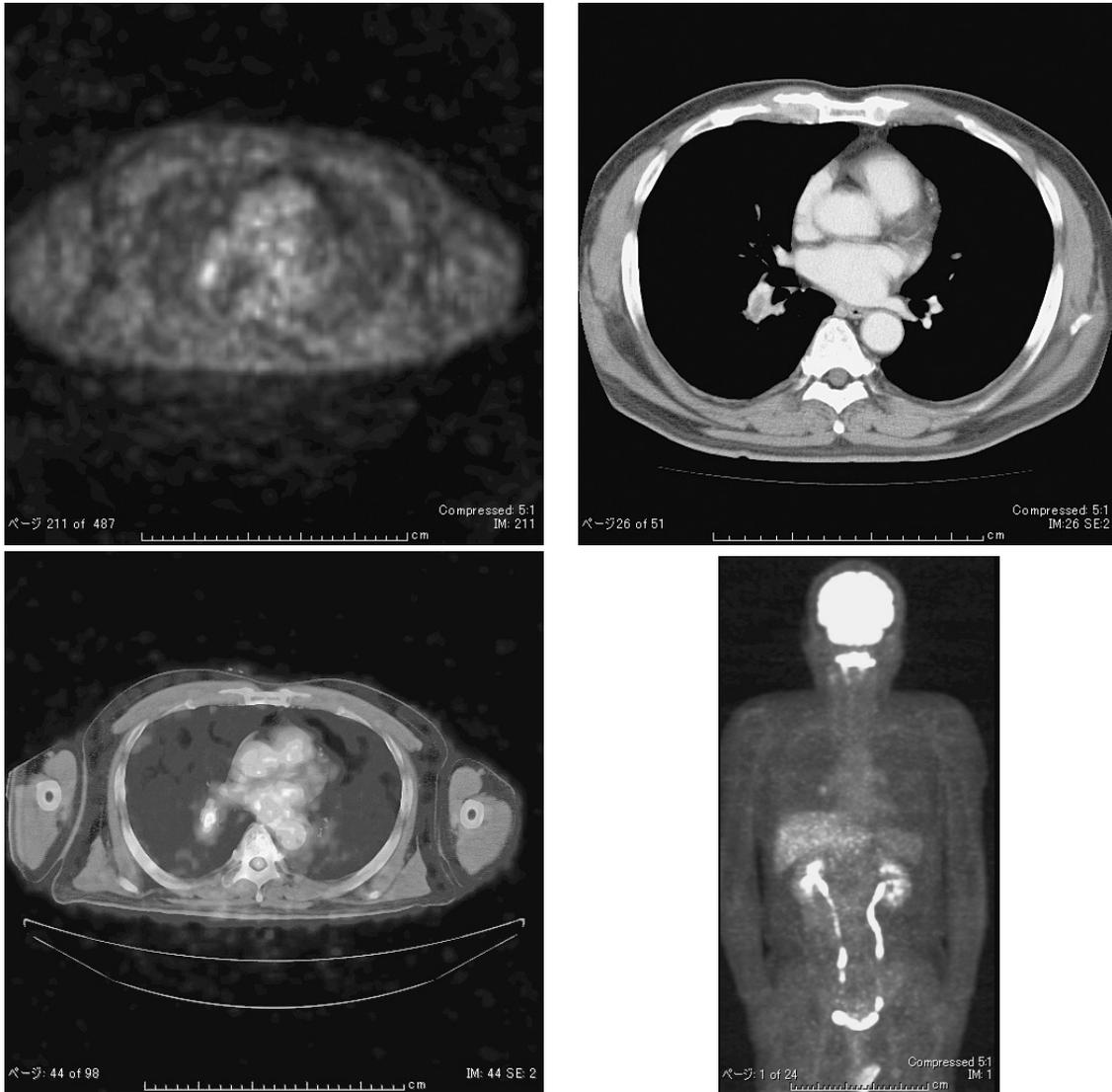


Fig. 1. [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) scan showed increased uptake of FDG [maximum standard uptake value (SUV_{max}) = 3.7] in the right hilar region. Enhanced computed tomography revealed a round, abnormal mass located in the right pulmonary lower lobe, extremely close to a pulmonary artery (**1a-1c**). Coronal view of FDG-PET scan showed no abnormal uptake of FDG elsewhere (**1d**).

gastrin-releasing peptide) and soluble interleukin-2 receptor (441 U/mL : normal range 220 - 530) were all within the normal ranges. However, because of the increased uptake of FDG and his smoking history (20 cigarettes per day for 43 years), a malignant tumor was strongly suspected. The location of the tumor made it difficult to perform a bronchoscopic examination, and therefore the patient was referred to our department for a tumor biopsy. Since the mass was very close to a pulmonary artery, the tumor biopsy was performed by posterolateral thoracotomy. The tumor adhered strongly to the A6-basal pulmonary artery and we were unable to detach the adhesion (Fig. 2). A right lower lobe lobectomy was subsequently performed and the frozen diagnosis was a “ne-

crotizing granulomatous lesion”, negating the need for lymph node dissection.

Permanent pathological findings are shown in Figs. 3a-3f. Grossly, the lesion was relatively well circumscribed, about 18 x 11 x 8 mm in size, and located mainly within the left pulmonary artery A6. Histologically, the lesion consisted of a conspicuous lymphoid infiltrate between the adventitia and endothelium of the A6 arterial wall. The lymphoid cells consisted of a large number of small lymphocytes without atypia and a small number of medium or large mononuclear lymphoid cells with slight atypia in a background of histiocytes and occasional plasma cells. Few eosinophils and neutrophils were present. The large lymphoid cells resembled

immunoblasts and some had double nuclei, but classic Reed-Sternberg cells were not found. Although necrotic areas were observed, well-formed epithelioid granulomas were absent. Vascular changes such as lymphocytic vasculitis were observed in muscular arteries around the lesion.



Fig. 2. Evidence of the tumor adhering strongly to a pulmonary artery (arrow).

A periodic acid-Schiff reaction, Grocott-Gomori methenamine-silver staining and Ziehl-Neelsen staining did not reveal any microorganisms. Bacterial cultivation was performed using tissue from the lesion, but no bacterium was identified. Immunohistochemically, most of the infiltrating small-sized lymphocytes were positive for CD3 (PS1; Nichirei; Tokyo; Japan), but the medium-to-large lymphoid cells were positive for CD20 (L26; Dako; Copenhagen; Denmark) and CD79a (JCB117; Dako). *In situ* hybridization for EBV-encoded small RNA was positive for the medium-sized lymphoid cells (< 5 per high power field), which were also immunoreactive for CD79a. However, clonality of *immunoglobulin heavy chain* gene rearrangements could not be demonstrated by PCR using a method described in the literature.¹ Taken together with other results, we concluded that the clinicopathological findings were consistent with features of LYG of grade I.

The patient's postoperative course was uneventful and he was discharged on postoperative day 11. Because the permanent pathological diagnosis was grade I LYG and there was no evidence of other lesions, adjuvant treatment was not given. The patient is currently well with no evidence of recurrence 13 months after the operation, but will continue to

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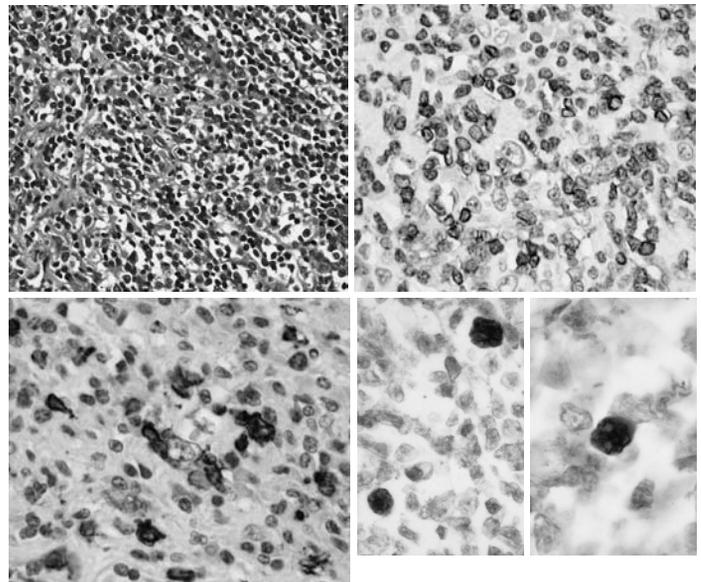
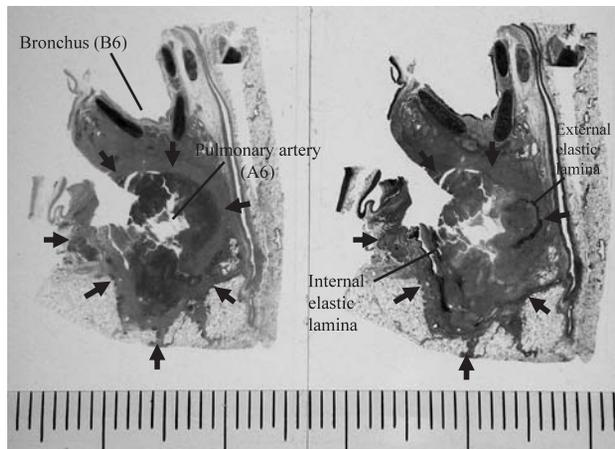


Fig. 3. Histology of lymphomatoid granulomatosis. (3a) Magnifying glass image showing a right pulmonary artery A6 lesion, consisting of lymphoid infiltrates and necrosis (arrows). The bronchus B6 was almost intact and no hilar lymph node involvement was detected. Elastica van Gieson stain delineated destruction of internal and external elastic laminae, suggesting that this lesion is an angiocentric and angiodestructive lymphoproliferative disorder. (3b) Microscopic high power view of the lesion showing predominance of small-sized lymphocytes interspersed by medium or large lymphoid cells [hematoxylin and eosin (HE) stain, original magnification $\times 100$]. (3c) Immunohistochemistry showing small-sized lymphocytes positive for CD3 (counterstained with HE, original magnification $\times 200$). (3d) Immunohistochemistry showing medium-or large-sized lymphoid cells positive for CD20 (counterstained with HE, original magnification $\times 200$). (3e) *In situ* hybridization showing lymphoid cells with slight atypia positive for Epstein-Barr virus-encoded small RNA transcripts (counterstained with HE, original magnification $\times 300$). (3f) Double stain showing a lymphoid cell positive for Epstein-Barr virus-encoded small RNA transcripts (counterstained with HE, colored brown, nucleus) and CD79a (colored red, cytoplasm) (original magnification $\times 500$).

receive careful, long-term follow-up. The patient provided informed consent regarding publication of the features of this case.

DISCUSSION

LYG was first described in 1972 by Liebow *et al.*² as a new disease that shared overlapping features with lymphoma and Wegener's granulomatosis (WG).³ Clinically and radiologically, the disease resembles WG, but biopsy findings are more suggestive of lymphoma.³ LYG is an extranodal angiocentric and angi-destructive lymphoproliferative disease that is also considered to be an EBV-associated B-cell lymphoproliferative disorder.⁴ It predominantly involves the lungs and extra-pulmonary involvement by LYG is also commonly found in skin (39%), as a neurological disorder (30%), and can be associated with splenomegaly (18%), hepatomegaly (12%), and lymphadenopathy (8%), in the absence of lung involvement.⁵ Age at onset is typically 30-50 years old and males are more susceptible than females, with a reported sex ratio of 1 to 6.5 males per female.⁶

Most patients with LYG present with chest symptoms, such as cough, and shortness of breath and/or systemic complaints such as fever, weight loss and malaise. However, asymptomatic cases have also been recognized⁵ and there is no striking pattern of laboratory abnormalities. Regarding pulmonary LYG, radiographic findings are various, but the most common are multiple rounded mass densities^{5,6} that are bilateral and predominate in the lower lobes. In contrast, unilateral or single nodules are unusual.⁶ Other findings are diffuse, fluffy alveolar shadows, diffuse reticulonodular infiltrate shadows, and hilar lymph node enlargement.⁵ Chest CT can show a peribronchovascular distribution of irregular coarse nodules, patchy coarse densities, cavitation, coalescent nodules,⁷ a thin-walled cavity,⁸ and mimicking of interstitial pneumonia.⁹

Histologically, LYG is a lymphoproliferative and granulomatous disease that is angiocentric and angi-destructive.² Many infiltrated cells have plasmacytoid characteristics; i. e., they consist of typical plasma cells and large cells with an intermediate appearance between plasma cells and reticuloendothelial cells.⁵ This includes histiocytes, plasma cells, many reactive T-cells and rare large, atypical cells of a B cell phenotype.⁴ EBV has been identified by PCR in most cases of LYG,¹⁰ and therefore LYG is considered to be an EBV-associated B-cell lymphoproliferative disorder.⁴ Guinee *et al.*¹¹ and Wilson *et al.*¹² suggested that LYG should be referred to as "T-cell-rich, EBV-associated, B-cell lymphoproliferative disorder (T-RELD)", but the exact origin of the infiltrated cells in LYG has not been determined.¹³

The term "angiocentric immunoproliferative lesion (AIL)" was proposed by Jaffe to encompass the histologic spectrum of the lesions in the lung and at other extranodal

sites.¹⁴ The histologic grading of AIL Grades I-III for these lesions is useful for determining prognosis and for guiding clinical management and therapy, with the grades defined as follows:¹⁴ Grade I: polymorphous cellular composition without cytologic atypia in the lymphoid cells, but the infiltrate has a striking angiocentric and angi-destructive character. Grade II: polymorphous cellular composition with considerable cytologic atypia in the small lymphoid cells. Large lymphoid cells or immunoblasts are more numerous than in Grade I. Necrosis due to vascular involvement is more readily observed. Grade III: monomorphism of the infiltrate and cytologic atypia are present in both small and large lymphoid cells. A polymorphous inflammatory background is usually inconspicuous, and necrosis is prominent.

One might assume that the current case is Grade II LYG because the lesion contained necrosis and large lymphocytes. However, our findings of infrequent large lymphoid cells, few EBV-encoded small RNA positive cells and lack of *immunoglobulin heavy chain* gene clonality led us to consider the lesion as Grade I LYG.

Guinee *et al.*¹¹ also assigned the disease to Grades I to III on the basis of the number of atypical EBV-positive B cells and the amount of necrosis, and reported that Grade III lesions had sheets of large atypical EBV-positive cells and should be considered as diffuse large B cell malignant lymphoma histologically. Wilson *et al.*¹² also reported that EBV was undetectable in Grade I lesions and most prevalent in Grade III lesions. The natural history of LYG is extremely variable. Katzenstein *et al.*⁵ found that 63.5% patients with LYG died within 36 months, with most LYG-related deaths due to extensive destruction of pulmonary parenchyma. Sepsis, massive hemoptysis, and central nervous system disorders were also seen. On the other hand, 76% of surviving patients had no evidence of disease from 9 months to 18 years after onset and 24% were alive with the disease after a period of 6 months to 4.5 years. However, 12% of LYG patients develop malignant lymphoma, and although the boundaries between "malignancy and benignity" and "monoclonality and polyclonality" remain poorly defined in LYG, the prognosis is generally poor.⁶

Jaffe¹⁴ reported that the histologic features in Grade I LYG are comparable to those of benign lymphocyte angitis and granulomatosis, and that LYG also has many clinical similarities with these diseases. Some patients with Grade I LYG had a benign clinical course, an excellent response to antibiotics, and spontaneous remission, but in others the lesions progressed to malignant lymphoma; therefore, although Grade I LYG seemed to follow a good clinical course, a risk of progression to malignant lymphoma was present and dissemination sites (skin, kidney, brain, and peripheral nerve) were also observed.¹⁴ The clinical course of Grade II LYG was more aggressive in its progression to malignant lymphoma. In Grade III LYG, the average B-cell

proliferation index was similar to that observed in large cell non-Hodgkin's B-cell lymphomas¹¹ and a Grade III lesion should be considered histologically as a diffuse large B cell malignant lymphoma.^{11,15}

There is no standard treatment for LYG and the optimal therapy is unknown, but observation alone, corticosteroid therapy, immunomodulatory therapy, anti-CD20 (rituximab) therapy, chemotherapy, and bone marrow transplantation have been tried.¹⁶ Katzenstein *et al.*⁵ reported patients with LYG who recovered regardless of the form of therapy and those who received no treatment or antibiotics but survived free of disease. In contrast, Drasga *et al.*¹⁷ suggested that since LYG resembles and can develop into malignant lymphoma, therapy for lymphoma might also be effective for LYG. Many chemotherapy regimens with a variety of agents have only been minimally successful, but Drasga *et al.* reported successful treatment of LYG with CHOP therapy (a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone) and also emphasized the importance of initial and aggressive treatment regimens for this disease.¹⁷ Wilson *et al.*¹² reported the efficacy of interferon- α 2b for LYG, and Guinee¹¹ suggested observation alone or use of an immunologic adjuvant for Grade I or II LYG and chemotherapy for Grade III. Success¹⁸ and failure¹⁹ with anti-CD20 (rituximab) monotherapy have also been reported in cases of LYG. And successful treatments of radiotherapy for localized pulmonary LYG, extrathoracic LYG also have been reported.⁶

In our case, the patient had no previous symptoms and no history of EBV infection. Chest X-rays showed no abnormal findings, but FDG-PET and enhanced chest CT revealed an abnormal mass with increased uptake of FDG ($SUV_{max} = 3.7$) in the right pulmonary lower lobe. Histologically, the lesion was an angiocentric and angiodestructive lymphoproliferative

disorder and no hilar lymph node involvement was detected.

There are few reports of FDG-PET findings in cases of LYG: a PubMed search gave only 6 publications using FDG-PET for LYG.^{8,15,16,18-20} Including our case, the clinical features of the 7 reported cases are summarized in Table 1. Yamauchi *et al.*⁸ described a strong accumulation of FDG (SUV_{max} unknown) at the cavity wall and in peripheral lesions of the lung, and Suzuki *et al.*²⁰ described similar findings in lung nodules, femoral muscle, and lumbar subcutaneous nodules (SUV_{max} unknown). Kawai *et al.*¹⁵ suggested that FDG-PET imaging with kinetic analysis is effective in brain LYG and shows increased hexokinase activity in the lesions, with the proposal that this phenomenon indicated malignant characteristics of LYG due to accelerated glycolytic metabolism in the tumor. Roarke and Nguyen¹⁶ reported findings of innumerable bilateral hypermetabolic coalescent lung foci in FDG-PET and suggested a correlation of the characteristics of LYG (lymphocytic, vasculitic, and inflammatory responses) with these findings and the usefulness of follow-up monitoring by FDG-PET.

In our case, chest CT and FDG-PET showed a round solitary mass in the lung with increased uptake of FDG, which is atypical for LYG. Thus, a tumor biopsy was required to establish the exact histological diagnosis. As far as we are aware, there are no detailed reports of the correlation of FDG-PET and LYG grade, but it is of interest that the FDG-PET scan in our patient with grade I LYG revealed increased uptake of FDG, which might be suggestive of other lesions, such as inflammation, tuberculoma,²¹ sarcoidosis²² and malignancies including lymphoma.²³ The exact etiology, treatment, and prognosis of LYG remain unclear, and further studies aimed at determining potential neoplastic characteristics are required.

Table 1. Characteristics of patients reported with [¹⁸F] fluorodeoxyglucose positron emission tomography (FDG-PET) findings in lymphomatoid granulomatosis

Case no.	Year	First author	Age	Sex	Site	Presenting complaints	Grade	SUVmax of FDG-PET	Treatment	Outcome
1	2002	Yamauchi Y ⁸	48	M	both lungs	fever, hemoptum	II	unknown	Prednisolone	Death at 78 days
2	2005	Jordan K ¹⁸	21	F	mediastinal	cough	II	high glucose uptake	Rituximab	Surviving at 20 mon
3	2005	Polizzotto MN ¹⁹	42	F	both lungs/skin/kidneys	dyspnea	unknown	intense FDG activity	Rituximab	Surviving at 2 wk with worsening
4	2006	Suzuki H ²⁰	46	M	both lungs/muscles/brain	fever, fatigue	unknown	strong accumulation	CHOP	Death at 39 days
5	2006	Kawai N ¹⁵	44	M	brain	disorientation	I	not significant increase	CHOP	Surviving
6	2007	Roarke MC ¹⁶	39	F	both lungs	cough	unknown	unknown	Rituximab	Surviving with relapse
7	2007	Present case	63	M	right hilar region	none	I	3.7	right lower lobectomy	Surviving at 13 mon

CHOP; cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisolone

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