

Measuring diffuse metabolic activity on FDG-PET/CT: new method for evaluating Langerhans cell histiocytosis activity in pulmonary parenchyma[☆]

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Abstract

Introduction: Pulmonary Langerhans cell histiocytosis (PLCH) is a rare cause of interstitial lung disease characterized by formation of nodules in the active phase of the disease that evolve into nonactive cystic lesions later on. To evaluate PLCH activity in patients, we developed a new method for measuring diffuse metabolic activity on fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) using a lung-to-liver activity ratio.

Material and Methods: We retrospectively studied a series of 4 FDG-PET and 23 FDG-PET/CT scans from 7 patients with PLCH and analyzed a sample of 100 randomly chosen FDG-PET/CT studies free from any known lung or hepatic diseases. Maximum standardized uptake value (SUVmax) in a spherical volume (6–8 cm in diameter) in the right lung was put into relation with SUVmax in a spherical volume (9–10 cm in diameter) in the reference liver parenchyma to set up the SUVmaxPULMO/SUVmaxHEPAR index. The index values were compared to the disease course in each patient.

Results: In patients with PLCH, a close correlation between the index value and the disease course was found in all seven subjects, where the increasing index values indicated disease activity, while decreasing index values were observed after therapy administration. In the group of 100 healthy control subjects, we found index values lower than 0.3 in 80% and lower than 0.4 in 96% [range: 0.14–0.43; 0.24±0.07 (100)].

Conclusion: Measuring SUVmaxPULMO/SUVmaxHEPAR values and their time-trend monitoring represent simple, noninvasive screening tools allowing an early diagnosis and treatment response follow-up assessment in patients with PLCH.

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Keywords: Langerhans cell histiocytosis; Interstitial lung disease; Positron emission tomography; Pulmonary function tests; High-resolution computed tomography (HRCT)

1. Introduction

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare condition, the symptoms of which are nonspecific and

include cough, chest pains and dyspnea, and sometimes, even pneumothorax may be its first manifestation. In the early stages of the disease, small nodules, evolving through cavitated forms into thick-walled, later thin-walled and eventually confluent cysts, start to build up in pulmonary parenchyma. These changes predominantly affect upper lung zones with relative sparing of the lung bases [1]. Radiological appearance of advanced PLCH on conventional radiographs or even high-resolution computed tomography (HRCT) scans may be difficult to distinguish from emphysema, which often leads to delays in getting the

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right diagnosis and initiating proper treatment. In addition, X-ray findings are sometimes inconclusive without any correlation to serious clinical symptoms (Fig. 1).

Langerhans cell histiocytosis limited only to pulmonary parenchyma is a smoke-related interstitial lung disease referred to as isolated PLCH, and it has a better prognosis than Langerhans cell histiocytosis with multisystemic involvement including lungs. Although having different prognoses and therapeutic approaches, these two entities present the same clinical, radiological and histopathological manifestations [2,3]. PLCH is responsible for 3%–5.5% of interstitial lung diseases [4–6]. Larger epidemiologic data are available from Japan [7], where the estimated crude prevalences in males and females are 0.27 and 0.07 per 100,000 population, respectively. Most patients with PLCH are young cigarette smokers between 20 and 40 years of age [1].

Diagnostics include surgical lung biopsy and bronchoalveolar lavage with CD1a+ elements (Langerhans cells) analysis [8]. Additionally, in the setting of multisystemic Langerhans cell histiocytosis, characteristic HRCT scan findings in the lungs may be sufficient for the diagnosis. Treatment is indicated in patients with multisystemic involvement or when a progression of pulmonary lesions

has been confirmed. The progression is characterized by increasing numbers of nodules, whereas formation and enlargement of cysts are only a natural disease development into its terminal, end-stage phase. HRCT scans and pulmonary function tests are routinely applied in the follow-up; however, determining the number of nodules on HRCT scans is extremely difficult and time consuming, and pulmonary function tests cannot always distinguish between end-stage cystic disease and active PLCH [6,9].

To facilitate the PLCH activity assessment, we developed and verified a new method for measuring diffuse metabolic activity on fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan imaging using the SUVmaxPULMO/SUVmaxHEPAR index. In this paper, we describe this methodology and verify its validity on a retrospective study of a PLCH patient cohort.

2. Materials and methods

2.1. Patients

During a 21-year period from November 1, 1989, to January 1, 2011, 23 patients were diagnosed with Langerhans

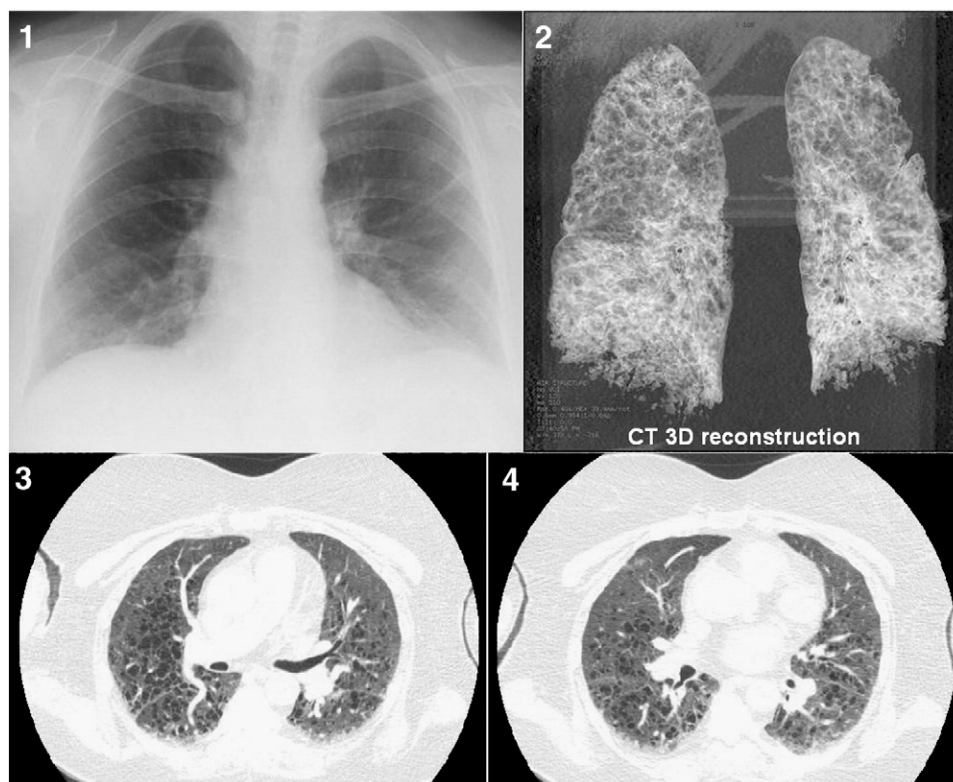


Fig. 1. Different radiological imaging modalities of the chest in a patient with multisystemic Langerhans cell histiocytosis with pulmonary involvement (female, born 1955). The patient presenting with fevers and dyspnea was admitted to hospital with suspected pneumonia in July 2010. There were no abnormalities seen on conventional radiography (1), in contrast to HRCT imaging (3 and 4) showing apart from hypostatic pneumonia also diffuse small cysts (4–15 mm in size) in both lung fields resembling emphysema, which was visualized using 3D reconstruction (2). Cystic lung disease, complicated by bacterial infection, was an accidental finding in this patient. However, retrospective analysis of the SUVmaxPULMO/SUVmaxHEPAR index in preceding four PET examinations (2004–2010) shows a high probability of a previous history of PLCH (Table 2).

cell histiocytosis and followed up at our department. Out of them, 15 patients had either single-systemic (nine patients) or multisystemic (six patients) disease without pulmonary involvement. The remaining eight patients were diagnosed with PLCH, of whom seven underwent FDG-PET scan imaging. In total, 4 FDG-PET and 23 FDG-PET/CT studies were performed between the years 2004 and 2010. The study follow-up period started with the first FDG-PET examination in March 2004.

The indications for FDG-PET or FDG-PET/CT scanning included: (a) searching for multiorgan involvement of an extrapulmonary (verified by bone, lymph node or skin biopsies) Langerhans cell histiocytosis (four scans) as well as (b) of known PLCH (two scans), (c) differential diagnosis of pituitary stalk infiltration (one scan) and (d) follow-up of patients (20 scans). The patients were free from any other active lung or liver disease at the time of PET scanning. The diagnosis of PLCH was based on pathological examinations (three patients) or pathognomonic HRCT scan findings (four patients). Patients who did not agree to the use of their medical records for research were not included in this study.

2.2. FDG-PET/CT scan imaging

In the PLCH patient cohort, we performed FDG-PET and FDG-PET/CT scanning in euglycemia after fasting for 6 h. FDG-PET scan images of the body, at the extent from the proximal thirds of femurs to the cranial base (with the head

included in four scans), were obtained 60 min after intravenous injection of fluorodeoxyglucose (range of applied activity: 312–409 MBq). Until 2008, data acquisition was performed on a PET scanner (ECAT ACCEL SIEMENS) in a three-dimensional (3D) mode and, later, from 2008, on a hybrid PET/CT scanner (True Point PET-CT Biograph 64 SIEMENS). Emission and transmission scans were reconstructed by using an iterative reconstruction algorithm. On acquired data, attenuation correction was applied. Due to repeated follow-up FDG-PET/CT scanning, in most studies, low-dose CT protocol reducing radiation load significantly was used. With the remaining studies, high-dose CT mode was applied. The scan field of view was 50 or 70 cm according to a patient's body habitus. The acquisition parameters for CT were as follows: slice 5 mm, collimation 24×1.2 mm, pitch 0.8 mm. To optimize lung parenchyma imaging, the following reconstruction algorithm was used: slice 1.5–2.0 mm, kernel B 80 f (ultra sharp), reconstruction increment 0.4 mm, window–lung. Maximum standardized uptake values (SUVmax) were measured for semiquantitative analysis.

2.3. SUVmaxPULMO/SUVmaxHEPAR index

Nodules in PLCH often measure several millimeters (4–6 mm) and are below detectable levels of used PET scanners (about 7 mm), which precludes direct measurement of their activity. Therefore, we tried to find these active lesions in a

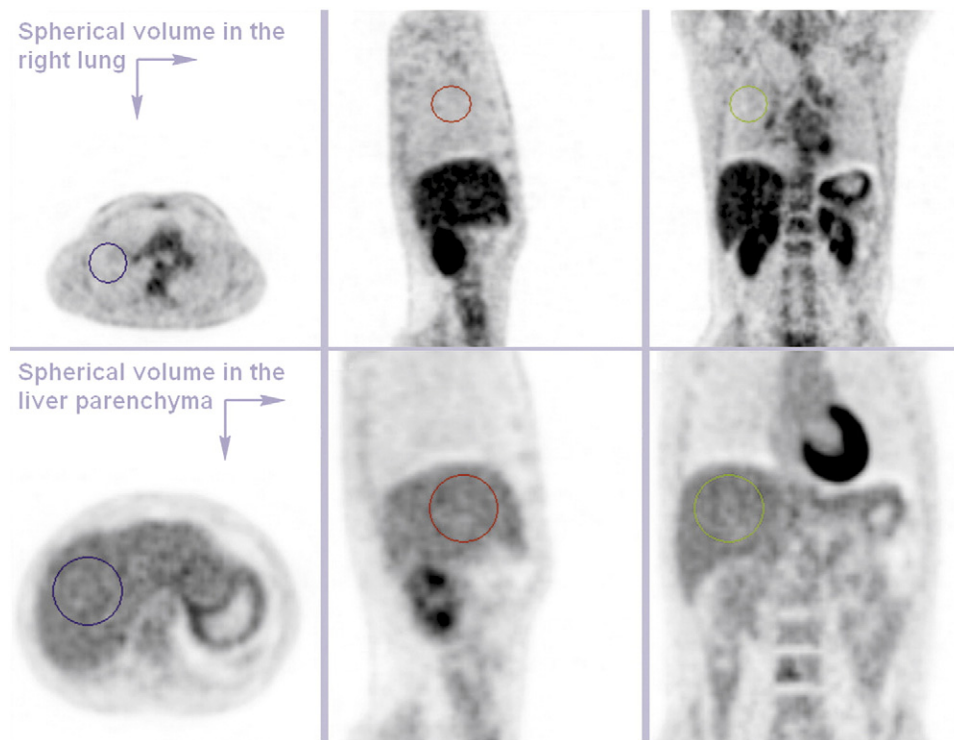


Fig. 2. SUVmax in a spherical volume (6–8 cm in diameter) in the right lung was put into relation with SUVmax in a spherical volume (9–10 cm in diameter) in the reference liver parenchyma to set up the SUVmaxPULMO/SUVmaxHEPAR index. Considering the topographical differences between the lungs and the liver, we were more limited in demarcating the volume of interest in the lung parenchyma, which therefore has smaller diameter.

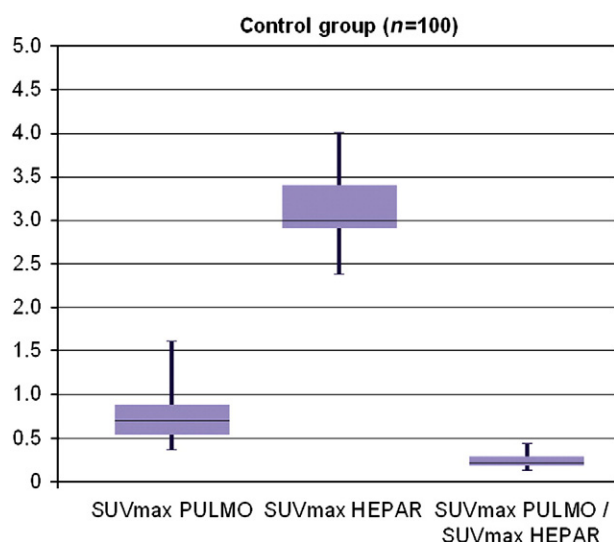


Fig. 3. Box plot of SUV data of control group: median SUVmaxPULMO=0.70 [range: 0.380–1.600; 0.74 ± 0.26 (100)], median SUVmaxHEPAR=3.00 [range: 2.40–4.00; 3.11 ± 0.35 (100)], median SUVmaxPULMO/SUVmaxHEPAR=0.22 [range: 0.14–0.43; 0.24 ± 0.07 (100)].

larger area. Considering the anatomical conditions, we chose the volume of interest shaped into spheres of 6–8 cm in diameter in the right lung. The metabolic activity was measured in the right upper and middle lung fields. These are the regions of predominant PLCH involvement. The right side without heart and pericardium is more suitable for demarcating the volume of interest and requires only the exclusion of the hilar structures and pleura, where the activity can be increased physiologically. Moreover, in the lower lung fields, numerous motion artifacts are common. This selection of size and location of the volume of interest strives to maximize the probability of occurrence of the majority of active lesions in the most anatomically suitable region while preserving an easy way of determination in a daily routine.

To decrease the variability between single examinations as well as to compare examinations from different scanners, lung-to-liver activity ratio was assessed. In the liver parenchyma, we chose volume of interest shaped into spheres of 9–10 cm in diameter following analogous principles as in the lungs (Fig. 2). Consequently, SUVmax in the right lung and SUVmax in the reference hepatic

parenchyma were measured, and their relationship expressed as the SUVmaxPULMO/SUVmaxHEPAR index was determined and used for PLCH activity evaluation.

In our analysis of a sample of 100 randomly chosen FDG-PET/CT studies free from any known lung or hepatic diseases, either oncological or nononcological, we found index values lower than 0.3 in 80% and lower than 0.4 in 96% [range: 0.14–0.43; 0.24 ± 0.07 (100)]. No index values higher than 0.5 were identified in the healthy population. The range of applied activity was 302–425 MBq [354.51 ± 32.12 (100)], and that of blood glucose levels was 3.1–8.1 mmol/L [5.00 ± 1.09 (100)]. Further SUV data are summarized in Fig. 3.

3. Results

Six males, all with a history of smoking, and one female, 31 to 48 years of age at the time of first FDG-PET scanning [39.7 ± 6.5 (7)], were included in this study. The mean follow-up period was 17 months [range: 9–79 months; 30.4 ± 29.0 (7)]. Six patients had a multisystemic Langerhans cell histiocytosis with pulmonary involvement and received at least one line of therapy. One patient had isolated PLCH, and this patient has not been treated yet. In patients with multisystemic disease, the following organs were affected: lungs (100%), skin (65%), bones (50%), brain (30%), ear (30%) and lymph nodes (15%). Respiratory symptoms (dyspnea, cough) were present in five patients (71%), of whom one patient suffered from recurrent pneumothorax. Demographic and clinical data are shown in Tables 1 and 2.

All patients underwent FDG-PET scan imaging (4 PET scans and 23 PET/CT scans). The acquired data, summarized in Table 3, were correlated to the clinical course of the disease, HRCT findings, pulmonary function tests and pathological examinations. In total, 18 HRCT studies [2.6 ± 1.3 (7)] and 13 pulmonary function tests [1.9 ± 1.5 (7)] were performed in seven patients. We have found a close correlation between the SUVmaxPULMO/SUVmaxHEPAR index values and the above-mentioned disease activity parameters (Table 2). Consequently, we worked with two variables, the index value and the metabolic tumor activity, and found a relationship with positive slope, i.e., increasing index value corresponds with increasing metabolic tumor

Table 1
Main demographic and clinical characteristics of seven patients with PLCH

Date of birth, sex	Smoking habitus	Disease onset (years)	Extrapulmonary involvement	Diagnosis of pulmonary involvement (years)
1972, M	Smoker	21	Bones	34
1974, M	Smoker	33	Skin, brain (pituitary stalk), ear	34
1969, M	Ex-smoker	39	Skin	40
1963, M	Active and passive smoker	43	Ear	45
1973, M	Smoker	34	Skin, bones, lymph nodes	35
1963, M	Smoker	45	Isolated PLCH	45
1955, F	Nonsmoker	22	Skin, bones, brain, ear	54

Table 2

Correlation between the SUVmaxPULMO/SUVmaxHEPAR index and disease course in seven patients with PLCH

Date of birth, sex	Date of PET/CT ^a	SUVmax PULMO/SUVmax HEPAR	Disease course and symptoms of pulmonary involvement	Interpretation of SUVmaxPULMO/SUVmaxHEPAR index in relation to disease course
1972, M	Mar 04	0.44	After 5 cycles of cladribine therapy, remission of bone lesions	High index value due to active smoking
	Jan 05	0.45	Lasting remission of bone lesions	Progression of PLCH Gradual remission of PLCH in accordance with relief of symptoms after cessation of smoking
	Feb 07	0.51	Dyspnea, cough	
	Jun 08	0.47	Smoking cessation leading to relief of symptoms	
	Jan 09	0.29		
	Feb 10	0.27		
1974, M	Mar 09	0.21	Screening admission PET/CT	Increased index value suggests progression in lungs
	Feb 10	0.27	Progression of pituitary stalk infiltration on brain MRI; therapy initiation	
	Jun 10	0.22	Regression of pituitary stalk infiltration after 3 cycles with cladribine	
1969, M	May 09	0.57	Disease activity (recurrent pneumothorax, 3 times); therapy initiation	High index value confirms PLCH
	Mar 10	0.22	After 6 cycles of cladribine therapy, partial remission of skin lesions	Therapy effective in PLCH as suggested by decreasing index value
1963, M	Mar 09	0.57	Screening admission PET/CT	High index value confirms PLCH
	Aug 09	0.53	After 4 cycles of cladribine therapy	Gradual remission of PLCH after successful cladribine therapy
1973, M	Mar 10	0.38	Follow-up PET/CT	High index value confirms PLCH Therapy effective also in PLCH Increased index value suggests relapse in lungs
	Jan 09	0.54	Screening admission PET/CT; dyspnea, cough	
	Jun 09	0.31	After 4 cycles with cladribine therapy	
	Nov 09	0.36	1st relapse (confirmed by lymph node and skin biopsies); cough	Remission of PLCH after chemotherapy Lasting remission of PLCH after autologous transplantation Increased index value suggests 2nd relapse in lungs
	Jan 10	0.27	After 2 cycles of salvage chemotherapy CHOEP; relief of symptoms	
	Jul 10	0.28	4 months after autologous transplantation	
1963, M	Oct 10	0.48	2nd relapse (confirmed by lymph node biopsy)	Slightly increased index value in patient with stable clinical manifestation, but still continuing his smoking habitus
	Jul 08	0.21	Screening admission PET/CT; intermittent cough	
	Feb 10	0.24	Stable disease not requiring therapy; lasting intermittent cough	
1955, F	Mar 04	0.42	Screening admission PET/CT; slight effort dyspnea	High index value suggests pulmonary involvement Therapy effective also in PLCH
	Jan 09	0.31	After several cycles with vinblastine, prednisone and etoposide	
	Mar 10	0.14	Progression in brain; therapy initiation	Further remission of PLCH
	May 10	0.17	After 2 cycles with cladribine	Lasting remission of PLCH
	Oct 10	0.38	Further progression in brain, chemoresistant disease	Increased index suggests progression of PLCH

CHOEP, cyclophosphamide+doxorubicin+vincristine+etoposide+prednisone.

^a Between 2004 and 2007, only PET scans were made.

activity and vice versa. The increasing trends of index values were seen in five patients, where they indicated PLCH activity (i.e., pulmonary symptoms, formation of nodules on HRCT or abnormal pulmonary function tests), whereas decreasing trends of index values were observed in six patients after therapy administration, signaling reduced metabolic tumor activity. Furthermore, in four patients, SUVmaxPULMO/SUVmaxHEPAR index values higher than 0.5 proved to be diagnostic for pulmonary involvement, demonstrating its role as a strong positive predictive marker. Fig. 4 shows the disease course with corresponding index values in one patient (male, born 1973).

Quantitative analysis of HRCT findings in patients with PLCH, consisting of assessment of the exact count of

nodules and cystic formations, is almost impossible to be obtained. Therefore, the PET/CT findings were correlated to a semiquantitative radiological evaluation of HRCT scans, and neither sensitivity, specificity, accuracy nor predictive values can be exactly calculated in our study.

4. Discussion

The clinical course of PLCH is very divergent and impossible to be predicted for an individual patient [2,3]. About 50% of patients with isolated PLCH have a favorable prognosis with total disease remission, i.e., reduction of pulmonary nodules either spontaneously or after corticoid

Table 3

An overview of PET/CT data in 7 patients with PLCH

Date of birth, Sex	Date of PET/CT ^a	Applied activity (MBq)	Blood glucose levels (mmol/L)	SUVmax PULMO	SUVmax HEPAR	SUVmax PULMO / SUVmax HEPAR
1972, M	Mar-04	327	4.4	0.80	1.83	0.44
	Jan-05	321	5.8	0.81	1.79	0.45
	Feb-07	335	4.1	1.02	2.01	0.51
	Jun-08	337	4.8	1.06	2.24	0.47
	Jan-09	315	5.2	0.92	3.22	0.29
	Feb-10	352	4.7	0.89	3.25	0.27
1974, M	Mar-09	414	4.6	0.93	4.39	0.21
	Feb-10	431	4.8	0.89	3.25	0.27
	Jun-10	466	5.4	0.78	3.53	0.22
1969, M	May-09	377	4.7	1.88	3.30	0.57
	Mar-10	393	5.2	0.78	3.53	0.22
1963, M	Mar-09	372	4.7	1.78	3.11	0.57
	Aug-09	421	4.9	1.79	3.36	0.53
	Mar-10	401	4.7	1.03	2.71	0.38
1973, M	Jan-09	330	6.3	1.34	2.49	0.54
	Jun-09	336	5.6	0.68	2.23	0.31
	Nov-09	330	5.3	1.18	3.24	0.36
	Jan-10	338	5.7	0.88	3.30	0.27
	Jul-10	317	5.5	0.75	2.72	0.28
	Oct-10	292	6.4	1.40	2.98	0.48
1963, M	Jul-08	338	4.7	0.69	3.30	0.21
	Feb-10	354	5.1	0.95	3.96	0.24
1955, F	Mar-04	344	4.4	1.02	2.45	0.42
	Jan-09	337	5.8	1.00	3.19	0.31
	Mar-10	357	6.7	0.48	3.49	0.14
	May-10	351	5.4	0.53	3.15	0.17
	Oct-10	386	7.0	1.45	3.80	0.38

^a Between 2004 and 2007, only PET scans were made.

therapy. Cessation of smoking proved to be essential in therapy management, leading to remission in many cases described [6,10,11]. Nevertheless, cystic lung damage is irreversible. Moreover, PLCH implies a higher risk of lung cancer, especially in smokers, and a higher risk of other malignancies as well [12].

The greatest challenge is the evaluation of PLCH disease activity and, consequently, therapy effectiveness. In recent years, based on a contrasting rate of glucose utilization between rapidly proliferating tumor cells and surrounding normal tissue, much attention has been devoted to the benefit of FDG-PET and FDG-PET/CT scan imaging for determining the extent of Langerhans cell histiocytosis and therapy response evaluation.

Derenzini et al. [13] used FDG-PET for evaluating the effectiveness of MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) chemotherapy in four patients. The FDG-PET scan was able to detect additional lesions missed by other modalities in two patients. A negative interim FDG-PET predicted a long-lasting remission in three of four patients. Phillips et al. [14] published the same experience as they compared the benefit of FDG-PET/CT to bone scans, CT, magnetic resonance imaging (MRI) and conventional radiography for determining the extent of Langerhans cell histiocytosis and evaluation

of therapy response in 44 patients (41 children and 3 adults). They concluded that whole-body FDG-PET scans can detect disease activity and early response to therapy with greater accuracy than other imaging modalities in patients with Langerhans cell histiocytosis affecting bones and soft tissues. Furthermore, FDG-PET is also beneficial for an early diagnosis of neurodegenerative Langerhans cell histiocytosis [15].

However, a MEDLINE literature search revealed only one paper evaluating FDG-PET scan imaging in PLCH, the work from authors Krajicek et al. [16], who described their cohort study with 11 patients. PET-scan-positive patients had predominantly nodular lung disease with more than 100 nodules usually under 8 mm in size, whereas PET-scan-negative patients had predominantly cystic lung disease with nodules numbering less than 25 in a field of examination.

In our study, all pathology in the lung parenchyma was below detectable levels of the PET scanner (less than 7 mm), and we did not find large active lesions. Notwithstanding the observations of Krajicek et al., we describe a new methodology for diffuse metabolic activity evaluation of the lung parenchyma and present the possibility to objectify the results by comparing them with the simultaneously measured activity of the reference liver parenchyma. The evaluation of pulmonary activity based on the index, the ratio

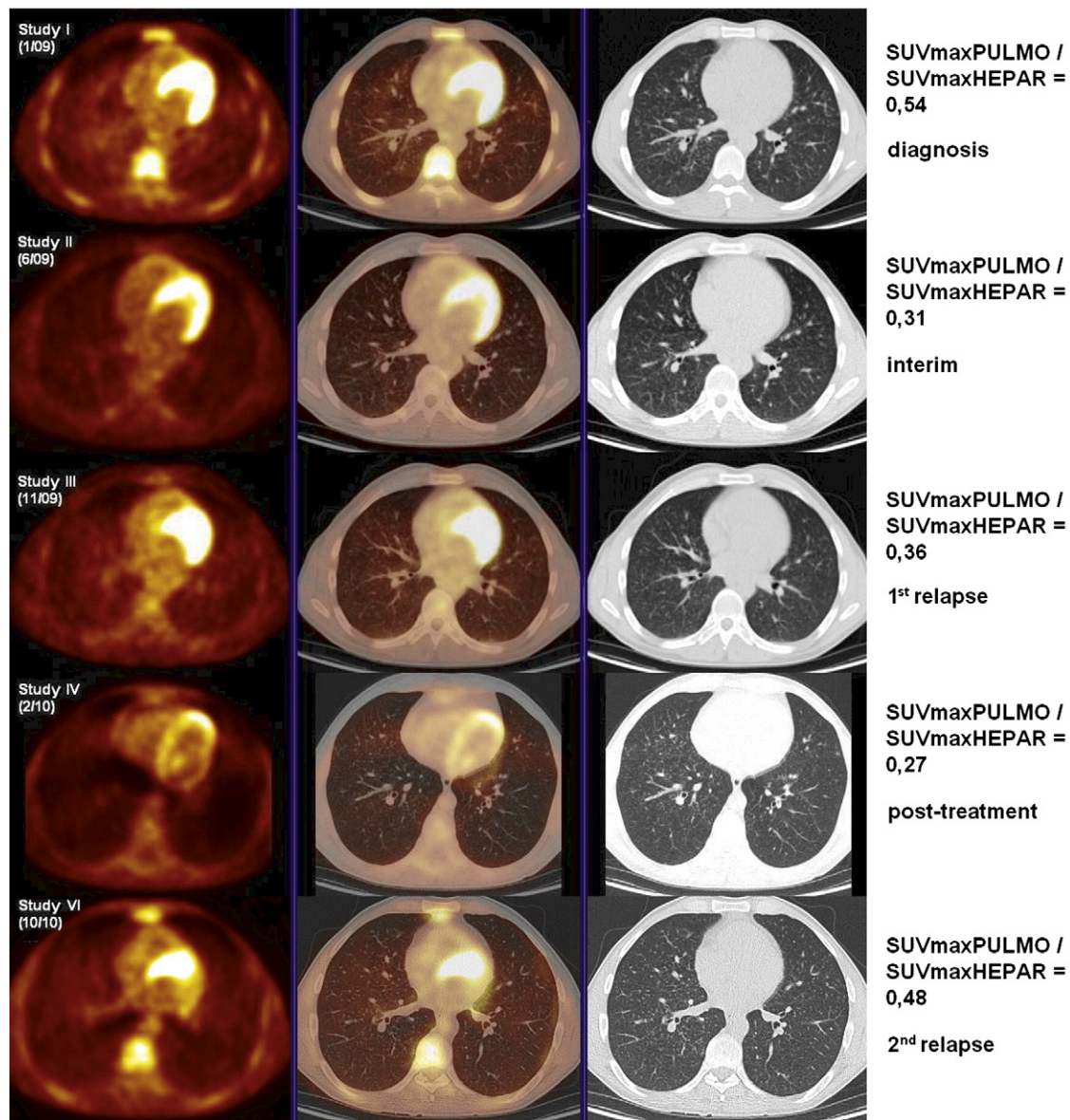


Fig. 4. Series of FDG-PET/CT images of a patient with multisystemic Langerhans cell histiocytosis with pulmonary involvement (male, born 1973). High index value on admission PET/CT together with pathognomonic HRCT finding (multiple small nodules with sporadic cysts) and clinical symptoms (dyspnea, cough) was diagnostic for PLCH. Interim PET/CT after two cycles with cladribine shows a therapy response which correlated with regression of lymphadenopathy and relief of the symptoms, including perianal pruritus and B-symptoms (night sweats, fever and weight loss). However, an aggressive form of Langerhans cell histiocytosis with recurrent relapses was the case. The index value corresponded closely with the disease course. We consider myocardial FDG uptake to be physiological.

of the measured SUVmax value in a spherical volume of the right lung to the measured SUVmax value in a spherical volume of the liver — the SUVmaxPULMO/SUVmaxHEPAR index — which we propose and which we have verified, has not been published so far. We are aware of the fact that the method we used is not common and, with such small lesions, it is negatively biased by the partial-volume effect characterized by increasing underestimation of SUV with decreasing lesion sizes [17]. The index may be influenced by concomitant factors affecting either lungs or liver (e.g., other interstitial lung diseases, benign tumors, active infections or noninfectious inflammations, cholesta-

sis, cirrhosis). Moreover, hyperinsulinemia [18], higher glucose level [19] and advanced age [20] were found to be related to increased FDG uptake by liver.

Currently, except for HRCT of the lungs and pulmonary function tests, there is no other modality that informs more accurately on PLCH activity. Traditional FDG-PET scan imaging is not possible due to the small size of nodules which cannot be reliably resolved by the PET scanner. Therefore, we consider the measuring and long-term monitoring of the index SUVmaxPULMO/SUVmaxHEPAR to be very useful additional tools for PLCH activity evaluation. Based on our analysis of a sample of 100

randomly chosen PET/CT scans, as mentioned above, and on this retrospective study, we found that SUVmaxPULMO/SUVmaxHEPAR index values higher than 0.5 bear high probability of pulmonary involvement in patients with Langerhans cell histiocytosis.

In conclusion, measuring the SUVmaxPULMO/SUVmaxHEPAR index and its time-trend monitoring represent simple noninvasive screening tools for PLCH, allowing us to optimize the therapeutic management in the patients. An early diagnosis of pulmonary involvement with a prompt initiation of therapy may prevent progressive cystic damage to the lungs. The index measurement also enables an effective monitoring of therapy response and follow-up of patients with PLCH.

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