The Utility of ^{18}F-fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography in Cutaneous B-Cell Lymphoma

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ABSTRACT: **Background:** Whole-body integrated positron emission tomography / contrast-enhanced computed tomography (PET/CT) scan is increasingly used in cutaneous lymphomas. However, the value of PET/CT in the detection of cutaneous lesions in primary cutaneous B-cell lymphoma (PCBCL) has barely been investigated.

Objectives: To investigate the diagnostic accuracy of PET/CT in tracking cutaneous involvement in PCBCL.

Methods: A retrospective study was conducted on 35 consecutive patients diagnosed with cutaneous B-cell lymphoma according to the World Health Organization classification who were evaluated with PET/CT as the initial staging procedure before treatment.

Results: Thirty-five patients met the study criteria. In two patients extracutaneous disease was detected by PET/CT and CT and confirmed by biopsy. Of the 33 patients with PCBCL, 26 (79%) had small cell PCBCL (18 marginal-zone, 8 follicle-center lymphoma) and 7 (21%) had large cell PCBCL (3 follicle-center, 3 leg-type, 1 indeterminate). PET/CT detected skin lesions in 3 of 26 patients (12%) with small-cell PCBCL as compared to 6 of 7 patients with large-cell PCBLC (86%), a 7.4-fold higher detection rate (95% confidence interval, 2.4–22, $P = 0.004$). The PET-positive subgroup was characterized by larger lesion size ($P < 0.001$) and a higher Ki-67 proliferation index ($P < 0.001$).

Conclusions: The sensitivity of PET/CT for detecting cutaneous involvement of lymphomas is low for small-cell PCBCL but high for large-cell types, and thus may facilitate therapeutic strategies.

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KEY WORDS: B-cell lymphoma, computed tomography (CT), cutaneous lymphoma, positron emission tomography (PET), primary cutaneous B-cell lymphoma (PCBCL)

Cutaneous B-cell lymphoma is a clonal proliferation of neoplastic B cells affecting the skin. In primary cutaneous B-cell lymphoma (PCBCL), the disease is limited to the skin, with no evidence of disease in other organs at the time of diagnosis. The involvement of other organs in addition to the skin at diagnosis is considered secondary cutaneous B-cell lymphoma (CBCL) and is generally indicative of an advanced stage disease.

According to the 2018 World Health Organisation (WHO)-European Organisation for Research and Treatment of Cancer classification for primary cutaneous lymphomas, PCBCL is divided into three main types: primary cutaneous marginal-zone B-cell lymphoma (PCMZL), which is a subgroup of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; primary cutaneous follicle-center lymphoma (PCFCL); and primary cutaneous diffuse large B-cell lymphoma-leg type (PCLCL-LT) [1]. PCMZL and PCFCL are clinically indolent and account for the vast majority of PCBCL [2]. PCLCL-LT is less common and characterized by intermediate aggressiveness [1]. Staging workup is mandatory for the correct classification of primary and secondary CBCL [2].

^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) is based on the increased metabolism of malignant cells. While there is no real use of FDG-PET alone, hybrid FDG-PET/ computed tomography (CT) systems were introduced into clinical practice over the last decade, allowing for the acquisition and fusion of the anatomical data provided by CT with the functional data provided by PET. ^{18}F-FDG PET/CT is currently the standard modality for staging and restaging of Hodgkin's lymphoma and non-Hodgkin's lymphomas in clinical practice, and it has also been found to be useful for monitoring tumor response to therapy and adverse effects of treatments [3,4].

A follow-up study with ^{18}F-FDG PET/CT after completion of therapy is of prognostic value and has been incorporated into the revised response criteria for aggressive lymphomas [3,5].

However, there is little evidence to support the use of ^{18}F-FDG PET/CT for monitoring the treatment of indolent lymphomas in the surveillance setting.

Over the past decade PET/CT has been applied for staging of cutaneous T-cell lymphomas as well as a variety of other cancers [6,7]. However, their use in PCBCL has barely been addressed [8,9]. The aim of the present study was to evaluate the value of PET/CT in detecting the extent of cutaneous involvement in PCBCL.

PATIENTS AND METHODS

The study was approved by the institutional ethics committee at Rabin Medical Center in agreement with the Helsinki Declaration. The study group consisted of 35 consecutive patients who were diagnosed with CBCL at the Department of Dermatology, Rabin Medical Center and were evaluated with PET/CT. The diagnosis of CBCL was based on the WHO classification [1]. All patients underwent routine workup, including complete blood count and blood chemistry with measurement of lactate dehydrogenase and beta-2 microglobulin levels.

PET/CT served as the initial staging procedure before treatment. It was performed at least one month after skin biopsy to avoid a false-positive interpretation in the presence of ^{18}F-FDG uptake in the surgical incision/regional lymph nodes. Patients in whom the entire skin lesions were removed for biopsy or treatment before the performance of PET/CT were excluded from the study.

The following parameters were extracted: age at diagnosis, sex, CBCL type, tumor location, extent and size, Ki-67 proliferation index, bone marrow biopsy, and ^{18}F-FDG avidity. The tumor, node, and metastases system was used to document cutaneous disease [10].

^{18}F-FDG PET/CT IMAGING PROCEDURE

Patients fasted for 4 hours before the procedure. FDG, 370-666 MBq (10–18 mCi), was injected intravenously. Oral contrast was added to improve discrimination between physiologic bowel activity and FDG uptake by abdominal tumor sites. Whole-body scanning was performed with the Discovery LS PET/CT system (GE Medical Systems, Milwaukee, WI, USA). Reduced-dose CT acquisition was performed first, with the following specifications: 140 kV, 80 mA, 0.8 seconds per CT rotation, pitch 6, and table speed 22.5 mm/s. Patients were not given specific breath-holding instructions. Immediately thereafter, PET emission scanning was performed (5–8 bed positions, 5 minutes each), without changing the patient's position. PET images were reconstructed using an OSEM algorithm. Findings were considered positive when increased focal uptake was observed in sites generally free of physiological uptake or when focal uptake in tissues that sometimes show physiological uptake was of higher intensity than the surrounding background activity. PET/CT interpretations were performed on Xeleris workstations (ELGEMS, Haifa, Israel) equipped with fusion software, which enable the display of PET images (with and without attenuation correction), CT images, and fused data of both modalities.

STATISTICAL ANALYSIS

Unpaired Student's *t*-test was used to analyze differences in FDG uptake in patients with different PCBCL subtypes. Clinical variables were correlated with positive and false-negative PET reports. A P value of < 0.05 was considered statistically significant. All analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp, Armonk, NY).

RESULTS

Thirty-five patients with CBCL were included in the study. In all, PET/CT detected nodal involvement in 2 of 35 patients (6%), confirmed by biopsy as follicle-center and marginal-zone lymphoma with secondary cutaneous involvement [Table 2]. Of note, case 33 had an uptake in a submandibular lymph node attributable to a reactive process (dental problem). Of the 33 patients (94%) with PCBCL, 22 were female and ranged in age from 17 to 85 years old (mean age 60). Eleven patients were male and ranged in age from 19 to 83 years (mean age 58) [Table 1, Table 2].

The pathologic diagnoses of PCBCL were as follows:

- PCMZL: 18 patients (55%), staged (T1 = 4 patients, T2 = 3 patients, and T3 = 11 patients) with lesions size ranging from 0.6 to 8 cm
- PCFCL: 11 patients (33%) (3 PCFCL-LC), staged (T1 = 2 patients, T2 = 5 patients, and T3 = 4 patients) with lesions size ranging from 0.5 to 10 cm
- PCLCL-LT: 3 patients (9%), staged (T1 = 1 patient and T2 = 2 patients) with lesions size ranging from 2.5 to 6 cm
- Diffuse large-cell lymphoma of indeterminate type: 1 patient (3%), staged T1 with 5 cm lesion size

PET/CT detected skin lesions of PCBCL in 9 of the 33 patients (27%), [Table 2, Table 3]. FDG avidity differed by lymphoma type: 2 of 18 (11%), PCMZL; 3 of 11 (27%), PCFCL (2/3 large-cell; 1/8 small-cell); 3 of 3, PCLCL-LT; sole patient with diffuse indeterminate PCLCL. Overall, only 3 of 26 (12%) small-cell PCBCL were FDG-avid compared to 6 of 7 large-cell PCBCL (86%), a 7.4-fold higher detection rate (95% CI, 2.4 - 22, $P = 0.004$).

Clinically, 4 of 5 (80%) positive and 19 of 24 (79%) negative avidity cases of PCMZL/PCFCL were staged ≥ T2. Positive avidity patients had larger tumor size (mean 5 vs. 1.54 cm, $P < 0.001$) and higher Ki-67 proliferation index (51% vs. 20%, $P < 0.001$) and were identifiable by physical examination. Two

Table 1. Summary of patients with PCBCL and negative PET/CT findings

Patient number	Age (years)/ sex	Diagnosis (large/small cell)	Site	T stage	Tumor size average (cm)	Ki67 staining (%)	PET	CT
1	59/M	PCMZL (small)	Back/ multiple lesions	T2	1	20	None	None
2	83/F	PCMZL (small)	Brow, forearm	T3a	2	15	None	None
3	62/F	PCFCL (small)	Forearms, back	T3a	1	30	None	None
4	37/F	PCFCL-LC (large)	Arm	T2a	1	40	None	None
5	69/F	PCMZL (small)	Back, forearm	T3a	1.5	15	None	None
6	19/M	PCMZL (small)	Limbs, back, nose	T3b	2	15	None	None
7	60/F	PCMZL (small)	Face, neck, chest shoulders, back	T3b	2	10	None	None
8	58/F	PCMZL (small)	Forearms, back	T3a	1	20	None	None
9	82/F	PCFCL (small)	Chest, back	T3a	1	25	None	None
10	17/F	PCMZL (small)	Upper limbs	T3a	1.5	15	None	None
11	50/M	PCMZL (small)	Forearm	T2a	3	50	None	None
12	49/F	PCFCL (small)	Forehead	T2a	2.5	30	None	None
13	67/F	PCMZL (small)	Arm	T1a	1.5	20	None	None
14	47/M	PCMZL (small)	Forearm, back	T3a	3	5	None	None
15	78/F	PCFCL (small)	Back	T1a	1	10	None	None
16	77/M	PCFCL (small)	Eyelid, back	T3a	0.5	20	None	None
17	26/F	PCMZL (small)	Forearms, back	T3a	1	12	None	None
18	50/F	PCMZL (small)	Eyelid	T1a	0.6	30	None	None
19	70/F	PCMZL (small)	Back	T2a	3	25	None	None
20	30/F	PCMZL (small)	Back, arms	T3a	0.8	10	None	None
21	82/F	PCFCL (small)	Flank	T1a	1	10	None	None
22	63/F	PCMZL (small)	Temple	T1a	1.5	5	None	None
23	67/F	PCMZL (small)	Forearm, chest	T3a	1.5	20	None	None
24	27/M	PCFCL (small)	Upper body, arms	T3b	1	30	None	None

CBCL = cutaneous B-cell lymphoma, CT = computed tomography, LC = large cleaved cells, PCFCL = primary cutaneous follicle-center lymphoma, PCMZL = primary cutaneous marginal-zone lymphoma, PET = positron emission tomography

of the five FDG-avid patients with indolent-type lymphoma had a long follow-up period of 2 (patient 29) and 6 years (patient 25) with periodic clinical examination and laboratory testing without disease progression. We found no discordance between PET and CT findings concerning systemic and cutaneous detection rate.

DISCUSSION

In the present study, we evaluated the efficacy of PET/CT to detect the extent of cutaneous involvement in PCBCL.

The role of PET imaging varies among lymphoma types. The detection rate of systemic B cell lymphoma, including Hodgkin's lymphoma and aggressive non-Hodgkin's lymphoma [such as diffuse large B-cell lymphoma, high-grade follicular lymphoma, and mantle-cell lymphoma] is as high as 98% to 100%, whereas the detection rate for low-grade systemic lymphomas, such as follicular and marginal-zone, is only 40 to 67% [11]. In a recent study that included 522 patients with low-grade CBCL, 3.6% and 8.8% of patients with MZL and FCL had systemic involvement. [12]. Similarly, in our cohort, consisting of patients with CBCL, only 2 of 35 patients (6%) had systematic nodal-involvement confirmed by biopsy. As systemic disease was suspected by CT in both cases, it remains unclear whether PET/CT had an additive value over CT for classification of patients with primary vs. secondary CBCL.

To the best of our knowledge this research is the first to evaluate the value of PET/CT in detecting the extent of cutaneous involvement in PCBCL. Previously, Shapiro and colleagues [13] described the first case of PCFCL staged with FDG-PET. They noted mildly increased cutaneous FDG uptake at sites of clinically apparent disease, without extracutaneous involvement. Overall, only 15 cases evaluating the cutaneous involvement of PCBCL by PET have been published to date [9,10,12–20]. Eleven of the 15 patients showed positive PET/CT findings in cutaneous lesions, most of them (8/11) had a large-cell phenotype, while 2 had PCFCL with no further information on cell size, and one with small-cell PCMZL. These findings suggest

Table 2. Summary of patients with CBCL and positive PET/CT findings

Patient number	Age, year/ sex	Diagnosis, (large/small cell)	Site (T stage)	Tumor size (cm)	Ki67 (%)	PET	CT
25	76/M	PCFCL-LC (large)	Abdomen, multifocal (T2a)	10	No data	Uptake in subcutaneous nodules in abdominal wall 2.2 cm	Subcutaneous masses in abdominal wall
26	65/M	Indeterminate PCLCL (large)	Forehead (T1a)	5	80	Uptake in forehead 0.6 cm	Mass in forehead
27	83/F	PCLCL-LT (large)	Chest (T1b)	6	60	Uptake in right upper chest	Lesion in rt. upper chest wall
28	83/M	PCLCL-LT (large)	Leg, ankle, multifocal (T2a)	3	70	Uptake in 3 foci in right shin and ankle	Skin lesions 0.5 cm
29	58/M	PCFCL (small)	Back, multifocal (T2a)	6	20	Uptake in 3 nodules on back	3 nodules on back 0.8 cm
30	61/F	PCLCL-LT (large)	Leg, multifocal (T2a)	2.5	80	Uptake in left leg	Skin lesions in left leg
31	85/F	PCMZL (small)	Arm, upper back, multifocal (T3a)	2	7	Uptake in small focus left forearm (subcutaneous nodule left forearm)	No data, probably negative
32	50/F	PCMZL (small)	Scalp, frontal (T1a)	8	10	Uptake in subcutaneous mass in scalp	Subcutaneous mass on the frontal region
33	81/M	PCFCL-LC (large)	Scalp, forehead (T2a)	3	80	Uptake in skin tumors up to 2.8 cm and rt. submandibular lymph node 1.9 cm*	Scalp masses
34	48/F	Secondary CBCL, follicle-center	Back	3	No data	Uptake in cervical and inguinal lymph nodes	Lymph nodes 1 cm
35	48/F	Secondary CBCL, marginal zone	Chest	3	No data	Uptake in inguinal lymph node	Lymph node 1.5 cm

*Attributable to a reactive process (dental problem)

CBCL = cutaneous B-cell lymphoma, CT = computed tomography, LC = large cleaved cells, LT = leg type, PCFCL = primary cutaneous follicle-center lymphoma, PCLCL = primary cutaneous diffuse large B-cell lymphoma, PCMZL = primary cutaneous marginal-zone lymphoma, PET = positron emission tomography

Table 3. PET/CT scan results for the various types of PCBCL

Diagnosis	Uptake positive	Uptake negative	Total	% positive
PCMZL	2	16	18	11
PCFCL	3 (2-LC; 1-small)	8	11	27
PCLCL-LT	3	0	3	100
Indeterminate PCLCL	1	0	1	100
Total	9	24	33	27

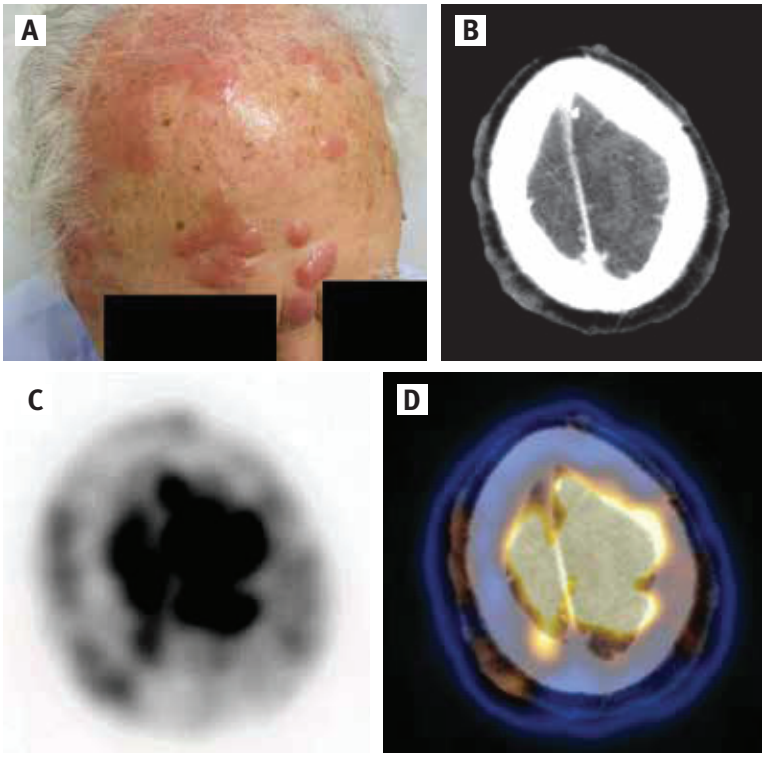
CBCL = cutaneous B-cell lymphoma, CT = computed tomography, LC = large-cleaved cell, LT = leg type, PCFCL = primary cutaneous follicle-center lymphoma, PCLCL = primary cutaneous diffuse large B-cell lymphoma, PCMZL = primary cutaneous marginal zone lymphoma, PET = positron emission tomography

that skin lesions of large-cell types of PCBCL are FDG-avid but are limited by small sample size.

Of the 33 cohort patients with PCBCL, 29 had indolent-type lymphoma, including PCMZL and PCFCL. Overall, skin lesions were detected by PET/CT in only 9 (27%) of the cases. We found PET/CT had a 7.4-fold higher detection rate for large-cell [Figure 1] compared to small-cell types of PCBCL (86% vs. 12% sensitivity). These findings are consistent with the published data on the role of PET in nodal and other extra-nodal lymphomas [21,22].

The differences in FDG avidity among the various types of lymphoma may reflect differences in glucose metabolism. It is generally accepted that indolent lymphoma cells exhibit lower glucose metabolic activity than aggressive lymphoma cells [23,24]. For example, systemic diffuse large B-cell lymphoma and high-grade follicular lymphoma showed a threefold higher FDG avidity than indolent low-grade follicular lymphoma and marginal lymphoma. We have shown that PET/CT detected 100% of cases of

Figure 1. Patient 33 with **[A]** primary cutaneous follicle center cell lymphoma-large type presenting extensive scalp and forehead involvement. **[B]** Axial CT showing the masses. **[C]** Axial PET showing increased pathological uptake of FDG. **[D]** Axial fusion PET/CT showing uptake in the masses



PET = positron emission tomography, CT = computed tomography

PCLCL-LT and diffuse large cell lymphoma, which are considered intermediate-aggressive types, and only 11% of PCMZLs and 27% of PCFCLs, which are indolent types. Given that PET/CT in our study detected mostly large-cell type CBCL, we assume that cell type is a major factor determining FDG avidity.

Ki67 is a marker for cellular proliferation. The fraction of Ki67-positive tumor cells (Ki67 labeling index) is often directly correlated with the clinical course of the disease [25]. In our study, higher Ki67 values were recorded for the more aggressive types of CBCL than for the indolent types, presumably indicating a higher metabolic activity. However, some cases of relatively high Ki67 values were PET/CT-negative (patients 4 and 11), whereas others, with low Ki67 values, were PET/CT-positive (patients 29, 31, and 32). Therefore, factors other than proliferation rate may also be important in determining glucose metabolism in lymphoma. The finding that PET/CT detected larger tumor masses more often than smaller ones is probably related to the correlation of tumor size with proliferative rate. The CT findings are probably related to the size of the lesions; small lesions were missed by CT while the larger lesions were mostly demonstrated [Tables 1, 2].

LIMITATIONS

Our results are limited by the study's retrospective design and a relative small sample size, particularly of patients with large-cell PCBCL. Additionally, comparison with secondary cutaneous lymphoma was not performed. Thus, further large scale prospective studies are in need to consolidate our conclusions.

CONCLUSIONS

The sensitivity of PET/CT for detecting cutaneous involvement of lymphomas is high for large-cell, aggressive, types of PCBCL, such as PCLCL-LT; but low for indolent, small-cell types, such as PCMZL and PCFLCL. PET/CT can facilitate the detection of the extent of skin involvement of large-cell lymphomas, which may involve the underlying subcutaneous and deep tissue, and thus may promote therapeutic strategies and treatment assessment.

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