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ORIGINAL ARTICLE

Unsuspected FDG–PET findings in the follow-up of patients with lymphoma

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Abstract 18F-Fluorodeoxyglucose–positron emission tomography (FDG–PET) plays an increasing role in the management of patients with lymphoma, for which it is successfully used for staging and treatment monitoring. We report seven patients with a history of lymphoma who presented a positive FDG–PET suggestive of lymphoma relapse and for which FDG–PET oriented biopsies revealed alternative diagnoses. Early in lymphoma follow-up, persistence of focal increased FDG activity corresponded to inflammatory or infectious lesions in two patients: one aspergillosis and one sarcoidosis. Later in the follow-up, five cases of secondary malignancies were identified (three lung cancers, one epidermoid carcinoma, and one villous tumor) in this particularly exposed population. The routine use of FDG PET to evaluate lymphoma significantly increases the probability of detecting unexpected diseases. These cases illustrate the potential pitfalls in PET follow-up. Because FDG is not lymphoma-specific, a relapse suspected only on FDG–PET imaging requires biopsy, as alternative diagnoses—infectious or malignant—are possible. Our data draws clinician's attention to potential false–positive FDG–PET findings, which may lead to therapeutic mistakes. Our data also suggests that FDG–PET might be a new imaging modality for long-term monitoring of late effects, especially second cancer occurrence.

Keywords 18F-Fluorodeoxyglucose (FDG) · Positron emission tomography (PET) · Lymphoma · Pitfalls · Second cancers

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Introduction

Based on the increased glucose metabolism of tumor cells, positron emission tomography using 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography (FDG–PET) plays an increasing role in the management of malignant diseases. In lymphoma, these roles include: initial staging, monitoring of the therapeutic response early in the course of a treatment regimen or at the end of a full course treatment [1], evaluation of a residual mass, and restaging in case of relapse suspicion [2]. However, its usefulness in the long-term follow-up of patients with lymphoma is still unknown.

In lymphoma patients with a high clinical suspicion of relapse, a positive FDG–PET is usually considered as a proof of persistent disease, so that image-oriented biopsy is not always performed before initiating a salvage chemotherapy. In this retrospective study, we evaluate the clinical value of FDG–PET findings unrelated to the primary diagnosis as well as we suggest clinical management of such lesions depending on the location and the follow-up time interval.

Patients and methods

From March 2000 to October 2002, nearly 200 FDG–PET were performed in 90 non-Hodgkin's lymphomas (NHL) and 11 Hodgkin's disease (HD). Among them, 43 were for initial staging, 53 for early assessment of treatment response, and 103 during the follow-up, mainly in case of relapse suspicion.

Patients were fasting for at least 6 h before their arrival in the PET facility. They received 375±50 MBq (range 300–440 MBq) FDG intravenously. Whole body emission scan from the upper legs to the head was recorded 99±27 min (range 63–136 min) later on a dedicated full ring PET scanner (ECAT EXACT HR+, CTI, Knoxville, Tennessee, USA) followed by a transmission scan for subsequent attenuation correction. Total scanning time was about 50 min. Images were reconstructed by means of iterative processing of both emission and transmission data, following the procedure described previously [3]; then interpreted on color monitors with simultaneous display of non-attenuated and attenuated images in the transaxial, coronal, and sagittal planes.

Results

Patient selection

Out of the 103 follow-up FDG–PET studies, 49 patients presented a positive FDG–PET suggestive of lymphoma relapse. We observed 42 true positives and seven false positives. We report in this study these seven patients in whom image-oriented biopsies revealed other diagnosis. A summary of their characteristics is presented in Tables 1 and 2, whereas their detailed clinical histories are described below.

Case reports

Case 1 A 68-year-old woman, previously treated by chemo- and radiotherapy for cervical transformed-follicular NHL, developed a jugal tumefaction and cervical lymph nodes highly suspicious of relapse. FDG–PET study showed increased tracer uptake in nasal fossa, jugal zones, and right pulmonary parenchyma. Right jugal mass biopsy showed giant cells consistent with sarcoidosis.

Case 2 A 64-year-old man with mediastinal diffuse large B-cell lymphoma had an early complete remission as assessed by FDG–PET after three courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (Fig. 1). At the end of treatment (six CHOP), FDG–PET showed abnormal uptake foci in the initial lymphoma localizations. A new transbronchic biopsy revealed an invasive aspergillosis.

Case 3 In 1994, a 55-year-old man was treated by chemotherapy for a peripheral T-cell NHL. Six years later, he presented a biopsy confirmed stage IV relapse (Fig. 2). Two months after BEAM chemotherapy with PBSCT, FDG–PET study showed a major regional extension of a lung nodule and new bone lesions biopsy proven to be nonsmall cell lung carcinoma (NSCLC).

Case 4 A 71-year-old man treated by chemotherapy in 1989 for a stage IV diffuse large B-cell lymphoma had 12 years later a pneumonia confirmed by computed tomography (CT) scan, which revealed additional right hilar and mediastinal adenopathies. These lesions were FDG avid and biopsy demonstrated NSCLC.

Case 5 Ten years after a cervical Hodgkin's disease treated by surgery and radiotherapy, a 53-year-old man presented a

Table 1 PET unsuspected findings

Cases	Initial diagnosis	Time interval	Secondary diagnosis	Reason of PET	Type of confirmation
Nonmalignant lesions		Mean=16.5 months			
1	B-NHL	27 months	Sarcoidosis	Clinical suspicion of relapse	Biopsy of jugal mass
2	B-NHL	6 months	Aspergillosis	Systematic EOT follow-up	Transbronchic biopsy
Malignant lesions		Mean=109.4 months			
3	T-NHL	72 months	NSCLC	Systematic EOT follow-up	Transbronchic biopsy
4	B-NHL	206 months	NSCLC	Fortuitous CT scan (pneumonia)	Biopsy of mediastinal lymph node
5	Hodgkin	155 months	Epidermoid carcinoma	Clinical suspicion of relapse	Biopsy of cervical lymph node
6	B-NHL	73 months	Villous tumor	Systematic EOT follow-up	Colonoscopic biopsy
7	B-NHL	41 months	SCLC	Clinical suspicion of relapse	Transbronchic biopsy

EOT End of treatment

Table 2 Initial patient characteristics, treatment, and evolution

Cases	1	2	3	4	5	6	7
Age (years)/sex	68/F	64/M	55/M	71/M	53/M	66/F	63/F
Histology	Transformed follicular B-NHL	Diffuse large B-cell NHL	Peripheral T-cell NHL	Diffuse large B-cell NHL	Hodgkin's lymphoma	Lymphocytic B-NHL	Follicular B-NHL
Ann Arbor stage	IA	IV	IIIB	IIIB	I	IV	IV
Performance status	1	3	2	1	0	1	1
LDH	Normal	Elevated	Elevated	Na	Na	Elevated	Elevated
1st line treatment	CHOP × 4 + radiotherapy	CHOP × 6	ACVBP × 4 + CT conso	Alternated VIM/ACVBP	Surgery + radiotherapy	Chlorambucil	CHVP + interferon
Lymphoma relapse	No	Yes	Yes	Yes	No	Yes	Yes
Best therapeutic response	CR	CR	CR	CR	CR	CR	PR
Last status, condition, delay from lymphoma diagnosis	Alive, CR1, 79 months	Alive, CR2, 57 months	Dead, evolutive, 72 months	Dead, evolutive, 206 months	Dead, evolutive, 155 months	Alive, PR, 70 months	Dead, evolutive, 55 months

F Female, *M* male, *NHL* non-Hodgkin lymphoma. *Na* nonavailable, *CT* chemotherapy, *CR* complete response, *PR* partial response, *EOT* end of treatment, *NSCLC* nonsmall cell lung cancer, *SCLC* small cell lung cancer

cervical lymph node positive on FDG–PET. The biopsy showed an epidermoid carcinoma probably of head and neck origin.

Case 6 A 66-year-old woman with B lymphocytic NHL, treated by chlorambucil for 6 years, underwent FDG–PET for staging. The imaging study was negative except for a focal increased tracer uptake in the rectum, which corresponded to a villous adenoma.

Case 7 A 63-year-old woman with a stage IV follicular NHL in 1996 never reached complete remission at follow-up. In 2001, she presented with alteration of general status, respiratory symptoms, hepatosplenomegaly, and disseminated lymphadenopathies. Bone marrow confirmed an involvement by the lymphoma cells, whereas transbronchic biopsy revealed a small cell carcinoma of neuroendocrine type, coexisting with NHL and indistinguishable on FDG–PET.

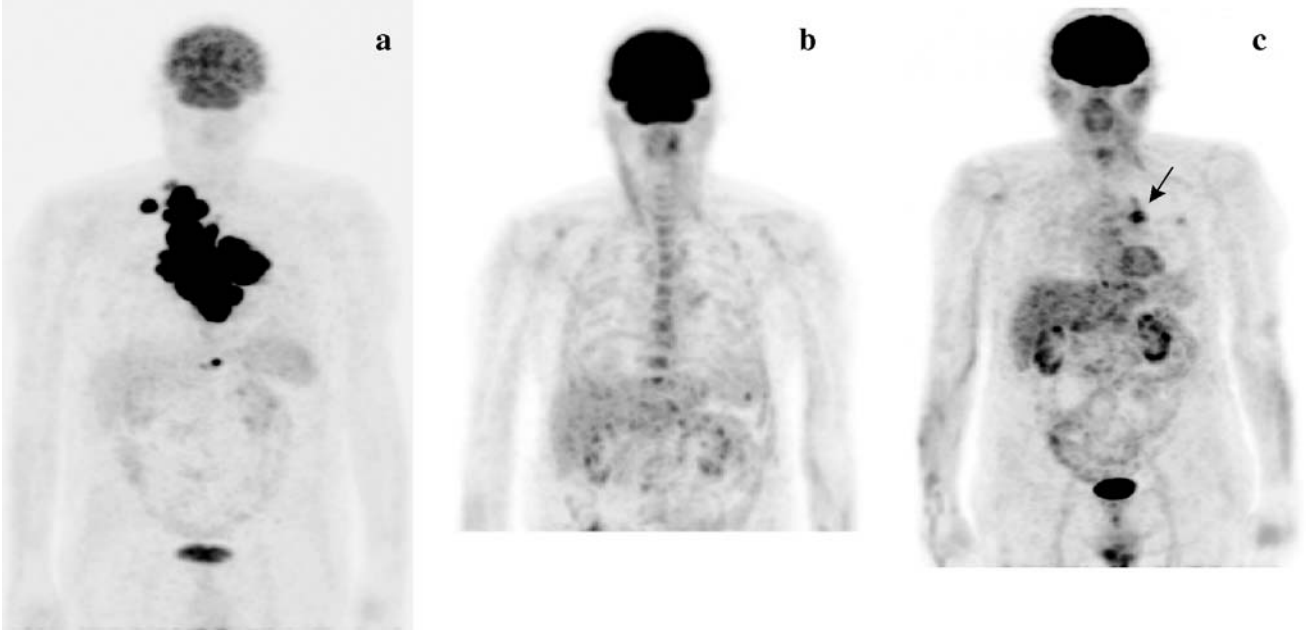

Fig. 1 Maximum intensity projection of the coronal FDG–PET images of a patient with diffuse large B-cell lymphoma (case 2) at initial staging (**a**), after three courses of CHOP chemotherapy (**b**), and after 6 months follow-up (**c**). At diagnosis, lung involvement, right supraclavicular; mediastinal and cardial lymph nodes are clearly visualized (Ann Arbor stage IV). Midtreatment a nearly complete response is observed, whereas the bone marrow signal is increased due to chemotherapy. At 6-month follow-up, a transbronchic-biopsy of the left suprahilar focus of activity (*arrow*) reveals an invasive aspergillosis

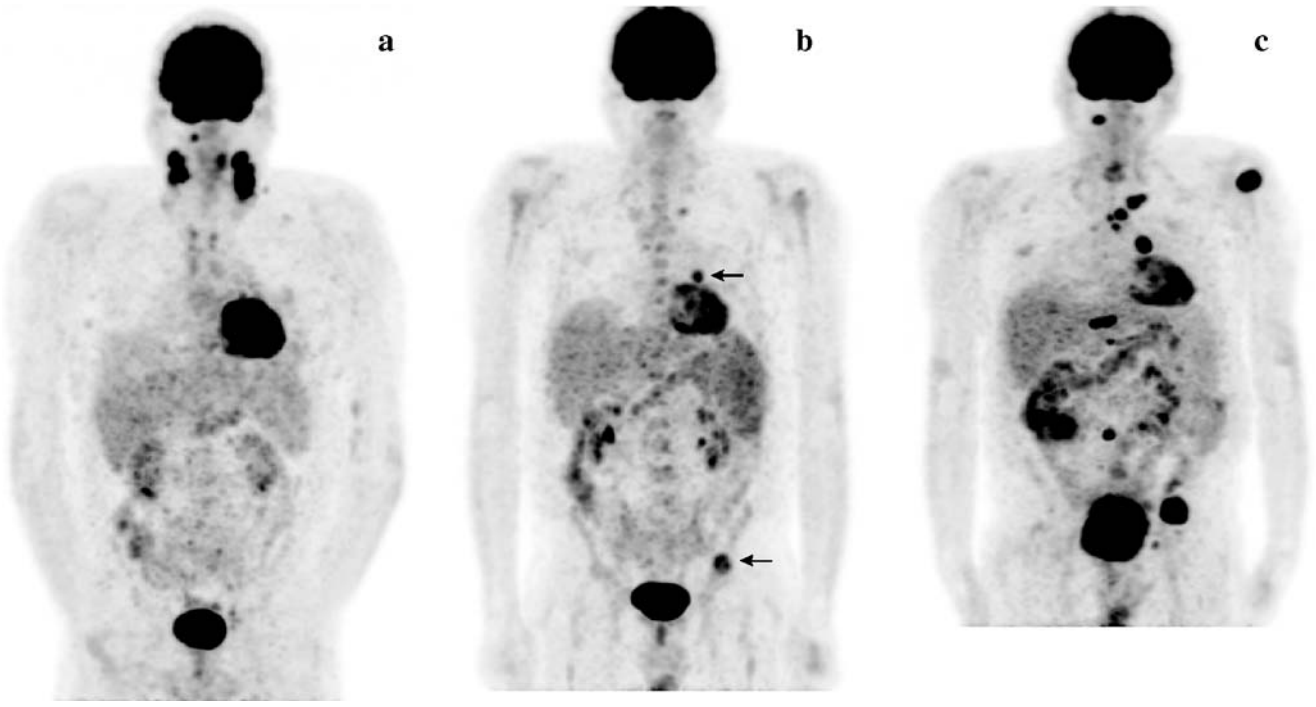

Fig. 2 Maximum intensity projection of the coronal FDG–PET images of a patient suspected of recurrence 6 years after the initial diagnosis of a peripheral T-cell NHL (case 3) at recurrence (**a**), before and 2 months after BEAM chemotherapy with peripheral blood stem cell transplantation (**b** and **c**, respectively). At recurrence, a stage IV is confirmed with supradiaphragmatic lymph nodes and cutaneous lesions (e.g., on the left arm). Before intensification, increased tracer uptake is visualized in the left lung and acetabulum (*arrows*), which extents to lymph nodes and other bones 2 months later. Lung and bone biopsies reveal a metastasised nonsmall cell lung carcinoma

Discussion

FDG–PET has been successfully used for diagnosis, staging, and monitoring of variety of malignancies, including lymphomas. However, increased FDG uptake is not specific of cancerous cells, so that FDG–PET has a low specificity [4]. FDG accumulates in several types of inflammatory cells such as lymphocytes, neutrophils, and macrophages because of their increased glucose metabolism [5–7]. The role of FDG–PET imaging is also evolving into a modality that can be effectively used for the diagnosis and monitoring of several nononcological diseases. A wide variety of infections or inflammatory processes can be successfully detected by FDG–PET [8, 9]. The technique has been shown to be very useful in other situations such as fever of unknown origin, acquired immunodeficiency syndrome, environment-induced lung diseases, atherosclerosis, vasculitis, back pain, transplantation... [10].

FDG–PET and infection

FDG–PET has demonstrated an interest in the diagnosis of various infectious diseases such as prosthesis infection [9, 11, 12], cytomegalovirus pneumonitis [13], helicobacter pylori infection [14], toxoplasmosis [15, 16], phlegmon [17], ... The uptake mechanism in infectious diseases has not been fully elucidated yet, but it appears to be related to the fact that glucose is the sole energy source of granulocytes and macrophages during their metabolic burst [6, 18].

Lymphoma patients are immunocompromised and thus predisposed to infectious complications due to various underlying conditions: chemotherapy, neutropenia, immunosuppression, and venous catheter... It is essential to recognize these infections, which can mimic malignant lesions on PET scan and not confuse them with active neoplastic disease. FDG–PET has demonstrated an interest in the management of invasive aspergillosis [19], for which it may serve to monitor the extent and activity of infection. In the case reported in this study, such a false–positive finding led to a radical new therapy: antimycotics in place of chemotherapy. It is unknown why an increased uptake of FDG occurred in the same locus than primitive localization of lymphoma, but it is possible that it was secondary to a local inflammatory process related to tumor necrosis.

FDG–PET and sarcoidosis

FDG–PET has demonstrated an interest in the diagnosis of sarcoidosis, to identify sarcoid lesions and to assess the extent and the degree of the disease in hilar lymph nodes

[20], lung parenchyma [21], abdominal organs [22], or heart [7, 8, 23, 24]. Sarcoidosis is a multisystem non-caseating granulomatous disease of unknown aetiology. Because lymph nodes harboring inflammatory and malignant cells appear with significant FDG uptake, this technique cannot distinguish sarcoidosis from diseases such as Hodgkin's or non-Hodgkin's lymphomas [25].

FDG–PET and lymphoma

Most of our cases illustrate the potential utility of FDG–PET to stage lymphoma patients and to find the best site for biopsy. All these information, provided by a single imaging modality, are needed to initiate the appropriate treatment. PET represents a major advance in both staging and restaging of lymphoma [26]. A recent analysis of the literature revealed that in the setting of restaging, 18F-FDG PET has a negative predictive value of 80–100%, but it has a variably low positive predictive value (19–60%) [4]. This means that this method is associated with a significant number of false–positive findings, which necessarily have major therapeutic implications.

Interpretation of FDG–PET studies may be hampered by limitations inherent to the PET system or to the degree of disease metabolism. False–negative results, equivocal findings, and potential pitfalls unrelated to cancer have to be considered. The most frequent false–positive PET findings are bone marrow activation by chemotherapy or cytokines, thymus hyperplasia, problems of attenuation, timing of the PET study in relationship to previous treatment... [2, 27]. Knowledge of these potential pitfalls is of particular importance in lymphoma, a multifocal disease that may involve any region of the body. Moreover, correct staging and localization of involved sites have a very important role in the future management of individual lymphoma patients.

FDG–PET is more often used for the efficient detection of lymphoma relapse [27]. Early diagnosis of relapse will lead to early administration of salvage therapy with potential for a better outcome [16]. In the setting of lymphoma monitoring, there is a trend to substitute all conventional evaluations (CT scan, endoscopy...) in this unique and rapid imaging modality. PET would offer obvious advantages such as a reduction of expenses both for the performance of the investigations and for hospitalization, and it would reduce the psychological stress for the patient [28].

FDG–PET and second malignancies

In a context of lymphoma patient, a positive FDG–PET staging may tempt the clinician to conclude immediately to a relapse. It would be particularly dangerous if the PET positivity is considered as the trigger of a new antitumoral treatment. Besides malignant tumors, the possibility of false positive findings must thus be kept in mind to prevent therapeutic mistakes. In this series, the majority of unsuspected PET findings occurred in lymphoma patients without clinical suspicion of relapse. Although relapse is not always associated with clinical symptoms, it is important to correlate PET interpretation with other anatomic imaging and with the patient's history. In case of positive findings on PET shortly after diagnosis, without or with few arguments in favor of relapse by clinical and other imaging investigations, the possibility of an infectious/inflammatory complication must be considered. Although relapse appears highly possible in a context of previous lymphoma, the feasibility of a new biopsy has to be discussed in all doubtful cases. The new pathological research done to confirm or inform the relapse can prevent unnecessary or inadequate therapy.

All cases described in this study showed that without pathological analysis, it was impossible to distinguish FDG–PET positive lesions between initial lymphoma diagnosis and the unsuspected findings. Even more, lymphoma cells can coexist with a second malignancy [29] as shown in this study for two cases (3 and 7).

Patients treated for Hodgkin's and non-Hodgkin's lymphoma tend to be at higher risk of second cancer as a late side-effect of the therapy [30, 31]. Our study highly suggests that FDG–PET could be helpful for detecting these secondary occult malignancies. It also emphasizes the need of a continuous monitoring of late toxicities. The incidental finding of a second cancer may have an important effect on the treatment and may prove to be very cost-effective. FDG–PET ability to detect various cancers (colonic [10], breast, lung cancer...) is another advantage of this technique.

In our study, late second malignancies occurred with a longer delay than infectious/inflammatory complications after the first diagnosis of lymphoma. Obviously, second cancer resulted in death in four out of five patients. There were one epidermoid carcinoma probably of head and neck origin and one villous tumor of the rectum. Lung cancer (two NSCLC and one SCLC) was the most frequent neoplastic complication. This is consistent with the literature which reports an increased risk of lung cancer in Hodgkin's and non-Hodgkin's patients, linked to radiotherapy, alkylating agents, and tobacco use [30, 31].

In conclusion, our results indicate that the time when FDG PET is performed may be useful to identify the aetiology of PET pitfalls. A relapse, suspected only on FDG–PET imaging, requires biopsy because alternative diagnoses are possible. Combined PET/CT scanners, in which structural and functional images are fused, should provide an integrated interpretation and diminish the risk of pitfalls [32, 33]. Early in the lymphoma staging, when

immunosuppression is high, persistent abnormal FDG uptake is highly suspicious for infectious or inflammatory lesions. Later in the lymphoma's course, particularly if the interval since diagnosis is long and if the site of relapse is unrelated to the initial staging, the occurrence of a second malignancy has to be suspected especially in those patients at risk.

In contrast to previous isolated case reports, the current study estimates that about 15% of follow-up studies suspicious of relapse revealed an unsuspected diagnosis [34]. Obviously, there are some limitations in this estimate. First, not all of the PET lesions accepted as possible relapses were biopsied again. Secondly, not all PET studies were made in a systematic routine control fashion: some patients were symptomatic, others not. The best moment to do the FDG–PET in a routine follow-up after lymphoma treatment is not standardized yet. Moreover, the place of PET during long-term follow-up is unknown. Our results, obtained in a heterogeneous population of lymphoma, suggest that FDG–PET may be helpful for long-term monitoring of late effects, especially second cancer occurrence. However, larger studies are warranted to evaluate the performance and the cost-effectiveness of FDG–PET in such a clinical setting.

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