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ORIGINAL ARTICLE

Early detection value of ^{18}F-FDG-PET/CT for drug-induced lung injury in lymphoma

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Abstract

Recent studies have not only shown better prognosis of lymphoma with the advancement of therapeutic drug development, but also suggested more attention should be paid to drug-induced lung injury. Early diagnosis is critical for treatment of drug-induced lung injury. ^{18}F-FDG-PET/CT, the standard imaging method for prognosis evaluation of Hodgkin's lymphoma and some non-Hodgkin's lymphoma, has also shown the potential for early detection of drug-induced lung injury in our study. A total of 579 lymphoma patients evaluated by ^{18}F-FDG-PET/CT between June 2016 and March 2018 are studied retrospectively. Clinical and imaging characteristics are described in 32 patients (average age of 55), who were diagnosed with drug-induced lung injury. The incidence of drug-induced lung injury was 5.53% (32/579); most of the chemotherapy regimens include rituximab (90.63%, 29/32). Twelve patients demonstrated fever, cough, and dyspnea, and the other 20 had no significant symptoms. ^{18}F-FDG-PET/CT showed multiple or diffused distribution of ground glass and patchy shadows, with increased FDG uptake in both lungs (SUV_{max} 2.28 ± 1.13, standardized uptake ratio-blood pool, SUR-BP = 0.59–4.07, median SUR-BP 1.32). SUV_{max} and SUR-BP in patients with symptoms (SUV_{max} 3.03 ± 1.33 and SUR-BP 2.12 ± 1.06) were significantly higher than in those without symptoms (SUV_{max} 1.84 ± 0.70 and SUR-BP 1.18 ± 0.48) ($P = 0.002$ for both SUV_{max} and SUR-BP). After temporary drug withdrawal, changing chemotherapy regimens, and corticosteroid usage, the pulmonary lesions in all patients were relieved, confirmed with chest CT. Drug-induced lung injury can be a co-finding during ^{18}F-FDG-PET/CT assessment of lymphoma. With positive correlation between FDG uptake and symptoms, ^{18}F-FDG-PET/CT provided value in early detection of lung injury in asymptomatic patients.

Keywords ^{18}F-FDG-PET/CT · Drug-induced lung injury · Lymphoma · Early detection

Introduction

As one of major non-solid malignant tumors, lymphoma presents severe threats to people's health and life. The prognosis of lymphoma has been gradually improved because of the development of drugs. More and more attention has been paid to drug-induced lung injury in clinical practice [1–6]. The diagnosis of drug-induced lung injury is exclusive; it usually appears shortly after chemotherapy with clinical symptoms such as fever, cough, and respiratory failure or imaging findings that cannot be explained by infection. Such symptoms can disappear by drug withdrawal and corticosteroid usage [7, 8]. Early diagnosis plays a crucial role for recovery. Previously, diagnosis of drug-induced lung injury was based on symptoms of respiratory systems and imaging findings, especially changes in chest CT [5, 9, 10].

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG-PET/CT) has become a standard imaging method for staging and evaluation of the chemotherapy effects for lymphoma, especially for diffuse large B cell lymphoma (DLBCL) and Hodgkin's lymphoma (HD). Early-stage drug-induced lung injury without obvious clinical symptoms was found in the routine follow-up PET/CT and has been reported in our previous study [11]. To expand the sample size, we selected lymphoma patients diagnosed with drug-induced lung injury in the past 6 years in our hospital. These patients share common characteristics, i.e., pulmonary abnormality was first identified during the routine ^{18}F-FDG-PET/CT examinations for evaluation of

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chemotherapy response. Their clinical and imaging features and the early detection value of ^{18}F-FDG-PET/CT in drug-induced lung injury were retrospectively analyzed.

Material and methods

General information

Nine hundred fifty-three ^{18}F-FDG-PET/CT scans for evaluation of chemotherapy response, from 579 lymphoma patients, performed in the Department of Nuclear Medicine in Peking University Third Hospital between June 2012 and March 2018 were included. Each patient had a baseline PET/CT before chemotherapy, though some baseline scan took place in other hospitals. Patients with new pulmonary lesions at the time of evaluation were screened as following criteria: (1) clinical symptoms appeared after chemotherapy; (2) unexplainable respiratory failure; (3) symptoms such as fever and cough cannot be explained by infection; (4) imaging findings cannot be explained by infection; (5) symptoms can disappear by drug withdrawal and corticosteroid usage. After the exclusion of other factors, patients diagnosed as drug-induced lung injury were selected and classified as lung injury group. Patients with matched genders and similar ages without obvious pulmonary lesions were selected as the control group. Their clinical and ^{18}F-FDG-PET/CT imaging features were analyzed. The final diagnoses of patients were based on clinical long-term follow-up. Informed consent was obtained from all patients for being included in the study.

Imaging protocol

The Siemens 52 ring biograph 64 PET/CT was used. ^{18}F-FDG was provided by the Institute of Isotope Research in China Academic of Atomic Energy with radiochemical pure > 90%. After fasting for more than 6 h, each patient was administered 5.55 MBq/kg (0.15 mci/kg) ^{18}F-FDG intravenously and imaged with routine PET/CT after 60 min. The CT scans were ranged from the skull base to the upper femur, with matrix of 512 × 512. Then, PET images were collected with matrix of 168 × 168 by 5–7 beds (2–2.5 min per bed). After that, maintaining the patient position, a deep inspiratory HRCT scan was performed using 64 × 1.25-mm detectors, with a pitch of 0.53 and 1.25-mm collimation (120 kVp and 100 mAs). PET images were reconstructed by OSEM, and later image fusion and evaluation were adopted by MedEx PET/CT image and information system.

Visual assessment

All images were independently visually evaluated from the MedEx PET/CT image and information system by two nuclear medicine physicians. To evaluate the remission status of lymphoma, purely visual interpretation of the lymphoma lesions was performed using the Deauville 5-point scale of 1 to 5 according to ^{18}F-FDG uptake. The lesion scores were graded by ^{18}F-FDG uptake according to the following criteria: score 1, no residual uptake; score 2, uptake ≤ mediastinum; score 3, uptake > mediastinum but ≤ liver; score 4, uptake moderately > liver; score 5, uptake markedly increased and/or progression of the lesions. Take the Deauville score < 4 as the PET negative standard and Deauville score ≥ 4 as the positive standard. The visual degree of uptake for the lung injury lesions was also assessed according to Deauville criteria. The pattern of lung uptake was analyzed, and chest CT findings were reviewed.

Quantitative analysis

Quantitative analysis of the lung lesions was performed using attenuation-corrected axial images. The maximum standardized uptake values (SUV_{max}) of a region of interest encompassing the FDG activity were recorded. Mean normalized uptake ratio of the ascending aorta (mean standardized uptake value, SUVmean) was used as the base of the mediastinal blood pool. Standardized uptake ratio-blood pool (SUR-BP) was calculated. The background SUVmean of lung in the control group was used as reference value, and the FDG uptake of lung lesions in patients was analyzed.

Statistical analysis

We compared the FDG uptake of lung lesions in lung injury group and uptake of lung background in control group. According to the clinical manifestations, patients in the lung injury group were divided into subgroups with or without symptoms. Then, we compared the SUV_{max} and SUR-BP of lung lesions between the two subgroups. Statistical analysis was performed using SPSS 22.0 software. For data conforming to normal distribution, two independent sample t tests are used, and Mann-Whitney U tests are used for data not conforming to normal distribution. $P < 0.05$ was considered statistically different.

Results

General characteristics

Thirty-two patients (19 males and 13 females, ages: min = 26, max = 83, median = 55) were diagnosed with drug-induced lung injury, with occurrence rate of 5.53%. There was lung involvement of lymphoma in one of the patients before chemotherapy. In the PET/CT scans for response evaluation, 4 patients were assessed as PET positive and 28 were negative. Twelve patients had fever, cough, dyspnea, and other

symptoms, while the other 20 had no obvious clinical manifestations. Patients received 2–12 courses (median 4) of chemotherapy before the occurrence of lung injury. Rituximab was the most common drug among the combination therapy regimen, accounting for 90.63% (29/32).

Among the 32 patients, lesions involved unilateral lungs in 3 patients and bilateral lung in 29 patients; while 14 patients had single or multiple localized lesions, 18 had diffused lung involvement. The lesions mainly manifested as ground glass density shadow, mesh shadow, slightly higher patchy shadow,

Table 1 General characteristic and PET/CT manifestation of patients

Number of patients	Diagnosis	Ann Arbor State	Regimen	Courses	Clinical symptoms	SUV_{max} of lesions	Deauville score of lung lesions	SUR-BP
1	DLBCL	IVA	BEACOP	4	Fever	3.70	3	2.64
2	DLBCL	IIIA	R-CHOP	4	No symptoms	2.00	3	1.28
3	DLBCL	IVB	R-EPOCH	2	No symptoms	1.40	2	0.85
4	DLBCL	IEA	R-CHOP	5	No symptoms	1.30	2	0.92
5	DLBCL	IA	R-CHOP	3	Cough	1.80	3	1.2
6	DLBCL	IA	R-BEACOP	8	Fever	1.70	3	1.3
7	DLBCL	IIA	R-CHOP	3	Dyspnea, fever	4.60	5	3.74
8	DLBCL	IVA	R-EPOCH	6	No symptoms	2.60	3	2.02
9	DLBCL	IVA	Cladribine	12	Dyspnea	4.80	5	4.07
10	DLBCL	IVB	R-GDP	8	No symptoms	3.30	4	2.28
11	DLBCL	IIIEB	R-CHOP	8	No symptoms	2.72	3	1.73
12	DLBCL	IVA	R-CHOP	5	Wheezing	0.90	2	0.59
13	T- LBL	IVB	Hyper-CVAD A*2, Hyper CVAD B*1, VDLD*1, CAM*1	5	Fever, cough	3.46	4	2.47
14	DLBCL	IVB	R-CHOP*1, R-EPOCH*2	3	No symptoms	1.04	2	0.77
15	AITL	IVA	CHOPE	3	No symptoms	2.29	3	1.44
16	DLBCL	IVA	R-EPOCH	2	No symptoms	1.68	2	0.76
17	DLBCL	IVA	R-EPOCH	3	No symptoms	2.00	2	1.06
18	DLBCL	IIA	R-COP*1, EPOCH*1, R-EPOCH*1, R-BEACOP*2	5	No symptoms	2.20	2	1.1
19	FL	IVA	R-CHOP	4	Dyspnea	2.24	3	1.48
20	FL	IB	R-CHOP*3, FMD*2	5	No symptoms	2.21	3	1.36
21	DLBCL	IEA	R-CHOP	6	No symptoms	1.12	2	0.74
22	DLBCL	IEA	R-EPOCH	5	Fever	3.11	4	2.16
23	DLBCL	IVB	R-CHOP	5	No symptoms	0.92	2	0.6
24	FL	IVA	R-CHOP	3	No symptoms	1.46	2	0.77
25	DLBCL	IIA	R-CHOP	4	No symptoms	2.25	3	1.11
26	DLBCL	IIA	CHOP*1, R-CHOPE*1, R-EPOCH*1	3	No symptoms	1.73	3	1.34
27	DLBCL	IVB	R-CHOP	2	Dyspnea, hypoxemia	5.04	5	2.77
28	DLBCL	IVA	R-CHOP*1, R-GDP*1, decitabine + R-GDP*2, R-BEACOP + bortezomib *1	5	No symptoms	1.09	2	0.77
29	FL	IIA	R-CHOP	2	No symptoms	2.74	3	1.92
30	FL	IIIA	R-CHOP*3, R-CHOPE*1	4	Chest tightness	2.24	3	1.36
31	DLBCL	IIA	R-COP	2	Cough, fever	2.71	3	1.68
32	HL	IVB	ABVD	2	No symptoms	0.75	2	0.77

FL, follicular lymphoma; *T-LBL*, T-lymphoblastic lymphoma; *AITL*, angioimmunoblastic T cell lymphoma; *R*, rituximab; *BEACOP*, etoposide, pirarubicin hydrochloride, cyclophosphamide, vincristine, prednisone, and methylbenzamide; *CHOP*, cyclophosphamide, doxorubicin, vincristine, and prednisone; *CHOPE*, cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide; *EPOCH*, etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide; *GDP*, gemcitabine, cisplatin, and prednisone; *Hyper-CVAD A*, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; *Hyper CVAD B*, methotrexate, cytarabine; *VDLD*, vincristine, daunorubicin, asparaginase, and prednisone; *CAM*, mercaptopurine, cyclophosphamide, and cytarabine; *ABVD*, epirubicin hydrochloride, dacarbazine, vincristine, diazepam, and bleomycin; *COP*, cyclophosphamide, vincristine, and prednisone

and consolidation with vague border, except for relatively clear boundary in 2 patients. Two patients had pleural thickening and pleural effusion. Also, 32 lymphoma patients of similar age and gender without pulmonary involvement were selected as controls. The uptake of FDG was significantly higher in patients with drug-induced lung injury compared to that in controls (SUV_{max} 2.28 ± 1.13 VS 0.37 ± 0.07, $P < 0.001$). Patients with drug-induced lung injury had SUR-BP ranging from 0.59 to 4.07 (median 1.32). Taking the Deauville 5-point scale as the criteria, 12 patients were rated 2 points, 14 patients were rated 3, 3 patients were rated 4, and 3 patients were rated 5. In the subgroup with symptoms, the lung lesions had SUV_{max} 3.03 ± 1.33 and SUR-BP 2.12 ± 1.06. In the subgroup without symptoms, the lung lesions had SUV_{max} 1.84 ± 0.70 and SUR-BP 1.18 ± 0.48. Both SUV_{max} and SUR-BP were higher in the subgroup with symptoms than in those without ($P = 0.002$ both) (Table 1).

Therapy and follow-up

Thirty patients had temporary drug withdrawal or changed chemotherapy regimens, and 20 of them took corticosteroid. Two patients continued their original chemotherapy and received oral corticosteroids at the same time. All patients received CT re-examinations after alteration of therapy (between 5 days and 3 months) and all showed obvious lesion absorption (Fig. 1).

Discussion

Drug-induced lung injury is not rare in patients receiving chemotherapy. The pathogenesis is generally considered to be chemotherapy drugs directly damaging the cells of lung tissues or causing anaphylaxis or immune responses. The pathological basis is the interstitial lung damage caused by chemotherapeutic drugs, including all subtypes of interstitial lung disease, such as diffuse pulmonary alveolar injury, chronic pulmonary fibrosis, organized pneumonia, eosinophilic pneumonia, and allergic pneumonia [8]. Drug-induced lung injury was traditionally found in patients with clinical symptoms and diagnosed by chest CT. Clinical manifestations include cough, fever, dyspnea, hypoxemia, and respiratory failure, and acute respiratory distress syndrome (ARDS) can happen when it is serious. The key criterial for diagnosis is to exclude other causes that may induce lung injury, although in many cases, this is very difficult. If early diagnosis can be made, the damage to the lung is reversible.

The role of ^{18}F-FDG-PET/CT in the response evaluation for treatment of some malignant tumors, especially lymphoma, has been well accepted [12]. However, in some of the lymphoma patients, the PET/CT scans used for routine assessment showed new lesions in the lungs while the primary lymphoma lesions were reduced or disappeared after chemotherapy. At that time, patients may not have respiratory manifestations. After clinical exclusion of other factors, some of the patients were diagnosed as drug-induced lung injury by clinician, and the pulmonary lesions were rapidly reduced after drug withdrawal and corticosteroid usage.

We retrospectively analyzed those cases with pulmonary lesions identified initially on ^{18}F-FDG-PET/CT for evaluation of lymphoma after chemotherapy and eventually diagnosed as drug-induced lung injury by clinicians. The purpose of this study was to summarize the clinical and imaging features and to assess the early detection value of ^{18}F-FDG-PET/CT in this disease.

The overall incidence of drug-induced lung injury was 5.53% (32/579) in our study. There is no big data analysis on the incidence of drug-induced lung injury in lymphoma patients yet. Some studies suggested that the incidence of drug-induced lung injury is about 0–21.1% in lymphoma [1, 3, 13–15]. Drug differences may contribute to the different incidence.

It is difficult to define the drug inducing lung injury, because most patients received combinatory therapy regimens. However, 29 cases (90.63%) of lung injury received chemotherapy

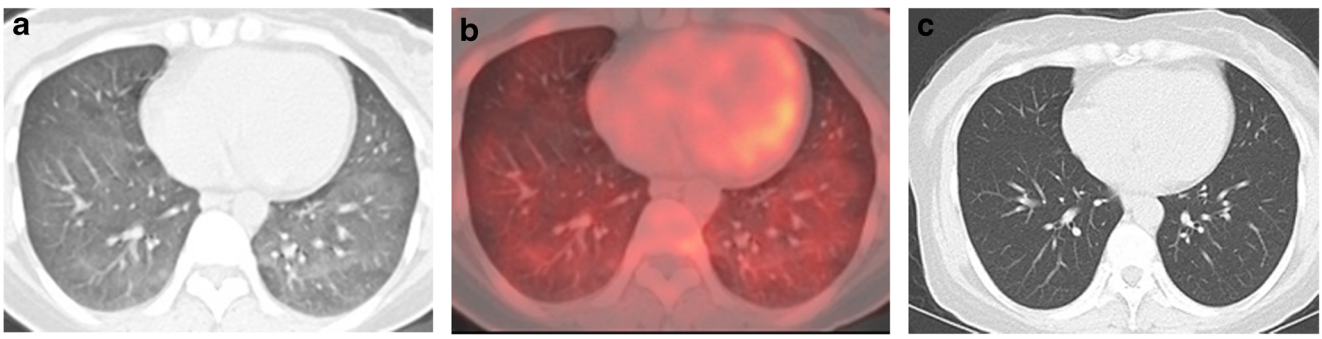

Fig. 1 PET/CT and chest CT scans for a 46-year-old woman with DLBCL. She had cough and dyspnea after four courses of R-CHOP. ^{18}F-FDG-PET/CT suggested diffuse distribution of ground glass shadows with increased FDG uptake (SUV_{max} 2.24). Drug-induced lung injury was diagnosed in clinical. The patient discontinued chemotherapy and used corticosteroid. After 20 days, the lung lesions were absorbed obviously (**a** CT; **b** PET/CT; **c** CT after 20 days)

containing rituximab, of which 12 cases were on R-CHOP regimen. In recent years, the application of rituximab has obviously improved the long-term survival rate of lymphoma such as DLBCL, and R-CHOP has become the first-line treatment for DLBCL. However, during the administration of rituximab, its effect on lung injury has gradually gained more attentions [1, 15–19]. Some studies suggested tumor necrosis factor (TNF-α) was involved in the process [20]. Our studies found R-CHOP and other chemotherapies containing rituximab were more frequent in causing lung injury.

Our study showed that patients received 2–12 chemotherapy courses (median 4) before lung injury, which suggested the lung injury could occur anytime during the treatment, with no evidence of obvious incident time.

The distribution of pulmonary lesions in ^{18}F-FDG-PET/CT imaging of the 32 patients was commonly bilateral diffuse or multiple localized. The most common features were ground glass density shadow, patchy shadow, and subpleural grid shadow, which were the characteristics of drug-induced interstitial and alveolar damage consistent with previous studies [21]. Also, our study showed that most patients with drug-induced lung injury had homogeneous and diffuse light-to-moderate FDG uptake with SUV_{max} 2.28 ± 1.13, which was similar to previous studies [13, 14, 22].

Although all patients with drug-induced lung injury in our study showed morphologic alterations in CT, we still believe that PET/CT provides additional valuable information, based on the following two points. First, for most lymphoma patients, PET/CT is a routine examination for post-therapeutic evaluation. Many patients without respiratory symptoms will not undertake chest CT, but they will generally receive a PET/CT examination after treatment for response evaluation. It is worth noting that, for some patients, when drug-induced lung injury happened, there was no apparent discomfort, but imaging changes were found during the routine PET/CT examination, which may be the only clue to the discovery of drug-induced lung injury. In our studies, 20 cases (62.5%) with pulmonary lesions and abnormal uptake were firstly manifested by PET/CT with no obvious clinical symptoms. We should pay more attention to these unexpected findings so that early clinical intervention can begin promptly. Second, according to our observation and statistics, for patients with lung injury after chemotherapy, FDG uptake in lung lesions is positively correlated with clinical manifestations; the difference is statistically significant. This suggests that FDG uptake may be related to the activity and severity of the disease. For patients with chemotherapy-induced lung injury, PET/CT provides additional metabolic information on the basis of CT. Patients without clinical symptoms may be at the early stage of lung injury. Falay et al. analyzed 13 patients with Hodgkin's lymphoma receiving bleomycin chemotherapy and found lung injury during 18F-FDG-PET/CT examinations and also confirmed the early detection value of ^{18}F-FDG-PET/CT for drug-induced lung injury [14]. The best way to intervene drug-induced lung injury is early diagnosis and treatment. Our results showed that PET/CT had a great value for early detection of drug-induced lung injury, and the FDG uptake level may be related to the severity of the disease. The imaging changes may occur before the appearance of clinical symptoms, and routine PET/CT for evaluation of chemotherapy effectively catch the evidence.

In conclusion, drug-induced lung injury can occur at any time of chemotherapy for lymphoma patients and often happens in chemotherapy regimens combined with rituximab. The clinical manifestations were not specific; sometimes, the patient has no clinical manifestations and lung damages were discovered in the routine ^{18}F-FDG-PET/CT scans for effect evaluation. ^{18}F-FDG-PET/CT showed interstitial changes in both lungs with mild-to-moderate FDG uptake which was positively correlated with the symptom. The early detection was useful for clinical intervention and prognosis improvement. In the future, more attentions should be paid to drug-induced lung injury discovered in the ^{18}F-FDG-PET/CT evaluation for lymphoma patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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