^{18}F-FDG-PET/CT Pulmonary Infiltrates in Non-Hodgkin's Lymphoma Patients Treated with Combined Immunochemotherapy: Incidence and Clinical Characteristics

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ABSTRACT: **Background:** Pulmonary infiltrates (PIs) detected in patients with non-Hodgkin's lymphoma (NHL) may present a diagnostic challenge due to their wide differential diagnosis, including infection, pulmonary lymphoma and immunochemotherapy-associated pulmonary toxicity.

Objectives: To characterize therapy-associated PIs by positron emission tomography/computed tomography (PET/CT) imaging.

Methods: We conducted a historical analysis of ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) PIs in NHL patients treated with combined immunochemotherapy including rituximab. Incidence of PIs, radiological features, patient characteristics, underlying NHL type, rituximab/chemotherapy dosing schedules, and symptoms were recorded. Therapy-associated PIs were defined as new or worsening PIs appearing after treatment onset, without evidence of active pulmonary lymphoma or infection.

Results: Among 80 patients who met the pre-specified criteria, therapy-associated PIs were identified in 17 (21%), 6 of whom had accompanying symptoms. Increased FDG uptake was observed in nine, and PI resolution in six. The incidence of PIs was higher in females and in patients with aggressive lymphoma who were at advanced stages and who had received treatment consisting of a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days (R-CHOP-14).

Conclusions: This characterization of therapy-associated PIs may support the clinician managing NHL patients. Further prospective studies are needed to establish the role of each therapeutic component and the natural history of this phenomenon.

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KEY WORDS: positron emission tomography/computed tomography (PET/CT), non-Hodgkin's lymphoma (NHL), pulmonary infiltrates (PIs), immunochemotherapy, pulmonary toxicity

Pulmonary infiltrates (PIs) are a frequent finding on various chest imaging studies of patients with non-Hodgkin's lymphoma (NHL) and often present a diagnostic challenge to the treating clinician. Differential diagnosis includes infections, persistent or recurrent lymphoma in the lung, and toxicity related to immunochemotherapy. The latter was recognized as a rare late complication of treatment with rituximab-containing chemotherapy, mostly presenting as interstitial lung disease [1]. This complication was reported based on cases of symptomatic lung injury that were usually reversible, although in some severe cases they were fatal. Diagnosis of therapy-related toxicity was supported by a lung biopsy in some of the cases [2-8], while others were based on the temporal relationship with rituximab treatment, characteristic computed tomography (CT) findings of diffuse infiltrates with lack of evidence of infection, reversibility following rituximab discontinuation and steroid treatment [9-11].

The incidence of such clinically significant pulmonary toxicity in patients receiving immunochemotherapy is thought to be rare. Rituximab-related interstitial lung disease was described in less than 0.03% of 540,000 patients [12], as reported by the manufacturer [9]. Lim et al. [13] reported severe drug-induced interstitial pneumonitis (DIIP) among 100 newly diagnosed lymphoma patients. In that study, 71 patients were treated with a

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combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days (R-CHOP-14) and 29 were treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) as an initial regimen. DIIP occurred in 7% of patients in the R-CHOP arm and in 3% of these in the CHOP arm [13]. Toxicity has rarely been reported in association with individual components of CHOP-combined chemotherapy, namely anecdotal cases of lung toxicity associated with vinca alkaloids including acute diffuse pulmonary infiltrates, respiratory failure, and cyclophosphamide lung toxicity, which is rare (< 1%) [14,15].

^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET), frequently combined with CT, is currently a routine imaging modality in the diagnosis and follow-up of NHL patients [16,17] and is used as a tool for assessment of therapy response [18]. Although ^{18}F-FDG PET may show abnormalities other than lymphoma activity, its role in the diagnosis and follow-up of symptomatic interstitial pneumonitis is uncertain. Subclinical infiltrates detected by PET/CT in NHL patients receiving immunochemotherapy without clinical symptoms have been described [19]; however, the incidence of this phenomenon has not yet been established [20].

This study was conducted in a historical cohort of consecutive NHL patients treated with immunochemotherapy regimens containing rituximab. The study goals were to evaluate the incidence of PIs detected by ^{18}F-FDG PET/CT imaging modalities to characterize the radiological findings, and to identify clinical correlates in patients with suspected rituximab/chemotherapy-induced lung toxicity, including patient characteristics underlying lymphoma type, rituximab and chemotherapy dosing schedules, and symptoms.

PATIENTS AND METHODS

In this historical cohort study, patients with NHL who were receiving rituximab combined with chemotherapy treatment between January 2007 and May 2009 in our center were identified based on queries of their electronic medical records. The requirement to obtain informed consent was waived by the institutional ethics review board. For each patient, the date of the first rituximab dose administration was defined as the baseline date on condition that it was within the study period. To be included, patients had to have undergone a CT or a ^{18}F-FDG PET/CT scan prior to baseline and at least one ^{18}F-FDG PET/CT scan after baseline. Cases of PIs were reviewed for symptoms and clinical outcomes up to the last reported follow-up visit.

PULMONARY INFILTRATES DEFINITION

Cases of therapy-associated PIs were defined as patients presenting with new or worsening PIs according to the CT scan; with alveolar, interstitial or ground-glass appearance; with or without FDG uptake; and without clinical evidence of pulmonary infection or active pulmonary lymphoma. Infiltrates found on ^{18}F-FDG PET/CT scans post-therapy that were not present on the baseline (pre-therapy) scan were defined as new PIs; worsening PIs were defined as PIs that increased in their extent (e.g., from focal to diffuse) or those with new appearance of FDG uptake. Lack of evidence of infection or active lymphoma was confirmed based on a review of the patient's medical chart, including medical follow-up and any culture, pathology or cytology findings.

SCAN REVIEW AND ANALYSIS

For each patient, all available chest scans underwent a structured review of the thoracic fields by two nuclear medicine physicians and a radiologist, who were blinded to the specific lymphoma type and treatment. For each patient, all available scans were reviewed in chronological order. FDG uptake was visually assessed by two nuclear medicine specialists and was considered to have increased when there was intense uptake compared to the background lung. The normal lung parenchyma usually shows low FDG uptake compared to mediastinum. The following findings were documented:

- PIs classified as ground glass, interstitial, alveolar or nodular
- Extent of the PIs documented as focal or diffuse
- Location of the documented as upper or lower lung and as central or peripheral

Adenopathy was classified as hilar or mediastinal, and pulmonary masses were documented. FDG uptake and intensity within lymph nodes or PIs was graded as low, medium or high. Other findings such as the presence of pleural or pericardial effusions, bronchiectasis or atelectasis were also recorded.

PET/CT SCAN ACQUISITION

All images were obtained with an integrated PET/CT scanner (Discovery ST, General Electric Healthcare, Milwaukee, WI, USA). Parameters for CT image acquisition were as follows: helical CT at 0.8 s/rotation 100–300 mAs, 120 kVp, section thickness 3.75 mm with 3.75 mm interval. Iodine contrast medium (1.5 ml/kg of iopromide, Ultravist 300®, Bayer Schering Pharma, Berlin, Germany) was administered intravenously. Patients with an iodine allergy or chronic renal failure and those who refused contrast administration were examined with unenhanced CT. Immediately after CT, PET was performed. The acquisition time for emission scans was 3–4 minutes per bed position with a one-section overlap. Six to eight bed positions from skull base to mid-thigh resulted in an acquisition time of 18–24 minutes. CT data were used for attenuation correction. Images were reconstructed with a standard iterative algorithm.

STATISTICAL ANALYSIS

Univariate analysis was performed by chi-square test or Fisher's exact test using SAS statistical software (version 9.1.3, SAS Institute, USA).

RESULTS

We identified 197 patients who had received immunochemotherapy containing rituximab for the treatment of NHL. Of this group, 117 patients were excluded due to the following reasons: 29 patients lacked a baseline scan, 78 patients did not have a follow-up PET-CT scan, 9 patients were not treated with rituximab within the prespecified study period and one patient was not treated with chemotherapy. The 80 patients who met prespecified eligibility criteria underwent review of their medical charts and CT and/or ^{18}F-FDG PET/CT scans. Patients' characteristics are described in Table 1. On average, three scans were reviewed for each patient. The average duration of follow-up was 5 months (from baseline date), range 1–19 months. Most patients had diffuse large B cell lymphoma (DLBCL, 61%), or follicular lymphoma (20%). Most patients had advanced stage disease at baseline. R-CHOP-21 therapy was given to 48 patients (60%) and R-CHOP-14 to 23 (29%). Twenty-nine patients (36%) had lymphoma-specific findings, either lymphadenopathy or pulmonary masses, in the thoracic cavity on their pre-treatment scan. We found PIs on the pre-treatment scan of 36 patients (45%) [Table 1].

We identified 23 cases with new or worsening PIs on follow-up PET/CT scans. Review of medical charts suggested that in three of these cases PIs were associated with infection, and in three cases with persistent lymphoma. Consequently, therapy-associated PIs were identified in 17 patients (21%). Of these, 14 patients had DLBCL (82%) and 3 (18%) had low-grade lymphoma, including follicular lymphoma, mucosa-associated lymphoma (MALT) and small lymphocytic lymphoma. Clinical and radiological characteristics are detailed in Table 2. An example of scans in Figure 1 depicts therapy-related PIs in a patient treated with R-CHOP. PIs were detected after an average of 3.8 cycles of combined immunochemotherapy (range 2–8). Infiltrates were detected during active treatment in 13 patients and after therapy had been completed in the remaining 4. The type of infiltrates was described as ground glass (n=11), interstitial (n=5) and/or alveolar (n=6). ^{18}F-FDG uptake was observed in 9 (52%) of the 17 cases, including 8 of the 14 patients with DLBCL and in 1 of the 3 patients with indolent lymphoma.

PIs were accompanied by one or more symptoms in 7 of the 17 patients, including cough (n=5), dyspnea (n=3) and fever (n=2). In three patients there was decreased diffusion capacity in pulmonary function tests. In four patients, symptoms resolved after treatment with corticosteroids and/or antibiotics and cessation of rituximab. One patient died shortly after amelioration of symptoms (cause of death unknown). No association between FDG uptake and patient characteristics or symptoms was identified: PIs were positive for FDG uptake in four of the seven symptomatic cases and in five of the asymptomatic cases. Follow-up scans revealed complete resolution within 2 to 6 months in five cases and partial improvement within 3 to 10 months in four cases. Persistent PIs were seen in six cases during a follow-up period of 5 to 12 months, while for two cases no further follow-up scans were available.

Table 1. Cohort characteristics and baseline imaging findings (80 cases)

Demographics		
Age (mean ± SD)	67 ± 12.9	
Gender	**No.**	**(%)**
Male	43	(54)
Female	37	(46)
Imaging		
Baseline scan		
CT	16	(20)
PET/CT	64	(80)
No. of scans per patient, mean (range)	3	(2-5)
Duration of follow-up, months, mean (range)	5	(1-19)
Lymphoma classification		
Diffuse large B cell lymphoma	49	61
Follicular lymphoma	16	20
Mantle cell lymphoma	8	10
MALT lymphoma	3	4
Small lymphocytic lymphoma	2	3
Anaplastic large cell lymphoma	1	1
Non-specified lymphoma	1	1
Stage at diagnosis		
I/II	22	27
III	15	19
IV	43	54
Regimen		
R-CHOP-21	48	60
R-CHOP-14	23	29
R-CHOP/R-DHAP	7	9
R-COP	2	2
Baseline imaging findings		
Lymphoma specific		
Hilar adenopathy	16	20
Mediastinal adenopathy	27	34
Pulmonary mass	1	1
Any lymphoma lung involvement	29	36
Pleural effusion	20	25
Pulmonary infiltrates		
Ground glass	11	14
Interstitial	13	16
Nodular	13	16
Alvelolar	7	8
Any infiltrate	36	45

PET/CT = positron emission tomography/computed tomography, MALT = mucosa-associated lymphoma, R-CHOP = treatment consisting of a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

Factors associated with therapy-related PIs were evaluated using univariate analysis [Table 3]. The incidence of PIs was higher in patients with lymphoma involving the thoracic cavity compared to patients without thoracic cavity involvement at baseline (29% vs. 14%, $P = 0.11$), in patients with advanced as opposed to early stage of disease (28% vs. 5%, $P = 0.03$), in patients with aggressive vs. indolent lymphoma (28% vs. 10%, $P = 0.06$), in females vs. males (30% vs. 14%, $P = 0.09$), and in patients who received R-CHOP-14 vs. R-CHOP-21 (35% vs. 16%, $P = 0.07$).

Table 2. Clinical and radiological characteristics of cases with therapy-associated pulmonary infiltrates

Age (years)	Gender	Diagnosis	Stage	Lymphoma lung involvement	Treatment	Clinical correlate	Treatment for pulmonary toxicity	Infiltrate type	^{18}F-FDG uptake	No. of R cycles after which PI appeared	Last follow-up: no. of months post-last R	Status at last follow-up
61	F	DLBCL	IV	No	R-CHOP21 × 6 + R × 2	None	–	GG	No	2	13	CR
69	F	FL	III	Yes	R-CHOP21X6 + R × 2	Fever	None	INT	No	2	20	CR
77	M	DLBCL	IV	No	R-CHOP21 × 3	Cough fever, interstitial pneumonitis on transbronchial biopsy, BAL negative for microorganisms	Antibiotics	GG	Yes	3	1	Deceased
75	F	DLBCL	IV	Yes	R-CHOP21 × 6 + Rx2	None	–	GG, ALV	Yes	3	15	CR
69	F	MALT	IIIE	Yes	RCOP × 6	Cough, no evidence of malignancy on transbronchial biopsy	None	GG, ALV	No	4	21	CR
55	F	DLBCL	IV	Yes	R-CHOP14 × 6 + 5R	Recurrent cough post-R	Stop R	ALV	Yes	3	13	CR
63	M	DLBCL	IV	Yes	R-CHOP14 × 6 + 2R	None	–	INT	Yes	2	8	CR
80	F	DLBCL	IV	Yes	R-CHOP21 × 6 + R × 2	None	–	GG, ALV	No	4	11	CR
77	F	DLBCL	IV	Yes	R-CHOP21 × 6 + R × 2	None	–	ALV	No	4	5	CR
61	M	DLBCL	IV	Yes	R-CHOP14 × 6	Cough	–	GG	Yes	6	8	CR
45	F	DLBCL	IV	Yes	R-CHOP14 × 6 + R × 1	Dyspnea	CS	GG, ALV	No	7	26	CR
61	M	DLBCL	IV	Yes	R-CHOP21 × 6 + R × 2	None	–	GG, INT	Yes	8	19	CR
73	M	DLBCL	IV	No	R-CHOP14 × 6	None	–	GG, INT	Yes	2	3	CR
38	F	DLBCL	IV	No	R-CHOP21 × 3 + R × 3	None	–	GG	No	6	15	CR
63	F	DLBCL	IV	Yes	R-CHOP21 × 6	None	–	GG	No	4	17	CR
62	M	DLBCL	IIE	No	R-CHOP14 × 6	Cough and dyspnea	CS & aerovent inhalations	GG	Yes	3	14	CR
80	F	SLL		Yes	RCOP × 6	None	–	GG, INT	Yes	3	28	CR

FDG = fluorodeoxyglucose, DLBCL = diffuse large B cell lymphoma, FL = follicular lymphoma, MALT = mucosa-associated lymphoma, SLL = small lymphocytic lymphoma, GG = ground glass, INT = interstitial, ALV = alveolar, R = rituximab, CS = corticosteroids, BAL = bronchoalveolar lavage, CR = complete remission, R-CHOP = treatment consisting of a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

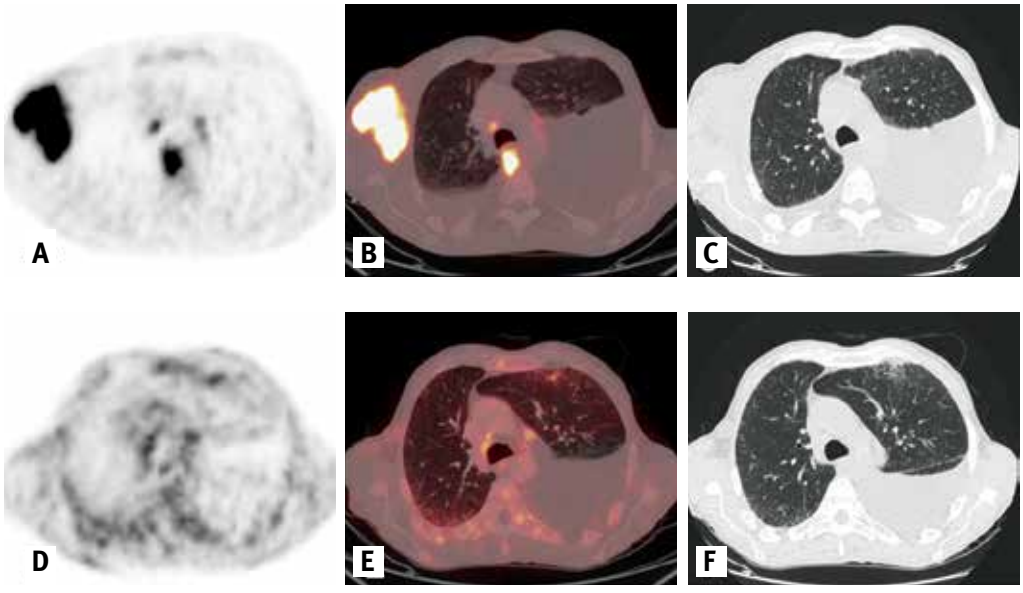

Figure 1. Therapy-associated pulmonary infiltrates in a patient with stage IV DLBCL treated with R-CHOP-21.

Upper panel: at diagnosis, showing intense increased ^{18}F-FDG uptake in lymphadenopathy in right axilla and mediastinum, large left pleural effusion: [**A**] PET, [**B**] Fusion PET/CT, **[C]** CT

Lower panel: after four cycles of R-CHOP-21 treatment. Lymphadenopathy resolved, but new pulmonary interstitial infiltrations occurred in the left upper lobe and right lower lobe, with increased uptake of FDG. [**D**] PET, [**E**] Fusion PET/CT, **[F]** CT

DLBCL = diffuse large B cell lymphoma; R-CHOP-21 = treatment consisting of a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone for 21 days; PET/CT = positron emission tomography/computed tomography; FDG = fluorodeoxyglucose

Table 3. Factors associated with pulmonary infiltrates, univariate analysis

	All (n=80) n	PIs (n=17) n	Frequency	*P* value*
Age				
< 69	40	10	25%	0.4
≥ 69	40	7	18%	
Gender				
Female	37	11	30%	0.09
Male	43	6	14%	
Lymphoma thoracic involvement				
Yes	38	11	29%	0.11
No	42	6	14%	
Lymphoma category				
Aggressive	50	14	28%	0.06
Indolent	30	3	10%	
Lymphoma stage				
I / II	22	1	5%	0.03**
III / IV	58	16	28%	
Elevated LDH				
No	42	8	19%	0.6
Yes	37	9	24%	
Immunochemotherapy				
R-CHOP-21	50	8	16%	0.07
R-CHOP-14	23	8	35%	

*χ^2 test

**Fisher's exact test

PIs = pulmonary infiltrates, LDH = lactate dehydrogenase, R-CHOP = treatment consisting of a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

DISCUSSION

This study evaluated pulmonary infiltrates in 80 consecutive NHL patients who had received combined rituximab/chemotherapy regimens at our institution. We found that 21% of the patients developed new or worsening PIs after initiation of therapy, with more than half being positive for ^{18}F-FDG uptake. The majority of cases (59%) were asymptomatic and transient, and most (76%) were detected before completion of therapy.

Several case series and small studies have addressed the issue of late pulmonary toxicity associated with chemotherapy containing rituximab in NHL patients, based on ^{18}F-FDG PET/CT scans. Nieuwenhuizen et al. [20] described four NHL patients with dyspnea related to chemotherapy with rituximab where the ^{18}F-FDG PET scan proved to be of diagnostic value. Biehn and colleagues [7] described three cases of rituximab-associated bronchiolitis obliterans organizing pneumonia (BOOP) positive for ^{18}F-FDG uptake on PET scans. Kalkanis and team [19] retrospectively reviewed clinical data and serial imaging studies of five patients with NHL treated with chemotherapy containing rituximab who developed new pulmonary abnormalities on routine follow-up ^{18}F-FDG PET/CT imaging without any accompanying symptoms and without evidence of pulmonary lymphoma or other pulmonary disease. Liu and co-authors [11] reported that 8% of their 107 patients with NHL coverage who received regimens containing rituximab developed all grades of interstitial pneumonitis manifested on CT scans.

We attempted to identify factors associated with therapy-associated PIs based on univariate analysis. Multivariate analysis was not carried out due to the limited sample size and event rate. A higher incidence of PIs was associated with lymphoma involving the thoracic cavity, with aggressive lymphoma, with female gender, and with R-CHOP-14 treatment. Huang et al. [21] published a retrospective study of DLBCL patients treated with rituximab who developed interstitial pneumonia in 4.9% of cases, predominantly males (80.8%), after a median of four cycles of immunochemotherapy. They found that low absolute lymphocyte count at diagnosis and combination with chemotherapy were independent risk factors for rituximab-associated interstitial lung disease (R-ILD). In a systematic review, Hadjinicolaou et al. [22] described 121 cases of suspected R-ILD occurring most commonly in the fifth and sixth decade of life, after a mean and median of four cycles of rituximab, similar to our findings and to those of Huang [21]. Contrary to our findings, they showed male predominance (56.5%), with only 20.7% of cases being asymptomatic at the time of diagnosis (as compared to 59% in our cohort). However, in accordance with our findings, DLBCL was the most common indication for rituximab treatment. These findings are intriguing considering the potential mechanism of rituximab lung toxicity [1].

One hypothesis for the pathogenesis of this toxicity suggests that rituximab, by attacking CD20-positive cells, induces B cell apoptosis. This in turn induces an inflammatory response in the lungs causing vascular and alveolar damage. This ongoing process may account for the latency between therapy and development of lung toxicity [23,24]. Perhaps this mechanism might contribute to the increased incidence of PIs in patients with lymphoma involving the thoracic cavity found in our cohort. Similarly, increased dose intensity in the R-CHOP-14 regimen compared to the R-CHOP-21 regimen may also augment the inflammatory response in the lungs. Use of hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) routinely used with R-CHOP-14, may further contribute to the inflammatory reaction.

Several limitations of this study merit consideration. This is a single-institution study based on a historical cohort of limited size. The timing for conducting the PET/CT scans was generally consistent with the practice patterns in our institution (pre-treatment staging, during therapy after 2–4 cycles, 4–6 weeks after completion of therapy, and 3 and 6 months post-treatment). On average only three scans were available per patient in our cohort. However, there was some variability between patients in the timing of PET/CT scans and in the length of follow-up. Inter- and intra-rater variability in radiologic assessment is also of concern. In some patients, baseline scan was a CT rather than a PET/CT, which could further contribute to variability. Since evaluation of pulmonary infiltrates in the immunocompromised

host can be challenging, with as many as 15% of cases undiagnosed on tissue biopsy [25], a notable drawback of our study is the fact that most patients did not undergo bronchoalveolar lavage or lung biopsy. Therefore, alternative etiologies for PIs such as infection or persistent lymphoma were not ruled out definitively. Nevertheless, no evidence of malignancy or infection appeared during several months of clinical follow-up which was available for most cases [Table 2]. Additional unaccounted factors may have contributed as well. Because all patients received rituximab in combination with chemotherapy, we could not separate between their relative contributions and the development of PIs. Similarly, the relative contribution of hematopoietic growth factors could not be established. Furthermore, some of the factors statistically associated with the development of PIs are not independent. Thus, disease stage and dosing regimen are related since R-CHOP-14 was given only to patients with aggressive and advanced disease, that is, a dose-dense regimen with growth factors. It is noteworthy that infiltrates were detected in 36% of the patients' pre-therapy chest scans. This finding may be related to increased sensitivity for documentation of lung findings in this study. Finally, whether cases of asymptomatic PIs and cases of overt pneumonitis share a similar pathogenesis with different manifestations, or whether asymptomatic PIs precede symptomatic pneumonitis remains to be elucidated.

CONCLUSIONS

To the best of our knowledge, this is the largest cohort study to date evaluating late pulmonary toxicity associated with rituximab-containing chemotherapy in NHL patients based on PET/CT scans, and the first to evaluate factors related to this relatively frequent phenomenon. PIs were more common in patients with lymphoma involving the thorax, in those receiving R-CHOP-14, and in those with advanced stage and aggressive lymphoma. In recent years, with the broadening routine use of PET/CT for response evaluation, dilemmas arising from the use of this modality are encountered by many practitioners. While the clinical implications and natural history of this phenomenon have not been elucidated, clinicians should be aware of its likelihood and consider it in their differential diagnosis along with infectious etiologies or disease progression. Further prospective studies are needed to establish the role of rituximab in the development of these findings, to compare between symptomatic and asymptomatic cases, and to define independent risk factors.

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