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Original Article

Computed tomography patterns of pulmonary and pleural involvement in lymphoma

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ABSTRACT

Background: Pulmonary and pleural involvement is fairly common in patients with lymphoma, especially in the setting of progressive or recurrent disease. Pleuropulmonary involvement in lymphoma may occur as a single pattern or as a combination of multiple patterns which can often mimic unrelated pathologies.

Methods: Review of our institutional database from 01 Jan 2015 to 04 Oct 2017 revealed 90 patients with pulmonary and/or pleural lesions attributable to lymphoma. These lesions were classified into various categories, and the pattern of involvement was evaluated.

Results: Pulmonary involvement was seen in 17.6% of patients with Hodgkin lymphoma (HL) and in 10.5% of patients with non-Hodgkin lymphoma (NHL), whereas pleural involvement was seen in 6.5% of patients with NHL. Almost all the patients in our study had findings belonging to multiple categories. Pulmonary involvement in patients with HL was seen in the form of nodules (51.6%), masses (51.6%), and direct extension from a mediastinal/hilar mass (45.2%). Patients with NHL had pulmonary involvement in the form of nodules (42.4%), direct extension from a mediastinal/hilar mass (25.4%), pulmonary masses (18.6%), and interstitial pattern (2.4%). Pleural thickening (61.5%), masses (30.8%), and effusion (15.4%) were the three patterns of pleural involvement.

Conclusion: Nodules and masses were the two commonest patterns of pulmonary involvement in patients with HL, whereas nodules were the commonest pattern noted in patients with NHL. Pulmonary masses were seen more commonly in patients with HL than in those with NHL. Pleural involvement was seen exclusively in patients with NHL.

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Introduction

Lymphomas are broadly classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) and have a worldwide incidence of 0.5% and 4.3%, respectively.^{1,2} A distinct increase in the incidence of HL and NHL has been noted over the past several years which has majorly contributed to a rise in the incidence of extranodal lymphomas.^{3–5} Marked improvement in treatment protocols over the years has also contributed to an overall increase in the disease prevalence. Lungs are not an uncommon site for lymphomas, with the secondary pulmonary lymphoma being more frequent than the primary pulmonary lymphoma.^{6–9} Pulmonary involvement is relatively more common in patients with HL; however, the significantly greater incidence of NHL translates to more cases of secondary pulmonary lymphoma being encountered with this entity.¹⁰ The computed tomography (CT) appearance of pulmonary lymphoma is diverse and may present as direct extension from nodal disease, nodules, or consolidation with air bronchogram.¹¹ Pleural effusions can be frequently seen but have doubtful prognostic significance unless associated with a pleural mass.^{6,12–14} Although pleuropulmonary involvement in lymphoma rarely causes distressing symptoms in a patient, it contributes significantly to staging of the disease and planning of an appropriate treatment.

Several studies have helped Fluorodeoxyglucose Positron Emission Tomography (FDG PET-CT) establish its role as the standard imaging modality for lymphoma with a major role to play in not only the initial staging of the disease but also the assessment of response to the treatment and in subsequent follow-up.^{15–25} In current clinical practice, patients with secondary pulmonary lymphoma are required to be subjected to tissue diagnosis from the lung lesions only if their FDG PET-CT study raises doubts of a lung pathology other than lymphoma.

To the best of our knowledge, no study based on PET-CT has been conducted till date for describing/categorizing CT patterns of pleuropulmonary lymphoma. Our primary objective of undertaking this study was therefore to evaluate the CT appearances of pulmonary and pleural involvement in lymphoma.

Material and methods

Study population and study group

This was a retrospective cohort study and was conducted at a tertiary care oncological referral hospital in New Delhi, India. The institutional review board (IRB) waiver was obtained to review the medical records and FDG PET-CT images of all patients with lymphoma who reported to this hospital between 01 Jan 2015 and 04 Oct 2017. The diagnosis of lymphoma in these patients had been established based on histopathological examination (HPE). The medical records of a total of 1055 patients were reviewed; however because the PET-CT images of 479 patients were not available for review, they had to be excluded from the study. A note was made of pulmonary and pleural findings in the remaining 576 patients—seen either at the initial PET-CT study or at a subsequent

scan performed for response assessment or as part of routine follow-up. A total of 146 patients with pulmonary and/or pleural findings were identified among these 576 patients. The inclusion and exclusion criteria given in the following were then applied, and a final study group of 90 patients was achieved.

There were 31 patients with HL and 59 patients with NHL in the final study group although within the pediatric subset of nine patients, seven had HL, and two had NHL. Tissue diagnosis from the pulmonary or pleural lesions was available in a total of 25 patients. Five patients with HL and 14 patients with NHL underwent a core biopsy from their pulmonary lesions, and two patients with NHL underwent a pleural biopsy. Pleural fluid cytology provided the supporting tissue diagnosis in four patients with NHL.

There were 392 (68.1%) male and 184 (31.9%) female patients among the 576 patients with lymphoma, whereas only 57 (63.3%) male and 33 (36.7%) female patients comprised the final study group of 90 patients who had pulmonary and/or pleural findings attributable to lymphoma. The age range in the study group was 8–85 years with nine pediatric patients (age < 18 years) and 81 adult patients. The mean age $\pm$ standard deviation (SD; in years) of adult patients with HL and NHL was 30.2 ± 10.5 and 51.3 ± 16.8 , respectively, whereas the mean age $\pm$ SD (in years) of pediatric patients with HL and NHL was 15.6 ± 0.9 and 10.0 ± 2.8 , respectively (Table 1).

PET-CT protocol

The scanning was performed using a combined PET-CT scanner (Siemens Biograph 40). After standard PET preparation and patient counseling, 6–10 mCi (296–370 MBq) of FDG was administered intravenously, and scanning was performed after 60–70 min. The scan area extended from the skull base to mid-thigh level. The CT scan was performed for attenuation correction and localization with a 5 mm slice thickness and 5 mm table feed. PET images were then acquired in 5–7 bed positions with time to record input set at 2 min per bed position. CT images were reconstructed at 3 mm in the mediastinal and lung window for evaluation of pleural and pulmonary parenchymal lesions, respectively.

The PET-CT images were reviewed independently by a radiologist and a nuclear medicine physician, and all relevant findings were noted. Any discrepancy in interpretation was resolved by discussion between the two.

Inclusion criteria

Pulmonary disease

All patients with an HPE of extrathoracic lymphoma who underwent a FDG PET-CT study and were found to have pulmonary pathology attributable to lymphoma based on the FDG uptake pattern and/or those patients with lymphoma in whom the HPE of the pulmonary lesions also proved to be lymphoma were included in the study.

Pleural disease

All patients with pleural thickening or pleural deposits which showed uptake on FDG PET-CT commensurate with

Table 1 – Mean age (in years) $\pm$ SD and gender distribution in the study group.

Age category	HL (n = 31)	NHL (n = 59)	P-value
All patients	26.9 $\pm$ 11.1 (years $\pm$ SD)	49.9 $\pm$ 18.2 (years $\pm$ SD)	<0.0001
Age < 18 yrs	15.6 $\pm$ 0.9 (years $\pm$ SD)	10.0 $\pm$ 2.8 (years $\pm$ SD)	0.004
Age $\geq$ 18 yrs	30.2 $\pm$ 10.5 (years $\pm$ SD)	51.3 $\pm$ 16.8 (years $\pm$ SD)	

HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; SD, standard deviation.

Bold value indicates p value <0.05 is considered statistically significant.

involvement in lymphoma, and/or those patients with HPE diagnosis of lymphoma from the pleural lesions were included in the study. Patients with pleural effusion which demonstrated atypical lymphoid cells on pleural fluid cytology were also included in the study.

Exclusion criteria

Pulmonary disease

All patients in whom the pulmonary lesions did not show FDG tracer uptake/pattern of involvement commensurate with the primary pathology of lymphoma were excluded from the study.

Pleural disease

Patients with pleural effusion who did not have a supporting pleural fluid cytology and patients with pleural thickening which did not show appropriate uptake on PET-CT were excluded from the study.

Definitions

For the purpose of categorization of findings in the study, the lesions were defined as follows. Pulmonary nodule was defined as a three-dimensional, soft-tissue density, pulmonary parenchymal lesion measuring <3 cm in the largest dimension. Pulmonary mass was defined as a three-dimensional, soft-tissue density, pulmonary parenchymal lesion measuring $\geq$ 3 cm in the largest dimension. Direct infiltration from mediastinal/hilar disease was defined as mediastinal/hilar pathology forming an irregular/lobulated contour with adjacent lung parenchyma which was not attributable to any normal structure in that location. Interstitial pattern was defined as the pattern of involvement corresponding to the anatomy of the pulmonary interstitium. Pleural effusion was defined as the fluid in pleural space as noted in a typical CT appearance. Pleural thickening was defined as diffuse circumferential thickening of pleura showing uptake on FDG PET-CT. Pleural deposit/mass was defined as focal thickening of pleura showing uptake on FDG PET-CT.

Statistical analysis

The summary of all categorical variables is presented in frequencies and percentages, whereas the summary of continuous variables such as age is presented in mean $\pm$ SD. A chi-square test is used to see the association between categorical variables. A two-sample independent t-test was used to find the significant difference for continuous outcomes. The reported p-values are two-sided, and a p value <0.05 is considered as statistically significant. All analyses were performed

using the statistical package for social sciences (SPSS) software, version 23.0.

Results

Among a total of 576 patients with lymphoma whose medical records and FDG PET-CT images were available for review, 176 (30.6%) patients had HL, whereas 400 (69.4%) patients had NHL. The study group of 90 patients which was achieved by applying the inclusion and exclusion criteria to the 146 patients with lymphoma with pulmonary and/or pleural findings had 31 (34.4%) patients with HL and 59 (65.6%) patients with NHL. Pulmonary involvement was seen in 31 (17.6%) of the 176 patients with HL (Fig. 1) and in 42 (10.5%) of the 400 patients with NHL. Pleural involvement was seen in 26 (6.5%) of the 400 patients with NHL, whereas none of the patients with HL had any pleural involvement. Among the 59 patients with NHL, nine (15.3%) patients had both pleural and pulmonary involvement, 33 (55.9%) patients had only pulmonary involvement, and 17 (28.8%) patients had only pleural involvement (Fig. 2).

An overwhelming proportion of patients in the study group (89 of the total 90) had pulmonary and pleural findings belonging to multiple categories with 56 patients having findings from two categories, 23 patients having findings from three categories, nine patients having findings from four categories, and one patient having findings from five categories of the described lesions.

HODGKIN LYMPHOMA (N=176)

Fig. 1 – Incidence of pulmonary findings in Hodgkin lymphoma (HL).

Among the 73 patients (HL + NHL) with pulmonary involvement, 41 (56.2%) patients had nodules, 29 (39.7%) patients had lung involvement secondary to direct extension from mediastinal/hilar mass, 27 (36.9%) patients had pulmonary parenchymal masses, and one patient (1.4%) showed an interstitial pattern of pulmonary parenchymal involvement. Nodules and masses were found with equal frequencies in the patients with HL—seen in 16 patients each (51.6%), whereas direct extension into lung parenchyma from a mediastinal/hilar mass was found in 14 (45.2%) patients (Fig. 3). Unilateral pulmonary involvement was seen in 17 (54.8%) patients with HL, whereas 14 (45.2%) patients with HL had bilateral pulmonary involvement. Nodules were also the commonest finding in the NHL group and were seen in 25 (42.4%) patients, whereas the next commonest finding was of direct extension into lung parenchyma from a mediastinal/hilar mass which was seen in 15 (25.4%) patients (Figs. 3–5). Pulmonary masses were seen in 11 (18.6%) patients with NHL, whereas the interstitial pattern was the least common finding and was found in only one patient (Fig. 6). Unilateral pulmonary involvement was seen in 23 (54.8%) patients with NHL, and bilateral pulmonary involvement was seen in 19 (45.2%) patients with NHL; this proportion of unilateral and bilateral involvement was quite similar to that seen in patients with HL. Cavitation in nodules/masses was seen in only five patients in our study—three patients with HL and two patients with NHL.

Pleural involvement was seen only in patients with NHL. Pleural thickening was the commonest pattern of pleural involvement and was seen in 16 (61.5%) patients, whereas pleural deposit/mass was seen in eight (30.8%) patients (Fig. 7). Pleural effusion was the least common pattern of pleural involvement and was seen in only four (15.4%) patients (Fig. 3). Unilateral pleural involvement was seen in 19 (73.1%) patients, whereas seven (26.9%) patients had bilateral pleural involvement.

NON-HODGKIN LYMPHOMA (N=400)

Fig. 2 – Incidence of pulmonary and pleural findings in non-Hodgkin lymphoma (NHL).

In the pediatric subset of nine patients, nodules were the commonest pattern and were found in seven patients (six with HL and one with NHL), whereas masses were found in five patients (all with HL). None of the pediatric patients showed direct extension of disease from mediastinal/hilar lesions. Pleural involvement was seen in one patient with NHL and was in the form of effusion.

Apart from the 90 patients who formed the study group, data analysis revealed a separate set of 27 patients in whom the only finding was pleural effusion. This pleural effusion was noted to have resolved in the posttherapy follow-up scans; however, no supporting pleural fluid cytology was available in these cases. Fourteen patients in the study group also had pleural effusions apart from their other pulmonary and/or pleural findings which resolved on institution of appropriate therapy. These pleural effusions could possibly represent a consequence of the disease secondary to lymphatic blockade and were probably not due to direct pleural involvement in the disease per se.

Discussion

The primary aim of this study was to evaluate the pattern of pulmonary and pleural involvement in patients with lymphoma on CT. All patients in our study were cases of secondary lymphoma as none of them fulfilled the defining criteria of primary pulmonary lymphoma. Pulmonary involvement in our study population was commoner in patients with HL (17.6%) than in those with NHL (10.5%), and this was found to be higher than in previously reported studies.^{26,27} Our study group had more patients with NHL ($n = 42$) with pulmonary lesions than patients with HL ($n = 31$) because the incidence of NHL in the study population was nearly 3.25 times higher than that of HL. Pleural involvement was seen only in 26 of the 400 patients with NHL reviewed for the study with isolated pleural involvement seen in 17 patients and combined pleuropulmonary involvement seen in nine patients. Most patients in our study had findings belonging to multiple categories with pulmonary nodules being the commonest pattern among the combined HL + NHL group as well as in the NHL group. Nodules and masses were the commonest pattern in the HL group and occurred with equal frequencies. On the other hand, only a quarter of the patients in the NHL group had the finding of pulmonary masses. Thus, a pulmonary mass was more commonly associated with HL than with NHL, and this observation was found to be statistically significant (Table 2). Unilateral pulmonary involvement was slightly more common than bilateral involvement in patients with NHL and HL. Pleural involvement was seen only in patients with NHL, with pleural thickening being the commonest pattern, followed by pleural deposit/mass, and pleural effusion was the least common. The findings of pleural thickening and pleural deposit/mass in patients with NHL vis-à-vis patients with HL were found to be statistically significant with p -values of 0.0001 and 0.00988, respectively (Table 3). Unilateral pleural involvement was almost thrice as common as bilateral involvement and was seen in 73.1% of the patients. The pediatric patients also exhibited multiplicity of findings, with nodules being the

Fig. 3 – Categories of pulmonary and pleural involvement in patients with lymphoma. HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

Fig. 4 – Case 89: Fused PET-CT image showing multiple nodules in both lungs with a mass in the inferior lingular segment.

Fig. 6 – Case 49: Fused PET-CT image depicting the interstitial pattern of parenchymal involvement in both lungs.

Fig. 5 – Case 46: Anterior mediastinal mass is seen infiltrating into the right middle lobe on this fused PET-CT image.

Fig. 7 – Case 66: Pleural thickening seen on the left side on the fused PET-CT image.

Table 2 – Pulmonary findings in the study group.

Category of pulmonary finding	HL (n = 31)	NHL (n = 42)	P-value
Nodules	16 (51.6%)	25 (59.5%)	0.50286
Masses	16 (51.6%)	11 (26.2%)	0.02642
Direct extension	14 (45.2%)	15 (35.7%)	0.41222
Interstitial pattern	0 (0%)	1 (2.4%)	0.3843

HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.
Bold value indicates p value <0.05 is considered statistically significant.

Table 3 – Pleural findings in the study group.

Category of pleural findings	HL (n = 0)	NHL (n = 26)	P-value
Pleural effusion	0 (0%)	4 (15.4%)	0.07672
Pleural thickening	0 (0%)	16 (61.5%)	0.0001
Pleural deposit/mass	0 (0%)	8 (30.8%)	0.00988

HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.
Bold value indicates p value <0.05 is considered statistically significant.

commonest pattern followed by pulmonary masses; lung involvement by direct extension from mediastinal/hilar mass and the interstitial pattern of pulmonary involvement were not found in this age group in our study. Pleural involvement was seen in only one pediatric patient with NHL and was in the form of an effusion.

Lewis et al⁷ in their retrospective study of 31 patients had found mass or mass-like consolidation to be the commonest pattern which was seen in 21 of the 31 (68%) patients and nodules in 19 of the 31 (61%) patients to be the second commonest finding; 94% of the patients had nodules and/or masses among their pulmonary findings. Multiplicity was also noted in their study with 21 of the 31 (68%) patients exhibiting abnormalities in three or more of the seven categories. Mass/mass-like consolidation was the commonest pattern in patients with HD (80%), and peribronchial/perivascular thickening was the commonest pattern in patients with NHL (69%). There were 10 of 31 patients in the category of masses of pleural origin, and 13 of 31 patients had pleural effusions with nearly equal distribution in HD and NHL. In our study, we found nodules to be commoner than masses which could possibly be due to the different size criteria for nodules used in our study—<3 cm vs <1 cm. Pleural involvement in the form of a mass/deposit, effusion, or thickening was also seen with lesser frequencies in our study which could be due to the inclusion/exclusion criteria used in our study requiring FDG uptake on PET-CT or an HPE/cytological support.

In a retrospective study of 161 pediatric patients with lymphoma, Maturen et al²⁸ identified 21 patients (10 HD + 7 NHL + 4 posttransplant lymphoproliferative disorder) with pulmonary parenchymal involvement. They found nodules (<1 cm) in 19 of the 21 (90%) cases, masses in 8 of the 21 (38%) cases, and interstitial-alveolar opacities in 4 of the 21 (19%) cases. Pleural masses and pleural effusions were seen in 2 of the 21 (9%) cases each. Our study included a smaller number of pediatric patients, and we used different size criteria for

defining a lesion as a nodule which could possibly account for some of the observed differences. However, we also found nodules to be the commonest pattern followed by masses, whereas no interstitial pattern or lung involvement by direct extension was observed in our study. Pleural effusion was seen in one patient with NHL, and no thickening/mass/deposit was noted in any patient in the pediatric age group.

Shuman et al¹⁴ in their study of 71 (47 HD + 24 NHL) patients with lymphoma found solid pleural manifestations in the form of nodules and plaques in 22 of the 71 patients—14 of the 47 (30%) patients with HD + 8 of the 24 (33%) patients with NHL. In our study, we found no pleural involvement in any of the patients with HL, whereas only 6.5% of the patients with NHL in the study population demonstrated pleural involvement; pleural thickening was the commonest pattern followed by pleural deposit/mass, and pleural effusion was the least common. These differences could be explained by the different inclusion/exclusion criteria used in our study.

Our study has revealed that nodules are the commonest pattern of pulmonary involvement in NHL, whereas nodules and masses occur with equal frequencies in HL. We also found that pulmonary masses were seen more commonly in association with HL than with NHL. Pleural involvement was found to be less common than pulmonary involvement in our study population of patients with lymphoma and also was seen only in patients with NHL.

This study has been conducted at a specialized tertiary care oncology referral hospital with a disproportionate number of patients with advanced or recurrent disease which could have possibly affected our study results. In addition, because our study is largely based on FDG uptake by lesions on PET-CT, which itself is plagued by certain inherent limitations, very small lesions, especially those which are not FDG-avid and patients with very minimal interstitial involvement could possibly have been excluded from the study group. The retrospective nature of the study and lack of tissue diagnosis from the pulmonary or pleural lesion in all cases have also contributed to limiting our study. Prospective studies on this subject using a larger study population are, however, required to further substantiate these findings.

Conflicts of interest

The authors have none to declare.

IRB statement

This is a retrospective descriptive study for which an IRB waiver was obtained before undertaking the study.

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