

# HRCT LUNG FINDINGS IN POST CHEMOTHERAPY PATIENTS - EMERGING CHALLENGE FOR RADIOLOGISTS

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Date Received:  
November 04, 2014  
Date Revised:  
November 12, 2015  
Date Accepted:  
December 14, 2015

## ABSTRACT

**Objective:** To characterize, diagnose and to differentiate various HRCT manifestations of lung abnormalities in post chemotherapy patients.

**Methodology:** This was a retrospective study of 50 patients conducted at Radiology department of Rehman Medical Institute, Peshawar. Duration of study was 6 months i.e from April 2013 to September 2013. Patients were investigated using 128-slice Multidetector Computed tomography (MDCT) scanner in the Radiology department of Rehman Medical Institute Peshawar. 0.5mm reconstructed images in lung window and 3mm images in mediastinal window were viewed on workstation in axial, coronal and sagittal planes. The data was processed using Microsoft excel 2007.

**Results:** A total of 50 patients were included. Age of the patients ranged from 6 to 70 years with a mean age of 35 years. In our study, we found five radiologic patterns on CT scan; (1) non-specific ground-glass attenuation 17(34%), (2) patchy distribution of ground-glass attenuation accompanied by interlobular septal thickening 7(14%), (3) multifocal areas of airspace consolidation 7(14%), (4) extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis 4(8%), and (5) nodules of variable sizes randomly distributed in both lungs 15(30%).

**Conclusion:** The most common pattern was found to be patchy areas of ground-glass attenuation. Pulmonary diseases that are induced by chemotherapy represent particular challenges for radiologists due to non-specific and atypical imaging features.

**Key Words:** Post chemotherapy lungs, High resolution computed tomography (HRCT), Multidetector computed tomography (MDCT)

This article may be cited as: Umer US, Alam S, Ghuas S, Gul S, Arif QA. HRCT lung findings in post chemotherapy patients - Emerging challenge for radiologists. *J Postgrad Med Inst* 2015; 29(4): 243-51.

## INTRODUCTION

Pulmonary diseases due to drug toxicity are common but probably not detected and reported frequently<sup>1</sup>. Thus, the true incidence of drug-induced respiratory disease is unknown, although it is estimated to be less than 10%<sup>2</sup>.

Chemo-therapeutic agents besides other drugs might be responsible for adversely affecting the lungs<sup>3-6</sup>. As their use is on the rise, physicians as well as radiologists will be facing a huge challenge. Symptoms are usually non-specific. Patients may present with shortness of breath, fever and cough which can appear even after a significant period of time has been lapsed after taking the drug. A low threshold for its diagnosis should be kept as it can mimic infection and underlying lung disease.

The most frequent radiologic features associated with chemotherapy are pulmonary infiltrates. However, in early stages, it can be asymptomatic. The ground-

glass infiltrates should not be ignored or misinterpreted as tumor progression<sup>7</sup>. Chemotherapy associated pulmonary infiltrates may develop due to a variety of reasons. Infection, inflammation, cardiogenic and non-cardiogenic interstitial edema are considered to be significant. Knowledge regarding chemotherapy agents which are mainly responsible for pulmonary toxicity may be helpful in assessing the most likely cause. Some of the older chemotherapy agents (bleomycin and carmustine) can lead to dose dependent pulmonary toxicity. Others (cyclophosphamide, busulfan, and carmustine) can cause it even years after completion of therapy<sup>8</sup>.

Standard plain chest radiograph is initially considered for assessing drug associated pulmonary toxicity in most of the patients. However, other imaging techniques are required due to the limitations of the pattern approach on chest radiography.

High-resolution computed tomography (HRCT) can

aid in early detection of lung toxicity, when it is still reversible. It can also help in differentiating drug toxicity from other lung pathology<sup>9</sup>. In symptomatic patients with normal or less distinct findings on chest radiography, HRCT can playkeyrole in the delineation of parenchymal abnormalities<sup>10,11</sup>.

## METHODOLOGY

This was a retrospective study of 50 patients conducted at Radiology department of Rehman Medical Institute, Peshawar. Duration of study was 6months i.e from April 2013 to September 2013. Approval from Rehman medical research committee of ethics and research was taken. Enrollment of OPD and indoor post chemotherapy patients coming for HRCT chest with age range of 6- 70 years (Mean age: 35 yrs) was done. Informed consent was undertaken from the patient. Nature and duration of the procedure, benefits and involved documented risks of the intravenous contrast were narrated in an easy /native language to the patients. HRCT chest was performed on a 128 slice Toshiba MDCT scanner (CT techniques: 128 slicer CT scanner, Toshiba Aquilion, Tokyo, 120kvp / 300mA, 150mAs, 500msec, 0.5mm thickness). Additional complimentary prone scanning was done when indicated.All 50 patients which were in-

cluded in the study were proven cases of malignancy on the basis of Biopsy and on chemotherapeutic treatment cycles. All data was entered and analyzed using SPSS version 10.0 and processed using Microsoft excel 2007.

Retrospective review of HRCT scans on vitrea workstation was done by four qualified radiologists for presence or absence of ground glass haze, airspace consolidation, reticulation and honeycombing, extent and zonal distribution of HRCT findings, severity of bronchiolectasis / bronchiectasis, architectural distortion or ancillary findings such as lymphadenopathy and associated pleural or cardiac changes.

## RESULTS

A total of 50 patients were included. Age of the patients ranged from 6 to 70 years with a mean age of 35 years. In our study, we found five radiologic patterns on CT scan. Their relative frequencies are shown in (Table1.)

Findings suggesting classical Tuberculosis(TB) were seen in 5 patients, out of which 4 had normal background whereas 1 patient had background lung changes of previous TB. Two patients had imaging features characteristic of Invasive Aspergillosis. (Table2.)

**Table 1: HRCT patterns in post chemotherapy lungs**

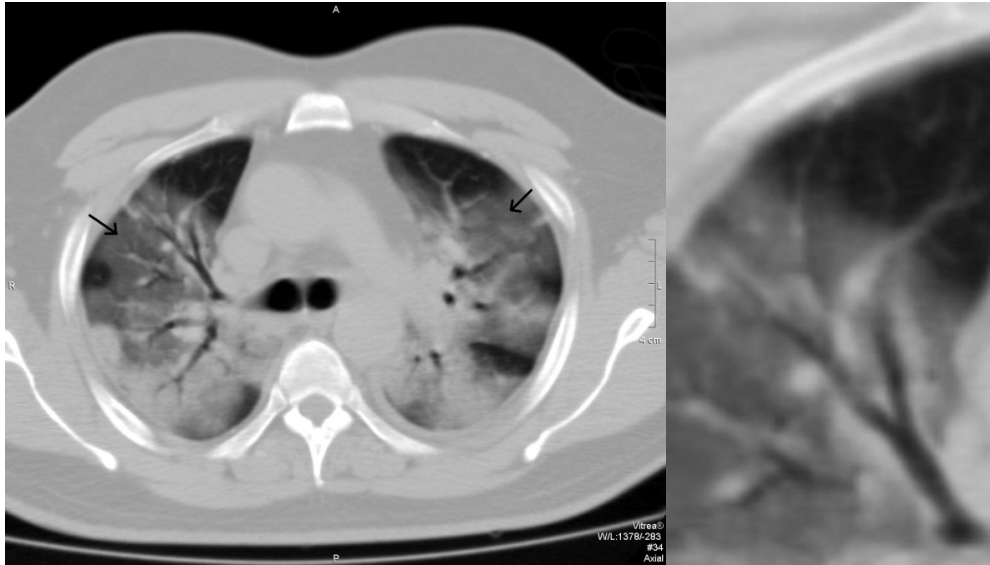
S.no	HRCT patterns	Number of patients (%)
1	Patchy ground glass haze(GGH)	17 (34%)
2	Patchy GGH with interlobular septal thickening	7(14%)
3	Multifocal areas of consolidation	7(14%)
4	Extensive bilateral GGH or consolidations with traction bronchiectasis ( like in NSIP)	4(8%)
5	Nodules of variable sizes randomly distributed in both lungs	15(30%)

**Table 2: Lung Disease patterns in post chemotherapy patients**

Disease pattern	Number of patients
Tuberculosis	5 (10%)
Invasive Aspergillosis	2 (4%)
UIP	3 (6%)
Lymphangitis	3 (6%)
Radiation Induced Fibrosis	1 (2%)
Metastatic Nodules	9 (18%)
Granulomas	6 (12%)
Nonspecific Patchy GGH only	17 (14%)
NSIP/Chemotherapy induced Toxicity	4 (8%)

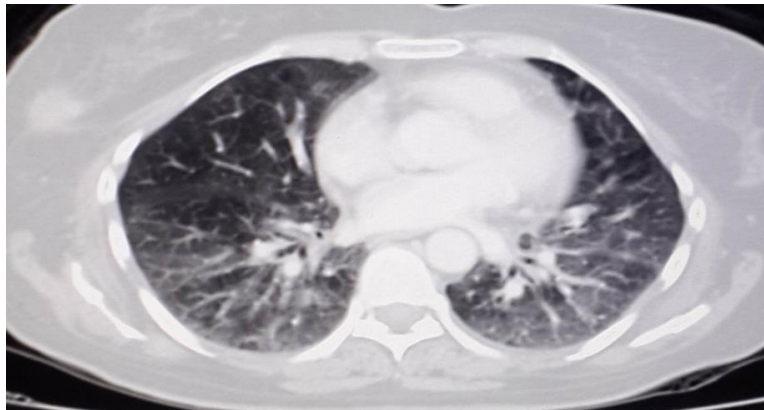
**Figure 1: (a&b) HRCT image of a 30 year old male showing bilateral patchy areas of ground glass attenuation (arrows) with visualization of underlying normal vessels and positive dark bronchus sign(fig1b)**

**1c: Drug induced toxicity in a 48 years old CA breast patient on chemotherapy. CT chest shows patchy areas of nonspecific ground glass haze. Nodular mass noted in right breast.**



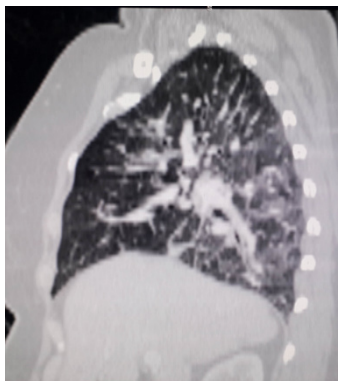
1a

1b

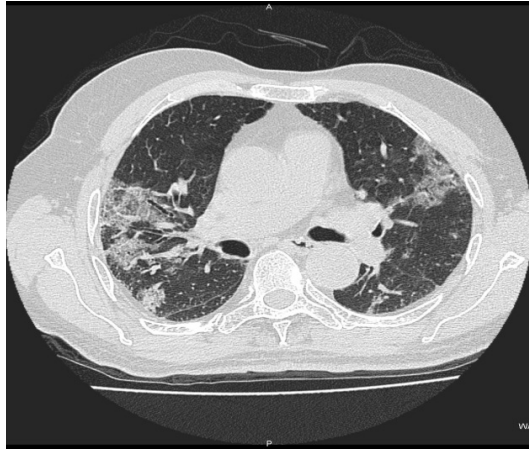


1c

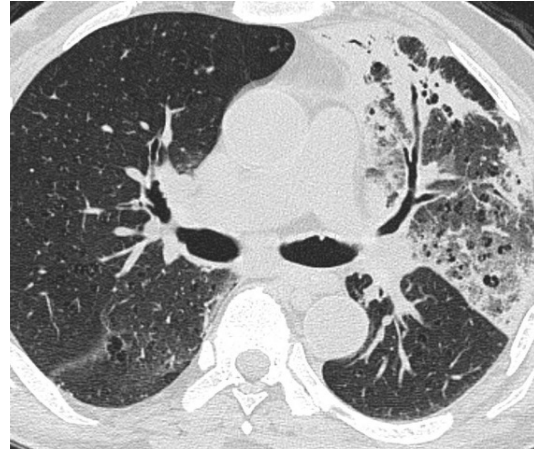
**Figure 2: CT chest sagittal image showing patchy areas of ground glass haze(GGH) more so in dependent segments of lungs, in keeping with pulmonary edema.**



**Figure 3: (3a) HRCT image showing patchy areas of ground glass haze interspersed with septal thickening (crazy-paving pattern). (3b) HRCT chest of another patient showing left upper lobe and lingular patchy ground glass haze and septal thickening. Few consolidating opacities also seen anteriorly. Tiny centrilobular bullae seen in both lungs, which are more clearly seen on left side due to background of GGH.**



3a

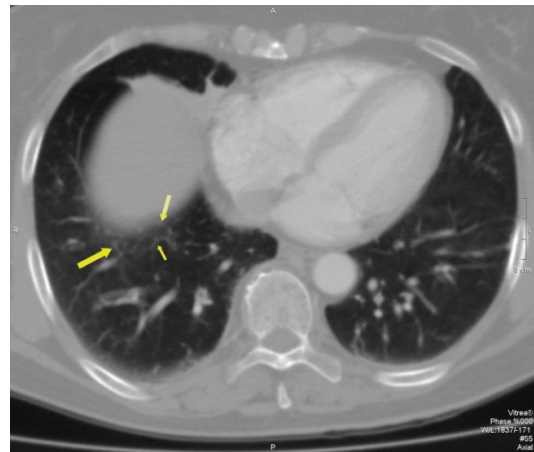


3b

**Figure 4: (4a)HRCT image of a 68 years old male showing both fine and nodular thickenings of interstitial tissue septa (arrows),in keeping with lymphangitis.(5b) HRCT image of another patient shows a small patch of septal thickening (arrows) in right lung base, highly suspicious for lymphangitic spread of disease (lymphangitis).**



4a



4b

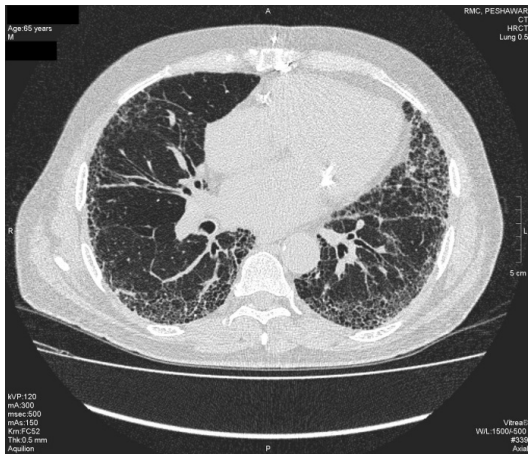
## DISCUSSION

Approximately 10% of patients receiving cytotoxic drugs develop drug-induced lung reactions<sup>12,13</sup>. Any chemotherapeutic drug can adversely affect the lung, but the most commonly implicated drugs associated with lung toxicity are bleomycin, methotrexate, carmustine, busulfan, and cyclophosphamide<sup>14-18</sup>.

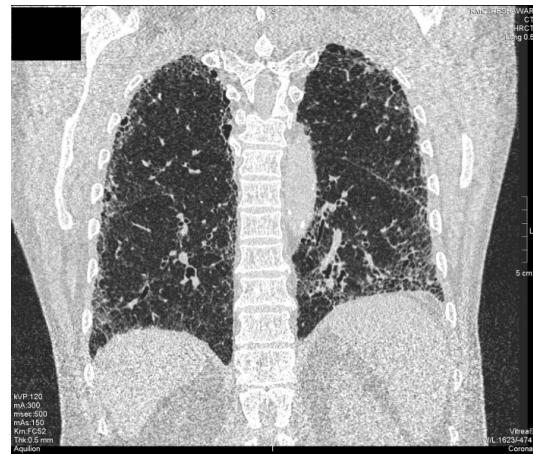
Currently,HRCT is considered the best non-invasive method to assess the presence of drug-induced lung disease. It may show abnormalities even in patients with normal radiographs<sup>19-21</sup>. An accuracy of 45% has been reported for HRCT by Cleverly et al<sup>22</sup>. Therefore, to predict the histological patterns in drug-induced lung diseases,HRCT may have limited ability<sup>22</sup>. However,HRCT is of great value in excluding alternative diagnoses and in monitoring response to treatments.



**Figure 5: HRCT chest images showing classic UIP pattern of bilateral sub-pleural areas of septal thickening, reticulations, clusters of tiny air cysts, honeycombing and tractional bronchiectasis with apicobasal predominance.**



5a

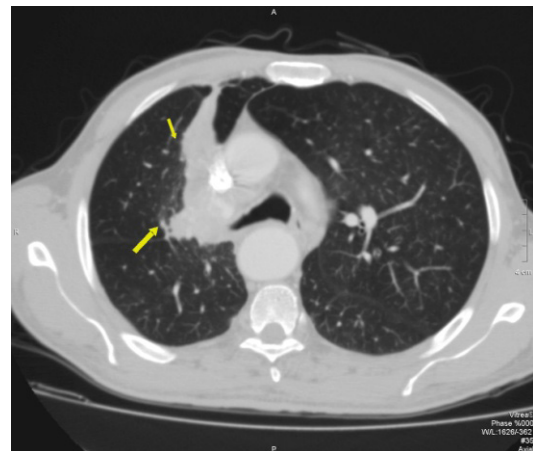


5b

**Figure 6: (a&b) CT chest of a patient with Right lung carcinoma showing a consolidation in right upper lobe. Mediastinal window reveals fluid filled bronchi in the consolidated lung. Lung window shows peri-consolidation areas of septal thickening (arrows), which are suggesting regional spread of disease. Right sided aortic arch seen with aberrant left subclavian artery.**



6a



6b

**(1) Patchy areas of ground glass haze (GGH)**

GGH is the slight increase of pulmonary attenuation, which permits seeing the underlying vessels and walls of the bronchi<sup>23</sup> (dark bronchus seen). (Figure.1) Its cause could be edema, cells like neutrophils or even early changes of fibrosis in which the underlying pulmonary alteration is below the limit of resolution of the HRCT image. Though non-spe-

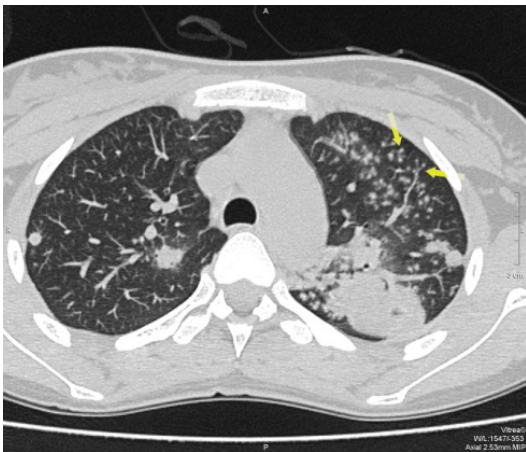
cific in itself, the sign is always very significant<sup>23</sup>. In our study patchy ground glass haze areas were divided into two groups, Patients whose GGH shifted on prone scanning were considered as dependent GGH like in pulmonary edema which is a side effect of long standing chemotherapy or illness(Figure.2). Inpatients whose GGH didn't shift with prone imaging were labelled as nonspecific GGH. These were the cases that were advised follow up HRCT.

**Figure 7a: CT chest of a 41 years old female,known case of CA stomach, showing small thick walled cavity and tree in bud branching opacities in posterior segment of right upper lobe. These findings are classical for active endobronchial Tuberculosis.**



7a

**Figure 7b: (1&2) HRCT chest axial and coronal images of another patient patient showing consolidations, multiple nodules and tree-in-bud like branching nodular opacities(arrow) in active endobronchial tuberculosis.**



7b1



7b2

**(2)Septal thickening with or without GGH.**

The combination of ground-glass opacities and thickening of interstitial septa can produce the crazy-paving pattern(Figure.3). The thickening of interstitial tissue septa could be either fine or nodular. The nodular thickening associated with GGH needs special concern to rule out lymphangitis carcinomatosa (Figure.4) and further histopathological workup should be considered. Fine septal thickening can be seen with tumour progression but it is very rare and mostly could be due to pulmonary edema or early changes of fibrosis with alveolitis .The CT findings in patients with leukemia consist mainly of ground-glass attenuation, centrilobular nodules and thickening of the bronchovascular bundles in the peripheral lung<sup>24</sup>.

In our study 02 patients showed HRCT findings of septal thickening with GGH, and for which strong concern for lymphangitis was raised. Patients with septal thickening without GGH were grouped according to the zonal predominance. Subpleural septal thickening with a predominant apicobasal gradient was labeled as usual interstitial pneumonia (UIP)(Figure.5). In our study we only had two patients with classical UIP like pattern. These were considered as incidental. There was a patient with focal patch of septal thickening in right anterior lung, which was considered as radiation induced fibrosis.

**(3)Patchy areas of consolidations**

Consolidations are areas of increased air space attenuation which obscure the underlying vascular

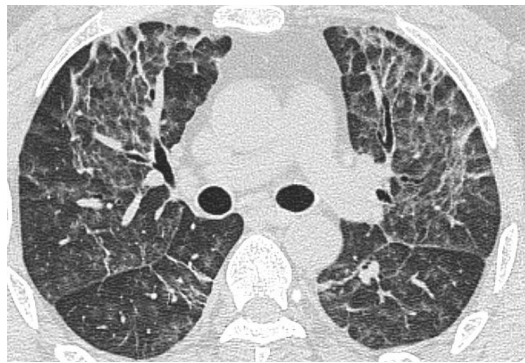
**Figure 8: (a,b&c) HRCT chest images showing imaging appearance of nonspecific interstitial pneumonia/ drug induced toxicity. Bilateral patchy areas of ground glass haze, sub pleural reticulations, septal thickening and tractional bronchiectasis seen with apicobasal predominance. Septal thickening with tractional bronchiectasis suggest early fibrotic changes, which are mostly irreversible.**



8a



8b



8c

markings<sup>23</sup> (Figure.6). These could be with or without air bronchograms. In our study, patchy consolidations were seen in 14% patients. In post chemotherapy patients, consolidating opacities in lungs could be infective in etiology i.e. with superadded infection (Bacterial, Mycobacterial – TB, Fungal), might be Lymphomatous deposits in cases of Lymphoma, Hypersensitivity pneumonitis due to drug induced hypersensitivity or of malignant etiology. In our series, consolidations were seen in lungs of 5 patients with associated branching nodular opacities and small cavities (Figure.7), which is a classical finding of pulmonary tuberculosis. In two cases, there were periconsolidation ground glass halos which strongly represented invasive aspergillosis. The other differential considered in these cases was cryptogenic organizing pneumonia (COP).

**(4) Extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis (like in NSIP):**

The chronic form of chemotherapy induced lung toxicity pattern manifests as a pulmonary fibrotic process,

often with no accompanying eosinophilia. In our series, 4 patients had classical imaging appearance of nonspecific interstitial pneumonia/Chemotherapy induced toxicity with patchy areas of extensive GGH, consolidations and septal thickening with tractional bronchiectasis with zonal apico-basal predominance (Figure 8).

**(5) Multiple nodules:**

In our study we characterized pulmonary nodules into three groups: i) Pulmonary granulomas. These are composed of macrophages reacting to various chemotherapeutic drugs, such as methotrexate and nitrofurantion. These can also be post infective or post tuberculous and not associated with chemotherapy effects. ii) Metastatic nodules: classic imaging features of metastatic nodules is a long list. Main features seen in our patients were positive feeding vessel sign, subpleural location, lobular spiculated margins and interval size and number progress. iii) Nodules with Equivocal features. These were suggested follow up. These nodules should be correlated with PET scan. There were few limitations in our study. Limited number of the study enrolled patients came for



follow up HRCT. No correlation of findings and changes on HRCT scan with clinical and functional parameters in most of the patients. No consideration of changes during the whole disease course that is, only comparison of initial and the recent follow up exams. They characterized CT findings into four groups whereas we divided our HRCT findings into five groups. Nodules are an important CT feature for assessing post chemotherapy lungs and should be a part of check-list in lungs. In our study most common finding was found to be patchy ground glass haze which was the same as study conducted by Endo et al in Japan. According to Santiago et al, Ground-glass haze is nonspecific, but highly significant finding since 60-80% of patients have an active and potentially treatable lung disease. Previous studies have evaluated the prognostic significance of HRCT in chemotherapy induced lung disease patterns. According to Wells and Gay et al, Response to treatment is better in patients with GGH and is correlated with the extent of GGH on HRCT<sup>25</sup>. Patients with more extensive fibrosis on HRCT have a worse prognosis<sup>26</sup>. Usually, GGH indicates active disease that is potentially reversible with the appropriate treatment.

Akira et al reported diffuse or multi-focal ground-glass opacities with intralobular interstitial thickening as the main feature in chemotherapy associated pneumonitis. On the contrary, in antibiotic-induced pneumonitis, predominant radiographic findings were patchy ground-glass opacities with centrilobular opacities and interlobular septal lines<sup>27</sup>.

Although HRCT findings are usually non-specific, diagnosis can be arrived by identifying the most common histo-pathologic and radiologic manifestations of drug-induced lung injury<sup>28</sup>.

Ground-glass opacities and mild fibrosis are frequently ignored on radiography<sup>29</sup>. Patients with non-specific patchy areas of ground glass haze on HRCT and that too without septal thickening (Figure.2c) must not be ignored as most of the times these early changes respond to treatment. Follow up scan must strongly be advised.

## CONCLUSION

The most common pattern was found to be patchy areas of ground-glass attenuation. Pulmonary diseases that are induced by chemotherapy represent particular challenges for radiologists due to nonspecific and atypical imaging features. Patients with nonspecific patchy areas of ground glass haze and that too without septal thickening must not be ignored as most of the times these early changes respond to treatment. Follow up scan must strongly be advised.

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#### CONTRIBUTORS

USU Conceived the idea, planned the study, and drafted the manuscript. SA helped acquisition of data and did statistical analysis. SG and QUAA drafted and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.