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Multi-detector Computed Tomography (MDCT) Findings of Chemotherapy-Induced Cardiopulmonary Changes

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Authors' contributions

This work was carried out in collaboration between all authors. All authors designed the study, wrote the protocol, wrote the first draft of the manuscript, managed the literature searches and analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: To evaluate the role of multi-detector computed tomography (MDCT) in detection & characterization of chemotherapy-induced cardiopulmonary changes.
Materials and Methods: This retrospective study included 400 patients with confirmed 14 extra-pulmonary malignancies and treated by standard chemotherapy regimens. Of the 400 patients, 234 complained of Non Hodgkin lymphoma (NHL). Thirteen other types of malignant tumors were enrolled in our study. All patients underwent CT scan using 64 MDCT scanner (Brilliance 64, Philips) before chemotherapy and 6 months after the last session of chemotherapy. Chest CT scans were evaluated for ground-glass opacities (GGO), fibrosis, consolidation, nodules, pleural effusion, cardiac dilatation, pericardial effusion and pulmonary embolism.
Results: Cardiopulmonary chemotherapy-induced changes detected in 36/400 patients. The most

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common finding was pneumonic consolidation detected in 18/36. GGOs, fibrotic bands, pleural effusion and pericardial effusion were detected in 10/36, 6/36, 6/36 and 2/36 respectively. More than one finding detected in 6 patients. These changes completely resolved on follow-up without medication.

Conclusion: MDCT can accurately detect and evaluate cardiopulmonary chemotherapy-induced changes, differentiate these changes from disease progression and /or superadded pathology. Pneumonic consolidation is the commonest finding. Awareness of chemotherapy-induced cardiopulmonary changes can help the radiologist to detect these at early stages, which helps in appropriate management.

Keywords: MDCT; chemotherapy; cardiopulmonary complication.

1. INTRODUCTION

Chemotherapy as the main nonsurgical remedy of cancer treatment is generally based on the cytotoxic effect of natural or synthetic agents taking advantage of a higher vulnerability of cancer cells as compared to normal cells. However, normal cells may be affected by cytotoxic chemotherapy as well [1].

The final effect of all these drugs is to inhibit cell division in rapidly diving cells and thereby reduce the cell turnover in cancer tissues. Unfortunately, these drugs can also affect the normal cells, especially those with rapid cell division, leading to significant complications.

Gastrointestinal tract (GIT) and bone marrow are more susceptible to injury in patients undergoing cytotoxic chemotherapy; however, it may affect any organ in the body [2].

Pulmonary toxicity may be seen with many of the newer cytotoxic chemotherapeutic agents. These agents may cause diffuse ground-glass changes accompanied by thickened septal lines, interstitial infiltrates, or diffuse alveolar infiltrates, which may sometimes be associated with acute respiratory distress syndrome and, rarely, death [3,4].

Chemotherapy-induced cardiovascular toxicity resulting in cardiomyopathy can be detected by the radiologist as a dilated heart or heart failure in the differential diagnosis of new-onset interstitial thickening. Cardiotoxicity may be worsened by radiation therapy. The most common cardiovascular toxicity of the molecular targeted therapies is arterial hypertension, which is directly related to inhibition of the vascular endothelial growth factor receptor pathway [5].

The purpose of this study was to evaluate the role of MDCT in detection and evaluation of chemotherapy-induced cardiothoracic changes, differentiation of these changes from the disease progression and/or superadded pathology.

2. MATERIALS AND METHODS

2.1 Patients

This study was approved by our institutional review board, and informed consent was waived. The study was carried out on 400 patients with extra-thoracic malignancies (194 male and 206 female with mean age 38 years). The primary tumors that enrolled in this study were 14 malignant processes (Table 1). Inclusion criteria included patients with malignant lesions treated by standard chemotherapy regimens and underwent three or more follow-up visits after post-chemotherapy CT chest examinations. Exclusion criteria include primary pulmonary tumor patients underwent less than three follow-up visits post contrast chest CT studies and contraindication to contrast media. Chemotherapy regimens have been used in the treatment of the patients shown in (Table 2).

All patients were evaluated by clinical assessment in the form of patient's history taking together with clinical examination. Twenty patients underwent bronchoscopy with bronchoalveolar lavage and were evaluated for respiratory viral and microbiological infections.

2.2 MDCT Imaging

Chest CT scans were performed using 64 multi-detector CT scanner (Brilliance 64; Philips Healthcare, Best, Netherlands). Standard CT was performed at end-inspiratory acquisition using the following parameters: 64 _ 0.65 mm detectors, 120 kVp, automatic mA adjustment, 3 mm slice thickness, 1 mm section reconstruction.

For contrast-enhanced CT, a total of 100 mL of iohexol (Omnipaque; GE Healthcare, Cork, Ireland) 350 mg/mL was given intravenously. The images were viewed on both lung (window width, 1600 HU; level, –600 HU) and mediastinal (window width, 350 HU; level, 40HU) setting. Pulmonary embolism protocol CT was performed in a fashion similar to standard contrast-enhanced CT but with appropriate scan timing. Scans were timed using bolus tracking with an ROI on the main pulmonary artery and a trigger of approximately 200 HU. The images were then transferred to a workstation (Extended Brilliance Workspace V3.5.0.2254; Philips Healthcare, Cleveland, OH, USA).

2.3 Image Analysis

All CT images were reviewed on a Picture Archiving and Communication System (PACS, Paxeramed, Paxeramed Corp, Oslip, Austria). The reader recorded the presence of each of the following findings: ground-glass opacities (GGOs), fibrosis, consolidation, nodules, pleural effusion, cardiac dilatation, pericardial effusion and pulmonary embolism.

Table 1. The primary tumors that enrolled in this study (14 malignant processes)

Primary lesion	Distribution according to sex of the patient		Total
	Male	Female	
NHL	134	100	234 (58.5%)
HD	26	22	48 (12%)
Breast	-	32	32 (8%)
Colon	8	6	14 (3.5%)
Ovary	-	20	20 (5%)
Stomach	6	8	14 (3.5%)
Bladder	2	-	2 (0.5%)
Pancreas	12	6	18 (4.5%)
Esophagus	-	2	2 (0.5%)
Germ cell	2	2	4 (1%)
CLL	2	2	4 (1%)
Osteosarcoma	2	-	2 (0.5%)
Neuroblastoma	-	4	4 (1%)
Endometrial carcinoma	-	2	2 (0.5%)
Total	194	206	400

Table 2. Chemotherapy regimens used in treatment of described malignancies

Chemotherapy regimen	Number of cases
CHOP	196 Patients (49 %)
DHAP	18 Patients (4.5%)
ABVD	34 Patients (8.5 %)
FAC	32 Patients (9 %)
ABVD + MINE	10 Patients (2.5 %)
DHAP + MINE	6 Patients (1.5 %)
ABVD + CHOP	6 Patients (1.5 %)
DHAP + ICE	8 patients (2 %)
BEA-COPP	8 Patients (2 %)
FOLFOX	12 Patients (3 %)
ECF	8 Patients (2 %)
CISPLATINE + TAXANE	20 Patients (5 %)
CISPLATINE + GEMZAR	26 Patients (6.5 %)
CISPLATINE + 5-FLUROURACILE	8 Patients (2 %)
CISPLATINE + ENDOXANE	8 Patients (2 %)
Total	400 Patients.

3. RESULTS

The most common primary tumor in patients enrolled in our study was NHL 234 patients (134 males and 100 females) with a total percent of 58.5% (Table 1), and the most common chemotherapy regimen used was CHOP, 192 patients received CHOP chemotherapy representing 49% (Table 2).

Follow up post-contrast CT chest studies of 400 patients were done. From 400 patients 246 patients had normal post-contrast CT chest follow-ups. The other 154 patients were carefully re-evaluated; CT chest findings were compared with the clinical data and laboratory investigations to evaluate whether these changes were related to the chemotherapy or progression of the disease and/or superadded pathology. Final results (by the exclusion of other possibilities) suggested that only 36/400 patients (9%) complained of cardiothoracic insult due to the effect of the chemotherapy. These changes were variable in radiologic finding, severity and ranged from just fibrotic bands up to diffuse ground glass opacity.

The clinical presentations of 36 patients with the chemotherapeutic cardiothoracic insult were variable. Some of them were asymptomatic and accidently discovered during routine follow-up, others complained of chest tightness and more than one complaint was present in the same patient, the majority of cases were complaining of dyspnea at the time of diagnosis of the chemotherapy-induced cardiothoracic changes with a percentage of 55.5% (Table 3). The clinical data and the radiologic findings for 36 cases with chemotherapy-induced toxicity were shown in Table 4.

Table 3. Clinical presentation at time of diagnosis of chemotherapy complication of 36 patients

Clinical presentation	N0. of cases	%
Asymptomatic	8	22.2%
Cough	14	38.8%
Dyspnea	20	55.5%
Fever	10	27.7%
Chest pain	0	0%

The different chemotherapy CT chest findings effects were shown in Table 5 and they were variable from mild effect in the form of fibrotic bands to more severe cases in the form of bilateral diffuse ground-glass opacity. More than one finding was detected in one patient. The most common finding was pneumonic consolidation detected in 18/36 (50%). GGOs, fibrotic bands, pleural effusion and pericardial effusion were detected in 27,7%, 16.6%, 16.6% and 5.5% respectively.

4. DISCUSSION

Chemotherapeutic agents are used extensively in solid and hematologic malignancies and are increasingly used for their immunosuppressive properties in the management of inflammatory disorders [6]. Cancer chemotherapy has evolved from cytotoxic agents and now includes several new agents that target specific molecules responsible for regulation of cell growth, nutrient supply, and differentiation. These molecularly targeted therapies have a different mechanism of action than do classic cytotoxic agents, which predominantly attack rapidly proliferating cells. Therefore, the toxicities of targeted and cytotoxic agents may differ in both clinical and radiologic presentation [5]. Universal criteria for the diagnosis of drug-induced pulmonary disease are not available. The diagnosis of cytotoxic lung damage generally depends upon an appropriate history of drug exposure, histologic evidence of lung injury and most importantly, the exclusion of other causes of the lung damage. Unfortunately, there is no single diagnostic test or tissue biopsy that definitively can confirm the diagnosis of chemotherapy-associated lung disease. Thus, a careful evaluation is needed to eliminate the possibilities of other conditions that produce these effects, particularly infection. Clinicians who care for these patients must be aware of the myriad of chemotherapeutic agents that can injure the lungs [6].

The main advantages of MDCT are; shorter scan duration to minimize the scan time, greater anatomic coverage in a single breath-hold allowing greater patient comfort and excellent 3D reconstructions. Faster imaging allows more consistent contrast enhancement with a single bolus of contrast, thus reducing the cost of examination [7]. In our study, after clinical and radiological evaluation of the 400 patients; 36 (9%) patients reported to have cardiothoracic changes related to treatment by chemotherapy. Thirty-four patients had variable pulmonary changes (fibrotic bands-consolidations-pleural effusion-ground glass opacity) representing a percent of 8.5%. This coincides with Limper [6] and Dimopoulou et al. [8] who reported increases risk of lung toxicity associated with the chemotherapy up to 10%.

Table 4. The clinical data and the radiologic findings in 36 cases with chemotherapy induced toxicity

List of cases	Age	Primary tumor	Radiologic findings	Chemotherapy	
				Type used	No. of cycles
Case No. 1,2	13,45	NHL	Bilateral diffuse ground glass opacity.	ABVD	8Cycles
Case No. 3,4	30,50	Cancer colon	Bilateral basal consolidations	FOLFOX	4Cycles
Case No. 5,6	31,34	NHL	Right side pleural effusion with bilateral basal consolidations.	CHOP	8Cycles
Case No. 7,8	28,48	Breast Cancer	Bilateral ground glass opacity	FAC	6Cycles
Case No. 9,10	45,58	HD	Bilateral ground glass opacity	ABVD MINE	8Cycles 3Cycles
Case No. 11,12	38,43	HD	Left sided pleural effusion with underlying consolidation	ABVD	8Cycles
Case No. 13,14	50,57	NHL	Patchy consolidation right lower lung lobe	CHOP	8Cycles
Case No. 15,16	23,28	HD	Mild to moderate pericardial effusion	BEA-COPP	6Cycles
Case No. 17,18	18,45	NHL	Bilateral diffuse ground glass opacity	BEA-COPP	6Cycles
Case No. 19,20	46,54	Breast Cancer	Right middle lobe atelectasis.	FAC	6Cycles
Case No. 21,22	22,48	NHL	Mild right sided pleural effusion	CHOP	8Cycles
Case No. 23,24	19,63	HD	Right basal patchy consolidation	DHAP	6Cycles
Case No. 25,26	46,48	NHL	Patchy consolidation in the right lower lung lobe	CHOP	8Cycles
Case No. 27,28	31,50	NHL	Bilateral basal consolidation with bilateral fibrotic bands	DHAP MINE	8Cycles 3Cycles
Case No. 29,30	25,35	NHL	Patchy consolidation in the left lower lung lobe	DHAP	8Cycles
Case No. 31,32	55,50	Cancer ovary	Right basal atelectasis with bilateral pleural thickening	Gimzar and cisplatin	6Cycles
Case No. 33,34	38,69	NHL	Bilateral patchy areas of consolidations.	ABVD	6Cycles
Case No. 35,36	48,56	NHL	Bilateral ground glass opacity	CHOP	8Cycles

Table 5. Different CT chest findings related to chemotherapy toxicities of 36 patients

CT chest finding	NO. of cases	Percent
Fibrotic bands	6	16.6%
Consolidation	18	50%
Pleural effusion	6	16.6%
Ground glass opacity	10	27.7%
Pericardial effusion	2	5.5%

In the present study, 36 patients had positive pulmonary findings related to chemotherapy administration, sixteen of them presented with pulmonary consolidation (44%) of pulmonary changes. Ground glass opacities were detected in 10 patients, fibrosis in 6 patients and pleural effusion in 6 patients. This cope with Cleverley et al. [9] who reported that the most common drug-induced abnormalities on high-resolution computed tomography (HRCT) are ground glass opacities, consolidation, interlobular septal thickening, and centrilobular nodules. Torrisi, et al., reported various radiographic patterns of drug-induced injury, including patchy, unilateral or bilateral reticular markings, ground glass opacities or consolidations. More than one finding may be presented in an individual patient. Pleural effusions and focal nodular consolidations that mimic tumor involvement may also be seen [5]. These findings are in agreement with our results.

In our study, most of the pulmonary changes tend to affect the lower lung zones which cope with Ellis, et al. [10] who reported that high-resolution CT findings of chemotherapeutic drug–induced lung disease tend to involve the lower zones of the lungs. The pulmonary changes reported in our study exclusively affect the lung parenchyma. This comes with Dimopoulou et al. [8] who reported that most novel antineoplastic drugs may induce pulmonary toxicity, which involves mainly the parenchyma, and less frequently the airways, pleura or the pulmonary circulation.

Akira et al. [11] reported diffuse or multi-focal ground-glass opacities with intralobular interstitial thickening as the main feature in chemotherapy associated pneumonitis.

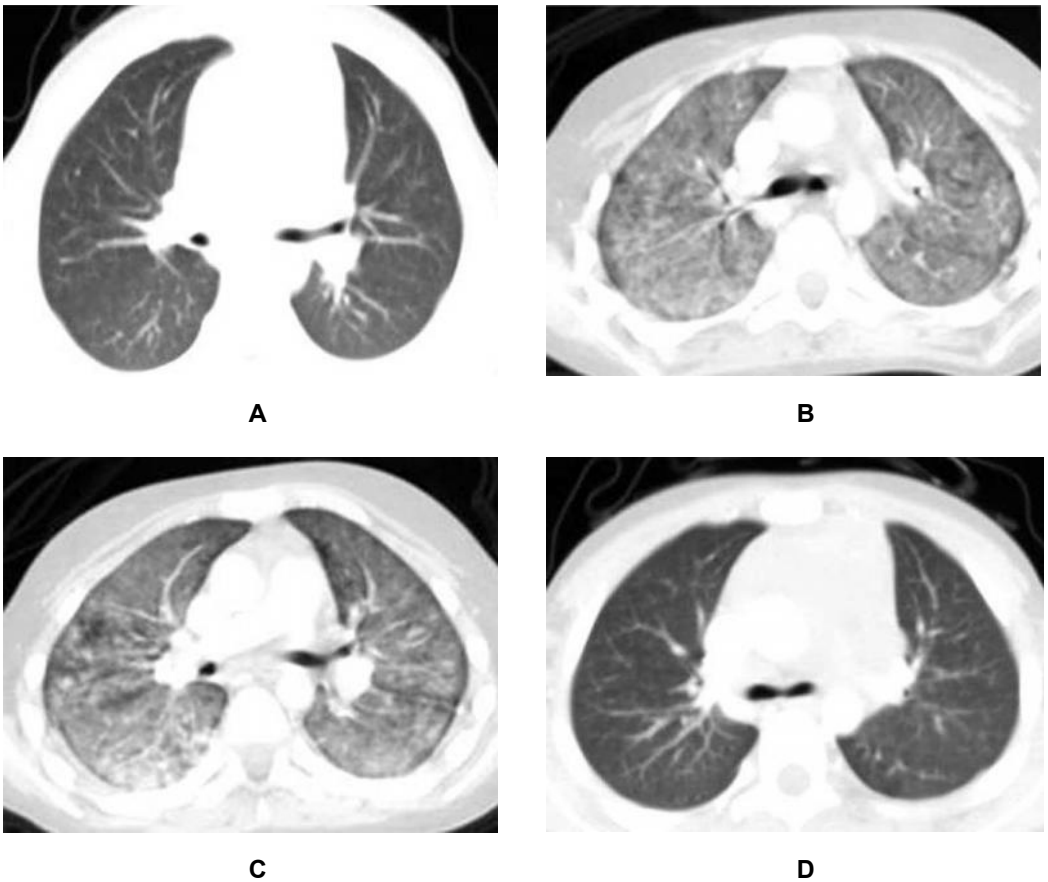

Fig. 1. 13-years-old male patient with NHL Patient received 8 cycles of ABVD. On follow up MDCCT chest. A- Before the start of chemotherapy. B&C-Bilateral diffuse ground glass opacity (GGO) following chemotherapy. D- Follow up after termination of chemotherapy complete disappearance of GGO

In study conducted by Tamura et al. [12] the HRCT findings were nonspecific pneumonitis 71%, hypersensitivity pneumonitis 14%, diffuse alveolar damage 11%, and organizing pneumonia 4%; in patients received anticancer chemotherapy gemcitabine.

In this study, CHOP chemotherapy regimen was used in the treatment of 198 patients (used alone in 192 patients and after ABVD regimen in 6 patients). Of the 198 patients, 10 patients reported having pulmonary changes with a percent about 5.05%. Lim et al. [13] reported pulmonary adverse effects in 4 patients (13.8%), the study was done on 29 patients receiving CHOP regimen for treatment of lymphoma, this doesn't match with our study results of pulmonary adverse effects. The difference may be related to a different number of patients, different age groups or concomitant disease.

Twelve patients received FOLFOX chemotherapy in our study; two patients of them developed pulmonary complication with a percent of 16%. This doesn't match with Shimura et al. [14] who conduct a study on 734 patient received FOLOFX for the treatment of colorectal carcinoma, only 11 patients developed chemotherapy-related pulmonary complication with a percent of 1.5%. This difference may be related to a small number of patients receiving FOLFOX chemotherapy screened in our study.

Two patients in our study reported to have a cardiac side effect of chemotherapy. These patients complained of HD and underwent BEA-COPP chemotherapy which includes doxorubicin and bleomycin. This copes with Folyd et al. [15] who reported that some of the agents used in chemotherapy of lymphomas need to be considered as potential etiologic factors of pericardial effusions.

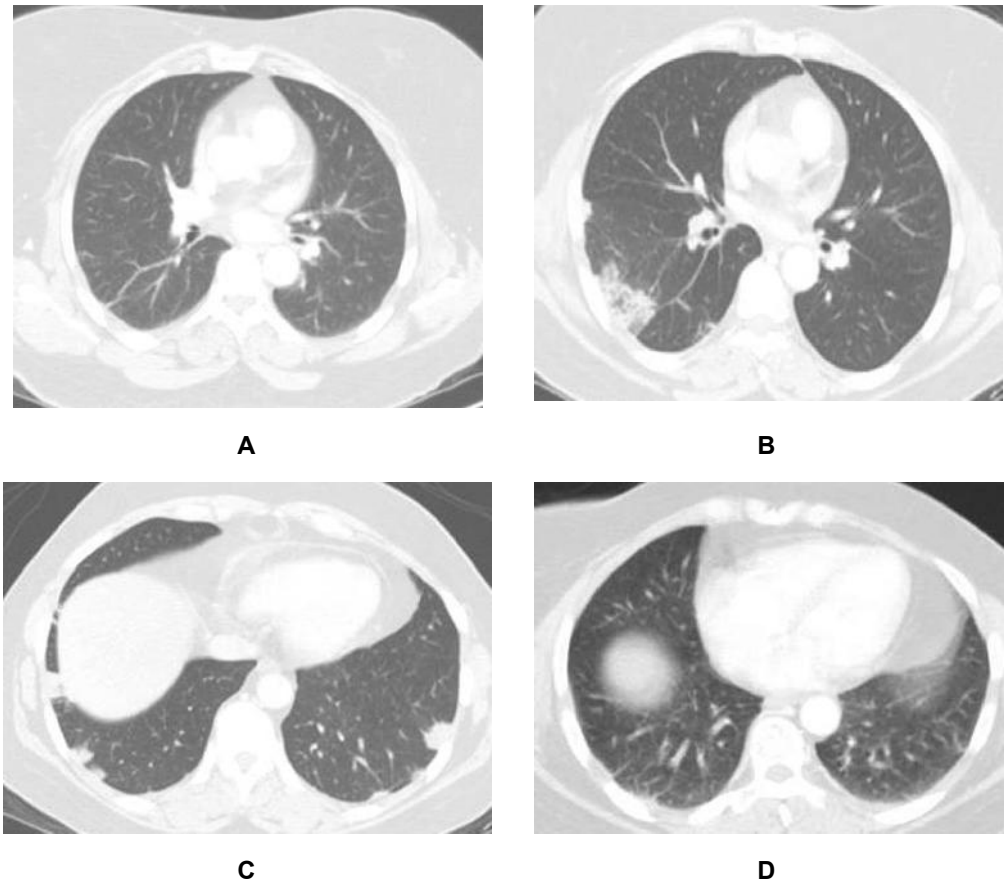

Fig. 2. 50-year old female patient with mucoid adenocarcinoma. Patient received 4 cycles of FOLFOX. Follow up MDCT of the chest. A- Before the start of chemotherapy. B and C-Bilateral basal consolidations following Chemotherapy treatment (FNAC proved). D- Follow up after termination of chemotherapy complete improvement of consolidation

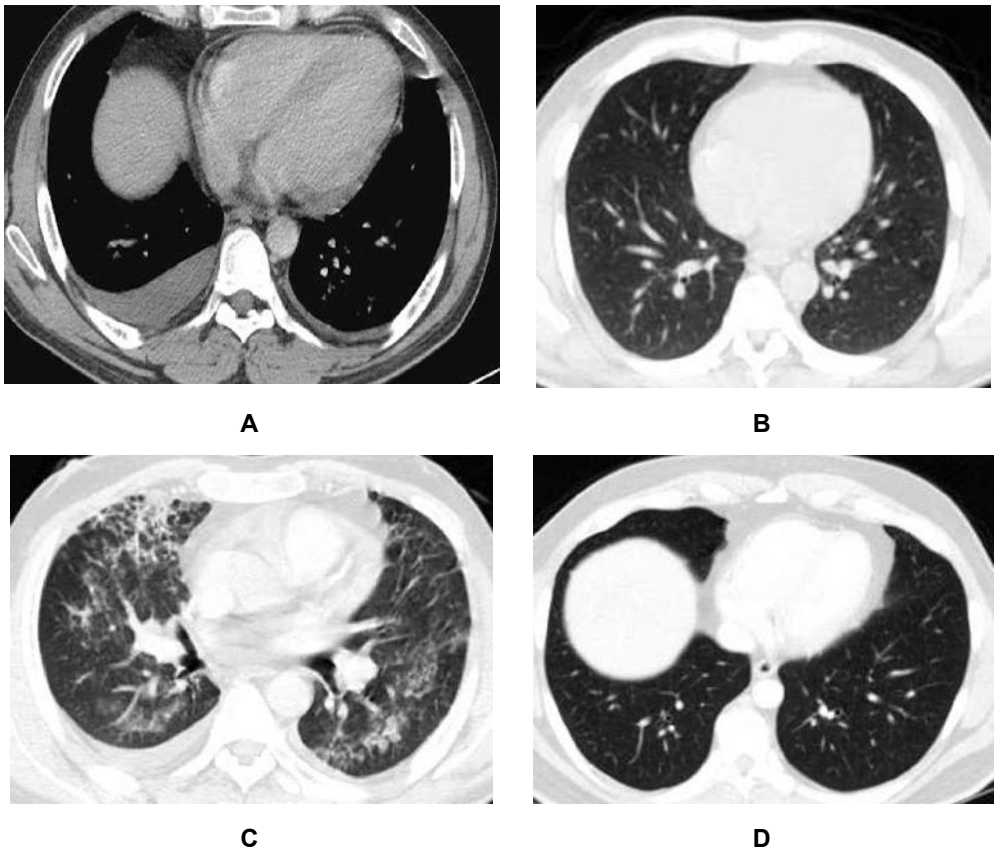

Fig. 3. 31-year-old male patient with NHL. Patient received 8 cycles of CHOP. Patient complains of dyspnea and cough. Follow up MDCT CT chest. A: Before the start of chemotherapy. B: (mediastinal window) & C: (lung window): Mild right sided pleural effusion with bilateral pulmonary consolidation and ground glass opacities following chemotherapy treatment. D: Marked improvement following termination of chemotherapy

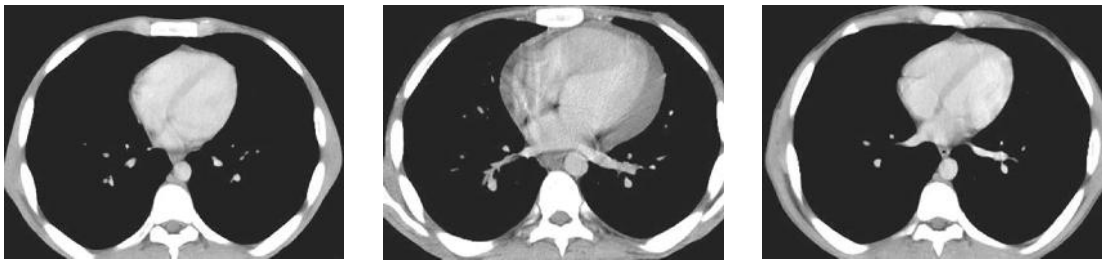

Fig. 4. 23-year-old male woth HD. Patient received 6 cycles of BEA-COPP. Follow up CT chest. A- Before the start of chemotherapy. B (mediastinal window). Mild to moderate pericardial effusion. C- Marked improvement after termination of chemotherapy treatment

Khorana et al. [16] reported that among 3003 patients treated with at least one cycle of chemotherapy, venous thromboembolism occurred in 58 (1.93%). This is not in agreement with our study where none of the 400 patients reported to have pulmonary embolism. The difference in the results may be referred to the difference in the type of primary malignancy and number of screened cases.

The limitation of our study was its retrospective and randomized nature. Prospective studies with larger number of patients are needed for further evaluation.

5. CONCLUSION

We concluded that most anti-neoplastic agents have the potential to induce cardiothoracic toxicity, which involves primarily the lung parenchyma. CT is a single comprehensive, non-invasive and accurate imaging modality used to detect these changes, to differentiate these changes from disease progression and /or superadded pathology. Awareness of these cardiothoracic toxic effects helps the radiologists to detect these changes at the early stage, which helps the clinician for appropriate management.

DISCLAIMER

The title of this manuscript was previously presented in the following conference.
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ETHICAL APPROVAL

The authors have obtained all necessary ethical approval from suitable Institutional Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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