HRCT findings in chemotherapy toxicity and pattern recognition

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Authors: D. K. Rajendran; Chennai, TAMIL NADU/IN
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Learning objectives

Cancer chemotherapy is the cornerstone of treatment success in patients with disseminated or non-resectable disease. These drugs inhibit cell proliferation at single or multiple steps in the cell-cycle. As such, they are more active against cells which are actively dividing.

The systemic administration predisposes other rapidly dividing cells to be affected by these drugs. The most common manifestations are seen in actively dividing cells of bone marrow and mucosa of gastro intestinal tract. Often, pneumocytes are also affected. Though chemotherapeutic side effects causing pneumocyte damage is rare, it is a well-documented phenomenon. The predominant effect is pulmonary fibrosis. bleomycin, methotrexate, carmustine, busulfan and cyclophosphamide.[1]

In this exhibit we aim to describe the spectrum of radiological findings in chemotherapy induced pulmonary toxicity; identify specific patterns of pulmonary damage caused by chemotherapeutic agents and to distinguish disease progression and other causes of pulmonary changes from drug induced damage.

It's paramount that radiologists are aware of the entity of drug induced pulmonary changes and the common patterns of pulmonary manifestation to identify and help in intervention before irreversible lung fibrosis results. Adequate differentiation of this entity from infective etiology helps in institution of steroids in treatment of the disease.

Background

Anatomy of secondary pulmonary lobule:[2]

In high resolution computer tomography (HRCT) the lung parenchyma can be resolved upto the secondary pulmonary lobule. This is a polygonal structure bounded by interlobar septa. Pulmonary veins and lymphatics are within the connective tissue forming the interlobar septa. Central portion of the lobe is known as centrilobular region and this comprises the axial interstitium. This contains the pulmonary artery and bronchioles.

Pathogenesis of pulmonary fibrosis:[3]

Endogenous or exogenous stimuli (chemotherapeutic agent)

--> Microscopic lung injury
Wound healing mechanism:
a. intact: lung homeostasis
b. aberrant: reactive fibroblast activation à pulmonary fibrosis.

The mechanism of lung injury:

1. Direct oxidant injury.
2. Vascular damage: increased capillary permeability.
3. Intra cellular phospholipid deposition: seen with amiodarone due to inhibition of phospholipase A.
5. Central nervous system depression: Neurogenic pulmonary edema.
6. Direct toxicity: DNA damage.

Classification of ILD:[4,7]

The American thoracic society and European Respiratory Society classification defines the guiding principles for classifying interstitial pneumonia. The various lung patterns defined are:

1. Idiopathic Pulmonary Fibrosis
   IPF - Histology: Temporally heterogenous interstitial fibrosis
   Radiology: i. Peripheral, subpleural with lower lobe predominance
   ii. Fibrosis (interlobar septal thickening, traction bronchiectasis and honeycombing)
   iii. Ground glass opacities.
2. Non-specific Interstitial Pneumonia
   NSIP - Histology: Temporally homogenous interstitial cellular infiltrates or fibrosis
   Radiology: i. Diffuse involvement with subpleural sparing, lower lobe predominance
   ii. Mild fibrosis (reticular opacities)
   iii. Ground glass opacities.
3. Lymphoid Interstitial Pneumonia
   LIP - Histology: Interstitial infiltration of lymphocytes.
   Radiology: i. Cystic spaces
   ii. Ground glass opacities
   iii. Nodules (centrilobular and subpleural)
   iv. NO BASAL PREDOMINANCE.
4. Respiratory Bronchiolitis- associated Interstitial Lung Disease
   RB-ILD - Histology: Centrilobular macrophage accumulation (involves axial interstitium).
   Radiology: i. Upper lobe predominance
   ii. Centrilobular nodules and peribronchial thickening
   iii. Patchy ground glass opacities.
5. Desquamative Interstitial Pneumonia
   DIP - Histology: Alveolar macrophage accumulation
   Radiology: i. Basal, subpleural.
   ii. Ground glass opacities.

6. Acute Interstitial Pneumonia
   AIP - Histology: Idiopathic diffuse alveolar damage
   Radiology: Exudative phase:
   i. Extensive bilateral ground glass opacities
   ii. Dependent consolidation
   Organising phase:
   i. Architectural destruction.

7. Bronchiolitis Obliterans Organising Pneumonia, Cryptogenic Organising
   Pneumonia, Organising Pneumonia
   BOOP, COP, OP -
   Histology: Distal airspace fibrosis with lack of interstitial fibrosis.
   Radiology: i. Atoll sign or Reversed Halo sign - ring shaped or crescentic
   opacities with central ground glass opacities
   ii. Consolidation or ground glass opacities - subpleural and/or peribronchial
   distribution.
   iii. Crazy paving pattern.

**Mechanism of action of chemotherapeutic drug**[^5, 6]

Drugs act directly on cells (cyto-toxic) or change hormonal milieu. Monoclonal antibodies
physically connect tumor cells with cells of immune system which cause targeted cell
destruction or block antigenic cell signaling mechanism.

**Patterns of lung involvement in chemotherapeutic drug toxicity**[^1]

10% of patients undergoing chemotherapy have adverse reaction to the lungs. The main
patterns of lung involvement due to chemotherapeutic drugs are IPF, (Hypersensitive
Pneumonitis)HP, Acute Respiratory Distress Syndrome (ARDS), OP.

**Findings and procedure details**

**Procedure:**

Patient selection: Patients presenting with dyspnea, shortness of breath and fever.

Scanner: 24 slice CT scanner was used for acquisition. Spiral acquisition with 1.5 mm
slice thickness and 1 mm pitch was done. HRCT reconstruction with 1.5 mm slice
thickness, at 10 mm interval and 80 kernels was done. The images were separately
reviewed on the console and a PACS workstation with optimum window settings (width 1200 to 1800; level -250 to -500 HU) and software filters (sharp filter settings).

**Findings:**

Causes of pulmonary findings in oncological patients can be grouped under:

a. **Chemotherapy induced changes,**

b. **Infections,** or

c. **Primary disease per se.**

**Chemotherapy induced changes:**

7 patients had pulmonary parenchymal changes with no evidence of infection on airway tube or blood or urine culture. These pulmonary presentation in these patients were consistent with drug toxicity. Distribution of patients according to drug received and other pulmonary pathologies is shown in Figure 1.

**Specific findings with each drug:**

<table>
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<td>Bleomyin</td>
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<td>Cyclophosphamide</td>
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<td>Treosulfan</td>
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<td>Paclitaxel</td>
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and ground glass opacity (OP)

The frequency distribution of lung parenchymal patterns observed in patients presenting with dry cough and dyspnea is represented in figure 11.

From our study we found the commonest pattern of pulmonary damage in drug toxicity is NSIP with a high propensity of honeycombing. The patients commonly presented with dry cough with dyspnea as early as 1 week to 4 months from institution of chemotherapeutic agent.

5 patients with similar presentation did not have drug toxicity. Two patients with primary bronchial malignancy presenting with similar clinical features had disease progression. On HRCT, they had lymphangitic spread (Figure & ). Both of them had a rapid downhill course of disease progression.

One patient underwent adjuvant chemo-radiation for colonic carcinoma. After 8 months of disease free status, she presented with dyspnea. HRCT revealed organizing pneumonia pattern of pulmonary involvement. However, she had not received any chemotherapeutic agents which are associated with pulmonary toxicity. Lung involvement in her case was considered as cryptogenic organizing pneumonia.

Two patients had fever in association with shortness of breath. Blood cultures showed Klebsiella pneumoniae and yeast like organisms in their blood and airway tube culture, respectively. This is due to the myelosupression associated with chemotherapeutic drugs and secondary pulmonary infection.

Images for this section:
Fig. 1: Figure 1: Distribution of patients according to the various toxic drugs and other pathologies
Fig. 2: Bleomycin toxicity: Extensive bilateral ground glass opacities with peripheral sparing (AIP - Diffuse alveolar damage)
**Fig. 3:** Bleomycin toxicity: Baseline radiograph (Left): Interstitial thickening better appreciated in the right mid and lower zones. Radiograph after 5 months shows resolution of interstitial opacities.

**Fig. 4:** Cyclophosphamide toxicity: Bilateral diffuse ground glass opacities (NSIP / HP)
Fig. 5: Cyclophosphamide toxicity: Resolution of ground glass opacities after steroid administration
Fig. 6: Treosulfan toxicity: Centrilobular nodules and peribronchial thickening with upper lobe predominance (RB-ILD)
Fig. 7: Paclitaxel toxicity: Interlobular septal thickening (Crazy paving pattern) with diffuse ground glass opacities and diffuse subpleural fibrosis (NSIP)
**Fig. 8:** Pemetrexed toxicity: Diffuse honeycombing in right lung (NSIP); rare unilateral presentation
**Fig. 9:** Rituximab toxicity: Centrilobular nodules with peribronchial thickening (OP)

**Fig. 10:** Rituximab toxicity (different patient): Focal areas of ground glass opacity and interstitial thickening (OP)
Fig. 11: The frequency distribution of lung parenchymal patterns observed in patients presenting with dry cough and dyspnea. Five patients having similar clinical presentation did not have drug related pulmonary changes.
Conclusion

Drug induced toxicity of lungs is a potential complication of chemotherapy. Radiologists should be aware of the pattern of pulmonary toxicity due to chemotherapy, agent specific as early recognition and diagnosis helps in the management which otherwise can be progressive and result in irreversible pulmonary fibrosis.

Even more important is awareness of other causes of pulmonary changes in oncological patients from drug toxicity for prompt institution of appropriate management.

Personal information

References

1. Ellis S.J, Cleverley J. R, Muller N.L; "Drug-Induced Lung Disease: High-resolution CT findings"; AJR Am J Roentgenol; 2000, October; 175:1019-1024