Pictorial Review of Chemotherapy-induced Pneumonitis in Oncologic Patients

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Chemotherapy-induced pneumonitis is an important cause of respiratory failure in oncologic patients.

Otherwise clinical presentations and radiographic features may be virtually identical to pulmonary infection or cancer recurrence. These conditions are not easily differentiated based on clinical and radiographic presentations.

Radiologists must be aware of general conditions of increased risk of pulmonary injury from chemotherapeutic agent.

The approach to diagnose, risk factors, imaging features with clinical manifestations are discussed to improve accuracy of diagnosis in this presentation.
Pathophysiology of Adverse Reactions to Drug

<table>
<thead>
<tr>
<th>Direct toxic action</th>
<th>Hypersensitivity Reaction</th>
<th>Neural humoral mechanism</th>
<th>Autoimmune reaction</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioactivation, conversion to various metabolites, or release of toxic oxygen species and free radicals</td>
<td>Type I reaction (immediate hypersensitivity) Type III reaction (immune complex)</td>
<td>Altering capillary permeability</td>
<td>Autoimmune response Type III or type IV hypersensitivity reaction</td>
<td>Drug induced</td>
</tr>
<tr>
<td>Diffuse alveolar damage Interstitial pneumonia Organizing pneumonia</td>
<td>Eosinophilic pneumonia Hypersensitivity pneumonitis</td>
<td>Non cardiogenic or neuronal pulmonary edema Drug induced asthma</td>
<td>Drug induced lupus Drug induced vasculitis</td>
<td>Alveolar hemorrhage Pulmonary hypertension Pulmonary thromboembolism</td>
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</table>
# Pathogenesis

<table>
<thead>
<tr>
<th>Histopathologic pattern</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse alveolar damage</td>
<td>Bleomycin, busulfan, carmustine (BCNU), Gefitinib, cyclophosphamide, methotrexate, methotrexate, mitomycin, melphalan</td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>Methotrexate, carmustine (BCNU), chlorambucil, cyclophosphamide, oxaliplatin</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>Bleomycin, methotrexate, cyclophosphamide, doxorubicin, thalidomide, trastuzumab</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>Oxaliplatin, bleomycin</td>
</tr>
<tr>
<td></td>
<td>More common in ACEIs, antidepressants, NSAIDS, etc. rather than in chemotherapeutic agent</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Gemcitabin, mitomycin, all-transretinoid acid (ATRA)</td>
</tr>
<tr>
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<td>More common in NSAIDs, transfusion, narcotics</td>
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<tr>
<td>Alveolar hemorrhage</td>
<td>Bevacizumab, cytosine arabinoside (Ara-c), cyclophosphamide, etoposide, gemcitabine</td>
</tr>
<tr>
<td></td>
<td>More common in anticoagulation</td>
</tr>
<tr>
<td>Pulmonary vasculitis</td>
<td>Mitomycin, all-transretinoid acid (ATRA)</td>
</tr>
</tbody>
</table>
Correct Identification of the drug

- Singularity of drug
- Temporal eligibility
- Clinical, HRCT, Bronchoalveolar lavage (BAL)
- Pathologic pattern
- Exclusion of other causes for the interstitial lung disease (ILD)

- Current or recent exposure to chemotherapy

- In case of several drugs, the respective likelihood is evaluated against the incidence rate and pattern of lung response

- Nonspecific
  - Cough, Fever, Dyspnea, Hypoxemia
- Maybe rapidly progressive
  - Respiratory failure,
  - Acute respiratory distress syndrome (ARDS)

- Elevated
  - WBC count
  - Erythrocyte sedimentation rate (ESR),
  - C-reactive protein levels (CRP)
  - Krebs von den Lunge-6 (KL-6) (>500U/ml)

- Variable results
  - Neutrophilia
  - Lymphocytosis
  - Rarely, eosinophilia
- To exclude atypical or typical infections

- Decreased DLco
  - Used to detect early onset of reaction
- Gallium ($^{67}$Ga) uptake
  - Increase in most of chemotherapeutic drug reactions

- Nonspecific
  - Nonspecific pneumonitis
  - Organizing pneumonia
  - Eosinophilic pneumonia
  - Pulmonary fibrosis
  - Diffuse alveolar damage
- Should not be considered diagnostic of drug induced lung disease

Transbronchial or open-lung biopsy

- BAL
- Lung function & Imaging

- Clinical Manifestations
- Laboratory finding

Recurrence
Risk Factors

1. Combination chemotherapy
   • Additive effect with higher frequency of pulmonary toxicity
2. Second or third line chemotherapy regimen
3. Preexisting ILD
4. Chronic obstructive pulmonary disease (COPD)
5. Radiation therapy
6. Extensive pulmonary metastatic disease
7. Poor functional status
8. High inspired oxygen concentration
   • May increase the incidence or severity of mitomycin-C-induced pneumonitis
9. Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) use
Virtually all patients who take chemotherapy are immune suppressed, from their underlying disease as well as from the chemotherapy agents. This makes susceptible to a variety of opportunistic infections, which may have overlapping radiologic manifestations with drug reactions.

- **Opportunistic Infections**: Pneumocystis Jiroveci Pneumonia (PJP), Cytomegalovirus (CMV) pneumonia
- **Challenging Conditions**: Lymphangitic metastasis, Mucinous adenocarcinoma
- **Drug-induced Lung**
  - Resolution of pneumonitis after corticosteroid and withdrawal of the presumed agent

The diagnosis of chemotherapy toxicity is a diagnosis of exclusion.
# Thin-section CT Findings

## Early-onset Chemotherapy-Induced Pulmonary injury

<table>
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<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Diffuse Alveolar Damage</td>
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<tr>
<td>(Acute Respiratory Distress Syndrome)</td>
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<tr>
<td>Pulmonary Edema</td>
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<tr>
<td>Diffuse Alveolar Hemorrhage</td>
</tr>
<tr>
<td>Hypersensitivity Pneumonitis</td>
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![CT Scan Images](image1.png) ![CT Scan Images](image2.png) ![CT Scan Images](image3.png) ![CT Scan Images](image4.png)
**Diffuse Alveolar Damage (DAD)**
*(Acute Respiratory Distress Syndrome, ARDS)*

**Risk Factors**
- Occur more often and be more severe in patients who receive multi-agent chemotherapy or in whom radiation therapy or oxygen are given concurrently
- Patients who are on a 2nd or 3rd line chemotherapy regimen

**Symptoms**
- Dyspnea, acute respiratory failure

**Histopathology**
- Hyaline membranes, dysplasia of type 2 pneumocytes, interstitial or alveolar edema
- Abnormal type 2 cells may be retrieved by BAL

**Associated antineoplastic agent**
- Antibiotics (bleomycin, mitomycin C)
- Alkylating agents (busulfan, cyclophosphamide, chlorambucil, melphalan)
- Antimetabolites (methotrexate, 6-mercaptopurine, azathiprine, cytosine-arabinoside, gemcitabine, fludarabine)
- Nitrosamines (BCNU, CCNU)
- Podophyllotoxins (etoposide, paclitaxel, docetaxel)
- ATRA, gefitinib, imatinib, irinotecan, interferon-γ, sirolimus, TNF-α

**Timing**
- Exudative phase: 1st week after lung injury
- Reparative phase: after 1-2 weeks

Most common histologic manifestations of pulmonary drug injury:
Observed most commonly as a reaction to chemotherapeutic
Diffuse Alveolar Damage (DAD)  
(Acute Respiratory Distress Syndrome, ARDS)

Imaging

• Extensive bilateral GGO with or without associated consolidation that tend to involve mainly the dependent lung regions
• Early exudative phase; GGO usually predominate and often have a patchy or geographic distribution with adjacent areas of lobular sparing
• GGO rapidly become confluent and are frequently associated with Crazy-paving pattern
• Organizing phase; Architectural distortion and traction bronchiectasis
• Chronic fibrotic phase; extensive reticulation and honeycombing
**Diffuse Alveolar Damage (DAD)**
*(Acute Respiratory Distress Syndrome, ARDS)*

Case I. ARDS in a patient (M/70) with gastric cancer

The patient was under 6th cycle of FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) chemotherapy. At the day of administration of chemotherapy, chest posteroanterior (PA) view showed clear lung fields (A). After 7 days, chest PA obtained at the time when he complained of dyspnea shows bilateral symmetric GGO and consolidation (B). Serial anteroposterior view showed rapid progression to extensive bilateral consolidation within a week.
Extensive bilateral GGO with or without associated consolidation that tend to involve mainly the dependent lung regions

- Early exudative phase: GGO usually predominate and often have a patchy or geographic distribution with adjacent areas of lobular sparing
- GGO rapidly become confluent and are frequently associated with Crazy-paving pattern
- Organizing phase: Architectural distortion and traction bronchiectasis
- Chronic fibrotic phase: extensive reticulation and honeycombing

Imaging

**Case I. ARDS in a patient (M/70) with gastric cancer**

Thin-section CT revealed extensive bilateral GGO with consolidation (A-B). Consolidation was predominant in the dependent lung region (B). He had respiratory failure and expired a few days later.
Diffuse Alveolar Damage (DAD)  
(Acute Respiratory Distress Syndrome, ARDS)

Case II. ARDS in a patient (M/70) with lung cancer in right lower lobe

After two weeks from initiation of docetaxel, the patient had dyspnea and fever. No cultural growth found both in sputum and blood. Thin-section CT revealed diffuse bilateral GGO with multifocal crazy-paving appearance. After administration of corticosteroid, pulmonary infiltrate showed resolution.
Acute Pulmonary Edema

**Clinical**

- **Symptoms**
  - Dyspnea, acute respiratory failure, Foamy tracheal exudate
  - Fever, obtundation, shock possible

- **Pathogenesis & Histopathology**
  - Non cardiogenic and result from drug related increase in capillary pulmonary permeability
  - Presence of proteinaceous fluid in the alveolar spaces and a near-normal interstitium

- **Lab**
  - Normal echocardiography, pulmonary capillary wedge pressure

- **Associated antineoplastic agent**
  - Cytosine arabinoside (Ara-C), bleomycin, mitomycin, cyclophosphamide, methotrexate, interleukin-2

- **Timing**
  - Can develop shortly (less than 1 minute) after drug administration
  - Also can occur unexpectedly later into treatment
  - Usually resolve fully 3-5 days after cessation of chemotherapy
**Acute Pulmonary Edema**

**Imaging**

- Confirmed by normalcy of heart size on imaging, and of cardiac echocardiography and capillary wedge pressure

- Indistinguishable from other forms of edema both in its radiographic appearance and in the rapidity of onset and clearing

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**Pulmonary edema in a patient (F/36) with breast cancer**

The patient who was under docetaxel and herceptin therapy complained of dyspnea without evidence of infectious sign.

CT revealed diffuse bilateral GGO, predominant in upper lungs (A-C).

Echocardiography was performed to prove normal cardiac function. After administration of diuretics, symptom and pulmonary infiltrate showed rapid improvement.
### Diffuse Alveolar Hemorrhage (DAH)

**Uncommon manifestation of drug toxicity**

#### Clinical

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Associated antineoplastic agent</th>
</tr>
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<tbody>
<tr>
<td>• Arthralgia, dyspnea, anemia  &lt;br&gt; • Hemoptysis is not a constant feature</td>
<td>• Methotrexate, high dose cyclophosphamide, mitomycin, cytarabine (Ara-C)</td>
</tr>
</tbody>
</table>

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<th>Pathogenesis</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diffuse and probably synchronous bleeding from pulmonary capillaries, with or without histologically demonstrable capillaritis  &lt;br&gt; • Can occur in isolation or in association with involvement of the kidney or other internal organs  &lt;br&gt; • Secondary due to thrombocytopenia</td>
<td>• Occurs during treatments with drugs &lt;br&gt; • Mitomycin causes a hemolytic-uremic syndrome after 4-8 months of therapy</td>
</tr>
</tbody>
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<tr>
<th>Lab</th>
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<tbody>
<tr>
<td>• Increase in DLco (KCO), suggesting freee hemoglobin in alveolar space  &lt;br&gt; • BAL demonstrates red cells, hemosiderin laden macrophages</td>
<td></td>
</tr>
</tbody>
</table>
**Diffuse Alveolar Hemorrhage (DAH)**

**Imaging**

- Extensive bilateral GGO with or without superimposed intralobular linear opacities (crazy paving pattern)

- Bilateral, scattered, or diffuse areas of GGO

**Diffuse alveolar hemorrhage in a patient (M/53) with lung cancer**

During administration of gefitinib (after 2 months of initiation), diffuse GGO and consolidation with geographic appearance was noted in CT. The patient developed hemoptysis and decreased level of hemoglobin.
Hypersensitivity Pneumonitis

Relatively uncommon manifestation of drug induced lung disease

Clinical

- **Symptoms**
  - Fever and peripheral eosinophilia suggest the diagnosis

- **Histopathology**
  - Indistinguishable from those commonly seen in hypersensitivity pneumonitis secondary to immunologic reaction
  - Cellular bronchiolitis, noncaseating granulomas, bronchiolocentric cellular interstitial pneumonia composed predominantly of lymphocytes

- **Associated antineoplastic agent**
  - Bleomycin, methotrexate, cyclophosphamide, docetaxel, paclitaxel

- **Timing**
  - Usually immediate and may become clinically apparent within hours or days after institution of drug
  - Withdrawal of the offending drug and administration of steroids usually results in prompt and complete resolution of symptoms
**Hypersensitivity Pneumonitis**

**Imaging**

- Diffuse bilateral GGO or small, poorly defined centrilobular nodules
- Lobular areas of decreased attenuation and vascularity that show air trapping on CT images at expiration

CT shows bilateral patchy GGO and poorly defined centrilobular GGO (arrows).

She was being treated with molecularly targeted agent and anti-estrogen therapy (exemestane, everolimus) and had eosinophilia (11%) in peripheral blood.
**Thin-section CT Findings**

**Late-Onset Chemotherapy-Induced Pulmonary Injury**

<table>
<thead>
<tr>
<th>Pulmonary infiltration of Eosinophil (Eosinophilic Pneumonia)</th>
<th>Organizing pneumonia (Bronchiolitis Obliterans Organizing Pneumonia)</th>
<th>Nonspecific Interstitial Pneumonia</th>
<th>Radiation Recall Pneumonitis</th>
<th>Miscellaneous</th>
</tr>
</thead>
</table>

![CT images of pulmonary findings](image-url)
**Pulmonary infiltration of Eosinophil**

*(Eosinophilic pneumonia)*

**Clinical**

- **Histopathology**
  - Accumulation of eosinophils, macrophages in alveolar space
  - Eosinophils, lymphocytes, plasma cells within alveolar septa and interstitium

- **Symptoms**
  - Dyspnea, dry cough, fever, chest pain, discomfort, skin rash, hypoxemia

- **Lab**
  - Peripheral eosinophilia
  - BAL eosinophil and lymphocytes
  - Serum Ig E level ↑
  - Sometimes lacking eosinophilia

- **Associated antineoplastic agent**
  - Bleomycin, oxaliplatine, methotrexate, DCNU, floxuridine, fotemustine, gemtuzumab, etc

- **Timing**
  - Maybe acute in onset or, more commonly, have an insidious course with progression over several months
  - Drug withdrawal may not translate into immediate improvement in extensive disease

- **Risk factors**
  - Prior atopy or asthma
  - History of allergic reaction to drugs
  - Repeated courses of treatment
Pulmonary infiltration of Eosinophil (Eosinophilic pneumonia)

Imaging

• Form of Eosinophilic infiltration
  • Localized, diffuse or migratory
  • Faint shadowing or a discrete diffuse ground-glass opacity (GGO)

Case I. Eosinophil infiltration in a patient (M/46) with osteosarcoma

After one week from the start of combination chemotherapy (bleomycin, cyclophosphamide, methotrexate, dactinomycin), multiple nodular GGO (B-C) and nodular consolidation with halo (A) developed with thin-section CT.

He had increased level of eosinophil at peripheral blood (8.6%) and BAL fluid (15%). He also showed increased serum Ig E.
Pulmonary infiltration of Eosinophil (Eosinophilic pneumonia)

**Imaging**

• **Form of Chronic eosinophilic pneumonia**
  - Bilateral areas of consolidation involving mainly the peripheral lung regions
  - Airspace consolidation > GGO
  - Peripheral region > Central region
  - Mainly upper lung zone > Lower lung

• **Associated Findings**
  - Small nodules, interlobular septal thickening, mild reticulation
  - Eosinophilic pleural effusion
  - Mediastinal lymphadenopathy

**Case II. Eosinophilic pneumonia in a patient (F/55) with breast cancer**

During the period of everolimus treatment, multifocal peripheral consolidation was developed at both lung fields (A).

Thin-section CT obtained after 3 months (B) and 4 months (C) show wandering consolidation at the same level.

He had increased level of eosinophil at peripheral blood (8.6%) and BAL fluid (15%). He also showed increased serum Ig E.
Organizing pneumonia (OP)
(Bronchiolitis Obliterans Organizing Pneumonia, BOOP–like Reaction)

**Clinical**

- **Symptoms**
  - Dyspnea, low grad of fever and, sometimes, lancinating or acute pleuritic chest pain

- **Histopathology**
  - Organizing granulation tissue in respiratory bronchioles, alveolar ducts, adjacent alveoli

- **Lab**
  - BAL lymphocytes and sometimes of neutrophils or eosinophils increased
  - Surgical approach is preferred to the transbronchial route for lung biopsy

- **Associated antineoplastic agent**
  - Bleomycin, cyclophosphamide, methotrexate, interferon

- **Timing**
  - Disease suspected when migratory opacities are seen on chest films that are taken sequentially over a few weeks or months
  - There may be intervening periods with a normal chest radiograph, despite continued exposure to the drug
  - Multiple relapses of OP can occur even if the drug was withdrawn several weeks earlier, especially during steroid tapering
  - Generally reversible after drug cessation or steroid therapy
Organizing pneumonia (BOOP-like reaction)

Resemble findings of idiopathic OP (Cryptogenic organizing pneumonia)

Mainly bilateral areas of consolidation that usually have a predominantly subpleural and peribronchial distribution

Asymmetric > symmetric
Consolidation frequently have associated GGO
GGOs are usually bilateral and asymmetric

Imaging

Case I. Organizing pneumonia in a patient (M/68) with cholangiocarcinoma

At CT obtained after a month having started the 6th course of 5-fluorouracil, multifocal areas of consolidation with subpleural distribution were observed at both basal lungs (A-B).

Bronchoscopy was performed without revealing infectious pathogens or malignant cells from BAL fluid. CT obtained after treatment with steroid revealed improvement of lesions (C-D).
Organizing pneumonia (BOOP-like reaction)

Imaging

- Resemble findings of idiopathic OP (Cryptogenic organizing pneumonia)
- Mainly bilateral areas of consolidation that usually have a predominantly subpleural and peribronchial distribution
- Asymmetric > symmetric
- Consolidation frequently have associated GGO
- GGOs are usually bilateral and asymmetric

Case II. Organizing pneumonia in a patient (M/74) with lung cancer

One month after having started the 2nd course of paclitaxel, he developed dry cough and dyspnea. CT showed irregular subpleural consolidation and GGO in both lungs (A-B).
### Nonspecific Interstitial Pneumonia (NSIP)

#### Symptoms
- Dyspnea and sometimes, marked chest pain and a friction rub are present
- Chronic respiratory insufficiency

#### Lab
- Lung biopsies usually show findings consistent with fibrotic NSIP

#### Histopathology
- Varying proportions of interstitial inflammation and fibrosis that are temporally uniform

#### Associated antineoplastic agent
- Bleomycin, busulfan, cyclophosphamide, carmustine (BCNU) and chloroethyl-cyclohexyl nitrosourea (CCNU), methotrexate, etoposide, gemcitabine, taxan derivatives (docetaxel, paclitaxel), multi-agent chemotherapy regimens

#### Timing
- Can develop during treatments
- Or later, up to several years after termination of treatment (eg, with cyclophosphamide, nitrosoureas)
- Response to steroids is unpredictable and often is limited in magnitude or duration

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**Common manifestation of drug toxicity**
**Nonspecific Interstitial Pneumonia (NSIP)**

**Imaging**

- Resemble findings of idiopathic form or with NSIP secondary to other causes
- Extensive bilateral GGO with or without associated fine reticulation, traction bronchiectasis, and bronchiectasis
- Diffuse, but most commonly involve mainly the lower lung zones
- Small number in peripheral regions of the upper lung zones, which is distinctive from that of other causes of NSIP

**Nonspecific interstitial pneumonia in a patient (M/69) with lung cancer**

CT obtained before the start of chemotherapy shows normal lung parenchyma (A). Shortly after having started the initial treatment of combination therapy (pemetrexed, cisplatin) 12 days later, he developed coughing. CT revealed subpleural line, GGO with fine reticulation at the peripheral region of both lower lungs (B-C).
Radiation Recall Pneumonitis

**Clinical**

- **Disease entity**
  - Unique complication of antineoplastic agents, seen in patients who received previous radiation therapy to the chest

- **Pathophysiology**
  - Unknown mechanism
  - Irradiation may cause subclinical injury to lung parenchyma, which may have an additive effect in precipitating lung injury when another pulmonary insult is encountered at a later date

- **Symptom**
  - Fever, cough, and dyspnea
  - Dermatitis, mucositis, myositis

**Timing**

- Shortly after the initiation of therapy with the antineoplastic drugs

**Associated antineoplastic agent**

- Adriamycin, carmustine (BCNU), doxorubicin, etoposide, gefitinib, gemcitabine, paclitaxel and trastuzumab

**Imaging**

- Pulmonary infiltrates in the same field as in previous radiation therapy
- Subsequent progression to diffuse bilateral pneumonitis in severe cases
Radiation recall pneumonitis in a patient (M/64) with lung cancer

The patient developed radiation pneumonitis after receiving 5400 Gy of radiation therapy at mediastinum and T spine (A-B) (Left upper lobe was resected). After 6 months, the lesions in right lung had resolved and curvilinear GGO in left medial lung had organized to consolidation with architectural distortion (C-D), which was considered to be a radiation fibrosis. After 4 more months, patchy GGO and consolidation re-developed in both paramedian lungs (E-F), while he was receiving 5th cycle of gemcitabine and cisplatin combination therapy. Extent of radiation fibrosis in left lung became larger (E-F), compared with 4 months before (arrows). Patchy peripheral consolidation was dominant in medial aspect of lung which was the field of radiation therapy (E-F).
**Drug-induced pulmonary thromboembolism**

- Associated with bevacizumab, thalidomide, lenalidomide

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**Recurrent pulmonary thromboembolism in the patient (F/63) with breast cancer**

She was being treated with tamoxifen and had no history of immobilization. Focal pulmonary thromboembolism was found at left lower segmental pulmonary arteries (blue arrow, A) After two weeks of anticoagulation therapy, CT showed resolution at initial area but new lesion developed at contralateral side (B, red arrow).
Conclusion

The diagnosis of chemotherapy-induced pneumonitis remains an exclusionary process, particularly with respect to atypical infections as well as tumor recurrence.

In many instances, chemotherapy-induced pneumonitis may respond to withdrawal of the offending agent and to the application of corticosteroid therapy.
Reference

Thank you !!!

If you have any inquiries or comments for the presentation,

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