Pulmonary involvement in patients with hematologic malignant diseases: differential diagnosis

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Learning objectives

To know the multiple lung diseases that can occur in patients with hematologic malignancies.

To show the radiological findings that allow making the differential diagnosis.

Background

Even with new chemotherapeutic agents which currently achieve high levels of healing and remission in hematologic patients, morbidity and mortality remains high. Immunosuppression caused by the disease and severe neutropenia due to powerful chemotherapy treatments significantly increase the risk of infection which is by far the leading cause of lung disease in these patients. However, noninfectious complications such as pulmonary haemorrhage, thromboembolic complications, pulmonary or cardiac toxicity postchemotherapy may also occur. Respiratory distress is a serious entity that occurs with some frequency, almost always as a complication of pneumonia or sepsis. Finally it cannot be overlooked that many hematologic diseases, especially lymphomas, can directly affect the lung. (Fig 1)

Images for this section:
Pulmonary diseases in patients with hematological malignancies

- **Infections:**
  - Bacterial infections
  - Fungal infections
  - Viral infections
- **Non-infectious complications:**
  - Graft versus host disease
  - Pneumonitis after radiotherapy
  - Drug induced complication
  - Cardiac toxicity
  - TRALI (Transfusion-related acute lung injury)
  - Pulmonary hemorrhage
  - Thromboembolic complications
- **ARDS: Acute Respiratory Distress Syndrome**
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  - Primary pulmonary lymphoma
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  - Non- Hodgkin’s lymphoma

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**Fig. 1**
INFECTIOUS COMPLICATIONS:

Neutropenia produced in patients treatments with leukemias and lymphomas, especially if it is severe (less than 500 cells) and maintained (more than 8 days) is a key factor in the risk of infection. The mechanisms of inflammation activation are altered so pneumonia is produced with clinically latent start and few symptoms mainly limited to fever and maintained cough. However, it has a high severity and mortality. Therefore, although empirical broad spectrum antibiotic is set in early treatment, the specific diagnosis is very important in order to establish promptly the most appropriate treatment.

Bacterias (pneumococcus, Haemophilus influenza, Pseudomonas, Nocardia, Legionella, Enterobacter, Staphylococcus, Acinetobacter baumannii, mycoplasma, etc.), fungi (Aspergillus, Candida, Pneumocystis jiroveci, etc.) or viruses (cytomegalovirus, herpes, influenza, adenovirus, etc.) may be the causative organisms of pneumonia.

Radiological findings in different causative organisms are usually similar and unspecific, although there are some characteristics that can guide about the possible etiologic germ. These are useful due to the fact that microbiological diagnosis with certainty is difficult and sometimes delayed, becoming necessary to establish early treatment.

They are classified into:

**Bacterial pneumonia**: (fig 2,3,4,5)

They are usually alveolar, segmental or lobar consolidations similar to pneumonia in immunocompetent but more prone to develop complications (cavitation, effusion, multilobar or diffuse extension). Sometimes small centroacinar nodules, "tree in bud" images and peribronchial thickening are present. In some cases atypical forms with patchy areas of frosted glass or diffuse involvement are observed. The acinetobacter baumannii is an opportunistic pathogen resistant to antibiotics that frequently affects patients from ICU and can give the latter pattern. It presents high mortality.

**Fungal pneumonia**: (fig 6,7,8,9)

Aspergillus is the filamentous fungus that most often affects neutropenic patients. There are many subtypes being Aspergillus fumigatus the most frequent. It presents high mortality.
The microbiological diagnosis is based on the detection of positive galactomannan and positive nucleic acid (in serum or in material obtained from bronchoalveolar washing) although the final diagnosis requires the fungus demonstration in tissular sample.

The presence of nodules surrounded by a peripheral halo in ground glass density is the characteristic radiology. This halo corresponds to peripheral hemorrhage. In other occasions a consolidation or pseudomass, also surrounded by halo, appears. The presence of wedge-shaped peripheral consolidations is also characteristic, which correspond to hemorrhagic infarcts. Cavitation with an air crescent sign may occur during the evolution towards healing.

Candida (fig 10) can cause pneumonia in these patients less frequently. It appears as focal areas of consolidation or sometimes as multiple nodules. They can cavitate. Organism demonstration in tissue is required for diagnosis.

Pneumocistitis jiroveci is considered a fungus. Its incidence has decreased due to preventive treatment, being infrequent in hematological patients except for transplanted patients with graft versus host disease, maintained corticoid treatment at high doses or acute myeloid leukemia.

Geographic areas of ground-glass opacities alternating with respected areas are the characteristic radiology. It typically respects the subpleural space. Sometimes septal thickening is superimposed giving the characteristic "crazy-paving" image.

**Viral pneumonia:** (fig 11)

It usually appears with interstitial involvement (sometimes micronodular) or in ground glass, patchy or diffuse.

The plain chest x-ray is the first choice diagnostic technique, but has a low sensitivity in early diagnosis. Also many times, due to patient acuity, a single supine frontal projection of lower quality is performed. The CT (high resolution or multislice) allows an early diagnosis of the lung disease presence or absence in these patients, and allows the assess of their characteristics. In some cases this will lead to their causes. Therefore, when the chest x-ray of a severe neutropenic patient with sustained fever is normal, lung CT (high resolution if possible) should be performed. Besides, using contrast IV is no required (unless pulmonary embolism is suspected) and the cost-benefit relation is very good, being cheap compared to the high cost of antibiotics and their potential adverse effects.

**NONINFECTIOUS COMPLICATIONS:**
**Graft versus Host Disease**: (fig 12)

It occurs as a complication of allogenic bone marrow transplantation. It can be acute or chronic. Pulmonary involvement occurs in chronic forms in up to 10% of patients. It appears 6 months after transplantation. Bronchiolitis obliterans occurs. Radiologically, geographical areas with mosaic pattern (alternating areas of higher and lower density) appear, which significantly increase in expiration indicating the presence of air entrapment. Clinically and radiologically differential diagnosis arises with viral pneumonia. Corticosteroids are required for treatment.

**Post-radiation pneumonitis**:

Acute pneumonitis occurs between three weeks and three months after radiotherapy and consists of areas of condensation or ground glass typically bounded by the radiation field. Clinically improves with corticosteroids.

Chronic pneumonitis appears later and is associated to fibrotic changes predominantly paramediastinal or in vertices.

**Pulmonary drugs toxicity**:

There are many cytotoxic and non-cytotoxic agents with potential pulmonary toxicity produced by various mechanisms. Examples of these drugs are Bleomycin, Methotrexate, Cytarabine, Cyclophosphamide and Rituximab (the latter is a monoclonal antibody recently used in B cell lymphoma in combination with chemotherapy).

They can produce diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), bronchiolitis obliterans, or even pulmonary hemorrhage.

**TRALI (Transfused Related Acute Lung Injury)**:

This rare complication occurs in polytransfused patients. It is defined as acute pulmonary injury associated to transfusions. Non cardiogenic pulmonary edema occurs due to pulmonary vascular endothelium injury which increases capillary pressure.

**Heart failure**: (fig 13)
In these patients pulmonary edema frequently occurs, due to multiple possible causes: cardiogenic, cardiac toxicity by medications (cyclophosphamide, anthracyclines, etc.), fluids excess, anemia, etc. Radiologically, bilateral alveolar pattern usually appears.

**Pulmonary hemorrhage:**

It is conditioned by thrombocytopenia, coagulation disorders or certain drugs.

**Thromboembolic complications:** (fig 14)

Patients with hematologic diseases present higher predisposition to them.

**RESPIRATORY DISTRESS:**

It is defined as persistent severe respiratory failure refractory to $O_2$ (Ratio $PO_2/ FiO_2 < 200mmHg$). It is a serious complication of some pneumonia, sepsis, post-chemotherapy or may appear with unknown cause. It presents high mortality.

Radiologically, alveolar condensation areas or bilateral ground glass appear with air bronchogram and without cardiomegaly.(fig 15)

**PULMONARY LYMPHOMA:**

Malignant lymphoproliferative diseases that affect the lungs can be primary (Primary pulmonary lymphoma), or secondary (Hodgkin and non-Hodgkin lymphomas).

Primary pulmonary lymphoma is rare. Most of them correspond to MALT lymphoma (mucosa-associated lymphoid tissue) which in the lung is sometimes called BALT (bronchus-associated lymphoid tissue). They are low-grade, clinically not very aggressive but there are also high-grade primary lymphomas (these are usually large cell lymphomas). Radiologically usually appears as a focal consolidation or single or multiple nodules that often have air bronchogram (fig 16). Lymphadenopathy is not associated to them. The diagnosis is histological.

The secondary pulmonary lymphoma is the most common form of pulmonary lymphoma. It occurs in Hodgkin lymphoma (HL) and in non-Hodgkin lymphoma (NHL). The incidence varies depending on the reference, with approximately 10% in the LH at the time of
diagnosis and up to 30% in the NHL, but it increases throughout the course of the disease and its recurrences. Clinical is unspecific mimicking sometimes an infectious process.

Pulmonary involvement may appear in several radiological ways, which can be grouped into four types:

- Single or multiple nodules: (fig 17,18)
  It is the most common presentation (sometimes they simulate metastases). Air bronchogram can occur in up to 50% of cases. It is said that this is due to tumor peribronchial infiltration without destruction of the bronchial wall.(fig 19)

- Consolidations or pseudomasses: (fig 20)
  They can be single or multiple. They simulate pneumonia.

- Direct extension from the hilum or mediastinum to the lung: (fig 21)
  This type of involvement is very characteristic of Hodgkin lymphoma.

- Diffuse interstitial pattern: (fig 22)
  Peribronchovascular and septal thickening (simulates lymphangitis) with small centrilobular nodules and sometimes frosted glass.

It should be noted that the mediastinal lymphadenopathy appears only in 30-50% of cases.

Although less characteristic, other radiological findings such as atelectasis, pleural effusion or pneumonitis can also occur.

Due to the wide variability of findings, it will almost always be required histologic confirmation of diagnosis, especially if it implies changes in the therapeutic approach.

Pulmonary involvement diagnosis indicates stage IV in lymphoma, which significantly worsens the prognosis although there are other factors that influence the prognosis such as the grade and cell type.

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**Fig. 1**
Fig. 2: Bacterial pneumonia is observed. Patient is a 71 years old man, with chronic lymphatic leukemia in progress despite several lines of treatment. TC: mediastinal lymphadenopathy and alveolar condensation in left lower lobe. Blood cultures + E. Coli. Exitus two days despite antibiotic treatment.
**Fig. 3:** Bacterial pneumonia. Patient is a 70 years old man, with myelodysplastic syndrome and maintained fever. Plain x-ray and CT: Bilateral consolidations and cavitary mass with multiple air-fluid levels. Cultives: Staphylococcus aureus

**Fig. 4:** Bacterial pneumonia: Patient is a 70 year old woman with chronic lymphatic leukemia admitted in the ICU for several days with polymicrobial antibiotic treatment. Fever persists. Plain x-ray and CT: diffuse reticular pattern. Cultives: Acinetobacter baumannii
**Fig. 5:** Bacterial pneumonia: *Mycoplasma pneumoniae*. Patient is an 18 year old female with relapsed HDK lymphoma in treatment. He goes to the hospital due to high fever. a) Alveolar-interstitial infiltrate with left predominance. b) Favorable evolution after treatment

**Fig. 6:** Fungal pneumonia: Aspergillosis. Patient is a 55 year old male with severe neutropenia and fever maintained for 11 days with no response to antibiotics. Rounded consolidation (pseudomass) with ground glass "halo". Multiple negative cultives. Galactomannan + for aspergillus.
**Fig. 7:** Fungal pneumonia: Evolution. Same case of the previous figure. Plain x-rays: unfavourable radiological developments despite antifungal treatment. Exitus at 35 days.

**Fig. 8:** Fungal pneumonia. Patient is a 68 year old man diagnosed with severe aplastic anemia, treatment for 1 month. Severe neutropenia and fever. Aspergillus pneumonia: fungus hyphae were demonstrated in the histological sample obtained from puncture of LSD. Despite antibiotic and antifungal treatment (amphotericin B and caspofungin that is changed by voricanazole later). The patient died after 30 days.
**Fig. 9:** TC of patient from previous figure: Multiple consolidations and bilateral nodules with halo.

**Fig. 10:** Fungal pneumonia: Candida. Acute myeloblastic leukemia M6. Rounded condensation with ground glass halo and incipient cavitation. Very similar to aspergillosis cases. Cultives of sputum, bronchoalveolar lavage, blood cultives and urine negative cultives. Only galactomannan + a candida (62.5). Favorable evolution with antifungal treatment.
**Fig. 11:** Viral pneumonia. Influenza A. Patient with chronic lymphatic leukemia in treatment, which presents maintained fever. TC: Areas of increased density in ground glass and micronodules: Viral pneumonia healed after treatment with oseltamivir in patient with a history of influenza A one year before (reactivation).
Fig. 12: Graft versus Host Disease (GVHD). Burkitt NHL treated 8 years before with chemotherapy and allogenic bone marrow transplantation in complete remission. Chronic severe GVHD refractory to several treatment lines. Severe CAFL (chronic air flow limitation) with FEV1 of 26%. Mosaic pattern in CT alternating areas of higher and lower density lung parenchyma consistent with bronchiolitis obliterans. In green: expiratory CT: findings are enhanced which indicates air trapping.
Fig. 13: Cardiac toxicity. Patient is a 68 year-old-man with large B-cell non-Hodgkin lymphoma which has finished chemotherapy two months before. He debuts with heart failure. Cardiology diagnosis: Dilated cardiomyopathy caused by chemotherapy.
Fig. 14: Pulmonary embolism: Patient aged 60 diagnosed with chronic lymphocytic leukemia. Adenopathic conglomerate in mediastinum and pulmonary thromboembolism in left lower lobar artery
**Fig. 15:** Distress (SRDA): Patient is a 58 year-old-male diagnosed with large B cell non-HDK lymphoma, which has completed chemotherapy 1 month ago. Admitted to hospital because of persistent fever and dyspnea. Severe respiratory failure which required ICU admission with mechanical ventilation. Diagnosis: acute respiratory distress syndrome secondary to bilateral pneumonia. No causative organism was demonstrated. (During the stay in ICU acinetobacter baumannii colonization is detected). Favorable evolution with discharge from the hospital after 40 days.

**Fig. 16:** Primary pulmonary lymphoma. Patient is a 60 year-old-woman with a history of Sjogren syndrome. a, b, c, d). Plain x-ray and CT: single focal consolidation with air bronchogram. e, f). Biopsy: MALT lymphoma: diffuse proliferation of B-lymphocytes invading the bronchial epithelium (black arrow) and the bronchial mucosa muscle layer (red arrow).
**Fig. 17:** HDK lymphoma with pulmonary involvement. Patient is a 28-year-old man with HDK lymphoma which enters with cervical and mediastinal lymphadenopathy, and multiple pulmonary nodules. The presence of pulmonary nodules indicates stage IV.

**Fig. 21:** HDK lymphoma with pulmonary involvement. Patient with relapsed lymphoma HDK: a) plain x-ray: mediastinal mass invading the lung. b) plain x-ray 3 months later: disease progression c) CT: direct lung infiltration from mediastinum with pleural invasion of chest wall. In biopsy lymphoma areas and foci of lipoid pneumonitis are observed.
Fig. 18: Non-HDK lymphoma. Patient is a 40 year-old-male under study due to arrhythmias. Casual detection of multiple pulmonary nodules. Biopsy: non-HDK lymphoma.

Fig. 20: Pulmonary lymphoma. Patient is a 58 year-old-male with dyspnea and fever. a, b, c, d). CT with multiple nodules and persistent consolidations. e) Hematoxylin-eosin:
monotonous lymphocyte proliferation. f) Immunohistochemistry CD 20 + indicating that they correspond to B-lymphocytes.

Fig. 19: Air bronchogram in three different patients. The air bronchogram is a common finding in consolidations and pulmonary lymphoma nodules. It is said that it is due to peribronchial invasion without bronchial wall destruction.

Fig. 22: Large B cell Non-HDK Lymphoma. a) CT with lung window: diffuse interstitial pattern with septal thickening. b) mediastinal lymphadenopathy.
Conclusion

Knowledge of the various entities that may appear in patients with hematological diseases and of their radiological findings facilitates the realization of the accurate diagnosis. It also allows early diagnosis of some cases, which is critical given the high mortality associated to them.

CT (or high resolution multislice) plays an essential role in these patients. Their implementation is indicated in every neutropenic patient with maintained fever and normal plain x-ray.

Although there are some characteristic radiological findings, when therapeutic approach changes, clinical, microbiological and histological correlation will almost always be necessary.

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