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UPDATE IN RADIOLOGY

Hematologic neoplasms: Interpreting lung findings in chest computed tomography[☆]



P. Calvillo Batllés^{a,*}, J. Carreres Polo^a, J. Sanz Caballer^b,
M. Salavert Lletí^c, L. Compte Torrero^d

^a Servicio de Radiología, Hospital Politécnico i Universitari La Fe, Valencia, Spain

^b Servicio de Hematología, Hospital Politécnico i Universitari La Fe, Valencia, Spain

^c Unidad de Enfermedades Infecciosas, Hospital Politécnico i Universitari La Fe, Valencia, Spain

^d Servicio de Neumología, Hospital Politécnico i Universitari La Fe, Valencia, Spain

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Abstract Lung disease is very common in patients with hematologic neoplasms and varies in function of the underlying disease and its treatment. Lung involvement is associated with high morbidity and mortality, so it requires early appropriate treatment. Chest computed tomography (CT) and the analysis of biologic specimens are the first line diagnostic tools in these patients, and sometimes invasive methods are necessary. Interpreting the images requires an analysis of the clinical context, which is often complex. Starting from the knowledge about the differential diagnosis of lung findings that radiologists acquire during training, this article aims to explain the key clinical and radiological aspects that make it possible to orient the diagnosis correctly and to understand the current role of CT in the treatment strategy for this group of patients.

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PALABRAS CLAVE

Neoplasias hematológicas;
Trasplante de precursores hematopoyéticos;

Neoplasias hematológicas: interpretación de los hallazgos pulmonares en la tomografía computarizada torácica

Resumen La patología pulmonar en la historia de un paciente con neoplasia hematológica es muy frecuente y variable en función de la enfermedad de base y la terapia recibida. La morbimortalidad asociada es alta, por lo que requiere un tratamiento correcto y precoz. La tomografía computarizada (TC) torácica, junto con el análisis de muestras biológicas, son las

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* Corresponding author.

E-mail address: pilarcalvillo@gmail.com (P. Calvillo Batllés).

Tomografía
computarizada
multidetector;
Enfermedad
pulmonar

herramientas de diagnóstico de primera línea empleadas en estos pacientes, y en determinados casos se requieren métodos invasivos. La interpretación de las imágenes exige el análisis de un contexto clínico en muchas ocasiones complejo. Partiendo del conocimiento que adquiere el radiólogo en su formación sobre el diagnóstico diferencial de los hallazgos pulmonares, el objetivo de este trabajo es explicar los aspectos clínicos y radiológicos claves que permiten orientar correctamente el diagnóstico y asimilar el papel actual de la TC en la estrategia terapéutica de este grupo de enfermos.

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Introduction

Hematologic neoplasms (HN) are characterized by being frequently disseminated at the moment of diagnosis, with bone marrow affectation. They are especially sensitive to chemotherapy or radiotherapy, therefore the patients usually receive aggressive chemotherapy and, in certain cases, hematopoietic precursors transplantation (HPT). The disease per se and its treatments cause prolonged pancytopenias, predisposing to very serious infections that make up a diagnostic and therapeutic emergency. Non-infectious pulmonary complications secondary to treatment are also frequent and determine prognosis. Pulmonary tumor disease includes infiltration due to HN, pulmonary neoplasm and post-HPT lymphoma. Chest computed tomography (CT) narrows down the differential diagnosis of these diseases. Their indications are reviewed, as well as the main clinical information that should be recorded in the radiologic application and interpretation of the findings based on the clinical context.

Indications of chest computed tomography

Performing helical chest CTs in patients with HN pursues two objectives: early detection of lesions not visible in the chest X-rays which require urgent treatment, and better characterization of the findings to outline diagnostic and therapeutic possibilities.¹ Reconstructions being < 1.5 mm cut thick and high resolution computed tomography (HRCT) are required since many of the pulmonary complications kick in as interstitial patterns.

The etiologic diagnosis of fever manifestations in patients with neutropenia and/or HPT requires the search for microorganisms and infectious markers. Chest HRCT plays a fundamental role—urgent when there are clinical signs of severity and early (<24h) in the absence of a response to antibiotics therapy in 72–96h because treatment of a possible invasive fungal infection (IFI) requires an early administration, a determinant factor for prognosis. In patients clinically classified as being in high risk of IFI^{2,3} antifungal drugs are administered empirically, while in subgroups of lower risk it is possible to delay treatment in cases of very likely clinical manifestations or early positive specific infection markers, which reduces the high costs and toxicity of these drugs.⁴ The markers usually used are the serum galactomannan test while the chest HRCT is performed early in a serial way.^{5,6} Galactomannan, a component

of the *Aspergillus* cell membrane, is falling into disuse as a marker due to its loss of sensitivity associated to antifungal prophylaxis.⁷ The HRCT gains more importance still as an urgent diagnostic test that allows starting an early therapy when pulmonary lesions characteristic of IFI are visualized. In addition, it can give rise to other etiologies and guide the acquisition of bronchoalveolar lavage (BAL) through bronchoscopy, thus speeding up the diagnosis of germs not covered by the initial empirical therapy.

In other respiratory manifestations HRCT is necessary to identify and characterize non-infectious complications, relapse and secondary neoplasms that can go unnoticed in radiographic tests or show similar patterns.

Key clinical information

When studying the HRCT of a patient with HN we need to know the clinical information and other fundamental data about the underlying condition as well as therapies and complications (Table 1).

Patients with Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL) receive a less intense polychemotherapy than those with leukemias, with shorter neutropenias so if pulmonary lesions are seen the possibility of tumor affectation should be taken into consideration.

It is not odd to find pulmonary neoplastic spread in autopsies of leukemias, but its radiologic manifestation is exceptional and the respiratory disease is mainly marked by infections. Acute myeloid leukemia (AML) deserves special attention, since pulmonary manifestations occur in all the stages of the disease, and it is possible to observe added to infections, more cases of hemorrhages due to thrombocytopenia and toxicity due to chemotherapy.

Multiple myeloma (MM) occurs mainly with bacterial infections due to humoral immunity deficiency and hypoventilation due to bone affectation. Pulmonary edema is very common while findings of pulmonary infiltration due to amyloids, plasma cells or light chain deposits are rare.

Chemotherapeutic drugs do not only depress immune function, but some of them are responsible for pulmonary toxicity, suspected by the radiologic pattern and its temporal relation with the treatment. Other therapeutic agents used can cause respiratory failure, often with a radiologic expression similar to alveolar damage, edema or hemorrhage.

In especially chemosensitive tumors (lymphomas and MM), the goal of autologous HPT is to allow the administration of high doses of chemotherapy with subsequent

Table 1 Request model for a HRCT.

Urgent <input type="checkbox"/>		Early <24 h <input type="checkbox"/>		Priority Early <48 h <input type="checkbox"/>		Planned <input type="checkbox"/>	
Reason for request							
History							
Diagnosis: Pulmonary history: No <input type="checkbox"/> Yes <input type="checkbox"/> (describe)				Relapse: No <input type="checkbox"/> Yes <input type="checkbox"/>			
Treatment and immune state							
Intensive chemotherapy <input type="checkbox"/> Date:				Radiotherapy <input type="checkbox"/> Date:			
Hematopoietic precursor transplantation (HPT) <input type="checkbox"/>							
Autologous <input type="checkbox"/> Allogeneic <input type="checkbox"/>							
Date:							
Pulmonary toxics <input type="checkbox"/> (describe)							
Date:							
Neutropenia <input type="checkbox"/>		Corticotherapy <input type="checkbox"/>		Graft vs host disease (GVHD) (immunosuppressant therapy) <input type="checkbox"/>			
Actual infectious prophylaxis <input type="checkbox"/>							
Wide-spectrum antibiotics <input type="checkbox"/> Antifungal <input type="checkbox"/> Prophylaxis <i>P jirovecii</i> <input type="checkbox"/>							

rescue of hematopoiesis thanks to the infusion of hematopoietic precursors obtained previously from the same patient. This prevents irreversible medullary failure and shortens the time of neutropenia. Pulmonary complications will be fundamentally the consequence of intensive chemotherapy not the consequence of the transplant per se.

The allogenic HPT is mainly used in patients with acute leukemias to re-establish hematopoietic and immunity functions. The cells are obtained from a family member with an identical HLA (Human Leukocyte Antigen) or else from someone unrelated but with a compatible HLA and they may come from the bone marrow, peripheral blood or the umbilical cord. Before the transplant the patient receives conditioning

with high doses of chemotherapy, with or without full-body radiotherapy, to suppress the bone marrow, destroy the malignant cells and prevent the host's rejection against the graft cells. Also a strong immunosuppressant treatment is later administered to avoid reverse rejection and when the hematopoietic function is reinstated the donor's cells recognize the recipient's tissues as foreign and they cause graft-versus-host disease (GVHD). Yet despite of this some patients develop GVHD and require a more extended immunosuppressant therapy. All of this explains why the allogenic HPT recipient suffers from a deep and prolonged immune deficit that leads to death in nearly 10–35% of patients.

Table 2 Moderate immunosuppression (disease onset, end of treatment, >180 days – late period – post-HPT^a).

Etiology	Nodes	Glass areas and/or consolidations
Infections	Opportunistic bacteria ++ ^a Conventional pyogenic bacteria Community respiratory viruses Very unlikely fungi	Conventional pyogenic bacteria ++ Community respiratory viruses (frequency based on seasonality)
Hematologic neoplasm	Lymphoma (HL > NHL) ++ relapse Primary pulmonary lymphoma Lymphomatoid granulomatosis	Primary pulmonary lymphoma Secondary lymphocytic infiltration
Malignancy	Post-transplant lymphoproliferative disease ^a Lung cancer Metastasis	Lung cancer
Other	Benign nodes: granulomas and other residual lesions from former infection	Organized pneumonia ^a Residual lesions from former infection

++ Most common etiology.

Opportunistic bacteria (that can make up granulomas): e.g., Nocardia, Rhodococcus, Mycobacterias (TB and atypical bacteria).

Conventional pyogenic bacteria: e.g. types Streptococcus, Staphylococcus, Haemophilus.

Community respiratory viruses: Influenza, Parainfluenza, syncytical respiratory virus, Rhinovirus, Coronavirus, Metapneumovirus, Adenovirus, Bocavirus and other.

^a Typical lesions of the post-HPT (hematopoietic precursor transplantation). In this table we can see a patient without graft-vs-host disease.

Table 3 High degree of immunosuppression.

	Chemotherapy -induction and consolidation- (neutropenia)	Post-HPT early pregraft <30 days (neutropenia)	Post-HPT postgraft 30–180 days (cellular and humoral immunity alteration)	Immunosuppressors due to chronic GVHD (cellular and humoral immunity alteration)
<i>Nodes</i>				
Infection	Filamentous fungi Nosocomial bacteria Non- <i>Candida</i> emerging yeasts	Filamentous fungi Nosocomial and opportunistic bacteria Non- <i>Candida</i> emerging yeasts	Filamentous fungi Bacteria: IRHC and opportunistic CMV and respiratory viruses	Filamentous fungi Encapsulated and opportunistic bacteria CMV and respiratory viruses
No infection	Neumonitis due to hypersensitivity Toxicity due to CHEMO (rare)	–	Post-transplant lymphoproliferative disease	Post-transplant lymphoproliferative disease Lung cancer Metastasis
	Nodes already present in CHEMO pretreatment: lymphoma or residual benign lesions	Nodes already present in CHEMO pretreatment: lymphoma or residual benign lesions	Nodes already present in CHEMO pretreatment: lymphoma or residual benign lesions	Nodes already present in CHEMO pretreatment: lymphoma or residual benign lesions
<i>Glass areas and/or consolidations</i>				
Infection	Nosocomial bacteria Filamentous fungi Non- <i>Candida</i> emerging yeasts	Nosocomial and opportunistic bacteria Filamentous fungi Non- <i>Candida</i> emerging yeasts	Bacteria: IRHC and opportunistic CMV and respiratory viruses Filamentous fungi <i>Pneumocystis jirovecii</i> (>day 100)	Encapsulated and opportunistic bacteria CMV and respiratory viruses Filamentous fungi <i>Pneumocystis jirovecii</i>
No infection	Toxicity due to CHEMO TRALI (6 h post) Toxicity due to rituximab (4 weeks post) Differentiation syndrome (2–47 day post-ATRA) Acute pulmonary damage due to G-CSF (first days post)	Pulmonary edema (2nd–3rd week post-HPT) HAD (12–15 days post-TPH) Pregraft respiratory distress syndrome (5–21 day post-TPH)	Neumonitis due to acute RT (3–6 weeks post-RT) Organized pneumonia Post-transplant lymphoproliferative disease	Organized pneumonia Post-transplant lymphoproliferative disease Lung cancer

ATRA: all-trans retinoic acid; CMV: cytomegalovirus; GVHD: graft vs host disease; G-CSF: granulocyte colony-stimulating factor; DAH: diffuse alveolar hemorrhage; IRHC: infections related to health care (including intra- and extrahospitalary), micro-organisms very similar to those of nosocomial origin characterized by multi- or panresistance to the usual antibiotics; post-HPT: post-hematopoietic transplantation; CHEMO: chemotherapy; RT: radiotherapy; TRALI: transfusion-related alveolar lung injury.

Filamentous fungi: *Aspergillus*; a lot less common, *Mucor*, *Fusarium* and *Scedosporium*.

Nosocomiales bacteria and IRHC: e.g., *Klebsiella*, *Serratia*, *Pseudomonas*, *Acinetobacter* and *Stenotrophomonas* (gram negative). *Staphylococcus* and *Streptococcus* (gram positive cocci).

Non-*Candida* emerging yeasts: e.g., types *Trichosporum*, *Cryptococcus*, *Saprochaeta* and *Geotrichum*.

Opportunistic bacteria (that can make up granulomas): e.g. *Nocardia*, *Rhodococcus*, *Mycobacterias* (TB and atypical bacteria).

Encapsulated bacteria: e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*.

Viruses: Cytomegalovirus (CMV), community respiratory virus (respiratory syncytial virus, *Adenovirus*, *Influenza*, *Parainfluenza*, *Metapneumovirus*, *Bocavirus*, *Rhinovirus*, *Coronavirus*) and less commonly the herpes simplex virus and varicella-zoster virus.

Based on at what specific moment in his history the patient is he will be included in one of these groups to approach diagnosis⁸ (Tables 2 and 3):

A. *Patient with moderate immune depression*. Does not receive active chemotherapy or immunosuppressants.

- a) Onset of disease.
 - b) End of treatment.
 - c) Late period (>180 days post-HPT) without GVHD.
- B. *Patient with a high degree of immune depression* because he is receiving:
- a) Active chemotherapy to treat his disease.

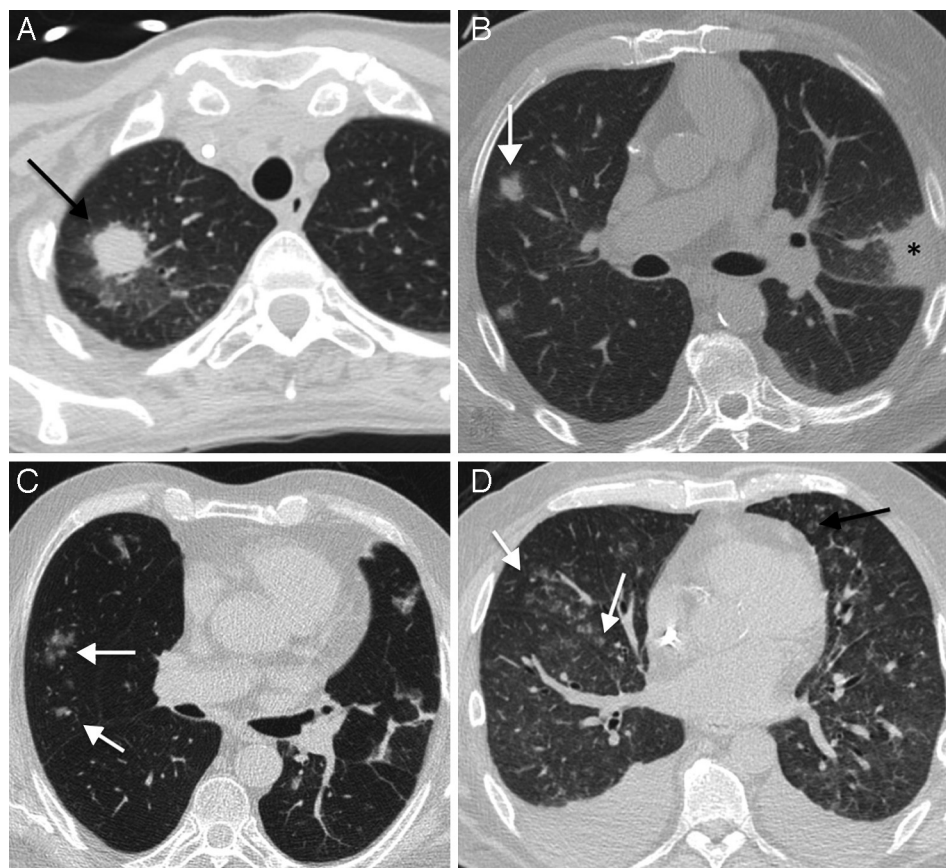


Figure 1 Infectious nodes. High-resolution computed tomography (CT). (A and B) Invasive fungal infection (IFI) due to *Aspergillus fumigatus*. Acute myeloid leukemia (AML) in early pre-graft period of hepatopoietic precursor transplantation (HPT). Nodes > 1 cm with halo (arrows), consolidation with pleural base and halo (asterisk). Infection due to respiratory syncytial virus (C) and cytomegalovirus (D). Low attenuation nodes < 1 cm (arrows) in patients in late stage post-HPT due to leukemia.

- b) Immunosuppressant therapy.
- Early pre-graft period (7 days of pre-infusion with chemotherapeutic conditioning–30 days post-HPT; neutropenia).
 - Early post-graft period (30–180 days post-HPT; alteration of cell and humoral immunity).
- c) Prolonged immunosuppressant therapy due to chronic GVHD. Late period (>180 days post-HPT).

Key pulmonary radiologic findings

Nodes and masses

See [Tables 2 and 3](#).

Infections

In the onset of the disease, before treatment, infectious nodes are uncommon. They are usually bacterial or viral and exceptionally, at the very moment of the diagnosis of AML with severe cytopenia or iron overload they can be fungal.⁹ In severely immunologically depressed patients, the nodes can be fungal, viral or bacterial ([Fig. 1](#)).

Filamentous fungi are common in prolonged deep neutropenias (over two weeks) especially during chemotherapy of an AML and in the early post-HPT period.⁸ In 94% of

invasive aspergillosis it is possible to observe nodes that are usually multiple-bilateral and at least one >1 cm.¹⁰ The ground-glass attenuation halo distinguishes them from bacterial nodes^{11,12} but it usually disappears during the first five days. Mucormycosis is suspected before aspergillosis if 10 nodes or more are observed as well as sinus affection, pleural effusion¹³ and/or the inverted halo sign,¹⁴ especially if the antifungal therapy did not cover that fungus. The HRCT is useful because there is no serological test available today for the diagnosis of mucormycosis.

Viral nodes often have poorly-defined edges and/or halos but they are distinguished by their small size (<1 cm) and the absence of cavitation.¹⁵ Bacterial nodes usually have better-defined edges.

Centrilobular nodes often represent unspecific infectious bronchiolitis, especially if accompanied by sprouting-tree images; however, diffuse symmetrical bilateral centrilobular nodes with predominance in upper fields and ground-glass attenuation, in the absence of other infectious findings, should lead to respiratory bronchiolitis by tobacco or pneumonitis due to hypersensitivity secondary to the treatment.

Pulmonary infiltration due to hematologic neoplasm

In NHL and HL infiltration is observed more often in relapses, increasing due to the greater survival of the patients with

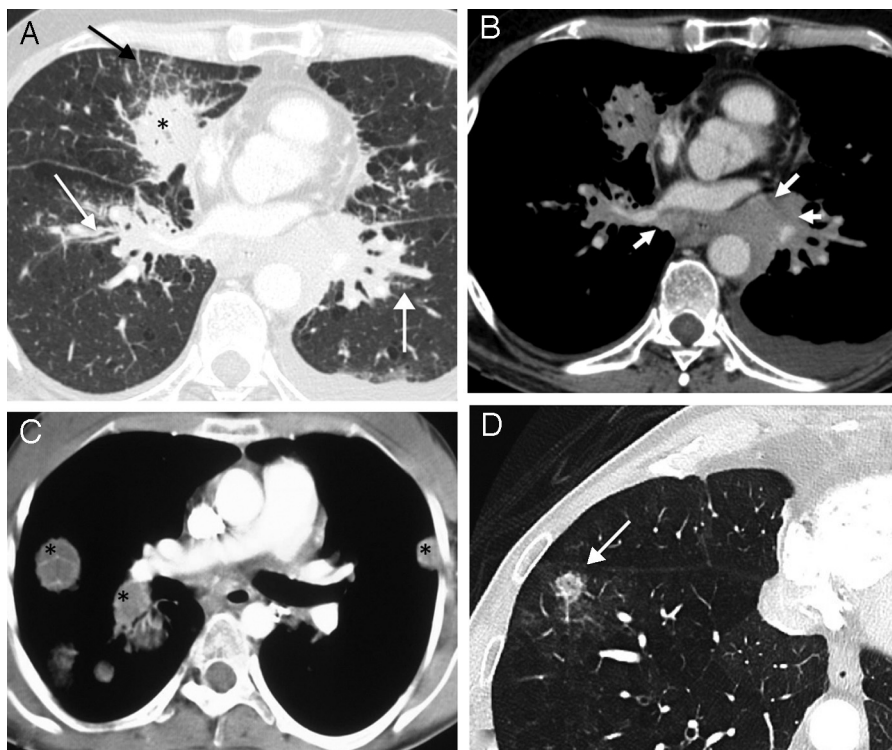


Figure 2 Hematologic neoplasms. (A and B) Non-Hodgkin's lymphoma with secondary pulmonary affectionation. High-resolution computed tomography (CT). Bilateral adenopathies (short arrows) and secondary pulmonary infiltration thickening the peribronchovascular and septal pulmonary interstitium (long arrows) making up one pulmonary mass (asterisk). (C) Pulmonary post-transplant lymphoproliferative syndrome. Chest CT. Bilateral pulmonary nodes and masses (asterisks) associated with bilateral hilar adenopathies (not shown). (D) Primary B pulmonary lymphoma of the mucosa-associated lymphoid tissue (MALT). High-resolution computed tomography (CT). It did not show any adenopathies. Courtesy of Dr. Flors (University of Virginia Health System).

the current therapies. It usually manifests itself as multiple pulmonary nodes <1 cm with irregular edges, consolidations and/or masses, which are more frequent in NHL and have worse prognosis. Primary pulmonary lymphoma occurs in patients of 55–60 years of age, it is usually non-Hodgkin of the B MALT type (mucosa-associated lymphoid tissue) and it shows as a nodule or peribronchovascular consolidation at the bronchogram test. These lesions can be single or multiple bilateral.^{16,17} They are characterized by the absence of mediastinal adenopathies at the moment of diagnosis and up to 3 months later, they grow slowly. Identical presentations to those of lymphocytic interstitial pneumonia have also been described (Fig. 2).

Myeloid leukemias and myelodysplastic syndromes can make up a blastic tumor called granulocytic sarcoma—extremely rare in the lung, where it can occur as a node, mass or consolidation.¹⁸

Exceptionally, MM can present nodes and/or masses, associated with adenopathies that simulate a lymphoma or a pulmonary cancer¹⁹ with a bad prognosis.²⁰

Lymphomatoid granulomatosis is an extranodal lymphoproliferative process associated with the Epstein–Barr virus (EBV) mainly affecting the lung and the central nervous system. It occurs as multiple pulmonary nodes in more than 80% of the cases, they are variable in number and size, and of basal predominance. Nodes can progress rapidly, coalesce

and cavitate, as well as disappear spontaneously, migrate or evolve making up the sign of the inverted halo sign.^{21,22}

Secondary neoplasms

Lung cancer has increased in survivors of HL, NHL and CLL, and its etiopathogenesis is being studied. Its appearance ranges from one to several years after the diagnosis of HN.

Patients receiving allogenic HPT can develop a post-transplant lymphoproliferative disorder (PTLD), usually during the first six (6) months, and up to a year, with a second peak at 4–5 years.²³ In PTLD and the HIV-associated lymphoma (most attributed to EBV) pulmonary nodes are usually bilateral, well-defined, and may associate a halo.²⁴ It is important not to take them for an IFI by taking into account the clinical context and the evolution of the lesions.

Cavitations

IFI nodes typically cavitate 2–3 weeks after the disease onset accompanying the recovery from neutropenia (neutrophils > 1000), making up the growing air image (crescent moon). Previously nodes can show low central attenuation²⁵ (Fig. 3).

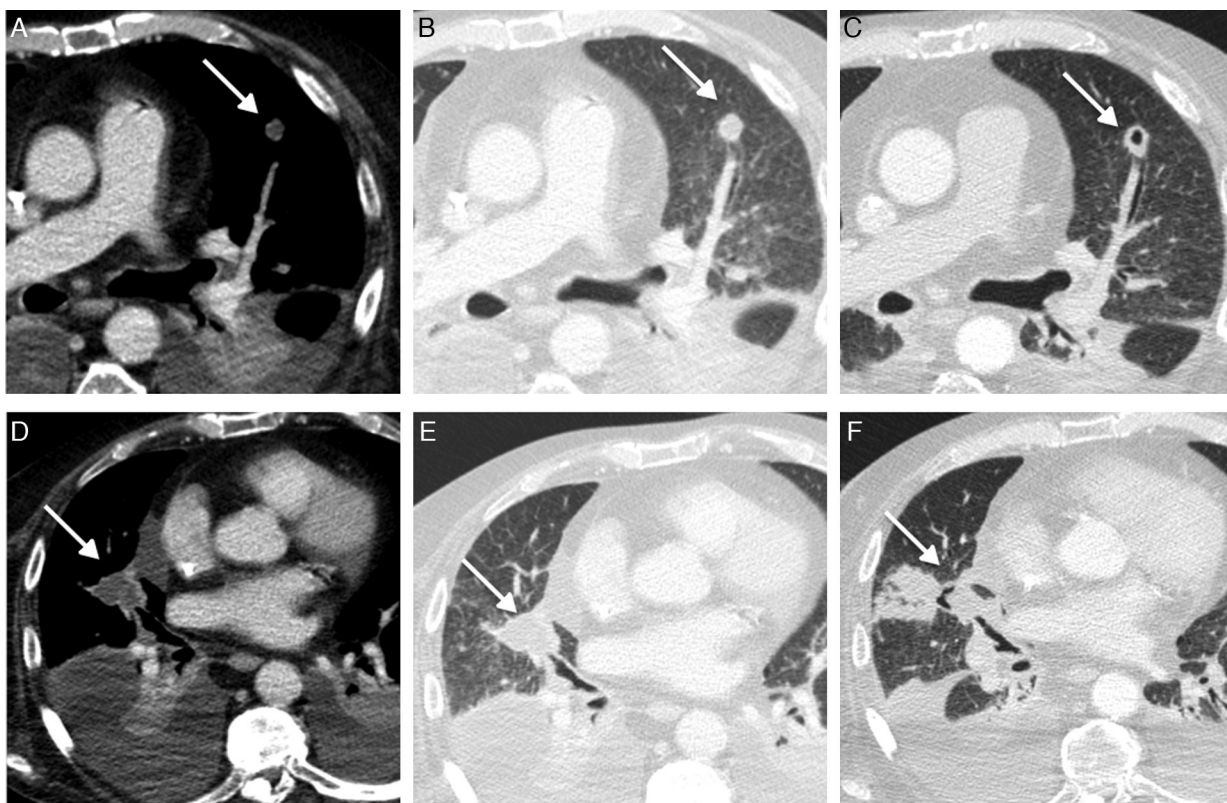


Figure 3 Low attenuation nodes. Invasive fungal infection (IFI) due to *Aspergillus*. Acute lymphoid leukemia and prolonged neutropenia. High-resolution computed tomography (CT). Upper cut (upper side images) and lower cut (lower side images). The nodes low attenuation can be seen in images with filter while the mediastinal window (arrows in A and D) is very typical of IFI due to necrosis prior to cavitation seen two (2) weeks later (C and F). Serum gactolamannan was positive one (1) month later.

Fungal and bacterial consolidations (especially staphylococcal or tuberculous ones) can also cavitate and less commonly nodes and consolidations due to lymphoma.

The appearance of cavitated nodes corresponding to Langerhans cell histiocytosis has been described in patients with HL and more rarely in leukemias; it is not known whether there is an actual association, but in any case tobacco plays a role in the etiopathogenesis.²⁶

Areas of attenuation in ground glass. Consolidations (Fig. 4) see Tables 2 and 3

Infections

At the disease onset and in the course of MM, it is possible to observe bacterial and viral bronchopneumonias similar to the rest of the population while in patients with severe immunodepression they are due to different germs (see Tables 2 and 3).

Segmental or lobar consolidations are most often bacterial. An IFI is suspected when they have a pleural base and halo,^{27,28} but the most sensitive diagnostic sign (100%) is vascular occlusion in the sinus of the lesions shown through pulmonary angio-CT.²⁹

Patched bilateral ground-glass opacities, whose size is very variable, are more typical of viruses and they can be accompanied by small nodes and consolidations.³⁰⁻³³ In

patients with HPT the paved pattern is of viral origin mainly and less commonly of a non-infectious cause.³⁴

Infection due to *Pneumocystis jirovecii* causes perihilar bilateral ground-glass attenuation areas in upper fields, usually after the 100th day post-HPT—a moment in which prophylaxis is usually withdrawn.

Respiratory colonization due to *Candida* is common in these patients, but pneumonia is exceptional except for in situations of spread candidiasis. Emerging “non-*Candida*” yeasts do cause infectious pulmonary consolidations and nodes.

Disease noninfectious complications

Pulmonary edema is frequent in the course of MM (due to PET, cardiac and/or renal amyloidosis) and AML (mainly as a consequence of treatment). At the onset and in the course of AML it should be differentiated from diffuse alveolar hemorrhage (DAH) due to thrombocytopenia and/or infection.

Secondary pulmonary lymphoid infiltration in leukemias is rare. It can be seen as ground-glass attenuation areas^{35,36} or consolidations similar to an organizing pneumonia,^{36,37} with adenopathies. In patients with CLL of years of evolution and adenopathies, the appearance of peribronchovascular consolidations, even endobronchial occupations, and clinical worsening, will make us suspect transformation into a high-grade lymphoma.

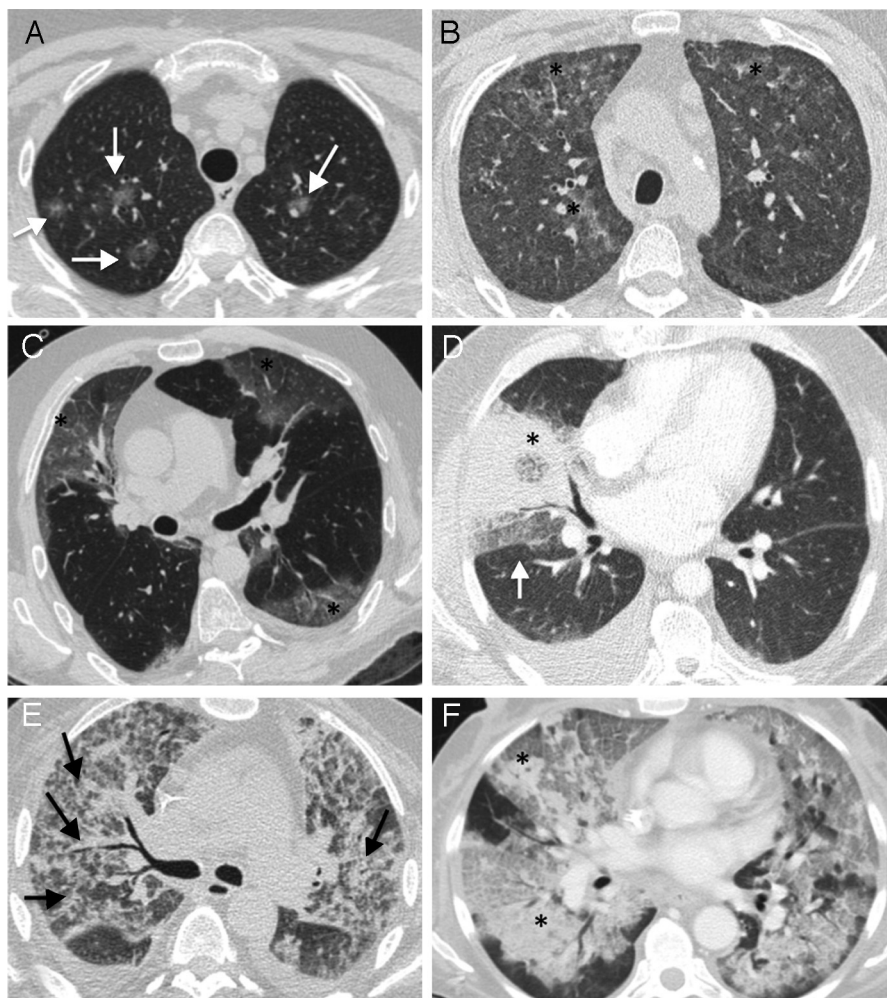


Figure 4 Attenuation areas of ground glass and consolidations. High-resolution computed tomography (CT). (A) Respiratory syncytial virus. Acute myeloid leukemia (AML) twelve (12) months post-hematopoietic transplantation (PHT). Small attenuation areas of ground glass (arrows). (B) Cytomegalovirus. AML ten (10) months post-PHT due to chronic GVHD. Extensive attenuation areas of ground glass (asterisks). (C) Influenza A (H1N1). Acute lymphoid leukemia (ALL) ten (10) months post-PHT under immunosuppressant treatment due to chronic GVHD. Bilaterally patched areas of attenuation of ground glass (asterisks). (D) Mucormycosis. AML relapse under treatment with intensive chemotherapy. Pleural base consolidation with halo (arrow) and inverted halo with thick ring (asterisk). The central area showed typical necrosis due to invasive fungal infection (IFI) in the next control (not shown). (E) Differentiation syndrome. Acute promyelocytic leukemia (APL) with active chemotherapy. Respiratory failure eighteen (18) days after treatment with trans-retinoic acid (all-trans retinoic acid, ATRA). Areas of ground glass peribronchovascular thickening (arrows) and pleural leak. Improved after treatment. (F) Generic acute lung injury. AML 60 days post-PHT. Paving pattern and consolidations (asterisks). No reduction in the levels of hemoglobin; the micro-organism could not be isolated.

Leukostasis (aggregation of blasts in pulmonary microvascularization) is exceptional and it will only be suspected in the diagnosis or relapse of an AML due to a rapid increase of the percentage of leucocytes in blood; it is characterized by respiratory and neurological failure kicking in with con pulmonary consolidations partly due to alveolar damage and hemorrhages due to plateletpenia.^{38,39} In MM, consolidations due to pulmonary infiltration of plasmatic cells causing respiratory distress of poor prognosis have also been described.^{20,40}

Noninfectious complications secondary to treatment

In the 6 h following the transfusion of blood products, the sudden appearance of consolidations simulating an edema

and accompanying a respiratory failure usually reflect acute pulmonary damage (APD) called TRALI (transfusion-related alveolar lung injury) which associates high mortality rates.⁴¹

Any courses of chemotherapy can cause pulmonary toxicity, although the most usual patterns are: organizing pneumonia (OP), unspecific interstitial pneumonia (UIP), pneumonitis due to hypersensitivity, eosinophilic pneumonia and diffuse alveolar damage. Carmustine (used in lymphomas and MM), which usually gives a UIP pattern⁴²; cytarabine (administered in high doses for the treatment of AML), that can cause non-cardiogenic pulmonary edema⁴³ and bleomycin (lymphoma treatment), causing diffuse alveolar damage and OP are among the most common drugs used.

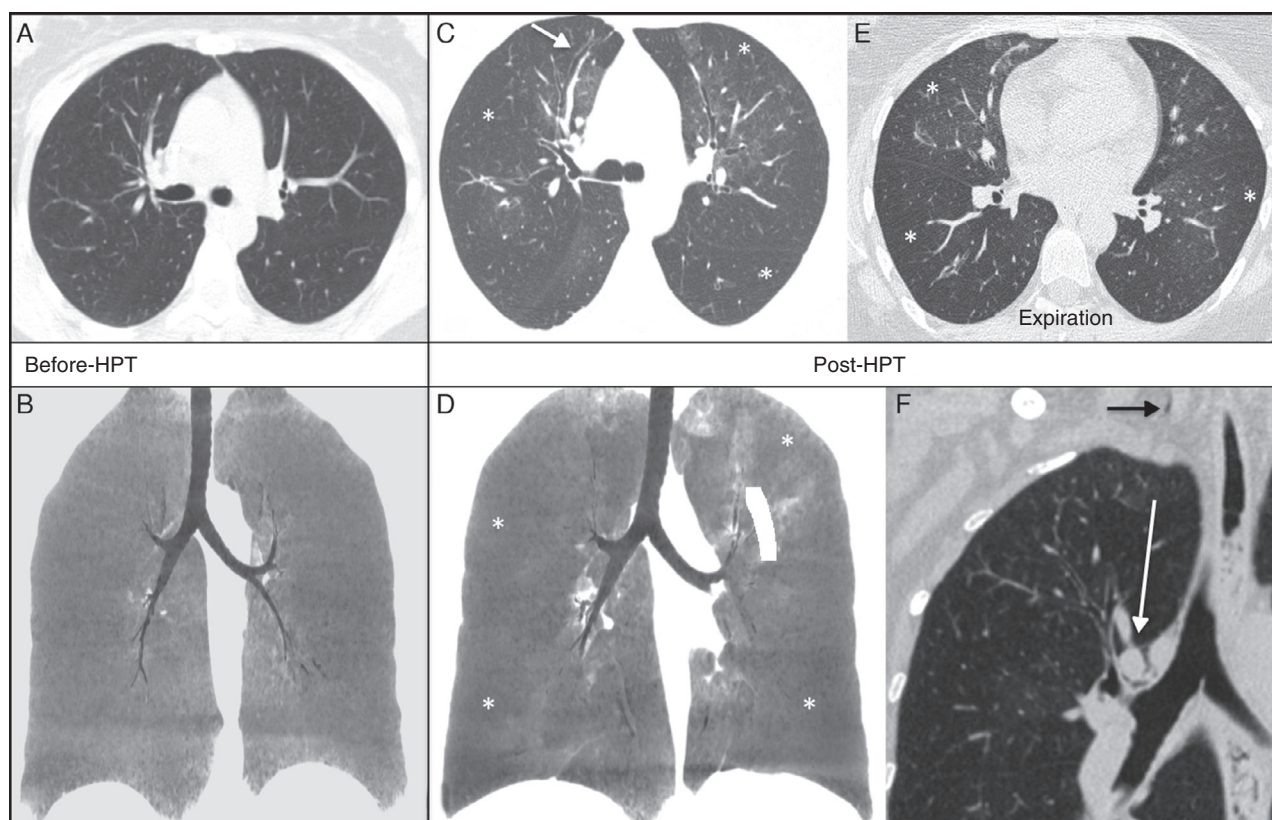


Figure 5 Bronchiolitis obliterans (BOS) and air leak syndrome. Acute myeloid leukemia (AML) before hematopoietic precursor transplantation (HPT). (A and B) Computed tomography (CT) before the HPT. (C–E) High-resolution CT twelve (12) months post-HPT. Comparatively in the axial images in inspiration (A and C) the post-HPT appearance of hyperinflation and perfusion pattern in mosaic with radiolucent areas (asterisks) and small bronchiectasias (arrows) is shown. Air entrapment (asterisks) can be confirmed in the study of expiration (E). Both coronal reconstructions and minimal intensity (MinIM) projections of thick cut (B and D) help us recognize the patched radiolucent areas (asterisks). (F) CT coronal reconstruction months later. Complication with BOS “air leak”. Interstitial emphysema around the bronchovascular axis (white arrow) and small pneumomediastinum (black arrow).

Rituximab is an anti-CD20 monoclonal antibody used in the treatment of lymphoproliferative B syndromes that have been associated to pulmonary disease due to a mechanism that has not been clarified yet after a median of four cycles and with a median time of appearance of 4 weeks after the last infusion. The ground-glass areas or bilateral diffuse pulmonary consolidations appear in weeks or months, and less commonly in hours or days, and they correspond histologically to inflammatory and lymphocytic infiltrates, among others. Most of them show hypoxemia of lethal evolution in 18%.⁴⁴

The granulocyte colony-stimulation factor (G-CSF) used in neutropenia recovery can rarely induce an APD during the first days of treatment displaying images similar to those of edemas or alveolar hemorrhages.¹²

All-trans retinoic acid (ATRA) and arsenic trioxide, used for the treatment of acute promyelocytic leukemia, can cause (20%) a “differentiation syndrome” consisting of respiratory failure manifestations during the following 2–47 days⁴⁵ probably due to the release of cytokines. Pleural effusion, ground-glass areas and bronchial wall thickening due to edema and hemorrhage can be seen.⁴⁶

The pre-graft early post-HPT period can become complicated with:

- Pulmonary edema-hydrostatic or due to increased patency (the most common non-infectious complication).
- DAH of multifactor etiology, characterized by large ground-glass attenuation areas that can evolve into paved patterns, in the absence of cardiomegalia and effusion; hemoptysis is only observed in 66% of the cases, but a drop in the levels of hemoglobin and the high rate of macrophages in BAL help us in the diagnosis.
- “Graft syndrome” or pre-graft respiratory distress—the consequence of an endothelial damage possibly due to the release of pro-inflammatory cytokines; it is similar to edema but without cardiomegalia and with clinical manifestations of fever and cutaneous exanthem.
- “Idiopathic pneumonia syndrome” defined by the American Thoracic Society as an acute respiratory failure and diffuse alveolar damage in the absence of cardiac or renal disease, iatrogenesis and responsible microorganism.⁴⁷ It is an exclusion diagnosis, probably of multifactor etiology or due to non-affiliated infections, such as it would happen with the recently discovered metapneumovirus.^{48,49}

In the late post-HPT period, peribronchovascular reticulation and ground-glass areas, and on occasion paved pattern ones, can represent an unclassifiable interstitial pneumonia,

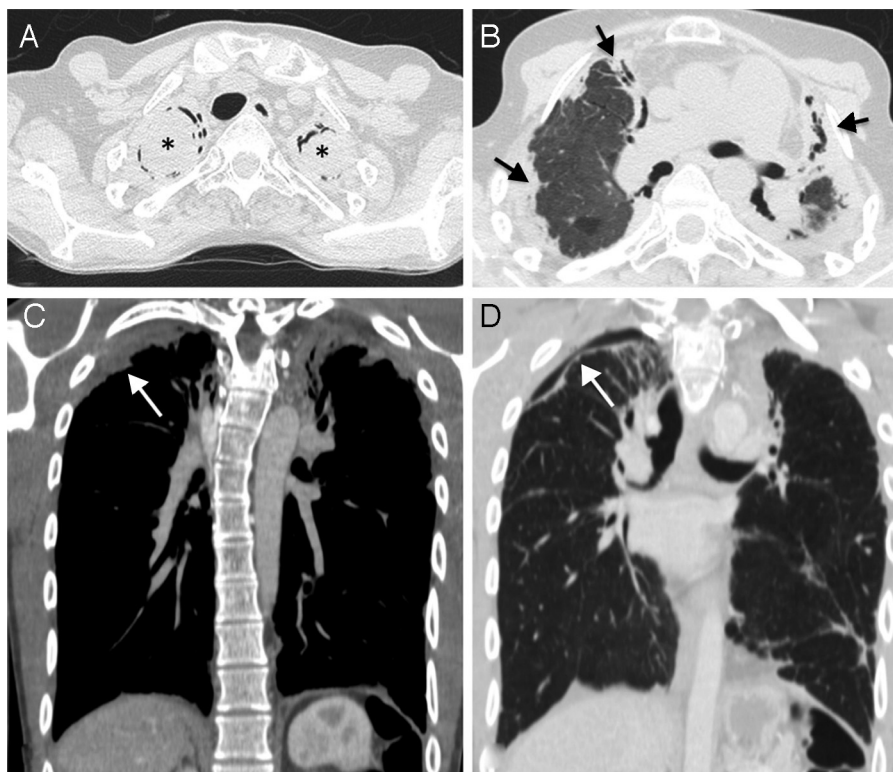


Figure 6 Post-radiotherapy fibrosis and complications. Chest computed tomography (CT). Irradiated mediastinic lymphomas. (A and B) CT axial images: paramediastinal subpleural apical fibrosis (arrows) with bronchiectasia. “Air crescent sign” due to the occupation of apical bronchiectasias with aspergillosis (asterisks); different meaning to the one observed in the invasive fungal infection (IFI). (C and D) Post-radiotherapy paramediastinal and pleuropulmonary apical fibrosis complicated with pneumothorax (arrows).

associated with rejection.⁵⁰ Histologically, it corresponds to a bronchioloalveolar lymphoplasmocytic infiltration that spreads toward peripheral regions and evolves into a fibrosis with traction and hive bronchiectasis.

OP can be secondary to infection, toxicity by drugs, radiotherapy or rejection; peripheral peribronchovascular and perilobular consolidations, and the inverted halo sign are characteristic findings in the appropriate clinical context. In a situation of neutropenia the inverted halo should lead us to consider mucormycosis¹⁴ in the first place which is different from the OP in that the thickness of its ring is >1 cm and also presents internal reticulation⁵¹ (Fig. 4).

Acute pneumonitis due to radiation can occur 3–6 weeks after mediastinal lymphoma radiotherapy and cause clinical and radiologic manifestations similar to those of a pneumonia. It is located in the irradiated area with a marked delimitation of the healthy parenchyma; it evolves into paramediastinal fibrosis.

Acute pulmonary rejection to HPT and pulmonary alveolar proteinosis due to leukemic infiltration or lately to treatment are extremely rare.^{52,53}

Tree in bud

These images represent bronchioles filled with mucous, liquid or pus; they usually correspond to an infectious bronchiolitis that can be due to many different germs.¹¹

Thickening of the bronchial walls

It can be due to unspecific respiratory infection, smoking, bronchiolitis obliterans, lymphoid infiltration or other bronchial conditions.

Perilymphatic interstitial thickening

Liquid retention and inflammatory or tumor infiltration of perilymphatic distribution translate into thickening of the bronchovascular axes, interlobular septa and the subpleural interstice.

The straight interstitial thickening can correspond to an interstitial pulmonary edema and a graft syndrome in the early post-graft period. In the 2–6 months following the HPT, pulmonary veno-occlusive disease can be a rare complication⁵⁴ leading to pulmonary hypertension with pulmonary congestion in the absence of left cardiac disease.

Secondary lymphatic tumor pulmonary infiltration can kick in as a straight or nodular thickening of the perilymphatic interstice^{35,55} and make up peribronchial consolidations (Fig. 2A). In most cases dissemination is retrograde from the hilar and mediastinal affectation, and can get to occlude the airways, especially in the CLL.⁵⁵

In MM, pulmonary amyloidosis can be seen radiologically as a septal interstitial thickening.

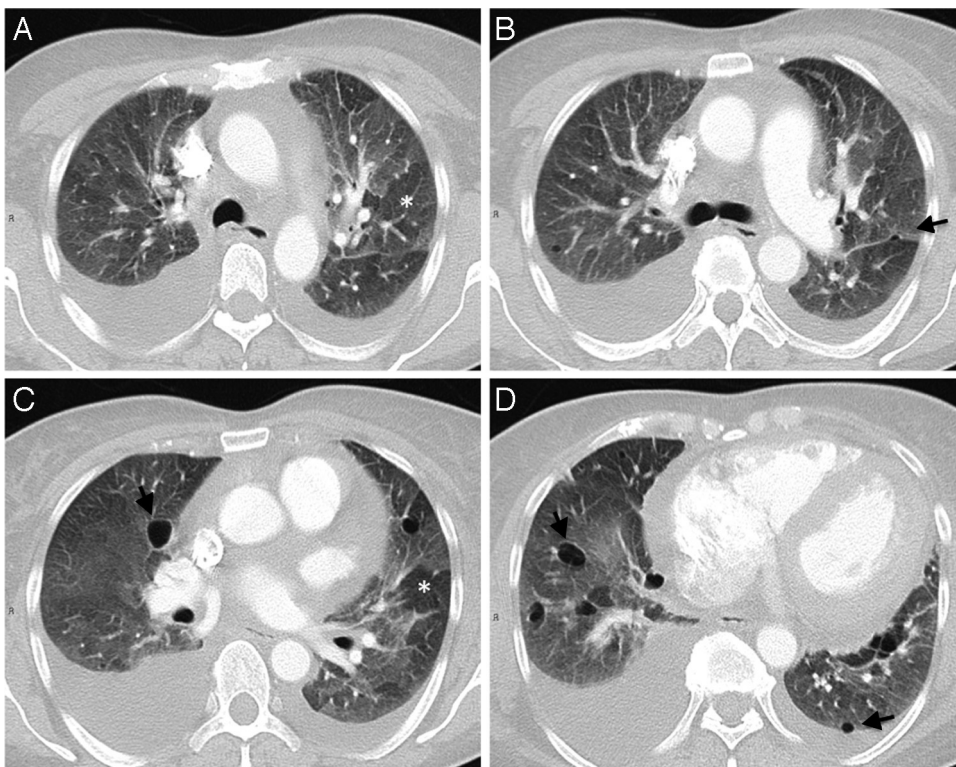


Figure 7 Multiple myeloma. Light chain deposit disease (LCDD) in bronchial alveolar and vascular walls. Chest computed tomography (CT) and mild mosaic patterns in expiration due to air entrapment (asterisks). Heart failure and pleuropericardial effusion due to cardiac and serous amyloidosis.

Obstructive bronchial lesions

Although the most frequent cause is pulmonary carcinoma we should not forget that they are a rare form of HL and NHL presentation. Also in the course of CLL, it is possible to see lymphoid growth in the lumen or bronchial wall making up obstructive endoluminal masses and cases of extra-osseous plasmacytoma as endoluminal masses have been published.⁵⁶

Air entrapment areas (Fig. 5)

It is a characteristic finding of bronchiolitis obliterans (BO), the most common (2–8%) and relevant complication 6–12 months post-HPT. It is considered a chronic GVHD defined by functional criteria of airway obstruction in the absence of active respiratory infection and confirmed through transbronchial and/or surgical biopsy. The “BO syndrome” can be diagnosed without histology when there is air trapping and/or bronchiectasis in HRCT and GVHD in at least one other organ.^{57,58} The images in forced expiration show air entrapment in 44–64% of the cases; on the other hand and yet despite the fact that this is the finding with the most diagnostic sensitivity, it is not very useful for the detection of early preclinical stages.⁵⁹ Bronchiectasis appears in more advanced stages and its progression has been associated with the forced expiratory volume in one second.⁶⁰ HRCT is a very useful addition to rule out airway infection or tumor infiltration, which can alter respiratory tests.

This disease causes slow functional worsening, especially if not detected early. Its treatment with corticoids and immune depressants causes infectious complications that will be the main cause of death.

Pulmonary fibrosis

It can be secondary to distress, toxicity, infection or radiotherapy (Fig. 6). In the late period after HPT it can correspond to an unclassifiable interstitial pneumonia or to a pleuroparenchymatous fibroelastosis⁶¹ likely as a consequence of chemotherapy, radiotherapy and GVHD.

The history, distribution and evolution of the findings will guide the etiological diagnosis.

Bronchial dilations

They can be seen in a transitory way in the sinus of infectious consolidations and be due to organizing pneumonia. Irreversible dilations (bronchiectasis) in areas of air entrapment are a characteristic finding of bronchiolitis obliterans unlike those observed in areas of fibrosis due to traction.

Interstitial pulmonary emphysema: air leak syndrome (Fig. 5F)

It is a typical complication of advanced post-HPT BO and a marker of poor prognosis. The increase of alveolar pressure leads both to its rupture and air leak around the

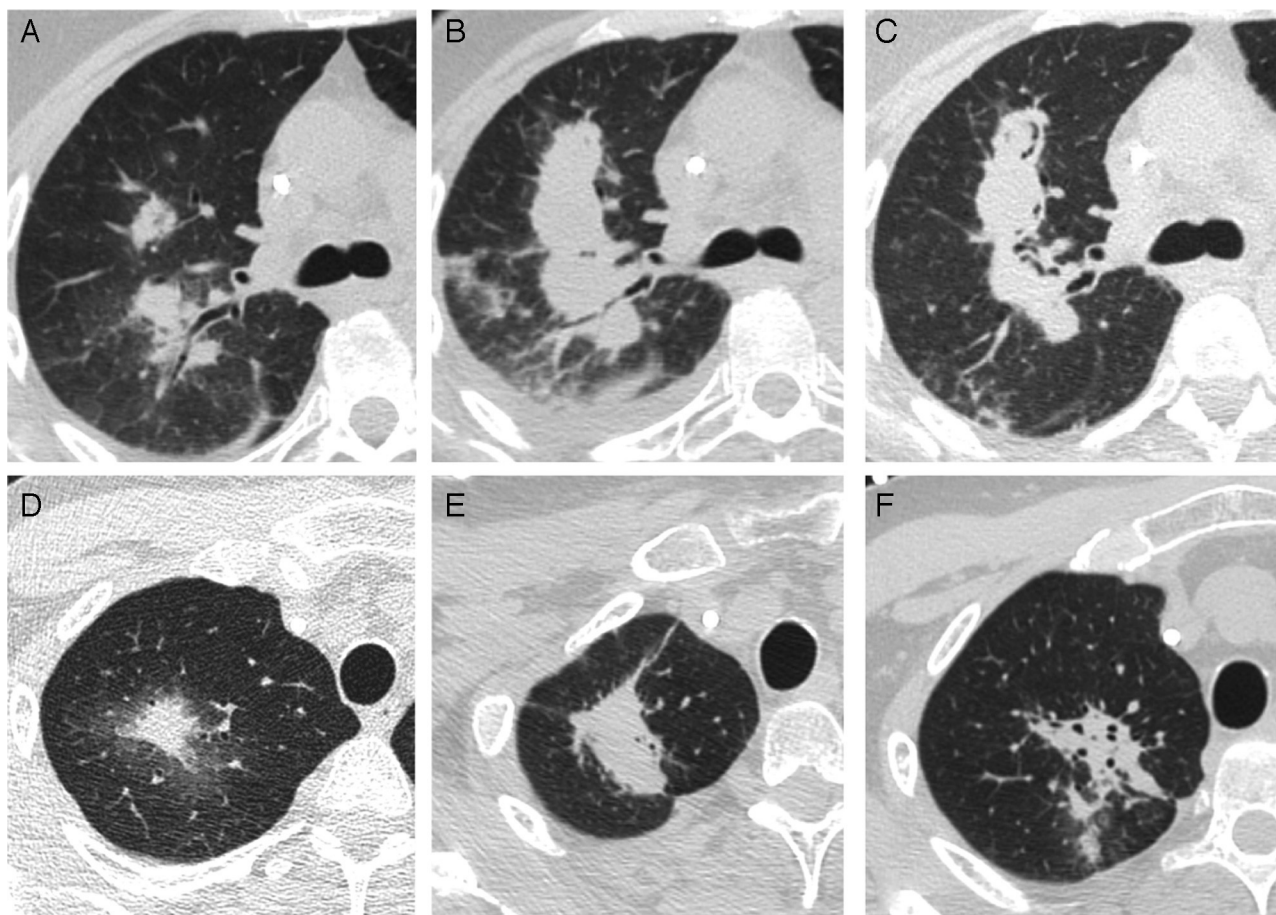


Figure 8 Evolution of an invasive fungal invasion due to *Aspergillus*. Acute myeloid leukemia (AML). High-resolution computed tomography (CT). (A) Nodes with a halo in the initial study (asterisks). (B) Loss of halo and size increase one (1) week later (normal evolution not meaning non-responsiveness). (C) Cavitation two (2) weeks later coinciding with a recovering neutropenia, air crescent sign (arrows). (D–F) A different patient. Consolidation (asterisk) with an initial halo (D); two (2) weeks later (E) size increase and disappearance of the halo; further size decrease with persistence of peribronchovascular consolidation with bronchial dilations (F) without resolution. The resection of lesion to guarantee the control of the infection before the hematopoietic precursor transplantation (HPT) showed organized pneumonia without micro-organisms or malignant cells.

bronchovascular axes due to retrograde dissection; it can reach the mediastinum, the subcutaneous tissue and the pleural cavity. The treatment is usually conservative except if the pneumothorax requires drainage.^{62,63}

Spontaneous pneumothorax

Pulmonary infiltration, radiotherapy and infection postulate as causes for a greater incidence of pneumothorax in Hodgkin's disease (Fig. 6). In the absence of radiotherapy or infection, the possibility of pleura-pulmonary infiltration described in lymphomas and MM should be taken into consideration.^{64,65}

In the late post-HPT period, the air leak syndrome due to BO or the rupture of apical vesicles due to a pleuroparenchymatous fibroelastosis should be taken into consideration.

Pulmonary cysts

Small cysts in the upper fields can correspond to pneumatoceles due to infection by *Pneumocystis jirovecii*.

Bilateral cysts, isolated or associated with nodes and adenopathies should make us think of the possibility of a pulmonary disease due light chains deposit disease in patients with MM or macroglobulinemia and obstructive functional pattern⁶⁶ (Fig. 7).

Follow-up of pulmonary lesions

In patients with a fever and active infection findings in the HRCT it is recommended that the examination be repeated until resolution of the findings:

- a) In cases of good clinical response, it is possible to wait for several weeks and even for 1 or 2 months—the estimated time for the resolution of the findings. During the first week of treatment the IFI lesions can grow worse which does not mean poor evolution (Fig. 8). Also it is convenient to recognize in any infection an immune reconstruction syndrome not to be taken for an absence of response. It is an inflammatory exacerbation secondary to neutrophil recovery or to the withdrawal of

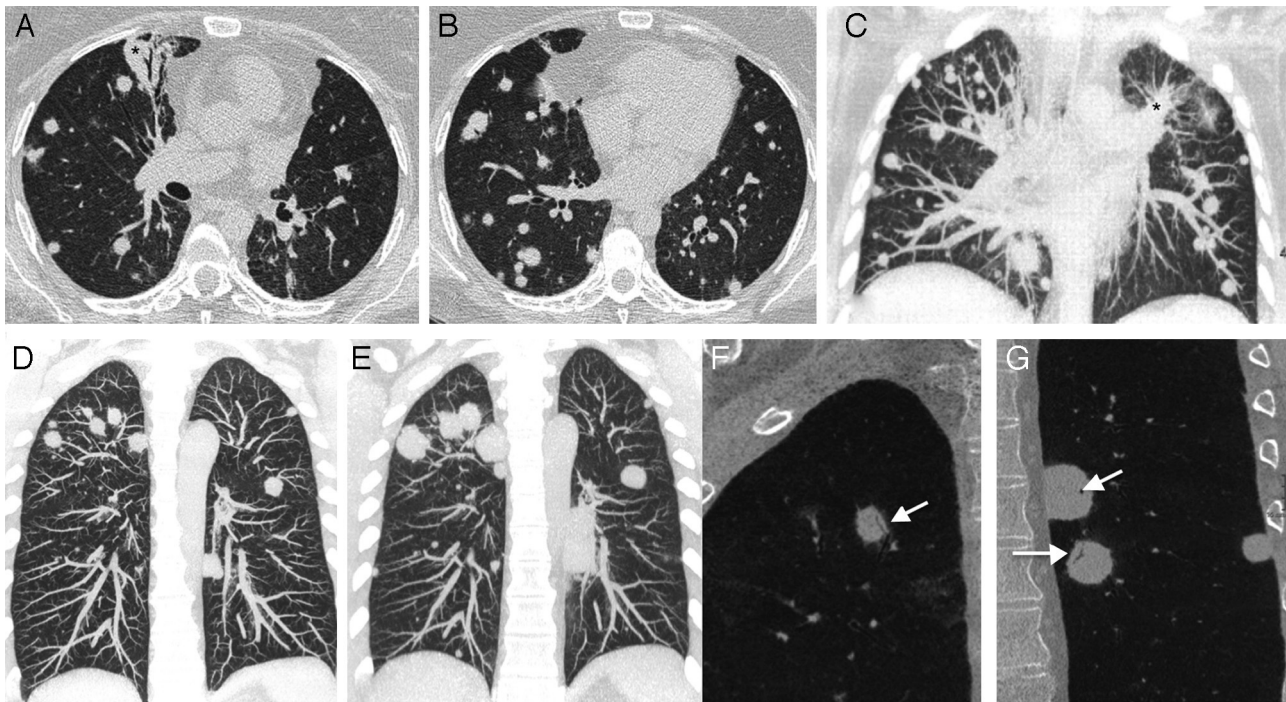


Figure 9 Pulmonary nodes due to lymphoma. High-resolution computed tomography (CT). (A–C) Hodgkin's lymphoma relapse. Axial images (A and B) and coronal resolution, maximum intensity projection (MIP) (C). Several bilateral pulmonary nodes and consolidations (asterisk) without adenopathies. The absence of infection symptoms and the high number of nodes made us suspect of lymphoma relapse later confirmed through CT-guided skin biopsy. (D–G) Hematopoietic precursor post-transplantation (post-HPT) lymphoproliferative syndrome. Acute lymphoid leukemia. Eight (8) months post-HPT. (D and E) Coronal reconstruction, MIP. Appearance of nodes in the context of a fever suspicious of invasive fungal invasion (IFI) (D). One (1) month later (E) lesions grow without cavitations being the bronchogram test (arrows) more evident in the minimal intensity image projection (MinIP) (F and G). This evolution together with the fever and the neutropenia made us suspect of post-HPT lymphoma later confirmed through a transthoracic ultrasound-guided skin biopsy.

immunosuppressant therapy which in turn translates into clinical worsening and lesion growth.⁶⁷

- b) If suspicion that there is not a good response (due to clinical and/or radiographic findings) it is important to repeat the diagnostic tests to rule out initially unidentified mixed infections.

If nodes are detected without infectious clinical manifestations, they should be compared with previous images to find out whether they are residues of an infection that occurred during periods of immune suppression. Indeterminate nodes can be followed up according to the recommendations made by the Fleischner society,⁶⁸ while the FNPA or the biopsy should be considered in lesions of suspected malignancy because of their characteristics, due to history of lymphoma and/or allogenic HPT, or because the lesions did not evolve as expected after therapy (Fig. 9). Preferentially the sample will be obtained through cutaneous (guided by CT or ultrasound) or transbronchial access, and surgery will be considered as a last resort or preferably videothoracoscopy if available.

The diffuse pulmonary disease of unclear etiology usually ends up requiring surgical or videothoracoscopic pulmonary biopsy due to its greater diagnostic yield.

¹⁸F-FDG PET-CT is not only useful for the staging and follow up of metabolically-active lymphomas⁶⁹ but also a

pathological uptake in the absence of pulmonary findings in the HRCT can raise early suspicion of drug toxicity^{70,71} or leukemic infiltration and it can be useful to differentiate active lesion scarring (whether toxic, infectious or tumoral).

Conclusion

In patients with HP the thoracic HRCT helps us come close to the differential diagnosis of infectious and non-infectious pulmonary complications by integrating image findings and clinical data. The HRCT needs to be performed in cases of acute clinical presentations and quickly when suspicion of IFI. It allows us to assess the response to treatment, detect malignancies and optimize the obtention of both the BAL and the pulmonary biopsy.

Contributors

1. Manager of the integrity of the study: PCB.
2. Study idea: PCB.
3. Study design: PCB.
4. Data mining: -
5. Data analysis and interpretation: -
6. Statistical analysis: -
7. Reference search: PCB, JCP, JSC, MSL, LCT.

8. Writing: PCB, JCP.
9. Critical review of the manuscript with intellectually relevant remarks: PCB, JCP, JSC, MSL, LCT.
10. Approval of final version: PCB, JCP, JSC, MSL, LCT.

Ethical responsibilities

Protection of people and animals. The authors declare that no experiments with human beings or animals have been performed while conducting this investigation.

Data confidentiality. The authors declare that in this article there are no data from patients.

Right to privacy and informed consent. The authors declare that in this article there are no data from patients.

Conflict of interests

The authors declare no conflict of interests.

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