CONTINUING EDUCATION PROGRAM: FOCUS...

Lung infections: The radiologist’s perspective

C. Beigelman-Aubry⁠,*, C. Godet⁠b⁠, E. Caumes⁠c

a Department of Radiodiagnosis and Interventional Radiology, CHUV, rue du Bugnon, 46, 1010 Lausanne, Vaud, Switzerland
b Department of Respiratory Medicine, Poitiers University Hospital, 2, rue de la Milétrie, 86800 Poitiers, France
c Department of Infectious Diseases, Pitié-Salpêtrière Hospital, 47–83, boulevard de l’Hôpital, 75013 Paris, France

Abstract Imaging plays a key role in lung infections. A CT scan must be carried out when there is a strong clinical suspicion of pneumonia that is accompanied by normal, ambiguous, or nonspecific radiography, a scenario that occurs most commonly in immunocompromised patients. CT allows clinicians to detect associated abnormalities or an underlying condition and it can guide bronchoalveolar lavage or a percutaneous or transbronchial lung biopsy. An organism can vary in how it is expressed depending on the extent to which the patient is immunocompromised. This is seen in tuberculosis in patients with AIDS. The infective agents vary with the type of immune deficiency and some infections can quickly become life-threatening. Clinicians should be aware of the complex radiological spectrum of pulmonary aspergillosis, given that this diagnosis must be considered in specific settings.

© 2012 Éditions françaises de radiologie. Published by Elsevier Masson SAS. All rights reserved.

Lung infections are a source of high morbidity and mortality, especially in the elderly and immunocompromised patients, who are growing in number [1,2]. The causative agent usually reaches the lung via inhalation of airborne droplets or organisms localised in the nasopharynx, by haematogenous contamination from an infectious site outside the chest, or by direct spread from a site of infection around the lungs or due to a penetrating trauma.

The main imaging investigations required for patients carrying or suspected of having a lung infection are chest radiography and CT. Although CT is not recommended for the initial assessment of these patients, it is much more sensitive and specific than plain film radiography [3]. It must be carried out when there is a strong clinical suspicion of pneumonia that is accompanied by normal, ambiguous, or nonspecific radiography, a scenario that occurs most commonly in immunocompromised patients. CT can confirm whether there are associated abnormalities such as lymphadenopathy, pleural effusion and/or empyema,

* Corresponding author.
E-mail address: catherine.beigelman-aubry@chuv.ch
(C. Beigelman-Aubry).

2211-5684/5 - see front matter © 2012 Éditions françaises de radiologie. Published by Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.diii.2012.04.021
and whether any cavities are forming. Furthermore, a CT scan can direct a bronchoalveolar lavage or guide a percutaneous or transbronchial lung biopsy. It also allows any underlying condition to be detected, especially if there is a tumour forming a bronchial obstruction in nonresolving pneumonia, which is defined as lesions resolving by less than 50% within 2 weeks or incomplete resolution after 4 weeks in spite of an appropriate antibiotic regimen. In a given clinical setting, the signs on CT can lead to a change in clinical management or give weight to clinical suspicion [1].

Epidemiology data (such as whether there are any current epidemics), clinical information (especially comorbidities), the patient’s immune status, medical history, history of the illness, physical examination, as well as laboratory test results and the patient’s response to treatment must always be considered together with the conclusions drawn from radiology, as the diagnoses proposed will vary depending on the setting. A given organism can express a range of imaging findings, especially in immunocompromised patients. For example, a Pneumocystis jirovecii infection may be demonstrated as bilateral ground glass radiodensities, areas of consolidation, or less commonly focal consolidation, nodules, miliary pattern or reticular opacification. Likewise, tuberculosis is expressed in different ways depending on the degree of immune deficiency in patients with AIDS. We provide an overview of the major ways in which lung infections present on radiology, the associated signs, and finally the specific characteristics of lung disease in immunocompromised patients.

Alveolar consolidation

Lobar pneumonia

General points

Lobar pneumonia is characterised on histology by the alveolar spaces being filled with an inflammatory exudate, with little or no tissue damage. This process typically spreads from one segment to another [4]. Involvement begins in the area of the lung adjacent to the visceral pleura. Lesions spread swiftly through the interalveolar pores (pores of Kohn) and the small airways in a centripetal pattern, with a relatively homogenous area of alveolar condensation building up either in the segments or lobes.

Signs on imaging

The typical appearance of acute community-acquired pneumonia (CAP) is one of a single subpleural area of alveolar consolidation with blurred margins that is restricted to the area next to the fissures, progressing to a systematised segmental opacity affecting one or several contiguous segments or a lobe, with or without the air bronchogram sign [5] (Fig. 1). Ground glass opacities adjacent to the alveolar consolidation caused by a partial filling of the alveoli may be present [6]. These are most often cases of bacterial pneumonia caused by Streptococcus pneumoniae [7]. They can also be infections due to atypical or allied organisms (Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci or Legionella pneumophila). Of the Gram-negative bacilli (GNB), only Klebsiella pneumoniae can cause CAP; the other GNB (Pseudomonas aeruginosa, Enterobacter cloacae, Escherichia Coli) are more often involved in nosocomial lung disease, especially when it is acquired under mechanical ventilation. Of the Gram-positive cocci, Staphylococcus aureus can cause CAP as a superinfection of flu for example. In this setting it is still sensitive to methicillin, at least in France. S. aureus can also cause nosocomial pneumonia and in this case it is methicillin-resistant. In immunocompromised patients, a P. jirovecii infection, a fungal infection, or mycobacteriosis must routinely be considered. Bilateral involvement that predominantly affects the lung bases with abscess formation is suggestive of a P. aeruginosa infection. An enlarged lobe with bulging fissures connected to voluminous oedema is a classic presentation of K. pneumoniae infection [7]. Round

Figure 1. Left lower lobe pneumonia with hypoxemia caused by a pneumococcal infection: a: standard radiography view. Opacity in the left lung that does not obscure the left lower heart contour with a double contour aspect; b: CT view (coronal reconstruction) of alveolar consolidation restricted by the fissure and containing the air bronchogram sign.
Lung involvement

Involvement of the parenchyma must be distinguished from involvement of the pleura which may be a loculated pleural effusion, with or without empyema. Atelectasis without the air bronchogram sign suggests a mucoid impaction. Aspiration pneumonia must be considered when the lower lung is affected, either on the right or bilaterally. Lobar or segmental consolidation may be secondary to an obstruction, a pulmonary oedema, or a haemorrhage. Alveolar consolidation can in addition be seen in organising pneumonia, radiation pneumonia, bronchioloalveolar carcinoma [9], lymphoma, pulmonary alveolar proteinosis, and acute interstitial pneumonia.

Bronchopneumonia

General points

Bronchopneumonia is an infectious process that initially centres on the epithelium of the small airways, defined on histopathology by acute bronchial inflammation with epithelial ulceration and the formation of an endoluminal and peribronchiolar fibrinopurulent exudate. These bronchiolar lesions are combined with peribronchiolar foci of inflammation with a patchy distribution. The inflammation can spread to the adjacent alveoli and go on to affect the lobules, segments, or lobes. The predominantly bronchiolar and peribronchiolar localisation of inflammation could be due to the presence of more virulent organisms, resulting in more significant tissue destruction and less abundant oedema formation, with the infection spreading more slowly to the lung [10]. The bacteria most often involved are *S. aureus*, *Haemophilus influenzae*, *P. aeruginosa*, anaerobes, and some species of fungus, especially *Aspergillus*. Bronchopneumonia is most commonly encountered in nosocomial infection and these cases are usually caused by a GNB, especially *P. aeruginosa* or *E. coli*.

CT signs

Thickening of the bronchial walls, centrilobular nodules, and the tree-in-bud sign are the expression of infectious bronchitis. The inflammation spreads to the peribronchiolar alveoli in the form of centrilobular nodules with blured margins that are generally smaller than 1 cm in size, with areas of ground glass opacity or peribronchiolar consolidation with an acinar pattern [11] that can progress to lobular, segmental, or lobar consolidation (Fig. 2). Involvement may be multifocal, multilobar, or diffuse. When the lobes are affected, the findings are similar to those seen in lobar pneumonia. There are no specific findings for different causative bacteria. Aspergillosis or atypical mycobacteriosis will be considered where the clinical setting supports it.

Differential diagnosis

Organising pneumonia appears in the form of alveolar consolidation and/or peribronchial and/or subpleural ground glass opacities. It can have a number of causes. Bronchioloalveolar carcinoma and lymphoma can present as multifocal alveolar consolidation. This finding is seen in 30% of cases of bronchioloalveolar carcinoma and corresponds to a mucinous histologic sub-type [9,12]. Depending on the context, multifocal alveolar consolidation may also be found in radiation pneumonia or acute hypereosinophilic syndrome. In case of chronic disease, the differential diagnoses also include pulmonary alveolar proteinosis, inflammation, granuloma, or lipid pneumonia [13].

Diffuse alveolar consolidation

General points

Diffuse alveolar consolidation is suggestive of diffuse alveolar damage [14]. An air bronchogram sign and small pleural

**Figure 2.** *Haemophilus influenzae* bronchopneumonia and herpes virus in a nosocomial infection: a: native axial view; b: the same anatomical area on an MIP view 5 mm thick. There are centrilobular micronodules with branching opacities and acinar pattern with lobular consolidation, both of which are better visualised on MIP (b).
effusions are common. Uncommon, unusual, or exotic organisms can be involved. Lesions not in the dependent lung are more suspicious for pneumonia than lesions in the dependent lung.

Differential diagnosis
Pulmonary oedema and Acute Respiratory Distress Syndrome (ARDS) must be distinguished from a picture of bronchopneumonia in case of diffuse involvement.

Ground glass opacity — Interstitial pneumonia

General points

Interstitial pneumonia is characterised by a mononuclear inflammatory cellular infiltrate in the alveolar septa and the distal peribronchovascular interstitium [4]. This interstitial inflammatory reaction is secondary to epithelial damage, with thickening in the peribronchial area and interlobular septa. The most common causes are viruses, *M. pneumoniae* and *P. jirovecii*.

Radiological findings

In viral infections and those caused by *M. pneumoniae*, the most common findings on standard radiography are reticular or reticulonodular opacities with blurred margins that may have a nodular or diffuse pattern predominating in the peripheral region, combined with peribronchial thickening with blurred margins [15]. On CT, signs of cellular bronchiolitis, ground glass attenuation and focal consolidation fitting with bronchopneumonia can be confirmed. In a patient who is not immunocompromised, respiratory syncytial virus or varicella infection should be considered in cases where ground glass opacities dominate. In immunocompromised patients, infection with *P. jirovecii* [16], CMV [17], or mycoplasma must be suggested. *P. jirovecii* infections appear on standard radiography as ground glass opacities with a fine reticulonodular pattern. On CT, a ground glass opacity that spares the pulmonary cortex (Fig. 3) and predominantly affects the upper region can be readily observed. In patients with immune deficiency not caused by AIDS, ground glass opacities are common but nonspecific, as they can be caused by viral or pyogenic infection [18].

Differential diagnosis

Ground glass attenuation is common but nonspecific finding in immunocompromised patients. It can be secondary to drug-induced toxicity, alveolar haemorrhage, pulmonary oedema, organising pneumonia, or hypersensitivity.

Nodules

Micronodules

General points

Bronchogenic distribution is demonstrated as centrilobular micronodules with branching opacities that are non-homogenously distributed and that spare the subpleural space [19]. This kind of pattern can be seen in bacterial, fungal, viral, mycobacterial, or mycoplasma infections. In reactivation tuberculosis (Fig. 4), the centrilobular micronodules and the branching opacities have increased density and distinct margins. They are readily found with cavititation, predominantly localised to the superior segment of the inferior lobes and the apicoposterior segment of the superior lobes. *Aspergillus* bronchopneumonia and/or bronchiolitis must be considered in immunocompromised patients [20]. Randomly distributed micronodules fitting with a haematogenous miliary pattern could suggest tuberculosis (Fig. 5), histoplasmosis, candidiasis, blastomycosis, or a viral cause (CMV, herpes, varicella), especially in immunocompromised patients.

Differential diagnosis

The differential diagnosis of infectious miliary nodules is miliary metastases.

**Figure 3.** Pneumocystosis revealing AIDS. Axial view of the middle regions of the lungs with lung window. Diffuse ground glass opacities with intralobular reticulation not affecting the peripheral cortex of the lung.
and candida, herpes simplex virus, cytomegalovirus, and in non-tuberculous mycobacteriosis [22–25]. Nodules with cavitation must routinely cause the clinician to suspect a septic embolism. The source site of infection may be tricuspid endocarditis, especially in intravenous illicit drug use, or where patients have peripheral venous thrombophlebitis, a central venous catheter, or pacemaker. The mechanism is one of endothelial damage combined with the formation of crumbling thrombi containing infective agents. Turbulence caused by circulating blood detaches fragments of thrombus which then migrate to the peripheral pulmonary arteries. Ischaemia then results in infarction and/or haemorrhage and the organisms release toxins causing necrosis to the parenchyma [4]. On imaging, mainly peripheral and basal nodules of varying size with blurred margins and often with cavitation are seen, as is pulmonary infarction (Fig. 7). Although feeding vessels are often demonstrated on axial views, it has been shown on multiple-plane reconstructions that most arteries have a lateralised trajectory around the nodule and the central vessels are the pulmonary veins [26].

Differential diagnosis

Nodules with a halo of ground glass opacity can be seen in Wegener’s granulomatosis, Kaposi’s sarcoma (in this case appearing with spiculated nodules), and in haemorrhagic metastases. Nodules with cavitation can also be seen in Wegener’s granulomatosis, metastases, or lymphoma.

Cavities

Abscesses, necrotising pneumonia, pulmonary gangrene, and pneumatoceles are all complications of bacterial pneumonia.
Pulmonary abscess

Pulmonary abscesses, possibly with bronchopulmonary fistula, are seen above all in infections caused by anaerobic bacteria. CT findings show single or multiple masses, between 2 and 6 cm in diameter, with central hypoattenuation or cavitation representing purulent liquefying necrosis, and peripheral enhancement after intravenous contrast medium injection. The internal wall of the abscess is usually smooth, with numerous air-fluid levels and consolidation in the adjacent parenchyma in half of all cases. The main localisations are those of aspiration pneumonia, which is commonly involved in these complications, namely the posterior segments of the right superior and left inferior lobe and the superior segments of the inferior lobes [4].

Necrotising pneumonia or pulmonary gangrene

Necrotising pneumonia or pulmonary gangrene can be secondary to acute community-acquired pneumonia or pulmonary tuberculosis. Abscesses caused by *S. aureus, K. pneumoniae* and *P. aeruginosa* are associated with higher mortality [27]. Anaerobic bacterial or even fungal infections can also be the cause. It should be noted that pleural and pulmonary complications in acute community-acquired pneumonia caused by *S. aureus* that secretes Panton-Valentine leukocidin, both in cases of methicillin-sensitive and resistant types, can be severe and rapid in onset (Fig. 8). On imaging, pulmonary gangrene usually starts with bilateral consolidation of the superior lobe, followed by the development of coalescent lucencies. The air crescent sign may also be present.

Pneumatoceles

Pneumatoceles manifest as single or multiple thin-walled air-filled lucencies located in areas of consolidation or ground glass opacity. These lucencies are associated with a recent infection, progressively increasing in size over the following days and weeks, and then resolving after weeks or months. They are most likely due to drainage of a necrotic site in the pulmonary parenchyma, followed by obstruction of an airway due to the check-valve mechanism. They usually occur in *S. aureus or P. jirovecii* infections (Fig. 3), but they can be seen in other infections including *E. coli* and *S. pneumoniae*.

Associated abnormalities

Mediastinal abnormalities

The most commonly found mediastinal abnormality is lymphadenopathy. Where there is necrosis, tuberculosis will be
considered, as should nocardiosis and candidiasis. The clinician should not forget differential diagnoses not involving infection such as lymphadenopathy in lymphoma, or necrotic metastases. In the setting of infection, clinicians should always look for abnormalities of the proximal tracheobronchial tree, especially in immunocompromised patients. The possibility of invasive aspergillosis of the respiratory tracts must always be considered where there is thickening of the trachea, with the specific risk of tracheal rupture.

Pleural abnormalities

Pleural effusions are seen in 20 to 60% of cases of acute bacterial pneumonia. Over 90% of parapneumonic effusions without pleural thickening resolve when treated with a suitable antibiotic regimen. Pleural loculation may be present. Where there is empyema, there is pleural thickening of the parietal and visceral layers after contrast medium injection, which points to an exudate, with the extra-pleural fat demonstrating hyperdensity. A pre-contrast sequence is useful in this context. This finding must be distinguished from that of a pulmonary abscess.

Other abnormalities

In principle, clinicians should check whether there is any damage to the bone, especially the spine, as well as to the chest wall or related sites. Spondylodiscitis or a cold abscess would give weight to a suspicion of tuberculosis.

Specific features of lung disease in immunocompromised patients

Lung disease in immunocompromised patients is common and serious, whether it is an infection or another pathology. The prognosis depends on disease severity, the patient's comorbidities, and the significance of the underlying immune deficiency. Management of this kind of illness requires multidisciplinary cooperation between clinicians in respiratory medicine, haematology, infectious diseases, radiology, microbiology, and intensive care in order to avoid any delay in diagnosis. CT scanning plays a very important role, especially in guiding interventions to take specimens for microbiology, whether the technique used is bronchoalveolar lavage or transthoracic needle biopsy.

Three main types of immune deficiency can be singled out: patients with aplasia following bone marrow or solid organ transplants, patients who have been treated with high-dose corticosteroids, and patients with AIDS. An emerging type of specific immune deficiency is caused by monoclonal antibodies, in particular TNF alpha inhibitors, which are associated with an increased risk of pulmonary tuberculosis.

Aplasia

General points

Aplasia is a profound immune deficiency that essentially affects phagocytosis. Profound neutropenia (<500 neutrophils) is connected to this picture. During the initial stage of aplasia, the infection-causing pathogens are mainly Gram-positive cocci, especially S. aureus, or GNB such as P. aeruginosa. When neutropenia persists, especially beyond five to seven days, fungal infections (aspergillosis, candidiasis, mucormycosis) develop. These patients present an unusual set of signs on imaging because a confirmed bacterial infection can be present with no damage to the parenchyma, as this only manifests when aplasia regresses. In contrast, fungal infections are seen on imaging but, as with bacteria, the findings do not correspond to the inflammatory reaction connected to the infection, but to the infiltration of the pulmonary parenchyma by, for example, aspergillus hyphae as well as to zones of infarction secondary to infiltration of the pulmonary vasculature.

Differential diagnosis

Although lung infections are the most common complication of aplasia, other pathologies must also be considered, especially intra-alveolar haemorrhage, pulmonary oedema due to fluid overload or heart failure, oedema due to acute respiratory distress syndrome (ARDS), and pulmonary medication-induced toxicity.

Immune compromised patients other than in AIDS and aplasia

Bone marrow transplant recipients

These patients who have usually undergone total body irradiation are similar to patients with asplenia and are very sensitive to pneumococci. After the conditioning, they can be grouped together with aplastic patients. For patients with aplasia, CMV and fungal disease such as aspergillosis and pneumocystosis pose the greatest threat [28].

Solid organ transplant recipients

These patients present complications connected to a lymphocyte deficiency. They are at risk of infection with intracellular bacteria such as L. pneumophila, Mycobacterium tuberculosis or Nocardia asteroides. Aspergillus and Nocardiosis account for two thirds of infections in patients who have had heart transplants. It must also be noted that lung transplant patients have an increased risk of CMV infection, while heart transplant patients are at greater risk of toxoplasmosis, especially patients who have not had a primary infection and whose donor was positive.

Patients treated with high-dose corticosteroids

These patients have a granulocyte function deficiency, which is essentially a lack of chemotaxis. There is an increased risk of pneumocystosis, and problems with differential diagnosis are common where there is a specific underlying
disorder as this can occur in collagen vascular disease, lymphoproliferative disorders, or in solid tumours treated with chemotherapy. The possibility of reactivated latent tuberculosis should also routinely be taken into account, as should disseminated strongyloidiasis in areas where there the risk exists and the patient has not taken preventive treatment.

Immune deficiency in AIDS

In AIDS, immune deficiency is essentially caused by the depletion of CD4 lymphocytes with a consequent reduction in their function. Although antiretroviral therapy has caused the number of opportunistic infections to fall by keeping patients at the HIV positive non-AIDS stage, they do still develop in patients who have not undergone testing. The most common infection in this setting is pneumocystosis. Pulmonary toxoplasmosis is less common. Tuberculosis, more common in the immigrant population, can develop at any stage of immune deficiency.

HR-CT is extremely useful for diagnosing and excluding infections like pneumocystosis. Pulmonary infections correlate with a fall in CD4 lymphocytes. Moreover, their appearance on radiology also depends on the degree of immune deficiency. For example, tuberculosis is expressed in a very similar way in immunocompetent subjects and those with slight immune deficiency, but when immune deficiency worsens it appears as a primary infection, and it takes on a miliary pattern and affects multiple systems in profound immune deficiency.

Conclusion

The CT scan indisputably plays a key role in pulmonary infections given that standard radiography alone is lacking in specificity. Immunocompromised patients are the group who are most affected, and in these patients clinicians must constantly bear in mind the possibility of infection with tuberculosis, aspergillosis, and pneumocystosis.

Figure 9. Axial views with lung window focused on the right inferior lobe (a, b). Axial view with mediastinal window (c).
Clinicians can routinely put forward theories about which microbe may be responsible in order to give weight to an empirical treatment, as it can take time to obtain the results of microbiology investigations. Moreover, some infections, especially bacterial ones, can very quickly become life-threatening. In view of this, in cases of acute necrotic pneumonia, an infection caused by *S. aureus*, Panton-Valentine leukocidin secretor should routinely be investigated in young patients with no medical history because it points to a very poor prognosis (70% mortality). The radiological spectrum of pulmonary aspergillosis must also always be borne in mind, as it can potentially be very serious in various types of immunocompromised patients. The CT scan therefore plays a key role in assisting clinicians managing these patients to make treatment decisions, especially in medical emergencies and immunocompromised patients.

**TAKE-HOME MESSAGES**

- The CT scan indisputably plays a key role in pulmonary infections given that standard radiography alone is lacking in specificity, especially in immunocompromised patients.
- In immunocompromised patients, the first conditions to be investigated should be tuberculosis, aspergillosis, and pneumocystosis.
- Some infections can very quickly become life-threatening.
- In cases of acute necrotic pneumonia, an infection caused by *S. aureus*, Panton-Valentine leukocidin secretor should routinely be investigated in young patients with no medical history because it points to a very poor prognosis (70% mortality).
- Pulmonary aspergillosis has a complex and non-homogenous radiological spectrum.
- The diagnosis of aspergillosis must be considered, depending on the findings, taking into account the patients immune status.
- The CT scan therefore plays a key role in assisting clinicians to make treatment decisions, especially in emergency and immunocompromised patients.

### Clinical case study

A 47-year-old male patient with no medical history of note who was not immunocompromised presented an unexplained fever. Here is the CT scan that was carried out (Fig. 9a–c).

### Questions

1. Describe the abnormal features visible on this CT scan.
2. Do these images fit into a picture of:
   (a) tuberculosis?
   (b) pneumocystosis?
   (c) septic emboli?
3. Could these lesions be caused by:
   (a) a *Staphylococcus* infection?
   (b) a viral infection?
   (c) a mycoplasma infection?

### Answers

1. Multiple nodules varying in size in the superior segment of the right inferior lobe, with internal density that is lower than that at the peripheries on parenchymal window; on mediastinal window, a hypodense centre, fitting with necrosis, is clearly visible.
2. (a) Cavitations due to tuberculosis have variable wall thickness and are accompanied by nodules with bronchogenic spread.
   (b) The cysts seen in pneumocystosis have thin walls and are found in areas of ground glass and reticulations.
   (c) The theory of septic emboli must be given greatest credence due to the rounded shape of the internal areas of necrosis.
3. These round images with central hypodensity that are suggestive of septic emboli could be caused by a *Staphylococcus* infection, because this bacterium readily causes septic emboli.

### Final diagnosis

This was a tricuspid endocarditis with septic emboli caused by methicillin-resistant *Staphylococcus* positive for Panton-Valentine leukocidin secretor secondary to a superinfected cutaneous wound.

### References


