CONTINUING EDUCATION PROGRAM: FOCUS

Infectious chest complications in haematological malignancies

S. Bommart a,*, A. Bourdin b, A. Makinson c, G. Durand a, A. Micheau a, V. Monnin-Bares a, F. Klein a, H. Kovacsik a

a Montpellier University Hospitals, Arnaud de Villeneuve Hospital, Medical Imaging, 371, avenue Doyen-Gaston-Giraud, 34295 Montpellier cedex 05, France
b Montpellier University Hospitals, Arnaud de Villeneuve Hospital, Department of Respiratory Medicine, 371, avenue Doyen-Gaston-Giraud, 34295 Montpellier cedex 05, France
c Montpellier University Hospitals, Gui de Chauliac Hospital, Department of Infectious and Tropical Disease, 80, avenue Augustin-Fliche, 34295 Montpellier cedex 05, France

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Abstract The management of infections in haematology is dictated by the patient’s type of acquired or induced immune deficiency (neutropenia, deficiency in cell-mediated or antibody-mediated immunity), and findings from clinical examination, laboratory studies, or morphologic investigations. The CT scan dominates in the initial management and follow-up of these patients, since clinical features very often appear to be non-specific. The radiologist’s role is to guide the clinician towards a specific diagnosis such as aspergillosis or pneumocystosis, or to point them towards a non-infectious cause: tumour localisation, hypervolaemia, bronchiolitis obliterans suggestive of GVH disease, drug toxicity, or embolism.

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Infectious complications are common in patients with haematological malignancies. They develop not only because of the immune deficiency that is intrinsic to haematological disease, but also because of the treatments used that cause immunosuppression or aplasia [1]. Around 50% of patients with a haematological malignancy will present a pulmonary infection during their management [2]. These events carry a heavy burden of morbidity that requires broad-spectrum anti-infective chemotherapy. They are the direct cause of almost 40% of deaths in this population. The prognosis correlates to how early diagnosis is made, meaning that quick access to cross-sectional
imaging is required: a key factor in the management of lung disorders is investigating the possibility of, for example, a fungal infection \[3\]. CT scanning has been shown to be superior to standard X-ray imaging for identifying localisation and spread of lesions as well as for an assessment of aetiology \[4\]. CT is currently recommended with evidence level A (one or more good quality meta-analyses or randomised clinical trials) when there is a suspicion of an infectious chest complication in a patient in haematological oncology \[5\]. It is also essential for carrying out or guiding biopsies, whether this is done by endoscopy or percutaneous needle biopsy. Microbiological diagnosis based on imaging features is of course only a signpost that will always have lesser sensitivity and specificity than the Gold Standard of microbiology testing. Nonetheless, the type and duration of immune suppression, when combined with certain specific morphologic findings, can point predominantly to particular pathogens and considering these factors together can assist with the decision-making process. Lungs are commonly not the only organs involved, and an associated infectious or non-infectious disease should always be searched (see Chapter of non infectious lesions).

Orientation and predisposing factors

There are three main mechanisms causing immunodeficiency in haematological oncology and these have recently been detailed by Godet et al. \[6\]. The emergence of pathogens depends on whether the patient has a deficiency in the type of immunity that is usually involved in controlling them, i.e. cellular-mediated or antibody-mediated immunity \[4\].

Three patterns are distinguished:

- neutropenia, which is usually caused by treatment, either chemotherapy or radiotherapy. This encourages bacterial or fungal lung infections to develop;
- deficiencies in cell-mediated immunity (immunosuppressant treatments, long-term corticosteroid use; lymphoproliferative diseases, bone marrow transplant). These encourage infections of intracellular bacteria, mycobacteria, viruses (Herpes virus), fungi (pneumocystosis), and parasites (toxoplasmosis);
- deficiencies in antibody-mediated immunity (splenectomy, hypo/ergammaglobulinemia and myeloma). They are usually associated with infections of *Streptococcus pneumoniae* or *Streptococcus haemophilus*.

Investigation technique

The chest CT scan can initially be carried out without injecting a contrast media. It will be carried out with contrast enhancement if there is a suspicion of pulmonary embolism or if the abdomen and pelvis are also to be examined. Where bronchiolitis is suspected, investigations are completed by taking expiration cross-sections using low-dose volume CT, or with four sequential staggered cross-sections. They can be acquired during breath hold in maximum expiration or during expiration (“breath, breathe, breathe”) \[7\]. To acquire a good quality expiration CT the patient needs to actively participate, as does the technician, so that the required functional information to characterise the distal airways is captured.

MRI is not currently indicated in this context.

**Imaging findings suggestive of infection**

**Bacterial infections**

Bacteria remain the most common infective agent causing lung disorders, or at least they are the pathogens that are most often identified on microbiology. These infections should routinely be treated with broad-spectrum antibiotics targeting staphylococci and Gram-negative bacteria \[8\]. Bacterial infections are usually non-specific, the radiological findings being an opacity or an uniform alveolar consolidation with air bronchogram (Fig. 1). This can be segmental, lobar, or spread across several lobes \[9\]. The description of the imaging features will attempt to define the spread and the associated abnormalities: underlying parenchyma or pleural effusion. Mediastinal lymphadenopathy can be found at the lymph nodes into which the infectious process is draining. More diffuse lymphadenopathy may present when there is tumour proliferation.

In general, the infection frequently gains entry via a central line catheter (Port a Cath, PICC line) \[10\]. Often blood cultures or bacteriology tests using specimens from the end of the catheter are used to check for infection after removal. In this specific case, the purpose of imaging is to assess the spread of septic localisations. The chest CT scan is especially useful for demonstrating relatively cavitated formations in the parenchyma that point to haematogenous dissemination of bacteria (or sometimes fungus). An assessment of the heart chambers forms part of the assessment of the spread of sepsis and this will look for thrombi of the valves pointing to associated endocarditis \[11\].

**Aspergillosis and other mycoses**

Many clinical entities connecting *Aspergillus* and the lung have been described, and these correlate with the level
of immune dysfunction that allowed them to develop: invasive aspergillosis, semi-invasive aspergillosis, chronic necrotising aspergillosis, aspergillus bronchitis, and finally allergic bronchopulmonary aspergillosis, which occupies the extreme end of this immunological and clinical spectrum. Aggressive opportunistic fungal infections can develop in patients who present neutropenia persisting beyond 1 week [12,13].

Invasive pulmonary aspergillosis (IPA) is at the forefront of these infections and it entails between 50 and 90% mortality. It complicates around 10% of allogeneic bone marrow transplants and induction cycles in acute leukaemia. This diagnosis is considered in the haematological oncology patients when they present severe infection that remains resistant to broad-spectrum antibiotics for 4 days or more. Aspergillus is a ubiquitous fungus and contamination is airborne, through the inhalation of spores. When the circumstances are favourable it can cause groups of cases. Aspergillus fumigatus is the most commonly found pathogen but other agents can produce similar pictures: zygomycosis [14], candidiasis (Fig. 2a and b). Imaging, and CT in particular, demonstrates non-specific pneumonia-like alveolar consolidation in fungal infections. One or more nodular lesions surrounded by a "ground glass" halo may point more specifically to this type of agent (Figs. 3 and 4). The ground glass opacity in this case relates to the presence of haemorrhagic areas peripheral to the central infarction. The halo sign is highly suspicious in this context, even though it has been demonstrated that this sign can also be seen in other infections (viruses, mycobacteria), inflammatory pathologies (Wegener’s granulomatosis), and tumours (metastases, lepidic growth pattern adenocarcinoma, Kaposi’s sarcoma) [15]. A reversed halo sign is, however, thought to be more suggestive of zygomycosis. The progression of CT features is marked by central necrosis and then retraction which then gives way to the air crescent sign (Fig. 5), and this usually coincides clinically with recovery from neutropenia [16]. As a general rule, the presence of well-delineated consolidation together with either a peripheral halo, an air crescent, or cavitation are the signs that point to probable IPA based

Figure 2. a,b: 56-year old female with respiratory decompensation within a relapse of M4 subtype acute myeloid leukaemia. Lung disease with central necrosis due to Candida tropicalis.

Figure 3. Forty-seven-year old female managed for acute lymphoblastic leukaemia. Severe sepsis following second cycle of induction chemotherapy. Diagnosis of invasive aspergillosis made after transthoracic needle biopsy. Indication for right upper lobectomy upheld when patient recovers from aplasia taking vascular connections into account.

on the current medical algorithms for the management of febrile patients with neutropenia [17].

Apart from guiding diagnosis, the role of the radiologist is to describe the relationships between these formations and the major vessels. This is because surgery may be indicated if localisations are found close to vascular structures, in view of the risk of massive haemoptysis.

Aspergillosis can readily affect the tracheobronchial tree, which translates into a thickening of the walls, debris filling the bronchi, or non-specific centrilobular opacities. This presentation occurs more easily in less severe forms of immunodeficiency [18].

Pneumocystosis

Pneumocystis jiroveci infection (formerly Pneumocystis carinii) is also a fungal infection due to recent
reclassification. A pneumocystosis infection in a patient living with HIV allows diagnosis of AIDS. It is however not specific to this kind of acquired immune deficiency and it can be seen irrespective of the cause of immune suppression, with a predilection for post-allogeneic transplant patients [19]. Imaging in pneumocystosis is highly distinct from that seen in other fungal infections. Indeed, the finding of extensive ‘ground glass’ opacities predominating in the upper zones is highly suggestive of pneumocystosis in this setting (Fig. 6). Other features classically associated with HIV (cystic lesions, crazy-paving sign) are less often found in haematological disease. These signs can be present when diagnosis has been delayed due to a subacute disease course [20].

Viral lung disease

Viral lung diseases caused by Herpes, cytomegalovirus or varicella-zoster virus (VZV) are usually conditions that are reactivated due to immune deficiency. Lung infections are presented as ‘ground glass’ or reticular opacities (Fig. 7) [21,22]. Alveolar consolidation or nodules are possible [22]. The development of a cough during an epidemic combined with findings of bronchial origin or ground glass opacities on CT points to a community-acquired virus.

Tuberculosis and atypical mycobacteria

When cell-mediated immunity is affected, this can cause a reactivation of tuberculosis that may be isolated or associated with other pathogens. Signs of this diagnosis are consolidation in the upper zones with nodular opacities associated with endobronchial spread (Fig. 8). Disseminated (miliary) forms occur most commonly when the patient has a severe immune deficiency. In these cases, multiple regular nodules distributed haematogenically may be observed.

Figure 4. Invasive aspergillosis, multiple nodule form.

Figure 5. Air crescent sign during a progressing invasive aspergillosis.

Figure 6. Repeat episode of fever two years after initial diagnosis. Ground glass opacities predominantly in the upper zones. Pneumocystosis (same patient as figure 1).
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Non-infectious lesions of the parenchyma

The non-infectious causes of parenchymal or vascular involvement can be presented on top of the signs of infection. A routine search should be made for them so that a disease that can be cured using methods other than antibiotics is not misdiagnosed.

Pulmonary oedema

A prescription of pre-treatment hyperhydration or the use of cardiotoxic chemotherapy such as anthracyclines can be the cause of pulmonary oedema. It is rarely difficult to diagnose clinically, although symptoms during the interstitial oedema stage of decompensated left heart failure can be more non-specific. If thickening of the perilobular septa is present, and all the more so if this is combined with pleural effusion, and even quite commonly mediastinal lymphadenopathy, this diagnosis must be considered, especially when it accompanies tangible signs of lung disease.

Parenchymal tumour localisations

Lymphomas can be present in the form of single or multiple areas of parenchymal consolidation and images may be misunderstood to be suggestive of an infectious cause. This finding is very typical in MALT lymphomas (Fig. 9a and b).

Specific case of pulmonary infiltration by leukemic blast cells

The finding of diffuse ground glass opacities together with acute dyspnoea can be explained by a build-up of circulating blast cells in the arterioles (pulmonary leukostasis), usually seen in acute myeloid leukaemia. This phenomenon is generally accompanied by multiple organ presentations and patients often make poor progress. Clinical signs and laboratory studies back up this diagnosis.

Figure 7. Lung disease with hypoxaemia in a 56-year old female being monitored for lymphoma. Predominantly diffuse pattern ground glass opacities: CMV lung infection.

Figure 8. B-lymphoma treated with CHOP in a 43-year old male. Alveolar consolidation has developed that is related to a site of hypermetabolism seen in the parenchyma on PET: atypical mycobacteria.

Figure 9. a,b: persistent alveolar consolidation with air bronchogram in a 79-year old male: non-Hodgkins lymphoma, MALT subtype.

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Infiltration of leukemic cells develops in the same setting but it can be distinguished because in this case tumour cells localise to the interstitium, which explains why some presentations mimic pulmonary oedema or appear to be lymphangitis [23,24].

**Drug or radiation-induced lung disease**

The presence of ground glass opacities with straight edges in the irradiated field that do not respect the pleural fissures, appearing during radiotherapy or in the following six months, is suggestive of acute radiation-induced lung disease.

Furthermore, there are many treatments used in haematological oncology that can cause an immune response leading to hypersensitivity reaction lung disease. The presentation can be extremely variable but shows involvement of the interstitium. The most classically seen forms are grouped together by drug on the website Pneumotox (http://www.pneumotox.com).

The purpose of multidisciplinary consultation is to exclude other diagnoses, to confirm the chronology of the patient’s treatments in order to establish which one the response may be attributed to using extrinsic information, and possibly to suggest other investigations for diagnosis.

**Alveolar haemorrhage**

Acquired or induced thrombocytopenia can predispose patients to alveolar haemorrhage. The filling of the alveolar space appears on imaging as ground glass opacities, sometimes combined with a reticular pattern (crazy-paving) [25]. The patient does not always expectorate blood (around 15% of cases) but when this clinical sign is present, it is another argument in favour of this diagnosis. If there is any doubt, fiberoptic bronchoalveolar lavage can confirm diagnosis. Alveolar haemorrhage can also complicate numerous other clinical settings (paraneoplastic syndrome, drug treatments, viral lung diseases etc.), principally pulmonary oedema, which is discussed above.

**Pulmonary alveolar proteinosis**

Pulmonary alveolar proteinosis or alveolar lipoproteinosis can be idiopathic or secondary to a haematological malignancy. It characteristically affects the interstitium, showing ground glass opacities combined with infralobular and perilobular reticular patterning (crazy-paving) (Fig. 10). The diagnosis is confirmed if milky fluid is collected on bronchoalveolar lavage [26,27].

**Pulmonary embolism**

With risk factors such as hyperviscosity syndrome, confinement to bed, and a malignant tumour occurring together, thromboembolic diseases become a common event in the management of haematological malignancies [28]. If a patient presents dyspnoea that has developed recently then the possibility of this diagnosis should be investigated.

**Bronchiolitis**

Bronchiolitis obliterans with organising pneumonia (BOOP, a name which has been replaced by cryptogenic organising pneumonia or COP in idiopathic cases) is a differential diagnosis identified by pathological and anatomical findings of subpleural alveolar consolidation that sometimes punctuates the course of a haematological malignancy (Fig. 11). The aetiology remains complex given that there are a multitude of factors that are potentially implicated (drug and physical treatments, underlying haematological disease, autoimmune response etc.).

Furthermore, 10 to 15% of allogeneic haematopoietic stem cell transplant recipients will present respiratory signs of rejection (Graft Versus Host Disease [GVHD]). Bronchiolitis obliterans is one way in which it may be identified.

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**Figure 10.** Ground glass opacities, intralobular and perilobular reticular pattern together forming the crazy-paving sign: secondary pulmonary alveolar proteinosis.

**Figure 11.** Fifty-eight-year-old female monitored for chronic lymphocytic leukaemia for 13 years. Invasive aspergillosis diagnosed and treated 3 years ago. Signs of recurrence in the alveoli. Transbronchial biopsy confirmed bronchiolitis obliterans, which resolved on corticosteroid therapy.
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Figure 12. a–d: air trapping in a 34-year old male with dyspnoea being monitored for acute myeloid leukaemia and allogeneic transplant: bronchiolitis obliterans due to GVHD.

This presents as dyspnoea and signs of obstructive disease on PFT. CT demonstrates mosaic lung attenuation that is more pronounced on images taken on expiration (Fig. 12) [29–31]. These presentations are very often associated with a series of non-respiratory symptoms linked to the rejection, mainly erythroderma and gastrointestinal disorders.

Conclusion

Chest infections are a common and serious complication in haematological oncology. The interpretation of CT findings, considered together with the setting, assists in therapeutic management by pointing towards a microbiological cause or to an intercurrent non-infectious pathology (Fig. 13).
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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