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Benefit of CT scanning for assessing pulmonary disease in the immunodepressed patient

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Abstract
Introduction: Management of pulmonary disease in immunodepressed patients requires a clear diagnostic and therapeutic strategy and multidisciplinary cooperation.
Discussion: The diagnostic approach should take into account the type of immunodepression, the clinical picture, the radiological signs and symptoms, and the microbiological, cytological and even histological examination of the pulmonary or extrapulmonary specimens. The high-resolution CT scan plays a central role and makes it possible to prioritize the diagnostic possibilities.
Conclusion: The analysis of the literature shows three important points: the chest X-ray has low diagnostic value; the CT scan of the chest can reveal lesions that cannot be detected on a standard chest X-ray; the CT scan is helpful for early detection and monitoring of invasive pulmonary aspergillosis.

The pulmonary diseases that occur in immunodepressed patients are common and serious. Their etiologies are numerous and may be infectious or noninfectious. Their management requires standardized pulmonary and immunohematological testing in order to suggest an appropriate choice of diagnostic tests and treatments. Multidisciplinary cooperation among pulmonologists, infectious disease specialists, oncologists, hematologists, radiologists, microbiologists, and intensivists is preferable. Such an organization is essential, since any diagnostic delay worsens the prognosis, which is dependent on the severity of the pulmonary disease itself, but also on the immunodepression and underlying comorbidities.

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The diagnostic process involves several factors:
- the type, duration, and degree of underlying immunodepression, which determines the microbiological possibilities to consider;
- the interview and clinical examination (nonspecific);
- the analysis of signs and symptoms on the standard chest X-ray (CXR) and especially the high-resolution CT scan (HR-CT), which makes it possible to determine the etiological possibilities;
- the results of microbiological or histological examinations, which sometimes make it possible to confirm the diagnosis.

Different types of immunodepression and principal etiologies of pulmonary conditions

Immunodepression is the result of a medical condition or treatment that impairs the body’s defense mechanisms for fighting infections. We can schematically define three major types of immunodepression: neutropenic patients, HIV-infected patients, and other types of immunodepressed patients.

Neutropenic patients

Neutropenia is an immune deficiency essentially involving phagocytosis. Profound neutropenia is defined as a decrease in the neutrophil count to less than 500/mm³.

During the initial phase of neutropenia, the causal pathogens are mainly bacteria of the Gram-positive cocci type, particularly *Staphylococcus aureus*, or Gram-negative bacteria such as *Pseudomonas aeruginosa*. When neutropenia lasts more than 5–7 days, fungal infections may occur (aspergillosis, candidiasis, mucormycosis). If there is a history of aspergillosis, it may occur earlier. From a radiological perspective, these patients have a particular presentation, since there may be an actual bacterial infection with no parenchymal opacity, which may not manifest until the neutropenia is corrected. Conversely, fungal infections manifest radiologically, since contrary to bacterial infections, the radiological image does not correspond to an inflammatory reaction associated with the infection, but to invasion of the pulmonary parenchyma by aspergillus hyphae (for example) and areas of infarction due to pulmonary vascular invasion. This pathogenesis explains the nodular or triangular (focal) nature of the opacity or radiological image at this stage, said image being most often surrounded by a halo of ground glass attenuation on the CT scan, indicating the hemorrhagic nature of the nodule. Furthermore, it is important to know that, while infectious pulmonary complications predominate during the aplastic phase, pulmonary opacities should also suggest other problems such as intraalveolar hemorrhages, hydrostatic or lesional pulmonary edema, and causes related to drug toxicity.

This is a major diagnostic challenge, since prognosis directly correlates with how quickly the underlying pulmonary condition is treated.

HIV-infected patients

Here, the immune deficiency is essentially linked to a quantitative and functional CD4 T-cell deficiency. Even though triple antiretroviral therapy has decreased the number of opportunistic infections that define onset of the AIDS stage, such complications are still common in undiagnosed patients and those in therapeutic failure. Infectious and noninfectious pulmonary complications in HIV patients correlate with CD4 T-cell levels. Pneumocystis is the most common infectious complication in patients with generally fewer than 200 CD4 T-cells/mm³. Tuberculosis occurs earlier in the course of HIV infection in patients with a higher CD4 T-cell level. Some emergent noninfectious pulmonary diseases have become important to know since the introduction of antiretroviral therapies: immune restoration syndrome, tumor conditions (Kaposi’s sarcoma, aggressive lymphoid proliferation, lung cancer, etc.), diffuse infiltrative disease (lymphoid interstitial pneumonia, organizing pneumonia, smoking-related diffuse infiltrative pneumonia, pulmonary drug toxicity, etc.) or even cardiovascular complications. The HR-CT appears to be a beneficial tool for the differential diagnosis of these pulmonary complications, since the analysis of signs and symptoms considerably reduces the number of diagnostic possibilities, guides the choice of endoscopic and biopsy specimens to take, and makes it possible to subsequently assess treatment response.

Bone marrow graft patients

Some patients who have undergone total body radiation resemble aplastic patients and are very vulnerable to pneumococcal infections. During conditioning, we find that the risks related to chemo-induced neutropenia are often prolonged; in particular, the risk of invasive pulmonary aspergillosis is especially high. Then, during bone marrow aplasia, these patients are particularly susceptible to cytomegalovirus (CMV) infections and mycoses such as pneumocystis. Later, in cases of graft-versus-host (GVH) disease, noninfectious diseases such as bronchiolitis obliterans, organizing pneumonia, interstitial lung disease, or pulmonary cytolytic thrombi should be considered.

Organ transplant patients

These patients have complications associated with cellular immune deficiency induced by immunosuppressant therapy. They are particularly susceptible to intracellular pathogens such as *Legionella pneumophila*, *Mycobacterium tuberculosis* and *Nocardia asteroides*. Aspergillus and *Nocardia* infections represent two-thirds of the causes of infection in heart transplant patients. Of note is the high risk of CMV infection in lung transplant patients and of toxoplasmosis in heart transplant patients, particularly in patients with no primary infection when the donor is seropositive. Furthermore, as in bone marrow graft patients and GVH, noninfectious entities such as bronchiolitis obliterans, organizing pneumonia, and interstitial lung disease may manifest.
Patients receiving high doses of corticosteroids

They have a granulocyte function deficiency essentially due to chemotaxis, but also a decrease in cytokine production and inhibition of T-cell activation. These patients are particularly susceptible to the risk of pneumocystosis, and frequent differential diagnosis problems versus a specific underlying condition in the context of collagen disease, lymphoproliferative syndromes, and solid tumors treated with chemotherapy. We compare them with patients treated with other immunosuppressants.

Diagnostic approach

The diagnostic approach should take several factors into account:
- the diathesis and underlying immunodepression, since the possibilities are different depending on type and duration;
- the clinical workup, which is necessary but nonspecific, and must determine the onset circumstances and nature of the respiratory symptoms as well as the associated signs;
- the radiologic signs and symptoms, where the HRCT scan plays a central role and makes it possible to prioritize the diagnostic possibilities based on the pattern or predominant semiotic component;
- the microbiological, cytological, or even histological examinations of pulmonary or extrapulmonary specimens, which sometimes make it possible to confirm the diagnosis.

Anamnèse

The nature of the underlying disease, the immunosuppressants taken, and the foreseeable duration and profundity of the neutropenia are all fundamental elements in the infectious risk assessment. One of the objectives is to draw up the patient’s immunosuppression profile in order to assess the pulmonary infection risks. Furthermore, it is important to thoroughly evaluate the chronology of the events, i.e., duration of the immunodepression and other potentially toxic therapies received (chemotherapy, radiation therapy, immunotherapy, immunosuppressant therapies, etc.). The stage of the underlying disease must be known, along with its complications, in order to prioritize the differential diagnoses. Examining the patient’s lifestyle (trips abroad, work and recreational activities, etc.) makes it possible to detect exposure to certain particular risks. Lastly, the nature and effect of anti-infective treatments received at the time of diagnosis of pneumonia, whether empirical, preemptive, or prophylactic, must be known, because they help guide the diagnostic approach and limit the number of possibilities.

Clinical presentation

The clinical examination is essential but nonspecific. Apart from fever, respiratory signs most often have little value in determining a cause of infection. The existence of extrathoracic signs can have great diagnostic value (pulmonary and brain involvement in a seropositive patient could suggest toxoplasmosis or cryptococcosis, for example). In addition, such extrathoracic locations may make it possible to take less invasive diagnostic specimens.

Microbiological diagnostic tests

Whether or not they are invasive, the benefit of a diagnostic tool should be assessed on a case-by-case basis: expected benefit versus benefit; impact of expected results on the patient’s prognosis and choice of therapy. A sputum test is useful for detecting bacteria, mycobacteria, and fungi. The induced sputum test is important for diagnosing pneumocystosis in patients who are seropositive for HIV. However, in some cases (mycobacteria or mold), it is difficult to distinguish between simple colonization and an actual infection.

The nasopharyngeal aspiration is cost-effective for diagnosing respiratory viral infections (molecular techniques) [1]. Detection of galactomannan in the serum or bronchoalveolar lavage (BAL) is very useful in diagnosing invasive pulmonary aspergillosis (IPA). However, the results reported by Weisser in 107 patients with IPA show that a CT scan provides an even earlier diagnosis [2]. Serological tests are also more likely to be positive in angioinvasive forms (80%) than in broncho-invasive forms (60%) [3].

Bronchoscopy, which is contraindicated in patients in acute respiratory failure, remains the gold standard for exploring pulmonary disease in immunodepressed patients [4]. That test makes it possible to perform guided BAL, but also bronchial and transbronchial biopsies, which improve its diagnostic performance [5]. Pulmonary biopsies can also be performed by transthoracically, guided by CT scan, and surgically (video-assisted or open chest surgery). Here too, the use of these diagnostic techniques in such immunodepressed and sometimes severely thrombopenic or neutropenic patients requires an assessment of the expected risk/benefit ratio [6].

Role of imaging

Standard chest X-ray

This is the first test required for immunodepressed patients suspected of having lung disease. It is helpful for detecting intrathoracic abnormalities, but it is difficult to interpret and its sensitivity is limited, as is its ability to determine an etiology. In a series of autopsies in 45 leukemia patients with lung involvement, CXR seemed helpful for diagnosing pulmonary abnormalities but very inadequate for establishing an etiological diagnosis, except in cases of acute respiratory distress syndrome and pulmonary hemorrhage [7]. In another series of immunodepressed patients not infected with HIV, a correct diagnosis was made based on an analysis of the CXR alone in 34% of cases [8]. The CXR was reported to be normal in 6% of HIV-infected patients with an infection such as pneumocystosis [9].

The CT scan of the chest

It can play an important role in the management of persistent fever in immunodepressed patients. The two
populations in which the differential diagnostic aid provided by a CT scan has been studied the most are HIV-infected and neutropenic patients. In HIV-infected patients, the HRCT is often essential for confirming or ruling out a pulmonary condition and sometimes provides etiological guidance [10–16].

In patients with febrile neutropenia, the HRCT is helpful for assessing a lung condition when the CXR is normal or subnormal. In that case, it helps determine the etiology and guide the collection of specimens such as BAL [17,18]. A study of 87 neutropenic patients with fever lasting more than 2 days while on broad-spectrum antibiotic therapy showed that more than half of the patients with a normal CXR had abnormalities suggestive of pneumonia on the HRCT [19]. Another series of 112 neutropenic patients with a persistent fever and normal CXR reported that the CT scan detected pneumonia in 60% of them [20]. In these two studies, the CT signs suggestive of pneumonia preceded CXR abnormalities by an average of 5 days. The authors concluded that any neutropenic patient with a resistant fever after 48–72 hours of broad-spectrum antibiotic therapy and a normal CXR should have a CT scan of the chest. In another study of 33 patients with febrile neutropenia in whom the CXR was interpreted as normal or subnormal in one-third and two-thirds of the cases, respectively, the CT scan resulted in a treatment change in one-third of the patients [21].

In neutropenic patients with IPA, even a repeated CXR has low sensitivity and low specificity. When the CT scan shows nodular opacities (and especially if those nodules are surrounded by a halo of ground glass attenuation or "halo sign"), an infection of fungal etiology (most often aspergillar) should be suspected [22]. During the correction of neutropenia phase, alveolar condensation with central hypodense area or presence of a nodule with an “air crescent” appearance are suggestive of IPA. If the CT scan is normal, an extrapulmonary etiology of the fever must be sought [22]. The high incidence of IPA and high morbidity and mortality from this disease in febrile neutropenia patients have led to numerous studies on the role of the CT scan in the early diagnosis of IPA [23–25].

Several studies suggest that early routine use of the CT scan in neutropenic patients provides a much earlier diagnosis of aspergillar infection [26,27]. In one of those studies, the time to diagnosis was reduced to 2–7 days [27]. Early diagnosis and aggressive management greatly determine the prognosis in these patients [23–28]. The approach combining early CT scan and detection of circulating galactomannan is probably the most successful [29]. Furthermore, contrast injection makes it possible to clarify the relationships between lesions and vascular structures (assessment of risk of hemoptysis), guide any diagnostic transpulmonary puncture biopsy, monitor changes in images during specific treatment, and take an inventory of residual lesions for purposes of potential "cleanup surgery". The HRCT also benefits other immunodepressed patients. Gulati assessed the diagnostic contribution of the HRCT in 21 kidney transplant patients suspected of having pulmonary infections; compared with a CXR, the CT scan rectified the etiological diagnosis in 11 patients (50%) [30].

The HRCT also clarified the etiology of pulmonary complications in febrile patients who received a hematopoietic stem cell transplant (HSCT). One team showed the CT scans were abnormal at least one week ahead of positive serological tests in these patients [31].

The possibility of noninfectious pulmonary complications should be borne in mind. These include specific conditions related to the underlying disease, drug- or radiation-induced toxicity, intraalveolar hemorrhaging, and hydrostatic pulmonary edema. The CT scan also makes it possible to suggest such complications when there is a nonspecific clinical presentation. Similarly, the HRCT is of major benefit for early diagnosis of the late noninfectious pulmonary complications that often mark the follow-up of HSCT patients and are often related to GVH disease. Recently, the HRCT proved its benefit for early screening of bronchiolar involvement in various diseases such as bronchiolitis obliterans after lung transplantation, before the onset of clinical or functional respiratory effects [32–36]. In fact, the CXR is most often initially normal and may remain so during the progression of bronchiolitis obliterans. The CT scan makes it possible to do a morphological analysis of the bronchi and bronchioli (dilatation, parietal thickness, etc.) and to screen for incipient bronchiolar involvement by showing air trapping during forced exhalation [34–40]. But air trapping during exhalation may also be due to other conditions, given the difficult medical history of HSCT patients (radiation therapy, chemotherapy, infection, etc.) [41,42].

Conclusion

Management of pulmonary disease in immunodepressed patients requires a formal analysis to establish the best diagnostic and therapeutic strategy and requires multidisciplinary cooperation. The initial diagnostic approach should take into account the diathesis and underlying immunodepression, the clinical examination, and the radiological signs and symptoms. Imaging, and especially the HRCT, plays a central management role, making it possible to prioritize the diagnostic possibilities based on the predominant pattern. Microbiological, cytological, and histological examinations of pulmonary or extrapulmonary specimens then sometimes make it possible to confirm the diagnosis.

**TAKE-HOME MESSAGES**

- Management of pulmonary disease in immunodepressed patients requires a clear diagnostic and therapeutic strategy and multidisciplinary cooperation.
- The diagnostic approach should take into account the type of immunodepression, the clinical picture, the radiological signs and symptoms, and the examination of the pulmonary or extrapulmonary specimens.
- The high-resolution CT scan makes it possible to prioritize the diagnostic possibilities and allows early detection of conditions that are not visible on the chest X-ray, such as invasive pulmonary aspergillosis.
• Any neutropenic patient with a resistant fever after 48–72 hours of broad-spectrum antibiotic therapy and a normal chest X-ray should have a CT scan of the chest.
• The injection of contrast clarifies the relationships between lesions and vascular structures (assessment of risk of hemoptysis).
• Pulmonary opacities in immunodepressed patients should suggest noninfectious diseases such as intraalveolar hemorrhages, hydrostatic or lesional pulmonary edema, and causes related to drug toxicity or conditions related to the underlying disease (tumors, systemic diseases, etc.).

References

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