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Rational approach to pulmonary infiltrates in leukemia and transplantation

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At present, a number of invasive diagnostic techniques can be used to diagnose the cause of lung infiltrates in patients with hematologic malignancies or hematopoietic stem cell transplantation recipients. Bronchoscopy with measurement of biomarkers in the bronchoalveolar lavage (BAL) will most likely become the preferred method to diagnose infectious causes of pulmonary infiltrates. However, there is no uniform approach regarding the technical parameters of the lavage procedure in cancer patients. Diagnostic protocols vary by region, center, and the expertise of the staff. This mini review discusses the issues surrounding diffuse pulmonary infiltrates and provides some recommendations to deal with these issues.

Introduction

Pulmonary infiltrates in hematologic malignancies is a broad and complicated topic and has been evolving over the last 50 years. From a classic autopsy study from the 1960s [1] and subsequent studies, a few general observations can be made in that patient population. First, as in all infections, neutropenic patients with pulmonary infiltrates often lack signs or symptoms, so their presentation is subtle and nonspecific. Thus, not uncommonly, such patients present late with manifestations with full blown pneumonia, unless there is a high index of suspicion. Second, not all infiltrates in patients with hematologic malignancies are due to infection. Their etiology is complicated and they can also be caused by pulmonary hemorrhage, drug toxicity, leukemic infiltration, and pulmonary edema. Third,

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multiple pathogens are not uncommon [2], making the diagnostic assessment with antigen-based assays or DNA-based assays complicated. And fourth, the radiologic pattern, although helpful, lacks specificity. Nevertheless, infection is always the major consideration [1]. The timing and rapidity of onset of the infiltrates, the radiologic pattern, immune status of the patient, local epidemiology, and diagnostic workup are important in determining appropriate treatment.

Initial evaluation

The first step in evaluating a leukemia patient with a pulmonary infiltrate is to assess the patient's immunosuppressive state. Immune defects vary according to the underlying malignancy. For example, a patient with chronic myeloid leukemia (CML) is not as immunosuppressed as the patient with refractory chronic lymphoblastic leukemia (CLL) or an elderly patient with refractory acute myeloid leukemia (AML). The number of episodes of neutropenia should also be assessed because each episode contributes to the cumulative immunosuppression. The dose, duration, and temporal sequence of immunosuppressive therapies also have an impact on the net immunosuppressive state of the patient. And metabolic factors should also be considered in the assessment. For example, hyperglycemia in the setting of steroids for treatment of GvHD is a risk factor for infection and results in a poor outcome independent of the type of antibacterial or antifungal therapy.

History of prior infections is also important to assess. For example, the immunosuppressive effects of viruses, for example cytomegalovirus (CMV) reactivation, are important in the setting of transplantation. CMV reactivation is commonly a harbinger for the development of subsequent aspergillosis in stem cell recipients. Exposure to construction sites or recent travel can also impact the patient's diagnosis and treatment, as can prior antibacterial or antifungal therapy the patient may have had. Clinical presentation, the tempo of the illness, and the timing of onset of the pulmonary process are all important considerations in the initial patient evaluation.

Radiographic findings in leukemic patients

Radiographic findings in leukemia patients can be categorized into consolidation, interstitial infiltrates, and nodular infiltrates, and each general category can be further subdivided into acute or subacute (Fig. 1). Typically, consolidating lung lesions in the acute setting are frequently due to bacterial infections and hemorrhage, particularly during remission/induction chemotherapy. Subacute consolidation findings are often due to bacterial and fungal infections. Radiographic findings in the category of acute interstitial infiltrates can include drug toxicity, bleeding, and non-cardiogenic pulmonary edema. The differential diagnosis in the subacute interstitial infiltrates can include viral infections, Pneumocystis, radiation-induced changes, and drug-induced changes. In the category of acute nodular infiltrates, bacterial infections such as *Staphylococcus aureus* and *Pseudomonas* can simulate fungal presentations. And for the subacute presentation of nodular infiltrates, fungal infections are prominent in the differential diagnosis. Studies have shown that if leukemia patients have nodular infiltrates, especially patients who are not in complete remission, about 80% of those are due to fungal infections; most are invasive pulmonary aspergillosis [3]. However, not all nodular infiltrates in leukemia patients are due to fungus. Sometimes they are caused by other conditions, such as lung cancers or chronic lung infections such as *Nocardia* or mycobacterial disease. Furthermore antineoplastic drugs can also induce lung infiltrates that may be confused with pneumonia, for example, interstitial pneumonitis, nonspecific interstitial pneumonitis, diffuse alveolar hemorrhage, and non-cardiogenic pulmonary edema.

Stem cell transplant recipients may also develop lung infiltrates that can be confused with pneumonia, pulmonary edema, engraftment syndrome, and other complications in the early (less than 100 days) posttransplant period. One hundred days after transplant, the etiology is usually due to bronchiolitis obliterans with organizing pneumonia (BOOP), posttransplant lymphoproliferative disease, delayed pulmonary toxicity, fungal infections, and late community-acquired viral infection [4].

Inflammatory immune reconstitution syndrome (IRIS) occurs infrequently during neutrophil recovery and can simulate worsening infection [5], as there is an influx of neutrophils to the area of