Pulmonary Infiltrates in the Immunocompromised Host

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Abstract

Patients with a compromised immune system suffer a wide variety of insults. Interstitial lung changes are one of the most common and serious complications in this group of patients. The morbidity rate reaches 50% and up to 90% if endotracheal intubation and mechanical ventilation are necessary. Opportunistic and bacterial infections are common causes of pulmonary infiltrates and must be distinguished from other conditions such as drug reactions, volume overload, pulmonary hemorrhage, and malignant diseases. Accurate and prompt diagnosis of potentially treatable causes can be life-saving. Non-invasive diagnostic methods for evaluation are often of little value, and an invasive procedure – such as bronchoalveolar lavage, transbronchial biopsy or even open lung biopsy – is therefore performed to obtain a histologic diagnosis. Yet, even when a specific diagnosis is made it may not improve the patient's survival. Numerous textbook and review articles have focused on the management of this condition. The present review attempts to provide a comprehensive and systematic picture of current knowledge and an integrated approach to these challenging patients.

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Evaluation of the immunocompromised host with diffuse pulmonary infiltrates can be difficult, frustrating and time-consuming. This common and serious problem results in significant morbidity and mortality, approaching 90% [1–3]. It is estimated that the lungs are involved in at least 75% of immunocompromised patients with any complication. At autopsy, well over 90% have pulmonary disease, at least histologically. However, in 15% of cases even the pathologist cannot make a definitive diagnosis, resulting in a non-specific diagnosis such as "diffuse alveolar damage," or "interstitial pneumonitis and fibrosis" [4,5].

Several series of trans-bronchoscopic lung biopsy, bronchoalveolar lavage, and even open lung biopsy resulted in similar failure rates (15–30%) in reaching a definitive diagnosis [3,5–15]. Yet even when a specific diagnosis is made, it may not necessarily improve the outcome [16–21]. The mortality rate varies between 15 and 90%, depending on the underlying disease, the severity of lung involvement, and the total impairment of host defenses [2,3,16,18,19,22–26]. This review provides clinicians with a systematic and organized approach to the evaluation and management of the immunocompromised host with diffuse pulmonary infiltrates.

Etiology

Infection is the most common cause of both acute and subacute lung impairment. However, many non-infectious etiologies may present in a similar fashion, further complicating the diagnostic process [1,16,27]. Table 1 lists the most common categories causing diffuse pulmonary infiltrates in the immunocompromised patient. Narrowing the diagnostic alternatives should minimize the need for risky, costly and possibly unnecessary diagnostic and therapeutic interventions.

The reported frequencies of these entities vary with the series, type of immunosuppression, age, and method of confirmation (i.e., BAL, TBB, OLB). The frequency depends as well on whether the definitive diagnostic procedure is performed early or after extensive empiric therapy. For example, a carefully taken drug history and review of past medical history may exclude drug or radiation toxicity, or it may help implicate underlying neoplastic disease as a cause. Pulmonary edema or congestive heart failure is rarely considered in young people who have never received cardiotoxic drugs and lack a history of cardiovascular disease. Yet, fluid overload syndromes related to occult cardiovascular disease might easily imitate infections in these patients.

Moreover, many of the clues and subtle clinical signs that are useful in non-compromised patients are not helpful and at times even misleading in immunocompromised patients with a similar

BAL = bronchoalveolar lavage
TBB = trans-bronchoscopic lung biopsy
OLB = open lung biopsy

Table 1. Differential diagnosis of diffuse pulmonary disease in the immunocompromised host

1.	Infection
2.	Drug induced pulmonary disease
3.	Recurrence of underlying disease
4.	Pulmonary hemorrhage
5.	Idiopathic fibrosis
6.	"Unrelated" disease
7.	Unusual complication
8.	Two or more of the above

clinical presentation. The presence or absence of fever, the productivity of cough, and even the radiologic pattern of infiltrates cannot reliably point to a diagnosis.

Pulmonary infection

Infection is the most frequent cause of pulmonary infiltrates in the immunocompromised host. A unilateral, localized process is very likely to be infectious in origin (90%), whereas diffuse disease is somewhat less frequent (75%) [1,26,28]. The lack of potent inflammatory response due to neutropenia or additional immune dysfunction may attenuate the classic signs of pulmonary infection such as fever and productive cough.

There are two main strategies in approaching the differential diagnosis. The first could relate the various organisms to the primary impairment in defense mechanisms. The second and the more clinically relevant would be to consider the probability of different pathogens in the context of the underlying condition (renal transplant, leukemia, human immunodeficiency virus, etc.). Most of them are well known to most clinicians. It is estimated that these pathogens account for over 90% of opportunistic infections. These organisms are summarized in Table 2.

Table 2. The most common organisms

Bacteria	Fungi	Viruses	Protozoa
Staphylococcus aureus	*Pneumocystis carinii*	Cytomegalovirus	*Toxoplasma gondii*
Streptococcus pneumoniae	*Candida* sp.	Herpes simplex	*Strongyloides stercoralis*
Staph. epidermidis	*Aspergillus* sp.	Herpes zoster	
Pseudomonas aeroginosa	*Hystoplasma capsulatum*	Respiratory syncytial virus	
Escherichia coli	*Blastomyces dermatitidis*	Influenza A	
Legionella	*Coccidiodes immitis*	Enterovirus	
Nocardia	*Cryptosporidium neoformans*		
Mycobacteria sp.			

Table 3. Drug-induced diffuse pulmonary disease

Chemotherapeutic drugs
1. Bleomycin
2. Methotrexate
3. Busulfan
4. Cytosine arabinose (AraC)
Non-chemotherapeutic drugs
1. Nitrofurantoin
2. Amiodarone

Drug-induced pulmonary disease and radiation pneumonitis fibrosis

Table 3 lists drug-induced pulmonary disease. The vast majority of these patients are febrile, usually without chills. The fever may be intermittent in nature. The onset of drug-induced pulmonary disease is usually insidious, developing over several weeks rather than acutely, although the latter has been reported with most drugs. Administration of multiple cytotoxic drugs, supplemental oxygen, as well as radiation therapy and preexisting lung disease, may potentiate the pulmonary toxicity. Patients should always be managed with the lowest FIO_2 that is sufficient to maintain hemoglobin saturation [16,27,28].

Recurrence of the underlying primary process

Recurrence of the underlying primary process may complicate the course in patients with hematologic malignancies [29]. It is difficult to diagnose by TBB brushing or BAL and may require OLB. However, a thorough examination of the patient may disclose a new lymph node warranting biopsy. Alternatively, bone marrow aspiration and biopsy may be sufficient to establish the recurrence of lymphoma.

The radiologic pattern of lymphoma involving the lung is extremely variable, ranging from a few nodules to a diffuse alveolar/interstitial process. It may progress rapidly or in a very indolent fashion. Pleural effusion is commonly present.

There is a high incidence of pulmonary complications in patients with leukemia. Possible causes of pulmonary infiltrates in the leukemic patient include:

- Opportunistic infection
- Infiltration of the lung by leukemic cells
- Adverse drug effect
- Hemorrhage
- Leukostasis from blasts cells (typically occurring when there are more than 40% blasts)
- Leukemic cell lysis pneumopathy
- Hyperleukocytic reaction.

The distinction between these entities is important, as some of them may be treatable.

Hemorrhage

Pulmonary hemorrhage is rare and is usually associated with clotting disorders and/or thrombocytopenia. It can be focal or diffuse and associated with fever. It infrequently results in massive hemoptysis. BAL will show hemosiderin-laden macrophages, however even such a finding may not preclude the coexistence of an additional etiology [1].

"Unrelated" disease

"Unrelated" disease may arise in the elderly patient with cardiopulmonary edema from asymptomatic coronary artery disease that is given a salt and fluid overload. Because of periods of prolonged bed-rest and hypercoagulability, this group of patients is predisposed to venous thromboembolism and multiple pulmonary emboli. The category of "unrelated" disease should always be kept in mind because most of the sources at least are treatable and many are reversible.

Unusual complications

Pulmonary alveolar proteinosis has been reported as a complication of hematologic malignancies. This diagnosis cannot be made unless it is suspected and the pathologist stains the tissue with a

periodic acid-Schiff stain. Non-traumatic fat embolization has been reported in the immunocompromised host, possibly related to the use of corticosteroids. It will also require the use of special stains for fat. Finally, pulmonary veno-occlusive disease has been reported as a complication of chemotherapeutic drugs, especially the nitroso-ureas and bleomycin, as well as after bone marrow transplantation. For obvious reasons, these entities are greatly under-diagnosed [1,27].

Two or more of the previously discussed causes

Unfortunately, establishing a specific single diagnosis, possibly through fairly simple means, does not rule out a second or even a third coexisting cause. This possibility is of particular importance in patients who are not responding to specific treatment as expected. The exact frequency of such overlap is unknown.

Diagnostic approach

The complexity and potential fatality mandates aggressive evaluation and quick identification of the underlying process. Moreover, it is practically impossible to cover all the diagnostic possibilities by empiric treatment. The non-invasive diagnostic methods include serologic tests, blood antigen detection, nasopharyngeal wash, sputum, and tracheobronchial aspirate cultures. It also includes chest X-ray, gram and Ziehl-Nielsen stain of expectorated sputum, and skin testing. These techniques are important because of their safe profile and relatively low cost [22,26,30,31], although most authors agree that they add little useful information [1,2,3,8,16]. It is recommended that they be performed as early as possible before the beginning of any empiric therapy. The diagnostic yield of non-invasive techniques is in the range of 10–30% [32–34].

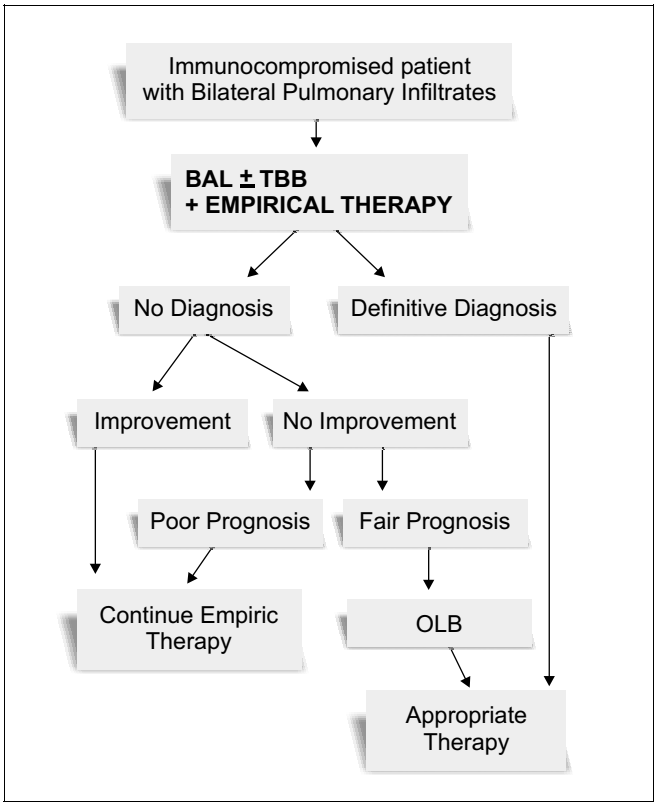
The diversity of etiologies, the non-specific nature of the clinical and radiologic finding, and the low yield of non-invasive procedures raise the issue of invasive diagnostic procedures. The risk benefit ratio is a major consideration in these critically ill patients. The least invasive procedure with a significant yield is BAL, which seems to be well tolerated even in critically ill patients [3,7–10,17]. In a recent, relatively small prospective trial, Gruson et al. [33] assessed the effect of fiberoptic bronchoscopy and BAL on the management and outcome of neutropenic patients with pulmonary infiltrates. They found that the use of routine BAL in this group of patients had a low complication rate (17%) and acceptable diagnostic yield (49%), but infrequently led to change in therapy and was not associated with improved survival. This lack of effect on mortality was attributed to the fact that most of the patients were already treated with broad-spectrum antibiotics prior to the diagnostic intervention. On the other hand, Rano et al. [3] reported that early invasive diagnosis (in the first week) and change of therapy did affect mortality (29 vs. 71%) in non-HIV patients with pulmonary infiltrates.

Unfortunately, some disorders that occur predominantly in the interstitium require a more invasive technique, such as transbronchial biopsy or open lung biopsy [10–15]. Open lung biopsy is regarded as the gold standard for the diagnosis of pulmonary infiltrates, and several studies have documented its use in specific patient populations [32]. In recent years an ongoing debate is reflected in the literature regarding the benefit of open lung biopsy. All these studies, however, showed that the procedure could be performed with a low mortality rate, even in seriously ill patients. Kramer et al. [11] demonstrated that the "benefit" (defined as change in therapy that resulted in survival) of open lung biopsy in this group of patients was 46%. This benefit was even higher when the patient had a reasonable prognosis. In fact the mortality rate in certain groups of immunosuppressed patients (e.g., bone marrow recipients with acute respiratory failure, or patients with respiratory failure plus two other organ failures) is so high that it is questionable whether a more invasive procedure should be routinely pursued [7,33–35].

Empiric therapy

Most investigators would agree that the first step in managing these patients is a quick non-invasive work-up followed by bronchoalveolar lavage. Typically, broad-spectrum antibiotics will be initiated based on clinical judgment and epidemiologic considerations. We would not recommend starting empiric therapy without making any diagnostic effort (such as BAL). An individualized approach should be tailored to each patient, considering all the pertinent clinical data that would dictate the extent and pace of additional interventions.

Our approach to the diagnosis and management of immunocompromised patients with diffuse lung disease is summarized in the following algorithm.



HIV = human immunodeficiency virus

Summary and conclusions

The management of immunocompromised patients with diffuse pulmonary infiltrates remains a common and stubbornly difficult problem. The range of diagnostic possibilities is wide. Non-invasive diagnostic procedures have little utility, and the drugs available for empiric therapy have toxic effects that are sometimes severe. Although guidelines for management have been developed, they may be predicated on data from a single institution or depend on diagnostic procedures and laboratory support that are not necessarily available to physicians in all locations.

Controversy still exists regarding whether making a definitive diagnosis in these patients has an impact on overall outcome. An individualized approach must consider local resources, the patient's age and prognosis, type of immunosuppression, opinions of the patient and his or her family regarding invasive measures and heroic support, and previous patterns of infection in the institution. Invasive procedures should be performed only if management is expected to change based upon results.

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