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Clinical Approach to the Compromised Host with Fever and Pulmonary Infiltrates

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1. The Febrile Pneumonitis Syndrome and Its Importance

The immunocompromised patient in whom fever and pneumonitis develop presents a formidable challenge to the clinician. On one hand, a legion of microbial invaders, ranging from common viral and bacterial pathogens to exotic fungal and protozoan agents, have been reported to cause pulmonary infection in these patients.[1–8] On the other hand, noninfectious causes of pulmonary inflammation—radiation lung injury, drug reactions, the underlying neoplasm, pulmonary embolic disease, leukoagglutinin transfusion reactions, pulmonary hemorrhage, atypical pulmonary edema, and alveolar proteinosis—may present a clinical picture similar to that produced by infection (i.e., the febrile pneumonitis syndrome).[2,3,5,9–11]

In addition to the broad differential diagnosis that must be considered, the clinician's task is further complicated in many patients by the subtlety of the clinical presentation. The impaired inflammatory response that is characteristic of so many immunocompromised states may greatly alter the clinical presentation of the process. Since physical findings, presenting symptoms, radiologic patterns, and even tissue pathology are largely determined by the inflammatory response to the inciting agent (particularly microbes), it is axiomatic that all these phenomena can be greatly modified in the compromised host. In particular, the manifestations of microbial invasion can be greatly attenuated until late in the disease process in patients with impaired inflammatory responses.[3,6,12,13]

Since survival of the immunocompromised host with pulmonary infection is determined in large part by the speed with which diagnosis is made and effective therapy instituted, even subtle clinical and radiologic findings must be carefully evaluated. For example, an unexplained cough in an individual with the acquired immunodeficiency syndrome (AIDS), even in the absence of physical findings or abnormalities on the chest roentgenogram, can represent significant *Pneumocystis carinii* pneumonia, demonstrable by nuclear medicine scan and diagnosable on induced sputum or bronchoalveolar lavage. Similarly, an unexplained fever in a leukemic patient with prolonged chemotherapy-induced neutropenia can be due to invasive pulmonary aspergillosis, despite a negative chest roentgenogram, that may be delineated on a computerized tomographic (CT) scan of the chest and diagnosed by percutaneous needle aspiration biopsy.

Of all the host-defense defects, severe granulocytopenia will have the most profound effect in this regard (although high-dose corticosteroids and advanced AIDS can have a similar impact). The incidence of cough and purulent sputum production, rate of development and progression of radiologic findings, occurrence of cavitation, and pleural space involvement are all markedly diminished in patients with profound granulocytopenia. In addition, the consequences of the pulmonary process in such granulocytopenic patients may also be modified.[3,6,12,13] For example, in children with acute leukemia and pneumonia who have absolute granulocyte

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counts of less than 1000/mm^3, the incidence of positive blood cultures has been reported to be 64%, with the incidence of positive cultures falling to 0% in children with leukemia, pneumonia, and absolute granulocyte counts greater than 1000/mm^3.[1,14] Similarly, although septic shock is a rare occurrence in an immunologically normal patient with pneumonia, it is not unusual in a severely granulocytopenic patient.[3]

The clinical importance of the febrile pneumonitis syndrome is illustrated by the following observations: The lungs are involved in at least 75% of immunocompromised patients who develop febrile complications, with autopsy evidence of pulmonary infection in more than 90% of patients who succumb.[5] As many as 58% of patients with cancer and profound granulocytopenia who die have been shown at autopsy to have clinically unrecognized and hence inadequately treated pneumonia.[14] Patients with significant lung injury from noninfectious processes have a high rate of secondary infection, which is often the immediate cause of death. This result is particularly likely if the primary lung injury required intubation for greater than 72 hr.[2] Mortality rates of 35–90% have been reported in immunocompromised patients with pneumonia, with the exact incidence depending on the underlying disease, the severity of the pneumonia at the time of diagnosis, and the degree of host-defense impairment.[10,15] For example, Poe et al.[15] have reported mortality rates that approached 100% in immunocompromised patients with pneumonia who demonstrated the following characteristics: a PaO_2 less than 50 mm Hg within 72 hr of admission, corticosteroid administration at the time of presentation, and the need for mechanical ventilation.

The foundation of the approach to the febrile pneumonitis syndrome in this patient population is the recognition of the clinical importance of this syndrome, an awareness of the subtlety of its clinical presentation, and the need for more intensive and invasive diagnostic procedures than in the normal host. Despite the obvious difficulties, a variety of clues are available to the clinician in approaching this clinical problem: (1) the clinical and epidemiologic setting in which the pulmonary process is occurring, (2) an understanding of the host-defense defects present, (3) the rate of progression of the illness, (4) the pattern of radiologic abnormality produced on chest radiography, and (5) the proper deployment and application of information gained from a series of increasingly invasive diagnostic techniques. A logical approach based on these elements will enable the clinician to arrive rapidly at the appropriate diagnosis. Such rapid diagnosis and appropriate institution of therapy can result, even in this population, in a gratifying rate of clinical response and meaningful patient survival.[2,3]

TABLE 1. Etiology of Febrile Pneumonitis Syndrome in 100 Cancer Patients and 51 Renal Transplant Patients at Massachusetts General Hospital[a]

Etiology	Number of patients: Cancer	Renal transplant	Total	Percent
Infectious causes				
Conventional bacterial infection	26	10	36	23.8
Viral infection	11	9	20	13.2
Fungal infection	10	6	16	10.6
Nocardia asteroides	5	8	13	8.6
Pneumocystis carinii	6	2	8	5.3
Mycobacterium tuberculosis	1	0	1	0.7
Mixed infections	14	1[b]	15	9.9
Total	73	36	109	72.2
Noninfectious causes				
Pulmonary emboli	3	9	12	7.9
Recurrent tumor	8	0	8	5.3
Radiation pneumonitis	7	0	7	4.6
Pulmonary edema	1	6	7	4.6
Drug-induced pneumonitis	5	0	5	3.3
Leukoagglutinin reaction	2	0	2	1.3
Pulmonary hemorrhage	1	0	1	0.7
Total	27	15	42	27.8

[a]Data taken and modified from Rubin[3] and Ramsey et al.[2]
[b]This one case was that of an aspiration pneumonia from whom mixed oropharyngeal flora were grown from a transtracheal aspirate. In addition, 23 renal transplant patients with a primary pulmonary process developed superinfection.

2. Overview of Infectious Causes of the Febrile Pneumonitis Syndrome in the Immunocompromised Host

The first concern of the clinician confronted with an immunocompromised patient with fever and pulmonary infiltrates is infection. Overall, 75–90% of episodes are due to infection, with particularly high rates of noninfectious causes of the febrile pneumonitis syndrome occurring in cancer patients and transplant recipients (Table 1).[2,3,5,8–11] Most published series devoted to pulmonary infections in immunocompromised patients have emphasized the importance of opportunistic gram-negative, fungal, protozoan, nocardial, and herpes group viral infections. Such series have been primarily concerned with infections in patients with acute leukemia or other illnesses undergoing intensive immunosuppressive therapy within the hospital environment. This emphasis on opportunistic infection is also appropriate in patients with AIDS. However, in all immunocompromised patients,

even the AIDS patient, common infections and noninfectious causes of pneumonitis must be considered (Table 1).[1,6–9,16]

It should also be emphasized that in some patients who are less intensively immunosuppressed, opportunistic infections are uncommon. Thus, *Streptococcus pneumoniae* is the single most common bacterial infection in the cancer and renal transplant patient population, as it is in the normal host, and influenza is the most common viral infection, other than cytomegalovirus.[2,3] These patients with pneumococcal and influenzal infection differ from those with more opportunistic infection in several respects. First, they acquire their pneumonias in the community when their primary disease is either in remission or relatively quiescent. Second, immunosuppressive therapy is often at a minimum. Third, there is a predominance of patients with stable renal transplants, solid tumors, or collagen disease and a dearth of patients with such conditions as acute allograft rejection or acute leukemia. Fourth, there is a relatively high level of influenza activity in the community and within their family units. Therefore, it is essential for the clinician to define the epidemiology of the infection as well as the status of the patient's host defenses early in the evaluation of the pulmonary process.[2,3,7,8]

Illustrative Case 1

A 32-year-old male renal transplant patient was admitted with a 4-hr history of fever, rigors, pleurisy, purulent sputum production, and shortness of breath. The patient had received a human leukocyte antigen (HLA)-identical kidney from his brother 18 months previously. Since then, he had had no episodes of rejection and was currently maintained on alternate-day prednisone, 30 mg qod, and azathioprine, 100 mg/day, with a stable serum creatinine of 1.2 mg/dl. One week prior to admission, he developed an upper respiratory infection characterized by low-grade fever, malaise, anorexia, myalgias, and nonproductive cough. Both his wife and one of his children had similar illnesses. He appeared to be getting somewhat better, when he was awakened early on the morning of admission with a shaking chill, pleuritic chest pain, an increased cough now productive of purulent blood-tinged sputum, and shortness of breath. Physical examination revealed a toxic, tachypneic gentleman with a temperature of 103.4°F (39.7°C) and a respiratory rate of 35. Herpes labialis was evident, and signs of consolidation were present at the left lung base. The renal allograft was of normal size and nontender. Laboratory data revealed Hct of 43%, WBC of 14,000/mm^3, with 80% polys, 14% bands, 3% lymphs, 3% monos. BUN was 26 mg/dl, and serum creatinine 1.3 mg/dl. Sputum examination revealed sheets of polymorphonuclear leukocytes and gram-positive diplococci. Sputum and two blood cultures grew *Streptococcus pneumoniae*. Chest radiography (Fig. 1) demonstrated a focal air space consolidation of the left lower lobe.

Comments. This is the classic presentation of community-acquired pneumococcal pneumonia following a viral upper respiratory infection. In this stable renal transplant patient receiving minimal immunosuppressive therapy, the community-acquired pulmonary infection is identical and presents in identical fashion to that seen in the normal host. Physical findings, chest radiography, and response to conventional penicillin therapy are typical for this type of infection.

2.1. Factors That Determine the Risk of Pulmonary Infection

The risk in the compromised host of invasive infection in general, and of pulmonary infection in particular, is determined largely by the interaction of two factors: the patient's net state of immunosuppression and the epidemiologic exposures he or she encounters. Thus, if the infecting inoculum is great enough, even a normal individual can develop life-threatening infection; conversely, if the degree of immunosuppression is great enough, even the most innocuous of commensal organisms can pose a severe threat.[17]

Certain defects in host defense render the individual particularly susceptible to infection with particular classes of microorganisms (Table 2). These correlations are especially useful in pediatric patients with congenital defects that are relatively "pure," such as isolated defects in antibody formation, complement function, or granulocyte function (see Chapters 2, 3, and 20).[18] In most individuals, however, the situation is far more complicated, with a variety of defects present in the same individual due to the effects of acquired disease and its therapy. For example, following a combination of splenectomy, radiation, and chemotherapy, patients with Hodgkin's disease, which itself is associated with profound defects in T-lymphocyte function and cell-mediated immunity, will develop marked B-lymphocyte dysfunction as manifested by low levels of serum immunoglobulin M and specific antibody against *Hemophilus influenzae* type B, poor response to pneumococcal vaccine, and an increased risk of life-threatening systemic and pulmonary infection with these two organisms.[19–21] Thus, in the majority of immunocompromised patients, the concern is the "net state of immunosuppression," rather than a single defect.

2.1.1. Net State of Immunosuppression

The net state of immunosuppression is a complex function determined by the interaction of a number of factors[17]:

1. Host-defense defects caused by the disease process itself.
2. Dose, duration, and temporal sequence of immunosuppressive therapy employed.
3. Presence or absence of neutropenia.
4. Anatomic integrity of the tracheobronchial tree (including the absence of such "foreign bodies"

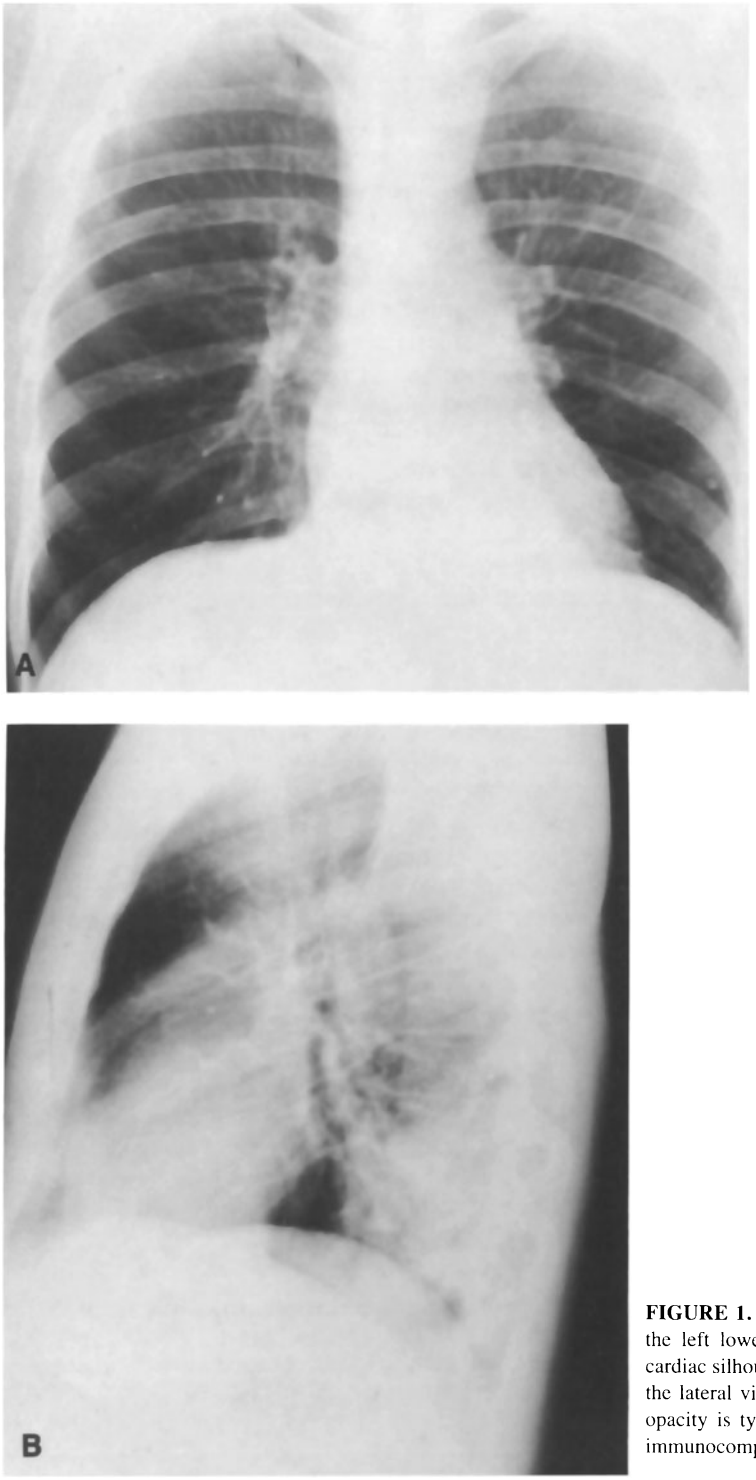

FIGURE 1. *Streptococcus pneumoniae* pneumonia. A consolidation in the left lower lobe of a renal transplant patient is obscured by the cardiac silhouette on the frontal view (A), but is more clearly visible on the lateral view (B). The peripheral, nonsegmental distribution of the opacity is typical of community-acquired bacterial pneumonia in the immunocompromised host.

as endotracheal tubes and obstructing tumor masses).

5. "Functional" integrity of the oropharyngeal and gastric mucosa in terms of their ability to resist the adherence of potential pathogens to these mucosal surfaces.
6. Such metabolic factors as protein–calorie malnutrition, uremia, and, perhaps, hyperglycemia.
7. Presence of infection with one or more of the immunomodulating viruses: human immunodeficiency virus (HIV), cytomegalovirus, Epstein–Barr virus, and hepatitis viruses B and C.

TABLE 2. Pulmonary Infections to Which Patients with Specific Host-Defense Defects Are Predisposed[a]

Host-defense defect	Pulmonary infections to which patient is predisposed
Oral and tracheobronchial ulceration or obstruction or both	Oral bacterial flora Enterobacteriaceae
Decrease in the number of fully functional granulocytes	Oral bacterial flora Enterobacteriaceae *Aspergillus* species *Pseudomonas aeruginosa*
Hypogammaglobulinemia	*Streptococcus pneumoniae* *Hemophilus influenza* type B (*Pneumocystitis carinii*)
Depressed cell-mediated immunity	Typical and atypical mycobacteria Fungi Viruses (CMV, varicella–zoster virus, herpes simplex, measles virus) *Pneumocystis carinii* *Toxoplasma gondii* *Strongyloides stercoralis*
Complement defects	*Streptococcus pneumoniae* *Hemophilus influenzae* type B

[a]Modified from Rubin.[3] Infections uncommonly associated with a particular defect are listed in parentheses.

The most important determinant of the net state of immunosuppression is the immunosuppressive therapy that has been and continues to be administered. A few general points regarding immunosuppressive therapy bear emphasis here: The first, and perhaps most important, is that the particular dose of immunosuppression being administered on a given day is less important than the dosages employed over a sustained period of time—"the area under the curve," so to speak. For example, although the highest daily doses of immunosuppressive therapy that are employed in organ transplantation are administered in the first 2–3 weeks posttransplant, the risk of opportunistic infection is extremely low until more than 4 weeks posttransplant, at which time the daily doses of immunosuppressive drugs have fallen significantly. We have suggested that immunosuppressive therapy is like buying something by credit card—if you increase immunosuppression, you have the immediate gratification of improved allograft function, with the bill coming due (in terms of infection) 3–4 weeks later.[17,22]

The second general point is that the effects of the entire immunosuppressive regimen must be considered—the net state of immunosuppression is determined not just by the summation of the effects of the individual agents, but also by the interactions of these different effects. For example, whereas antilymphocyte antibody treatments and cytotoxic therapies are capable of reactivating such viruses as cytomegalovirus and Epstein–Barr virus from latency, cyclosporine is not. However, once virus is reactivated, cyclosporine will greatly amplify the effects of these viruses by specifically blocking the virus-specific cytotoxic T-cell response, the key host defense. Thus, from the point of view of the host, the worst possible scenario is to reactivate virus with antilymphocyte antibody therapy and then accentuate the effects of the virus that has been reactivated with cyclosporine. Reversing this order of immunosuppression will greatly decrease the infectious disease consequences. Indeed, if the first sequence of therapy is utilized, then specific antiviral therapy needs to be administered concomitantly (see Chapter 24).[23–25]

More than 95% of the pneumonias that occur in the immunocompromised patient follow the delivery of sufficient numbers of virulent microorganisms to the lower respiratory tract via the tracheobronchial tree. In most cases, this infection occurs following the aspiration of gastric or oropharyngeal flora, thus emphasizing the importance of microbial colonization patterns in the pathogenesis of pneumonia,[26,27] particularly bacterial pneumonia (although even in the cases of invasive pulmonary aspergillosis,[28,29] there is evidence that preceding nasopharyngeal colonization may play a role in the pathogenesis of this form of infection as well). In addition, inhalation of aerosolized pathogens that are present in unusually high amounts in the patient's environment can be responsible for the microbial challenge to the lungs (see Section 2.1.2).[17,22]

There is increasing evidence that the stomach can be an important source of gram-negative bacillary pneumonia in the compromised host. The normal production of acid by the stomach maintains a low bacterial count. However, as gastric pH rises, the level of microbial contamination (particularly with gram-negative organisms) rises, serving as a reservoir for both the oropharynx and the respiratory tract.[30–32] Two therapies commonly employed in compromised hosts facilitate gastric gram-negative colonization: (1) The use of H_2 blockers and other measures that raise gastric pH for the prevention or treatment, or both, of ulcers, gastritis, and gastrointestinal hemorrhage will facilitate these events,[32–34] with retrograde colonization extending from the stomach to the trachea occurring in at least 30% of such individuals[35]; (2) the use of enteral feedings, many of which have a pH between 6.4 and 7.0, will also favor gram-negative colonization.[36] Recently, it has been suggested that impaired gastric and small intestinal motility result in bacterial overgrowth in the duodenum. This overgrowth is followed by duodenal–gastric reflux, with further amplification of bacterial growth caused by elevated gastric pH.[37]

The normal bacterial flora of the oropharynx is predominantly gram-positive and sensitive to a broad range of antibiotics. In particular, the prevalence of gram-negative oropharyngeal colonization in a normal population is on the order of 2%, and even challenging normal individuals with gram-negative organisms will rarely induce sustained colonization with these antibiotic-resistant, virulent bacterial species.[26,27,35,38,39] In contrast, sustained colonization with one or any combination of Enterobacteriaceae, *Pseudomonas aeruginosa, Staphylococcus aureus,* or *Candida* species is the rule in many immunocompromised patient populations, particularly cancer patients being treated with cytoreductive chemotherapy. Although environmental exposures, the use of antimicrobial therapies, the deployment of respiratory therapy equipment, and other factors will contribute to the rate of colonization, the crucial factor is the alteration in the surface characteristics of the mucosal epithelium. This alteration then facilitates the attachment of these organisms to the mucosal surface. Such gram-negative oropharyngeal colonization is recognized as the critical first step in the pathogenesis of gram-negative pneumonia.[35,40]

Adherence of bacteria to epithelial cells is mediated through specific interactions between adhesins on the surfaces of bacteria (particularly specialized appendages termed *pili* or *fimbriae*) and receptors on the surface of the epithelial cells. Oropharyngeal epithelial cells from individuals colonized with gram-negative organisms have been shown to support an increased rate of gram-negative adherence when compared to epithelial cells from uncolonized individuals.[35,39–41] The mechanisms involved in this change in adherence patterns are still being delineated, although the ubiquitous glycoprotein fibronectin appears to be a critical determinant of the microbial flora of the oropharynx. Normally, fibronectin coats this epithelial surface, promoting the attachment of gram-positive organisms and enhancing the bactericidal function of phagocytic cells directed against other microbial species. This causes a selective disadvantage for gram-negative bacteria, impeding colonization with these organisms. Destruction of this fibronectin coat, or inadequate production, as occurs in a variety of disease states, malnutrition, dehydration, and in response to chemotherapy, will have at least two adverse effects: (1) It will impede the attachment of the desirable normal flora and (2) it will expose epithelial cell surface receptors for a variety of gram-negative bacterial surface adhesins. The net result is gram-negative overgrowth of the oropharynx.[40–48]

Once gram-negative oropharyngeal colonization is established, it tends to persist. The next step is aspiration of these organisms into the lower respiratory tract. Pharyngeal secretions are aspirated in the majority of normal individuals during sleep and in 70% of individuals with a decreased level of consciousness. The impact of the aspiration episode(s) is increased by depressed gag and cough reflexes, with further amplification in the presence of endotracheal and nasogastric tubes. Two statistics emphasize the importance of these observations: (1) Approximately 90% of patients with gram-negative pneumonia have had prior oropharyngeal colonization with the same organism; (2) pneumonia develops 5–8 times more frequently in individuals colonized with these virulent gram-negative organisms. Hence, the ability of the host's epithelial surfaces to resist colonization with virulent microbial species is an important determinant of the net state of immunosuppression.[35,40,48]

2.1.2. Epidemiologic Aspects

The epidemiologic aspects of pulmonary infection in the immunocompromised host can be divided into two general categories: pulmonary infections related to exposures occurring within the community and pulmonary infections related to exposures within the hospital environment. There are four major considerations when considering the possibility of community-acquired pulmonary infection in the compromised host: (1) the geographically restricted, systemic mycoses (blastomycosis, coccidioidomycosis, and histoplasmosis), (2) tuberculosis, (3) *Strongyloides stercoralis* infection, and (4) acute infection with such respiratory viruses as influenza and parainfluenza.[17,22]

In the case of the systemic mycoses and tuberculosis, which share a similar pathogenesis (primary infection of the lungs following inhalation of a sufficient inoculum that escapes the initial nonspecific inflammatory response, the possibility of postprimary dissemination to other bodily sites, limitation of the extent of infection by the development of specific cell-mediated immunity, and later reactivation of disease at local sites with the possibility of secondary dissemination, due to local anatomic factors or waning of immunity), three general patterns of infection are being observed in immunocompromised individuals: progressive primary infection, reactivation with secondary dissemination, and reinfection with dissemination in an individual whose immunity has been ablated due to disease or its therapy. The end result in many compromised patients is disseminated infection, with either or both extensive pulmonary disease and evidence of metastatic infection to such sites as the skin, central nervous system, and bones and joints. Because of the great importance of cell-mediated immunity in controlling these infections, patients with AIDS (and, to a lesser extent, transplant patients and those with

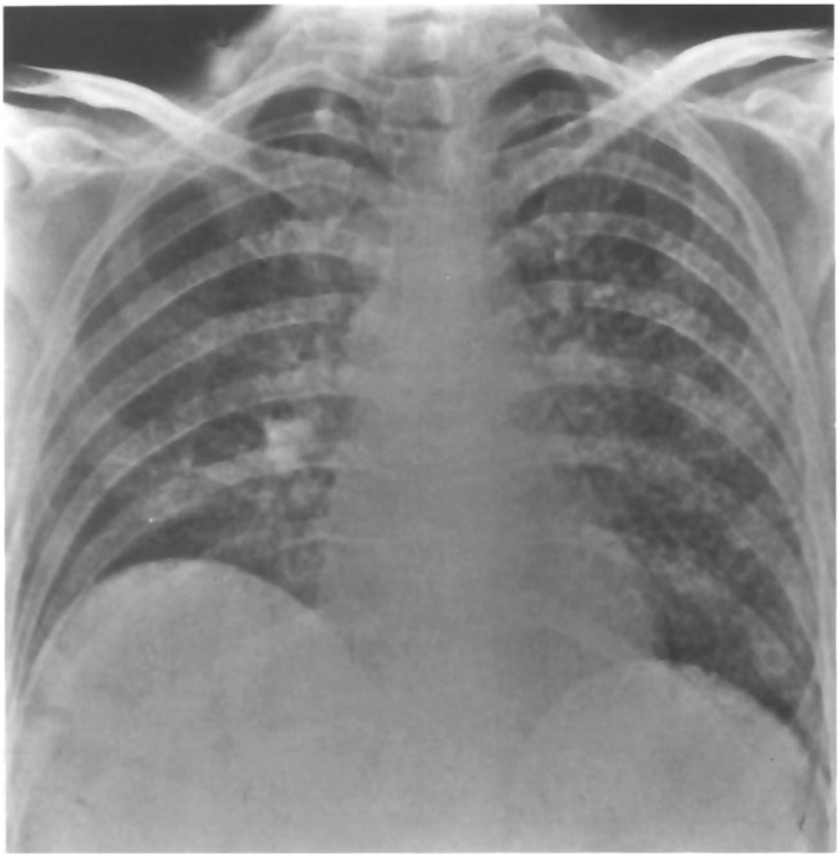

FIGURE 2. Miliary tuberculosis. Diffuse miliary opacities of 2–4 mm diameter due to miliary tuberculosis. The diffuse, tiny, nodular opacities are characteristic of blood-borne mycobacterial or fungal infection.

lymphoma) are at greatest risk for these events.[49] In particular, the coexistence of tuberculosis, especially drug-resistant tuberculosis, in populations with a high incidence of HIV infection is now recognized as a particular threat not only to these patients, and other, immunocompromised patients, but also to the community at large.[17,22,50–54]

Illustrative Case 2

A 37-year-old Hispanic male, who worked at a municipal hospital as an emergency ward attendant, presented with fevers, a nonproductive cough, and increasing shortness of breath of several weeks' duration. Although several friends and lovers had previously been diagnosed with AIDS, he had refused HIV testing for himself. Over the past year, he had sought treatment outside his place of employment for recurrent anogenital herpes and oral thrush. On physical examination, his temperature was 102.2°F (39°C), his respiratory rate was 24, and his blood pressure was 110/70. He appeared thin and chronically ill, with oral thrush, a painful 2×3 cm ulceration adjacent to his anus, and a slightly enlarged liver and spleen. Laboratory studies revealed the following: Hct 29%; WBC 3400/mm^3 with 65% polys, 14% bands, 12% monocytes, 9% lymphs; SGOT 110; alkaline phosphatase 3 times the upper limits of normal; bilirubin 2.4/3.0. Chest X ray, which was initially interpreted as negative, revealed a faint, diffuse miliary infiltrate (Fig. 2). Subsequently, his HIV antibody test was shown to be positive, and he was shown to have a CD4 count of 61. *Mycobacterium tuberculosis,* resistant to isoniazid and rifampin, was isolated from an induced sputum and from Dupont isolator blood cultures. On admission, he was placed in isolation and, following evaluation, begun on therapy with isoniazid, pyrazinamide, rifampin, ethambutol, and streptomycin, as well as anti-HIV therapy. Unfortunately, he continued to decline, and expired 2 weeks after admission, even before the suspected diagnosis of miliary tuberculosis, possibly drug-resistant, could be confirmed.

Comment. This case was part of a cluster of cases of drug-resistant tuberculosis involving immunocompromised individuals at this municipal hospital and graphically delineates our current public health dilemma. This Hispanic man with undiagnosed AIDS could have contracted his drug-resistant tuberculosis within his community, or occupationally. The extent and pace of his illness were greatly amplified by his HIV infection, and both within the community and within the hospital he posed a significant risk to other individuals, particularly other immunocompromised individuals, with whom he came into contact. The extent of his illness was underestimated by the initial evaluation of his chest radiograph (presumably due to the limited inflammatory response he was able to mount), thereby increasing the hazard to both himself and others.

Illustrative Case 3

A 46-year-old man with non-Hodgkin's lymphoma previously treated with radiotherapy and chemotherapy, but for the past 6 months with prednisone and weekly vincristine, entered with a 2-week history of a "cold." He had been relatively well until the gradual onset of fever, night sweats, anorexia, and 10-pound weight loss, increased fatiguability, and headaches. He did not complain of chest pain, but had

noted some dyspnea on exertion. There was no history of past tuberculosis or tuberculous exposure. Although he had been a resident of New England for the past 10 years, he had lived and worked for more than 30 years of his life on a farm in the San Joaquin valley of California. Physical examination revealed a chronically ill man with a respiratory rate of 18, temperature of 101°F (38.3°C), coarse rhonchi over the right upper chest posteriorly, and an enlarged spleen. Laboratory data revealed Hct of 32% and WBC count of 11,000/mm^3, with 85% polys, 3% bands, and 12% lymphs. Both second-strength PPD and *Candida* skin tests were negative, as was a skin test with coccidioidin. Sputum examination revealed abundant polymorphonuclear leukocytes and normal throat flora. Lumbar puncture revealed 52 leukocytes/mm^3, 89% lymphs and 11% polys, a sugar of 31 mg/dl (simultaneous blood sugar of 110 mg/dl), and a protein of 76 mg/dl. Chest radiograph revealed a cavitary lesion in the right upper lobe. Complement-fixing antibody to *Coccidioides immitis* was positive in both the serum and the cerebrospinal fluid.

Comment. This is an example of disseminated coccidioidomycosis years after the patient had been primarily infected, due to the immunosuppressive effects of his malignancy and its treatment. The important clue to the diagnosis lay in the patient's epidemiologic history, with the diagnosis established by serologic testing. A negative coccidioidin skin test and a positive serologic test constitute the characteristic pattern observed in this circumstance.

Strongyloides stercoralis is of particular concern, because of its life cycle. Unique among the intestinal nematodes that affect humans, *S. stercoralis* possesses an autoinfection cycle that can take place entirely within a person's GI tract. As a result, chronic asymptomatic GI infestation can be maintained for decades after the person has been exposed in an endemic area. With the onset of depressed cell-mediated immune function, due either to disease or to its therapy, overwhelming systemic invasion by this organism can occur. Hemorrhagic pulmonary consolidations or diffuse, bilateral alveolar opacities, often with accompanying GI complaints, may develop. Alternatively, systemic strongyloidiasis may be accompanied by the adult respiratory distress syndrome (see Chapter 10).[55,56]

The final community exposure that merits comment here is that related to respiratory viruses in the household, workplace, and general community. As increasing numbers of immunocompromised individuals (e.g., transplant and lymphoma patients) are being rehabilitated and restored to a normal life, it is axiomatic that they will be susceptible to those infections being circulated in the general community. Thus, there are increasing reports of the impact of influenza, parainfluenza, adenovirus, and other viruses on these patients. In general, immunosuppressed patients with these infections have a higher attack rate for viral pneumonia, superinfecting bacterial pneumonia, and prolonged illness than the normal population. Hence, increased efforts need to be made to protect these individuals by contact precautions, and vaccination and antiviral therapies need to be carefully studied in these individuals.[57–59]

As important as community exposures are in the evaluation of immunocompromised hosts with the febrile pneumonitis syndrome, exposures within the hospital are even more important. Nosocomial exposures to aerosols of *Pseudomonas aeruginosa, Klebsiella pneumoniae* and other Enterobacteriaceae, *Legionella* species, and *Aspergillus* species have resulted in epidemic pulmonary infection in immunocompromised patients.[22,28,29,60–77] Although *Pneumocystis carinii* pneumonia is usually thought to represent reactivation of old, dormant infection, there is evidence in animal models, and some epidemiologic observations in humans, that person-to-person spread of *P. carinii* among immunosuppressed individuals can occur.[1,78] Because of this possibility, it is our policy to isolate patients with *Pneumocystis* pneumonia from other immunosuppressed hosts.

Two epidemiologic patterns of nosocomial clusters of pulmonary infection have been noted in immunocompromised patients: domiciliary and nondomiciliary. The term *domiciliary* is used to describe outbreaks in which the patient is infected on the ward or in his or her hospital room. Such epidemics of *Legionella, Aspergillus,* and *Pseudomonas* infection have been not uncommon and are relatively easily identified because of temporal and spatial clustering of cases of opportunistic infection. The exposures have been shown to be due to construction, aerosolization of standing water laden with gram-negative bacilli or *Legionella,* or contamination of the air-handling system for the ward or the patient's room. Such outbreaks are effectively prevented by the provision of high-efficiency particulate air (HEPA) filtering in hospital locations where immunocompromised patients are housed. As one measure of the effectiveness of this approach, our experience with intubated transplant patients is very striking. In the absence of HEPA-filtered air, the incidence of gram-negative or *Aspergillus* superinfection in transplant patients requiring more than 3 days of tracheal intubation and ventilatory support approached 100%; at present, when care is administered in HEPA-filtered rooms, the incidence of secondary infection of the lungs does not become significant for at least a week, and we have successfully cared for immunosuppressed patients who required intubation for 4–6 weeks. Thus, an adequately filtered air supply is directly translated into a lower incidence of pulmonary infection and a decreased mortality due to opportunistic pulmonary infection.[2,22,61,79]

Although reports of domiciliary outbreaks of nosocomial pulmonary infection among immunocompromised patients are not uncommon, *nondomiciliary* exposures and outbreaks are actually a greater problem. These infections occur when patients are taken from their rooms through the hospital to the radiology, endoscopy,

or operating suites for essential procedures, with exposures occurring along the way or at the site of the procedure. Again, construction within the hospital environment has been the major cause of air contamination. Thus, we have observed an outbreak of invasive pulmonary aspergillosis among transplant patients, leukemic patients, and patients receiving immunosuppressive therapy for collagen vascular disease due to construction in the central radiology suite.[79] Similarly, cardiac transplant patients have acquired this infection while waiting outside the cardiac catheterization laboratory for a routine endomyocardial biopsy procedure. The use of routine surgical masks to protect these patients has not been effective. Because of this hazard, Dr. Richard Wenzel at the University of Iowa and our group have designed prototype portable HEPA-filtered transport equipment to protect patients when they must travel off the protected environment of the transplant or oncology units.[80]

Illustrative Case 4

An 11-year-old girl in remission after induction chemotherapy for acute myelogenous leukemia entered the hospital for a scheduled round of chemotherapy. Five days postadmission, she spiked a fever, and an infiltrate was noted on chest CT scan. Needle aspiration biopsy yielded a pure growth of *Aspergillus fumigatus*. Amphotericin therapy was instituted, with a good response after a prolonged hospitalization. That month, six other immunocompromised patients (three transplant patients, an adult oncology patient, and one patient being treated with high-dose corticosteroids for systemic lupus erythematosus) from different locations within the hospital developed invasive pulmonary aspergillosis. The epidemic was traced to construction in the central radiology suite. With cessation of the construction, the epidemic came to an end.

Comment. This is a well-documented nondomiciliary outbreak of invasive pulmonary aspergillosis. Such nondomiciliary exposures are probably quantitatively more important than domiciliary exposures, but are more difficult to identify because of the lack of temporal and spatial clustering. Constant surveillance of immunocompromised patients for such excessive epidemiologic hazards is essential. Suspicion regarding such a nondomiciliary, nosocomial exposure should be aroused whenever opportunistic pulmonary infection is identified in a patient whose net state of immunosuppression should not be great enough for such an infection to occur unless the patient had experienced an unusually intense exposure. For example, the occurrence of invasive aspergillosis in the first 3 weeks post–organ transplantation or in the first week of cancer chemotherapy should be cause for an epidemiologic investigation.

We have compared immunocompromised patients to "sentinel chickens" placed in the swamps to monitor the level of mosquito-borne arbovirus infection. In this context, it is our contention that immunocompromised patients are sentinel chickens placed in the swamps of our hospital environment. Any excess traffic in microbes will be seen first and most severely in these individuals, and constant attention is required to protect these patients. The lesson for the clinician is twofold: Constant surveillance to effect early identification and correction of hazards is important to prevent infection; in addition, the clinician must be aware of the prevalent nosocomial problems at any point in time to facilitate the care of the individual patient.[81]

2.2. Pathology of Pulmonary Infections in the Immunocompromised Host

The evaluation of pulmonary biopsy material for possibly treatable infection is an important part of the assessment of many immunocompromised patients with the febrile pneumonitis syndrome. The histologic patterns of pulmonary injury observed following microbial invasion in this patient population have been classified by Nash[82] into six general patterns, each with its own differential diagnostic considerations: Acute nonnecrotizing pneumonia, acute necrotizing pneumonia, diffuse alveolar damage, diffuse alveolar damage with foamy alveolar exudate, granulomatous pneumonitis, and bronchiolitis obliterans–organizing pneumonia (BOOP).

2.2.1. Acute Nonnecrotizing Pneumonia

Acute nonnecrotizing pneumonia is caused by a variety of bacterial agents, most commonly *Streptococcus pneumoniae*. It is characterized by a fibrinopurulent exudate filling airways and airspaces, without destruction of the alveoli. In most instances, the causative agent can be isolated from the respiratory secretions and lung tissue, and effective antimicrobial therapy can result in complete healing of the process. Indeed, lung biopsy is usually not necessary to make this diagnosis.[82]

2.2.2. Acute Necrotizing Pneumonia

Acute necrotizing pneumonia adds the element of pulmonary tissue destruction to the previous pattern of acute inflammation. The distribution of the lesions depends on the route by which the organisms invade the lung: Organisms that reach the lung via the tracheobronchial tree and invade at the level of the bronchi and adjacent airspaces produce a pattern of bronchopneumonia (e.g., *Staphylococcus aureus*), whereas those that invade the lung at the level of the distal airspaces produce an airspace consolidation that can progress to a full-blown lobar pneumonia (e.g., *Klebsiella pneumoniae*).

Hematogenous spread of organisms to the lung typically produces a nodular focus of necrotizing pneumonia that is located in the periphery of the lung and has no relationship to the segmental anatomy of the tracheobronchial tree. Such lesions are caused by a variety of virulent organisms once they enter the bloodstream, ranging from *S. aureus to Candida albicans, C. tropicalis,* and *Aspergillus fumigatus.*[82]

The most common bacterial infections that produce acute necrotizing pneumonia in the immunocompromised host are *S. aureus, K. pneumoniae, P. aeruginosa,* and *Legionella* species. In the case of *Pseudomonas* infection, in addition to the nonspecific necrotizing features, so-called *Pseudomonas* vasculitis characterized by masses of bacteria surrounding and invading blood vessels is a common finding. In the case of *Legionella* infection, the inflammatory exudate usually contains numerous macrophages in addition to the neutrophils seen with the other bacterial processes, and extensive leukocytoclasis of alveolar inflammatory cells may be observed.[82,83] *Candida, Aspergillus,* and Zygomycetes are the fungal species most commonly associated with pulmonary necrosis—both because of direct effects of these organisms and because of their propensity for invading pulmonary arteries, causing infarction and hemorrhage (as well as a propensity for hematogenous dissemination). The opportunistic bacterial pathogen *Nocardia asteroides,* the clinical effects of which resemble those of *Aspergillus,* can likewise produce necrotizing changes in the lung.[82,84] Finally, the herpes group viruses and adenoviruses can cause necrotizing pneumonias associated with a neutrophilic exudate. Cytomegalovirus (CMV) and adenovirus infection may be associated with two pathologic patterns: a necrotizing pneumonia (in the case of adenovirus, bronchiolitis, and bronchitis as well) and diffuse alveolar damage. In the case of CMV, enlarged cells exhibiting the characteristic cytopathic CMV changes may be present, although the absence of these cells does not rule out this diagnosis: Both viral culture and immunofluorescent staining are more sensitive in diagnosing CMV pulmonary infection than the demonstration of the "cytomegaly cells" with their intranuclear inclusions.[82,84]

2.2.3 Diffuse Alveolar Damage

Diffuse alveolar damage is a nonspecific response to a variety of insults and is the pathologic finding seen in the adult respiratory distress syndrome (ARDS), such as that caused by gram-negative sepsis. The term *diffuse alveolar damage* is given to a pathologic pattern of damaged alveolar capillary endothelium and alveolar epithelium, interstitial edema, and hyaline membranes. Over a few weeks, this acute exudative picture evolves into an organizing (proliferative) phase characterized by interstitial fibrosis, chronic inflammation, and regenerating alveolar epithelium. This lesion is the characteristic one caused by a variety of viruses, most notably influenza, but also including CMV and adenovirus.[82,84]

2.2.4. Diffuse Alveolar Damage with Foamy Alveolar Exudate

Diffuse alveolar damage with eosinophilic alveolar foam is the classic pathologic finding with *Pneumocystis carinii* pneumonia.[85] Typically, at the time of biopsy, evidence of the organizing phase of alveolar damage is already present, with the organisms being demonstrable within the alveolar foam with such special stains as the methenamine–silver stain or by immunohistochemical methods. It should also be emphasized, however, that the absence of the alveolar foam does not rule out pneumocystosis, with organisms still being demonstrable in association with nonspecific diffuse alveolar damage with the special stains. As with other infections that occur in the AIDS patient, the burden of *Pneumocystis* organisms is far higher in this group of immunosuppressed individuals, and the consequences of the *P. carinii* infection are often greater in AIDS patients than in other immunocompromised patients with this infection: a higher likelihood of developing changes of ARDS, a higher incidence of severe interstitial fibrosis, and the not uncommon occurrence of pneumatocoeles or bullae as a consequence of the *Pneumocystis* infection—unusual events in the non-AIDS patient.[82,84]

2.2.5. Granulomatous Pneumonitis

Granulomatous pneumonitis is characterized by a nodular infiltrate composed of epithelioid histiocytes, multinucleated giant cells, and surrounding areas of fibrosis and chronic inflammation. Varying degrees of central necrosis may be observed. This is the classic pathologic lesion observed with *Mycobacterium tuberculosis, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis.*

In saying this, however, two points must be particularly emphasized: (1) Prior to the development of the established granuloma, an acute neutrophilic response is the first line of defense against invasion with these microbes. Therefore, the exact mix of acute and granulomatous inflammation seen will depend on the age of the lesion biopsied. (2) Even more important in determining the exact pathologic picture observed with these organisms is the ability of the host to generate an inflammatory response. For example, depending on the level of

cell-mediated immune response possible, the pathologic pattern may range from a fully developed granulomatous response to the presence of organisms in the lung without any inflammatory response.

Hence, when an etiologic diagnosis is not immediately apparent after careful examination of the biopsy material, a broad range of special stains and probes aimed at delineating specific organisms should be employed, recognizing that the more immunocompromised the individual, the greater the likelihood of an atypical pathologic response.[82,84]

2.2.6. Bronchiolitis Obliterans–Organizing Pneumonia

The term bronchiolitis obliterans–organizing pneumonia (BOOP) encompasses a pathologic entity consisting of fibrous organization of an inflammatory exudate. As such, it is the end result of a variety of infectious and noninfectious inflammatory processes that affect the lung and is a not uncommon finding on biopsy—*particularly if the biopsy is carried out relatively late in the disease process*. Cultures are usually negative from tissue with this pathologic pattern. Since this pattern is a "final common pathway" for a variety of processes, this finding is of little use in terms of etiologic diagnosis and therapy, although the extent of the fibrotic reaction may have important prognostic implications as to the reversibility of the pulmonary injury.[82,86]

2.3. Clinical Clues to the Diagnosis of Pulmonary Infection

An important component in constructing a differential diagnosis for an immunosuppressed patient with possible pneumonia is an understanding of the "temporal" aspects of the underlying disease. That is to say, whether the patient's immunocompromised state is due to antileukemic chemotherapy or HIV infection or cyclosporine-based immunosuppression post–organ transplantation, the duration of the immunosuppressed state is an important determinant of what microorganisms are likely to be present. Thus, patients with acute leukemia who have pneumonia on first presentation almost assuredly have either bacterial infection or leukemic infiltrates, rather than opportunistic infection, and almost never require a lung biopsy before initiating effective antimicrobial therapy. In contrast, this same patient with fever and pneumonitis after 3 weeks of chemotherapy-induced neutropenia and broad-spectrum antibacterial therapy is at high risk for invasive fungal infection. Thus, the understanding of the expected "timetable of infection" for each of the immunocompromising illnesses (see Chapters 15, 16, 19, and 21–24) can play an extremely useful role in constructing the differential diagnosis.

Perhaps the most useful clue to the correct diagnosis in patients with the febrile pneumonitis syndrome comes from an assessment of the mode of onset and rate of progression of the pulmonary process. Thus, an acute onset over less than 24 hr of symptoms severe enough to bring the patient to medical attention would suggest conventional bacterial infection (and, of the noninfectious causes, pulmonary embolic disease, pulmonary edema, a leukoagglutinin reaction, or pulmonary hemorrhage). A subacute onset over a few days to a week would suggest viral or *Mycoplasma* infection, *Pneumocystis,* or, in some instances, *Aspergillus* or *Nocardia*. A more chronic course over one or more weeks would suggest fungal, nocardial, or tuberculous infection (as well as tumor or radiation- or drug-induced pneumonitis). When the mode of clinical presentation is combined with the radiologic finding, the range of etiologic possibilities becomes considerably smaller and much more manageable for the clinician (Table 3).[2,3]

Additional useful information may also be obtained by measuring the arterial partial pressure of oxygen (Pa_{O_2}) while the patient is breathing room air. Most of the disease processes that cause the febrile pneumonitis syndrome in the compromised host are associated with significant impairment in oxygenation early in the clinical course (room air Pa_{O_2} <65 mm Hg). By contrast, most patients with pulmonary disease caused by fungi, tuberculosis, *Nocardia,* and tumor will have relatively well-maintained oxygenation (room air Pa_{O_2} >70 mm Hg) until very late in the course, despite extensive consolidation on chest radiography. Although a rare patient with these three forms of infection will have an acute overwhelming pneumonia resembling acute bacterial infection in both clinical presentation and arterial blood gas findings, the great majority will have subacute or chronic presentations associated with well-preserved oxygenation. For example, among more than 25 organ transplant recipients with primary fungal or nocardial pulmonary infections, all but two had a Pa_{O_2} value of greater than 70 mm Hg. The two exceptions had concomitant congestive heart failure and chronic obstructive pulmonary disease to explain their low Pa_{O_2} values.[2,3]

The hypoxemia in patients with acute bacterial and viral infection and the noninfectious causes of the febrile pneumonitis syndrome results from a large shunt combined with regions of low ventilation–perfusion (V/Q) ratios in the involved lung tissues. Maintenance of the Pa_{O_2} in the fungal, nocardial, tuberculous, and, presumably, tumor patients appears to be due to diversion of obstructed blood flow to the involved lung, thus mini-

TABLE 3. Differential Diagnosis of Fever and Pulmonary Infiltrates in the Compromised Host According to Roentgenographic Abnormality and the Rate of Progression of the Symptoms[a]

Chest radiographic abnormality	Etiology according to the rate of progression of the illness	
	Acute	Subacute–chronic
Consolidation	Bacterial (including Legionnaires' disease) Thromboembolic Hemorrhage (pulmonary edema)	Fungal Nocardial Tuberculous Tumor (Viral, drug-induced, radiation, *Pneumocystis*)
Peribronchovascular	Pulmonary edema Leukoagglutinin reaction (bacterial)	Viral *Pneumocystis* Radiation Drug-induced (fungal, nocardial, tuberculous, tumor)
Nodular infiltrate[b]	(Bacterial, pulmonary edema)	Tumor Fungal Nocardial Tuberculous (*Pneumocystis*)

[a]Modified from Rubin.[3] An acute illness is one that develops and requires medical attention in a matter of relatively few hours (<24). A subacute–chronic process develops over several days to weeks. Note that unusual causes of a process are in parentheses.

[b]A nodular infiltrate is defined as one or more large (>1 cm² on chest radiography) focal defects with well-defined, more or less rounded edges, surrounded by aerated lung. Multiple tiny nodules of smaller size, as sometimes caused by such an agent as CMV or varicella–zoster virus, are not included here.

mizing V/Q mismatch. The pathogenetic mechanism for this obstruction may be thrombosis, vascular obstruction, direct invasion of the blood vessels, or a strong, unopposed reflex arteriolar vasoconstriction in response to regional alveolar hypoxia.[2,3]

3. Overview of Noninfectious Causes of the Febrile Pneumonitis Syndrome

The occurrence of noninfectious causes of the febrile pneumonitis syndrome in the compromised host is related to the underlying disease and how it is treated. Thus, in the patient with malignant disease, the major causes of this syndrome are radiation pneumonitis, drug-induced pulmonary injury, parenchymal tumor invasion, and, rarely, an unusual form of alveolar proteinosis. In the organ transplant patient, in the patient receiving corticosteroids, and in other groups of patients immunocompromised by nonmalignant disease, the major considerations are pulmonary emboli and pulmonary edema. In the patient with HIV infection, noninfectious causes of pulmonary infiltrates of particular importance include Kaposi's sarcoma, non-Hodgkin's lymphoma, and the two unusual forms of interstitial lung disease of unclear etiology, lymphoid interstitial pneumonitis (particularly in children with AIDS) and nonspecific interstitial pneumonitis. In addition, AIDS patients with advanced disease can develop ARDS as a result of systemic sepsis, and are at risk for such drug-induced pulmonary diseases as that induced by bleomycin employed to treat the secondary malignancies that complicate the course of the AIDS patient (Table 4). Less commonly, any patient with a major clotting or platelet disorder can develop pulmonary hemorrhage, and any transfused patient is at risk for the development of a leukoagglutinin reaction (Table 1).[8,10,11]

3.1. Radiation Pneumonitis

Radiation lung injury is of two types: (1) an acute type, *radiation pneumonitis,* which begins at the end of a course of radiation therapy or up to 6 months later; (2) a chronic type, *radiation fibrosis,* which may follow acute disease or begin without previous symptoms 6 or more months following the completion of therapy. Pathologically, radiation pneumonitis is characterized by the desquamation of bronchiolar and alveolar cells and by the formation of protein-rich hyaline membranes as a result of the exudation of plasma into the alveolar spaces through injured pulmonary capillaries. Engorgement and

TABLE 4. Cytotoxic and Noncytotoxic Chemotherapeutic Agents Known to Induce Pulmonary Disease[a]

Cytotoxic	Noncytotoxic
Azathioprine	Bleomycin sulfate
Belomycin sulfate	Cytosine arabinoside
Busulfan	Methotrexate sodium
Chlorambucil	Procarbazine hydrochloride
Cyclophosphamide	
Hydroxyurea	
Melphalan	
Mitomycin	
Nitrosourea (BCNU, CCNU, methyl-CCNU)	
Procarbazine hydrochloride	

[a]Modified from Rosenow et al.[5] Note that although both bleomycin and procarbazine are associated mainly with cytotoxic reactions, noncytotoxic reactions have also been observed, albeit uncommonly.

thrombosis of capillaries and arterioles are evident, and the alveolar septa are thickened by lymphocytic infiltrates and immature collagen deposition. Changes in surfactant production and metabolism may be particularly striking during this phase of radiation injury. This exudative phase is manifested on CT scan by findings of a homogeneously increased attenuation that progresses over time to patchy and then more dense consolidation. Particularly in the early exudative phase, corticosteroid administration is associated with rapid resolution of these CT scan findings.[87–93]

Radiation fibrosis is characterized by the replacement of normal pulmonary parenchyma and architecture by dense connective tissue. Clinically, radiation pneumonitis begins insidiously with fever without rigors, nonproductive cough, progressive dyspnea, and a characteristic pattern of pulmonary infiltrates on chest radiography (see Illustrative Case 5 below). Radiation fibrosis, as its name suggests, is not associated with symptoms of ongoing inflammation: It is usually asymptomatic, and when symptoms are present, they are related to the progressive pulmonary fibrosis (dyspnea, orthopnea, cyanosis, clubbing, and cor pulmonale).[87–91]

The incidence and severity of radiation lung injury are largely determined by the characteristics of the radiation administered: the volume of lung exposed, the total dose, and the rate at which the radiation is delivered. The greater the volume of lung exposed, the higher the dose, and the shorter the period of time over which the therapy is administered (fractionation of therapy permits repair of sublethal damage between doses), the higher is the incidence of radiation lung disease. It has been suggested that with the therapy protocols in current use, radiation pneumonitis is rarely seen at doses below 30 Gy, may develop at doses between 30 and 40 Gy, and is almost always evident with doses above 40 Gy. Evidence of radiation pneumonitis can be found an average of 8 weeks after a 40-Gy dose, appearing 1 week earlier for each 10-Gy increase in dose above 40.[94,95] Because of the nature of the radiation therapy administered, symptomatic radiation injury of the lung is most common in patients receiving radiotherapy for breast cancer, lung cancer, and lymphoma, with clinical manifestations developing in 3–15% of these individuals.[87,96–100]

Certain modifying factors greatly enhance the risk of radiation damage, the most important of such factors being previous radiotherapy to the lung, abrupt withdrawal of corticosteroid treatment, and the concomitant administration of cytotoxic cancer chemotherapy. Surprisingly, preexisting chronic obstructive pulmonary disease appears not to play an important role. Finally, there appears to be individual variability in susceptibility to radiation injury, as there are several reports of severe pneumonitis developing after relatively small doses of radiation.[96–105] One might question whether such increased susceptibility is related pathogenetically to the rare occurrence of extensive radiation pneumonitis beyond the radiation field. A trivial explanation for these events is that they result from technical errors involving radiation port placement. However, particularly in the rare cases of bilateral pneumonitis following unilateral irradiation, it has been suggested that a delayed hypersensitivity reaction to an antigen generated or released by radiation injury is responsible.[97,98,106,107] Gibson et al.[107] have carefully studied a group of patients who developed pneumonitis after unilateral thoracic irradiation for carcinoma of the breast: When bronchoalveolar lavage was carried out, there was an increase in total number of cells and percentage of lymphocytes from both lungs; in addition, the gallium scan showed increased uptake in both the irradiated and the nonirradiated lung. The long latent period, the involvement of nonirradiated tissue, the idiosyncratic occurrence of the process, and the clinical response to corticosteroid therapy that is seen are all consistent with the hypothesis that a hypersensitivity reaction can play a role in the pathogenesis of radiation pneumonitis. However, the observation that nonsteroidal anti-inflammatory drugs can provide significant protection in experimental models of radiation pneumonitis would argue that a significant component of the radiation injury to the lungs is not immunologically mediated.[107–111]

In sum, then, the clinician should be highly suspicious of the possibility of radiation pneumonitis in a patient with one of the tumor types noted who has a subacute–chronic onset of respiratory symptoms during or following the completion of a course of radiotherapy and from whom a history of one or more of the adjunctive factors can be obtained. Early diagnosis by biopsy can lead to effective therapy with corticosteroids, although such therapy will be ineffective if significant delay occurs. The potential therapeutic role of nonsteroidal anti-inflammatory drugs in humans with radiation pneumonitis remains to be delineated.

Illustrative Case 5

A 41-year-old woman with known Hodgkin's disease presented with a 3-week history of increasing dyspnea, nonproductive cough, fever, night sweats, and malaise. Stage IIIB Hodgkin's disease had been diagnosed 6 months previously and was treated with 5000 rads to the mediastinum and para-aortic lymph nodes followed by cyclic MOPP chemotherapy (nitrogen mustard, vincristine, prednisone, and procar-

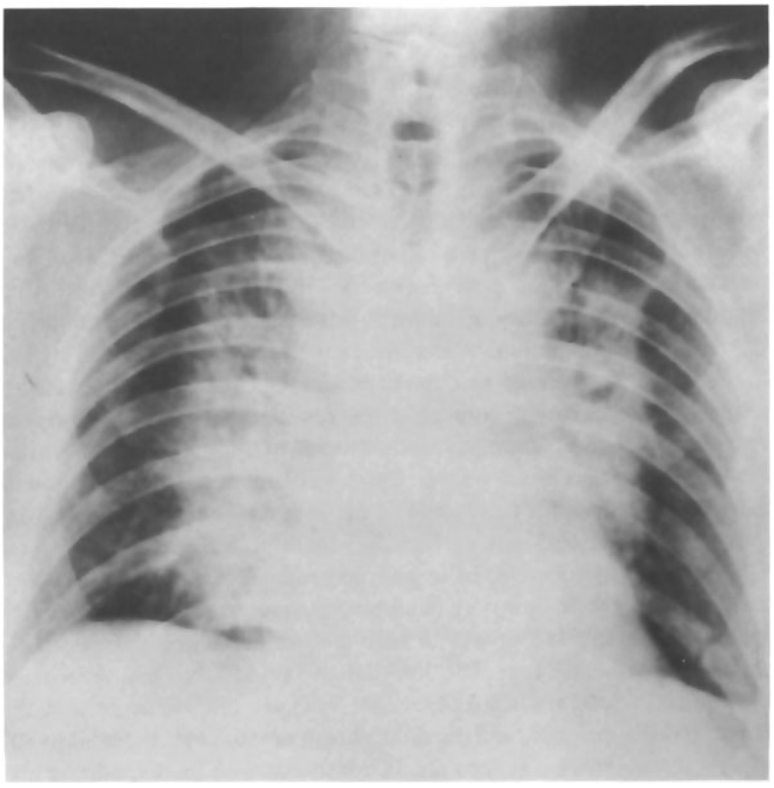

FIGURE 3. Radiation pneumonitis. Nonanatomic perimediastinal lung opacity 2 months after cessation of radiotherapy corresponds to the shape of irradiation portals and is typical of radiation pneumonitis.

bazine), the most recent cycle having been completed 2 weeks previously. The patient noted the insidious onset of fever, nonproductive cough, malaise, and dyspnea on exertion. Although she was quite dyspneic by the time she sought medical attention, she could not designate any one time when a major change in her clinical status occurred. No significant travel exposures had occurred, and there were no illnesses in her family. Physical examination revealed a dyspneic woman with a temperature of 101°F (38.3°C) and a respiratory rate of 35. General physical examination was unrevealing. Laboratory data included Hct 34%, WBC 5400/mm^3 with 82% polys, 11% lymphs, 7% monos. Room air arterial blood gases revealed a Pa_{O_2} of 42 mm Hg, Pa_{CO_2} 28 mm Hg, and pH 7.52. Chest radiography revealed mixed diffuse consolidative and peribronchovascular opacities predominantly central in distribution (Fig. 3). The diagnosis of radiation pneumonitis was made by transbronchial biopsy through the fiberoptic bronchoscope. The patient was treated with corticosteroids with marked improvement. Two weeks after the initiation of steroids, room air arterial blood gases were Pa_{O_2} 90 mm Hg, Pa_{CO_2} 36 mm Hg, and pH 7.45.

Comment. This is a classic case of radiation pneumonitis—an insidious onset of the febrile pneumonitis syndrome in the appropriate clinical setting, with a typical chest radiograph. Because of the need for corticosteroid therapy, concomitant infection needed to be ruled out—particularly *P. carinii* and a variety of viruses, including CMV. This was done, and the patient had a gratifying response to therapy.

3.2. Drug-Induced Pneumonitis

Several chemotherapeutic agents, most notably bleomycin, busulfan, mitomycin (with and without vinca alkaloids), cyclophosphamide, and chlorambucil produce pulmonary injury akin to that caused by radiation (see Table 4). It should be assumed that all alkylating agents have this ability because of their radiomimetic and mutagenic capabilities. In the lung, these effects cause injury, particularly to the lining epithelium of the alveoli and to the alveolar capillary endothelium, resulting, as with radiation lung injury, in two clinical syndromes: (1) a progressive interstitial pneumonitis characterized by fever without chills, as well as dyspnea, nonproductive cough, and progressive hypoxia usually beginning weeks to months after significant amounts of the drug have been administered; (2) a chronic interstitial fibrosis that may follow symptomatic inflammatory lung disease or occur insidiously without previous warning. Some patients may have symptoms due to drug-induced lung injury, but negative chest radiographs. In these instances, a decrease in diffusing capacity, a positive Ga 67 scan, or findings on CT scan can be very helpful.[3,5,10]

The inflammatory manifestations, like early radiation pneumonitis, may be responsive to the cessation of the provoking drug and the initiation of steroid therapy, whereas the chronic fibrotic process often is not. Again, as with radiation pneumonitis, both the dose of the agent administered (and the time course over which it is administered) and individual susceptibility to lung injury appear to be important in the pathogenesis of this pro-

cess. Given the similarities between drug-induced and radiation lung injury in presumed pathogenesis, radiographic and histologic appearances, and clinical presentation, it is not surprising that the combination of these treatment modalities is associated with a greater risk of pulmonary disease than when either type of agent is used alone.[99–106,112–114] It has been suggested that both these drugs and radiation induce the local production of oxygen radicals such as hydrogen peroxide and superoxide anions, which then produce lung injury. Consistent with this hypothesis is the observation that administration of oxygen to a patient receiving bleomycin will accelerate drug-induced pulmonary toxicity.[115–117] In addition, in an animal model, deficiency of vitamin E (an antioxidant) can accentuate the toxic effects of such drugs as bleomycin.[118] Both types of lung injury are associated with restrictive defects and lowered diffusing capacities on pulmonary function testing.[119–121] Studies of bleomycin toxicity in animal models suggest that disturbances in surfactant production play a role in the genesis of the pulmonary functional defect.[122] Given the subacute onset of symptoms, the interstitial pulmonary infiltrate, and the clinical setting, the major differential diagnostic considerations are *P. carinii* infection and viral pneumonitis. Usually, these conditions can be distinguished only by lung biopsy.[123–130]

Of all the cancer chemotherapeutic agents, busulfan and bleomycin are the drugs most commonly implicated as causes of pulmonary injury. In the case of busulfan, pulmonary injury is usually observed in patients placed on maintenance long-term therapy with this agent in the treatment of chronic myelogenous leukemia or, less commonly, polycythemia vera. In these patients, pulmonary disease may develop as early as 1 year after the initiation of such therapy, but more commonly requires up to 4 years.[131,132] The incidence of busulfan lung injury is not well established, but appears to be less than 5%. For example, in one series of 23 well-studied patients followed for an average period of approximately 2 years, only one patient developed clinical pulmonary disease, and this patient received a smaller dose of busulfan than did several of the other patients. Pathologically, intra-alveolar fibrosis and large atypical alveolar mononuclear cells may be seen in a much higher percentage of patients receiving chronic busulfan therapy.[133–136]

In part because of its efficacy as a chemotherapeutic agent for a wide variety of tumors, bleomycin is the single most common cause of drug-induced pulmonary injury. In an estimated 2.5–13% of patients receiving this agent, symptomatic pulmonary disease develops, and the reported mortality has been as high as 50%.[125–142] Clinically manifest lung injury will occur in most patients receiving a cumulative bleomycin dose greater than 500 mg.[138] In addition, there have now been several reports of life-threatening pulmonary disease when as little as 50–180 mg has been administered.[141,143,144] Early pulmonary injury may be detected by the demonstration of a decrease in diffusing capacity and vital capacity at a time when the chest radiograph is still normal.[139,143] An important clue for the clinician is the relatively high rate of bleomycin toxicity in patients who have received prior radiotherapy. For example, in one study of 101 patients receiving bleomycin therapy, 5 of 12 who had received previous radiotherapy developed pulmonary disease, whereas only 4 of 89 not receiving radiotherapy developed comparable levels of pulmonary injury.[140,141]

The nitrosourea compounds (BCNU, CCNU, and methyl-CCNU) have also emerged as important causes of cytotoxic drug-associated pulmonary injury akin to that caused by busulfan and bleomycin.[145,146] Less commonly, cyclophosphamide and chlorambucil appear to be associated with the same process.[112,147–153] The recent report of a high incidence of PCP in patients with necrotizing vasculitis or leukemia being treated with cyclophosphamide and prednisone underlines the clinician's dilemma: The clinical and radiologic presentations of *Pneumocystis* pneumonia and cytotoxic drug-induced pneumonitis are identical. Invasive studies for a precise diagnosis, rather than empiric therapy, are therefore essential in this clinical situation.[154]

Illustrative Case 6

A 51-year-old man with Hodgkin's disease was admitted with a 2-week history of fever, night sweats, and increasing shortness of breath. Two years earlier, Hodgkin's disease was diagnosed and was treated with splenectomy, total nodal irradiation, and several cycles of MOPP therapy for Stage IIIA disease. Eight months previously, recurrent disease involving the lung, liver, and bone was diagnosed, and bleomycin was begun. A total dose of 340 mg had been administered by the time of this admission. Over the 2 weeks prior to admission, fever, night sweats, nonproductive cough, and slowly increasing dyspnea were noted. On physical examination, his temperature was 100.6°F (38.1°C), respiratory rate was 30, and pulse rate was 90. He was a chronically ill-appearing man in mild respiratory distress. Fine rales were heard over both lung bases. Laboratory evaluation revealed Hct 34%, WBC 3200/mm^3 with 83% polys, 4% lymphs, 13% monos. Room air arterial blood gases revealed a Pao_2 of 54 mm Hg, Pco_2 32 mm Hg, and pH 7.50. Chest radiography revealed a diffuse peribronchovascular infiltrate in both lung fields, most prominent at the bases (Fig. 4). Transbronchial biopsy via the fiberoptic bronchoscope yielded characteristic changes of bleomycin-induced lung disease, with no evidence of infection. Therapy with corticosteroids was associated with symptomatic improvement and an increase in room air Pao_2 to approximately 60–65 mm Hg. Over the next 3 months, he remained stable with respect to pulmonary function and radiographic findings. However, he succumbed to progressive Hodgkin's disease. At postmortem examination, a mixed pulmonary picture consisting of exten-

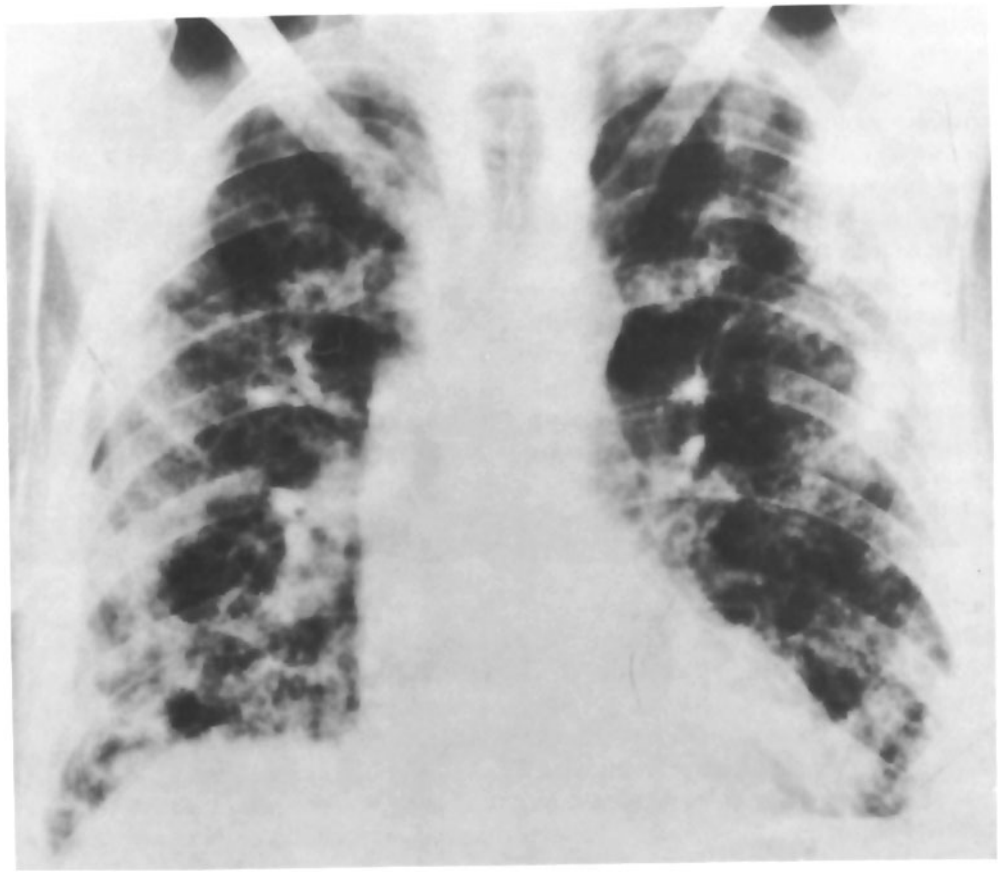

FIGURE 4. Bleomycin lung. Multiple irregular opacities are present throughout the periphery of the lungs. This is the most characteristic appearance of bleomycin lung.

sive intra-alveolar fibrosis and interstitial pneumonitis with frequent large atypical alveolar mononuclear cells was observed—the typical picture of bleomycin (and busulfan) lung injury.

Comment. This was a typical presentation of bleomycin-induced lung disease in a patient predisposed to its development by the previous radiotherapy he had received. The dose of bleomycin he received, although not excessive, was clearly in the range associated with at least a 5–10% risk of pulmonary toxicity. Again, the treatable differential diagnostic possibilities lay chiefly between bleomycin lung disease and *Pneumocystis*. Transbronchial biopsy provided an easy, well-tolerated means of diagnosis. Only a moderate response to corticosteroid therapy was observed in this case.

Methotrexate (MTX), a folic acid antagonist (antimetabolite), is widely used in the treatment of leukemia, lymphoma, and other neoplastic conditions, in bone marrow transplantation, and, increasingly, in the management of such nonmalignant conditions as psoriasis and rheumatoid arthritis when these entities are unresponsive to more conventional therapies. MTX can also produce subacute and chronic pulmonary injury syndromes, but in most instances, these syndromes differ from those caused by radiation and the alkylating agents: MTX appears to cause an acute, allergic, granulomatous reaction that may subside despite the continuation of therapy (or not reappear after cessation of the drug and subsequent rechallenge), although progressive, chronic interstitial fibrosis may also develop. The duration of MTX therapy before the onset of symptoms can range from less than 1 month (in at least one reported case, with a total dose of 12.5 mg) to more than 5 years with an average weekly dose during this period of 25–50 mg. In addition, it can occur weeks after the drug has been discontinued.[155–171]

Clinical disease and radiographic findings resemble those seen with the other agents. However, eosinophilia is commonly present, and bronchoalveolar lavage in patients with MTX-induced pneumonitis (as opposed to those receiving MTX without pulmonary effects) reveals evidence of a lymphocytic alveolitis with a predominance of CD4 cells—both findings suggesting an immunologic rather than a toxic reaction. Not surprisingly, preceding radiation therapy appears to play no role in predisposing patients to this form of pulmonary injury.[172] Rarely, bleomycin, cytosine arabinoside, and procarbazine can produce lung injury with an MTX-like pathologic picture, presumably due to a similar allergic rather than cytotoxic mechanism. Con-

versely, there is an occasional case of pneumonitis associated with MTX use in which the pathology and clinical course more closely resembles a bleomycin-like toxic reaction than the more common, presumably allergic disease.[5,163,172]

Other agents to which compromised patients may be exposed that may be associated with the production of either (or both) the febrile pneumonitis syndrome and chronic interstitial fibrosis include melphalan,[173] azathioprine,[174] diphenylhydantoin,[175] amitriptyline,[176] parenteral gold therapy,[177] D-penicillamine,[178] nitrofurantoin,[179] and amiodarone.[180] This last, a potent antiarrhythmic agent, has been a particular problem in heart transplantation, where we have observed patients who were receiving amiodarone at the time of transplant develop an acute ARDS syndrome, probably due to the combination of amiodarone, cyclosporine, and the other circumstances that obtain during cardiac transplantation. Our policy, at present, is to attempt to wean patients from amiodarone prior to transplantation.

3.3. Neoplastic Pulmonary Invasion

Fever and a clinical presentation suggesting pneumonia caused by neoplastic invasion of the lung may sometimes occur, particularly in patients with lymphoma. Pulmonary involvement occurs in 20–30% of patients with Hodgkin's disease, with most having the nodular sclerosis type of tumor. Almost invariably, Hodgkin's disease of the lung is associated with mediastinal lymph node involvement (or at least a history of previously treated mediastinal disease). In the rare Hodgkin's disease patient with pulmonary invasion in the absence of mediastinal adenopathy, there is almost always evidence of extrathoracic disease.[181–184]

Primary intrathoracic disease is uncommon in patients with non-Hodgkin's lymphoma (4% in one series of 1269 patients[185]), but in approximately half of these patients, thoracic disease will eventually develop. Primary pulmonary disease accounts for only 10% of these thoracic cases. Unlike the situation in Hodgkin's disease, a significant proportion of these patients may have pulmonary involvement in the absence of mediastinal nodal disease.[184–187]

Leukemia patients may occasionally have leukemic infiltrates in their lungs with associated fever, especially patients with acute monocytic and chronic lymphatic leukemia. Necropsy studies would suggest that as many as 25% of such patients will have leukemic pulmonary invasion. Occasionally, particularly in leukemic patients with WBCs greater than 200,000/mm^3, and a high percentage of blast cells, leukostasis and occlusion of pulmonary vessels may produce pulmonary symptoms and even infiltrates on chest radiographs. Superinfection of such areas is quite common. Because of decreased compliance within small blood vessels, leukemic blast cells may be particularly important in the pathogenesis of the intravascular leukostasis.[5,188–190] A variation of this process is what has been termed *leukemic cell lysis pneumopathy*, in which persons with large numbers of circulating leukemic blasts develop fever, respiratory distress, and patchy lung infiltrates within a few days of rapid chemotherapy-induced destruction of blasts. It has been suggested that this occurrence represents either diffuse alveolar or pulmonary capillary damage due to enzymes released locally by the destroyed blast cells.[5,191] However, infiltrates in such patients sufficient to cause radiographic abnormalities are much more frequently the result of infection, hemorrhage, or heart failure, and the clinician should proceed on this basis rather than pass off such infiltrates as being caused by the leukemia.[192,193]

Perhaps the most common association between neoplastic pulmonary invasion and the febrile pneumonitis syndrome is related to endobronchial lesions from primary or metastatic cancer that may cause bronchial obstruc-tion, distal atelectasis, and bacterial infection. Bronchoscopic demonstration of such lesions can be quite useful and lead to effective surgical or radiation therapy.[184]

3.4. Other Noninfectious Causes of the Febrile Pneumonitis Syndrome

Even in immunosuppressed patients without neoplastic disease, noninfectious causes of the febrile pneumonitis syndrome account for as many as 25% of such cases. Here, pulmonary emboli and atypical pulmonary edema are the major causes. Such difficulties have been particularly prominent in renal transplant patients.[194,195] In these patients, surgical manipulation of pelvic or lower-extremity venous structures is especially associated with pulmonary emboli, acute allograft failure, oliguria, and fluid overload (rather than primary cardiac disease) in patients with pulmonary edema. The administration of such antilymphocyte antibody therapies as OKT3 can lead to a febrile pulmonary edema picture due to cytokine release.[196,197]

A major difference between immunosuppressed patients and normal patients with these forms of primary pulmonary disease is the high rate of superinfection in the immunosuppressed patient. For example, in one series of renal transplant patients,[2] 8 of 9 patients with pulmonary embolic disease developed life-threatening superinfection, with rates of superinfection nearly as

high being noted in patients on high-dose corticosteroids, those with lymphoma, and those with other causes of significant immunosuppression. We have found that the restriction of immunocompromised patients to HEPA-filtered rooms after primary lung injury has had a major impact in preventing secondary superinfection of the injured lungs, *particularly if the patient is intubated.*

An unusual cause of fever and pulmonary infiltrates in the compromised host is a leukoagglutinin reaction. Leukoagglutinin reactions result in a syndrome of febrile pulmonary edema of noncardiac origin characterized by the abrupt onset of fever, chills, tachypnea, nonproductive cough, and respiratory distress in the first 24 hr following blood transfusion (and most commonly during the transfusion or in the first few hours following it). Such reactions are initiated by the interaction of preformed agglutinating antibodies with antigens on leukocyte surfaces, probably of both HLA and non-HLA type. The antibodies are usually present in the patient's serum because of sensitization by past transfusions or pregnancies and are directed against leukocytes transfused with the unit of blood; rarely, the antibodies may be present in the plasma of the blood being transfused, and they then act against the patient's leukocytes.[198–201]

Illustrative Case 7

A 22-year-old woman with a relapse of acute myelogenous leukemia developed fever and acute respiratory distress 4 hr after a blood transfusion. The patient had been well until 7 months previously, when she presented with fever and ecchymoses, and a diagnosis of acute myelogenous leukemia was made. Full remission was induced with cytosine arabinoside, daunorubicin, and thioguanine therapy after a stormy course requiring multiple red cell and platelet transfusions. Once in remission, she remained well until a few days prior to admission, when a bone marrow aspiration revealed recurrent disease, and she was found to be anemic and thrombocytopenic with a guaiac-positive stool. She was admitted to the hospital and given 2 units of packed red blood cells and 15 units of platelets. Approximately 4 hr after the initiation of the transfusion therapy, she complained of a shaking chill, spiked a fever, and developed progressive respiratory distress. Physical examination revealed an acutely dyspneic young woman with a temperature of 103.4°F (39.7°C), respiratory rate of 40, and diffuse rales and rhonchi over both lung fields. Cardiac examination revealed a regular tachycardia, no gallops, and a grade 2/6 pulmonic flow murmur. Room air arterial blood gases revealed a Pao_2 of 39 mm Hg, $Paco_2$ 28 mm Hg, and pH 7.52. Chest radiography revealed a normal size heart with a diffuse patchy infiltrate consistent with pulmonary edema (Fig. 5A). Sputum examination revealed no polymorphonuclear leukocytes or organisms. The patient was treated with intubation, positive end-expiratory pressure, and oxygen supplementation as needed. At 12 hr after intubation, she was extubated, and by 24 hr, her chest radiograph had returned to normal (Fig. 5B).

Comment. Noncardiogenic pulmonary edema secondary to a leukoagglutinin reaction is evident in this case. The therapy here does not include digitalization or diuresis, but rather is centered on adequate respiratory support with oxygen, positive end-expiratory pressure, and intubation as needed. As in any immunosuppressed host, extubation should be carried out as soon as possible.

Pulmonary alveolar proteinosis is characterized by the accumulation within the alveoli of eosinophilic, proteinaceous, periodic acid–Schiff-positive material that is surfactant-like in character.[202–204] It has been suggested that there are two forms of alveolar proteinosis: a primary form, in which the proteinacous material is derived from surfactant, and a secondary one, in which cellular debris and fibrin are significant components of the intra-alveolar material. The secondary form occurs in association with leukemia, lymphoma, metastatic melanoma, chemotherapy, primary immunodeficiencies, and as a consequence of infection, and may be seen in patients with AIDS.[205,206] On one hand, a defect in the macrophage clearance of surfactant components from the alveoli has been postulated as the cause of this condition (with secondary forms of alveolar proteinosis developing as a consequence of macrophage injury). On the other hand, defects in alveolar macrophage migration and macrophage metabolism are inducible by bronchoalveolar lavage material obtained from patients with alveolar proteinosis. These macrophage defects probably play a role in the relatively high rate of secondary infection, particularly with *Nocardia asteroides,* that occurs in patients with this condition.[202–209]

Symptomatically, patients with alveolar proteinosis commonly present with the subacute complaints of the nonproductive cough, fever, and slight dyspnea on exertion. More acute symptoms raise the possibility of superinfection. The usual radiographic manifestations are those of air space disease, with a minimum of air bronchograms. Typically, the chest radiograph reveals a bilateral, diffuse, perihilar, or central infiltrate that is more prominent at the lung bases, although atypical radiographs can occur.[207]

4. Radiologic Clues to the Diagnosis of the Febrile Pneumonitis Syndrome

Although no particular chest radiologic pattern is specific for a given pathologic process or microbial invader, particularly in the immunosuppressed patient, certain patterns are more characteristic of some processes than of others. Recognition of particular patterns can aid greatly in narrowing the range of differential diagnostic possibilities. The following radiographic characteristics are useful descriptors of radiologic patterns for clinical–radiologic–pathologic correlations[2]:

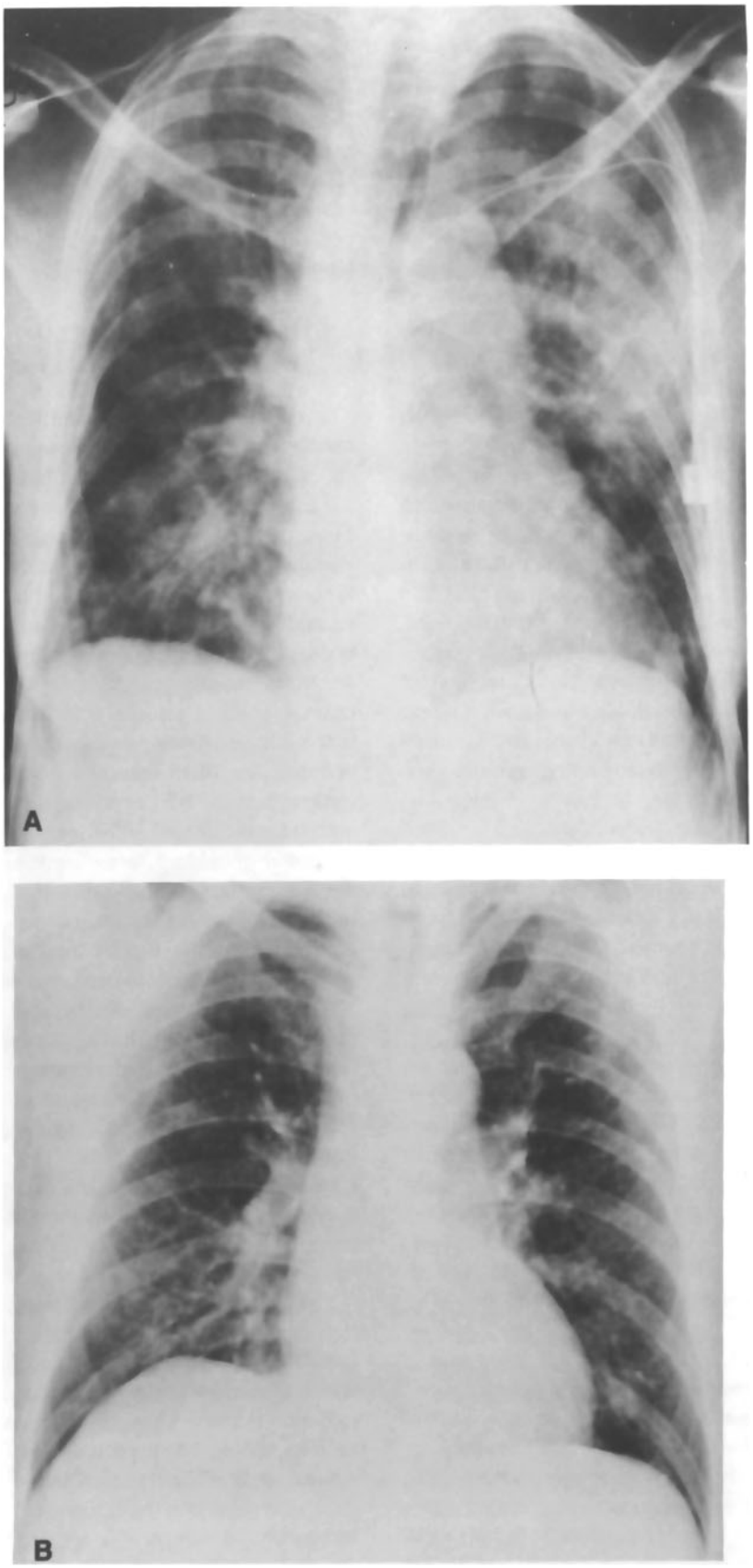

FIGURE 5. Leukoagglutinin reaction. (A) The appearance of patchy multifocal consolidation several hours after an intravenous transfusion is characteristic of the leukoagglutinin reaction. (B) At 24 hr later, the lung spontaneously cleared.

1. Time of appearance, progression, or resolution of new chest-imaging abnormalities as correlated with clinical findings.

2. Distribution and location of radiologic abnormalities. An opacity or small group of opacities confined to one anatomic area (e.g., segment or lobe) is considered *focal* [see Fig. 1 (Section 2)], whereas widespread or innumerable lesions are considered *diffuse* [see Fig. 2 (Section 2.1.2) and Fig. 5A]. Abnormalities that are distributed in more than one area, but are not so numerous as to be too numerous to count, are termed *multifocal* [see Fig. 4 (Section 3.2)]. As visualized on CT, abnormalities may be located *centrally* or *peripherally* or both.

3. Lung opacities, which are divided into three major groups: In the first group are *consolidations* in which there is substantial replacement of alveolar air by tissue density material. Air bronchograms and peripheral location are characteristic of consolidative lesions. On CT, a dense consolidation usually exhibits air bronchograms. Incomplete consolidation results in ground-glass opacification. On CT, ground-glass opacification is recognized as regions with slight increase in lung attenuation where the underlying vasculature remains visible and air bronchograms are absent. On radiography, ground-glass opacification results in subtle, or barely visible, lung opacity.

In the second group are *linear* and *peribronchovascular* (or *interstitial*) *opacities*. Interstitial opacities are predominantly oriented along the peribronchial or perivascular bundles. On CT and radiography, interstitial opacities are recognized by bronchovascular irregularity, or by thickened or irregular septa, or by both.

In the third group are *nodular opacities* that are subdivided into the following types: miliary, acinar, lobular, and macronodules. Tiny nodules with diameters of less than 3 mm are termed *miliary,* and are often indicative of interstitial granulomas, e.g., miliary tuberculosis. *Acinar opacities* are usually ill-defined nodules 4–8 mm diameter and are indicative of air-space disease prior to frank consolidation. Well-defined nodules of acinar size may be caused by interstitial nodules, e.g., metastases or large granulomas. *Lobular nodular opacities* (10–15 mm) with septal margins are seen in consolidation of secondary pulmonary lobules (i.e., groups of acini). These lesions may be seen in pulmonary infarcts and aspiration (Fig. 6). *Macronodules* (i.e., >15 mm) are generally space-occupying, nonanatomic lesions with well-defined, more or less rounded edges surrounded by aerated lung. Occasionally, small, well-defined, peripheral consolidations may take on the appearance of macronodules. The nodules of Kaposi's sarcoma are variable in size from acinar to lobular to macronodular (Fig. 7).

4. Other characteristics that should be looked for include pleural fluid, atelectasis, cavitation, lymphadenopathy, and cardiac enlargement. Pleural fluid is a clue to congestive heart failure and fluid overload when bilateral, and to necrotizing or granulomatous infection, especially when associated with lymphadenopathy or cavitation, when unilateral.

4.1. Correlation of Radiologic Findings, Rate of Progression, and Clinical Signs

By combining this classification with information concerning the rate of progression of the illness (acute vs. subacute–chronic), as outlined in Table 3 (Section 2.3), a useful differential diagnosis is then generated. Thus, focal or multifocal consolidation of acute onset will quite likely be caused by bacterial infection; similar lesions with subacute–chronic histories are most likely secondary to fungal, tuberculous, or nocardial infections. Macronodules are usually a sign of fungal or nocardial disease, particularly if they are subacute in onset. Subacute disease with diffuse abnormalities, either of the peribronchovascular type or miliary micronodules, are often caused by viruses or *Pneumocystis* (although in the AIDS patient, disseminated tuberculosis and systemic fungal infection are also considerations). As noted in Table 3, noninfectious causes are added to the differential diagnosis when the history is appropriate, the radiologic findings are consistent, and ancillary radiographic signs (such as hilar adenopathy in patients with Hodgkin's disease) are present.[2,3]

Additional clues can be found by examining the pulmonary lesion for the development of cysts or cavitation or by carefully delineating the location of the opacity or opacities. Cavitation suggests necrotizing infection such as that caused by fungi, *Nocardia,* certain gram-negative bacilli (most commonly *Klebsiella* and *Pseudomonas*), and *Staphylococcus aureus,* or necrotic tumor.[2,3,82] Apical cysts may be found in AIDS patients treated with inhaled pentamadine who develop *Pneumocystis carinii* pneumonia (Fig. 8).

The best clues to the radiologic diagnosis of radiation pneumonitis are the timing of onset with respect to radiation treatment and the location of the infiltrate, which is almost always confined to the outlines of the radiation portals. Thus, the diagnosis of radiation pneumonitis should be suspected when radiography demonstrates an infiltrate (particularly a peribronchovascular one) with relatively sharp margins that do not correspond to bronchopulmonary anatomy but adjoin the edges of the radiation field [see Fig. 3 (Section 3.1)]. Changes that occur outside this area should be minor. Since many cases of radiation pneumonitis follow mediastinal irradiation, the infiltrates are often central in location, in

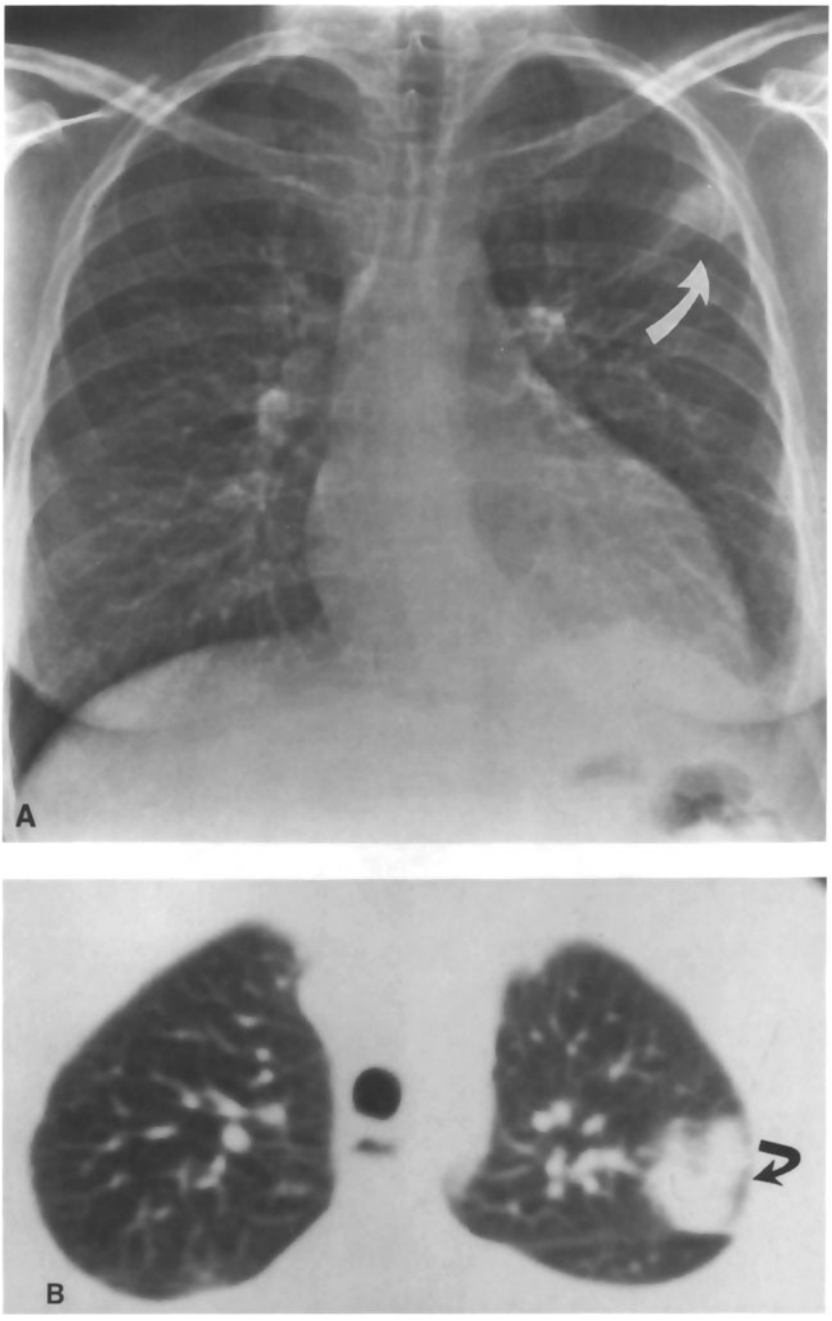

FIGURE 6. Pulmonary infarct. (A) A small opacity in the periphery of the left upper lobe of a diabetic with fever and a foot ulcer is due to a pulmonary infarct. The opacity is caused by a hemorrhagic infarct in a secondary pulmonary lobule. A straight interface along the bottom of the opacity is caused by a marginating interlobular septum. (B) A CT scan confirms the presence of the peripheral opacity. Other scan sections demonstrated additional bilateral infarcts and a left pleural effusion.

contrast to the usual peripheral location of most other processes that affect this population.[87–91,95,97,98,106]

The depressed inflammatory response of the immunocompromised host may greatly modify or delay the appearance of a pulmonary lesion on images. This depression is most frequently seen in patients with severe neutropenia (particularly those with an absolute granulocyte count $<100/mm^3$),[210–212] but is also seen with steroid treatment.[213] When such severe neutropenia is present, atelectasis may be the only radiologic clue to the presence of clinically important pulmonary infection. In particular, radiologic evidence of fungal invasion, which normally excites a less exuberant inflammatory response than does bacterial invasion, will often be very slow to appear. By contrast, in patients recovering from neutropenia, there may be a paradoxical increase in the radiologic findings (and sputum production) as the granulocyte count recovers, despite a good clinical response to antimicrobial therapy.[210–212]

CT of the chest has revolutionized the evaluation of the immunocompromised host with the febrile pneu-

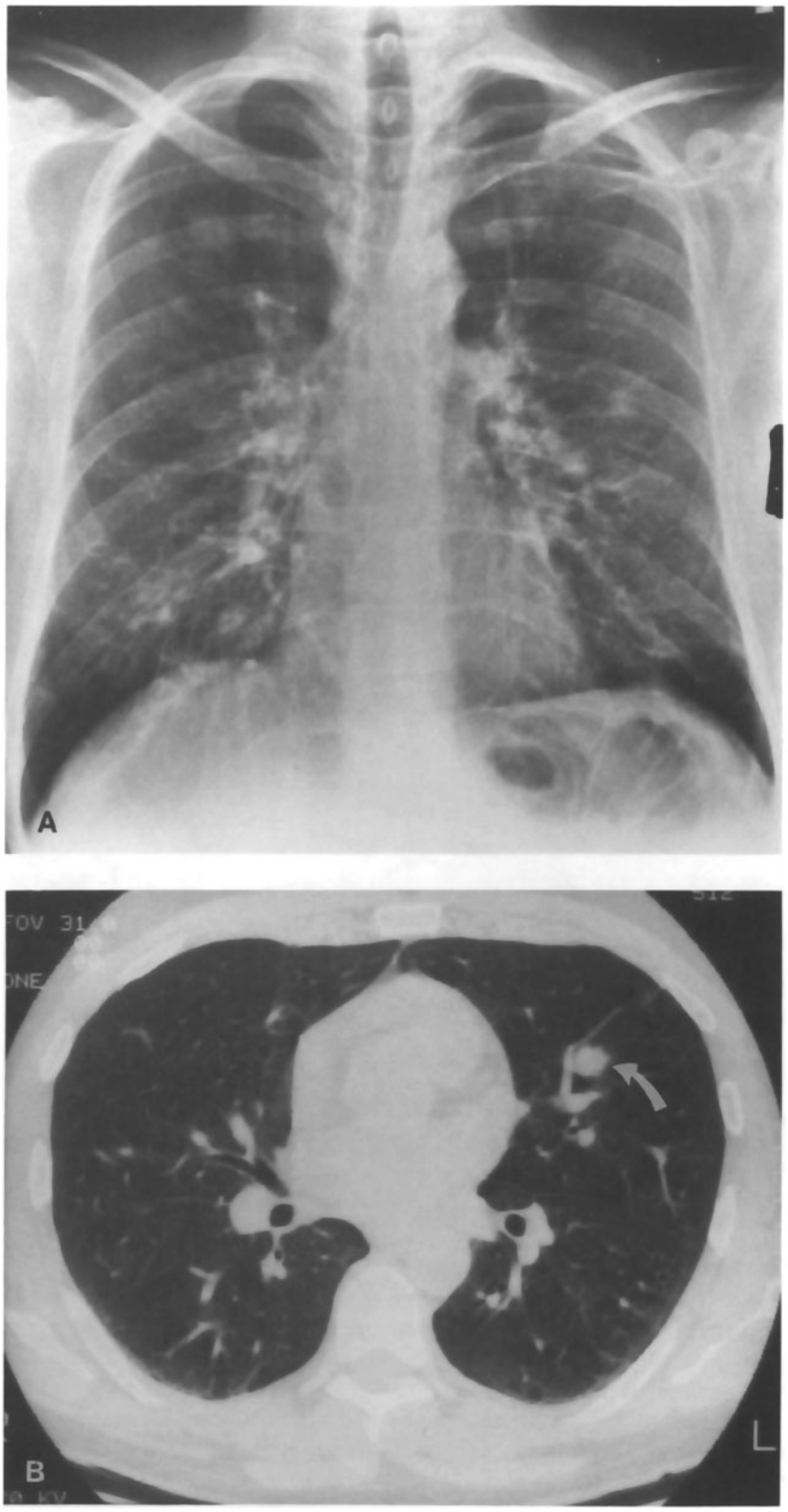

FIGURE 7. Kaposi's sarcoma. (A) Subtle multifocal peripheral opacities are suggested by a chest radiography in an AIDS patient with mucosal and skin lesions of Kaposi's sarcoma. (B) A single section from a CT scan shows one of many nodular lesions (➪) characteristic of Kaposi's sarcoma.

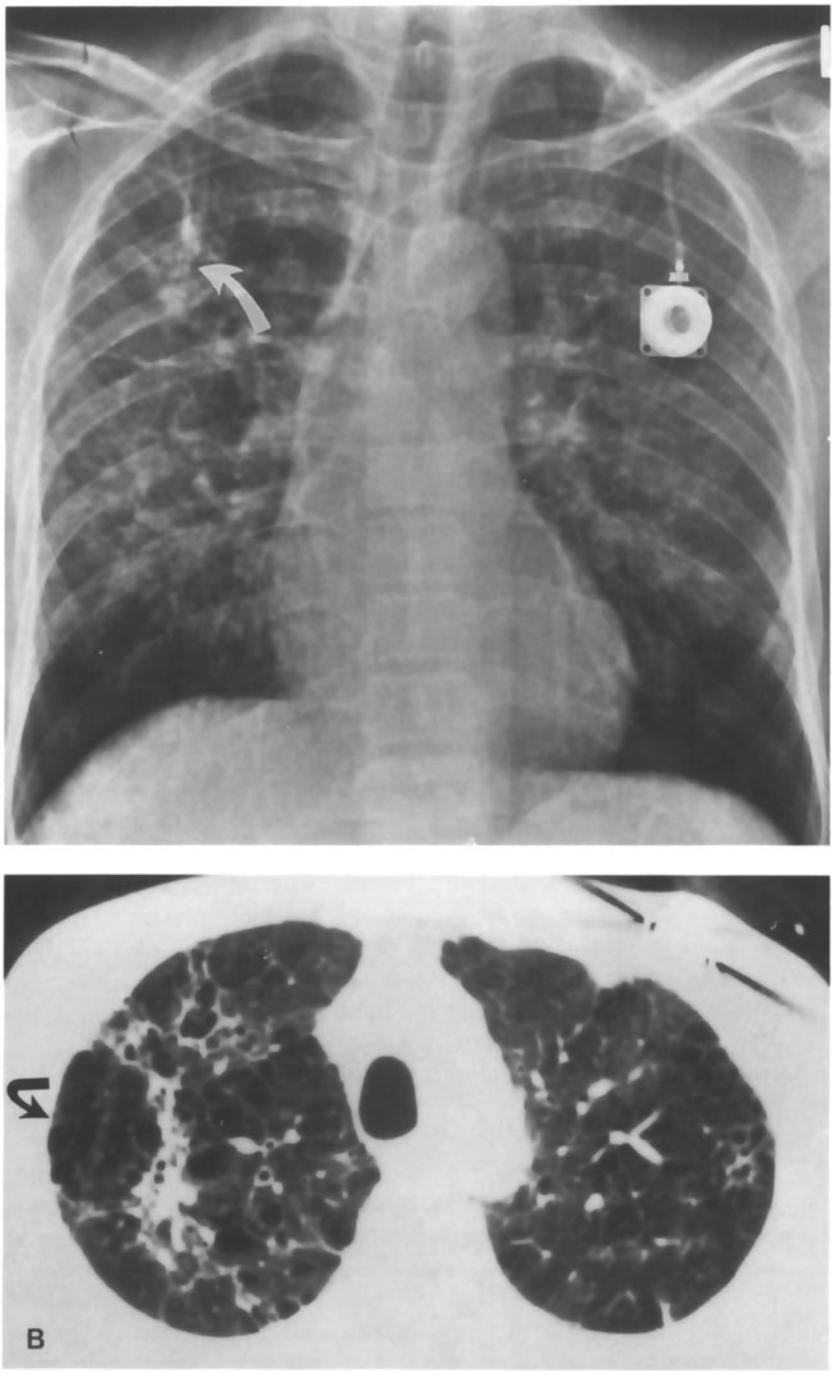

FIGURE 8. Cystic apical *Pneumocystis carinii* pneumonia. (A) Cystic lung regions of *Pneumocystis* pneumonia are most evident in the right apex of an HIV-positive patient treated with aerosolized pentamidine. (B) A CT scan confirms cystic lesions with well-formed walls, characteristic of post–aerosolized pentamidine *Pneumocystis* pneumonia, and unlike bullous emphysema.

monitis syndrome. This has become even more true as technical advances have resulted in the rapid acquisition of high-quality CT images, thus reducing breathing artifacts associated with tachypnea. Although conventional chest radiography remains the first procedure for evaluating immunocompromised patients for possible pulmonary disease, the high sensitivity and precise anatomic localization possible with CT scanning can result in earlier diagnosis and treatment. Thus, CT provides a greater chance of survival from opportunistic infection.[214,215] Clinical experience indicates that CT is more sensitive and effective than chest radiography in diagnosing disease in the immunocompromised patient.[216] CT is especially useful when the chest radiograph is negative or when the radiographic findings are subtle or nonspecific. Since localizing pulmonary symptoms are often absent, CT may also be a great aid in localizing disease for biopsy. CT may be more specific than radiography in

the diagnosis of opportunistic infection. For example, CT can often differentiate between infections with *Aspergillus* species and infections with bacterial or viral species.[217] Thus, CT is now of primary importance in the evaluation of the immunosuppressed patient in the following situations:

1. In the evaluation of febrile, severely neutropenic patients with negative or subtle chest radiographic findings, CT is far more sensitive in the detection of potentially treatable opportunistic infection, particularly fungal pathogens, such as *Aspergillus* species. Intrathoracic complications of bone marrow transplantation, for instance, are found with CT in 57% of patients in whom radiographs are negative.[218] Thus, CT has become the established imaging method of choice for the diagnosis of occult or subtle disease because the limited sensitivity of conventional radiography is exaggerated by the impaired inflammatory response of the neutropenic patient.

Similarly, equivocal chest radiographs of patients receiving exogenous immunosuppressive therapy (e.g., organ transplant patients) are best reevaluated with chest CT. We have seen a number of patients with asymptomatic pulmonary nodules due to such organisms as *Cryptococcus neoformans* that were clearly seen on chest CT evaluation after very minimal abnormalities were detected on chest radiograph (Fig. 9). Cure of such individuals is far more easily accomplished than after systemic dissemination and CNS seeding has occurred. Nodules detected with CT are strongly suggestive of fungal, nocardial, or tuberculous infection in the transplant patient. By the time radiography becomes definitely abnormal, the disease process is often far advanced.

In the AIDS patient, CT appears to be of value in evaluating patients for *Pneumocystis carinii* pneumonia who have negative chest radiographs. Since 10–20% of *Pneumocystis* patients have normal chest radiographs, CT may help to detect otherwise subtle disease.[219]

2. Although an abnormal chest radiograph may lead to the diagnosis of infection, it may greatly underestimate the extent of the disease process. Particularly with opportunistic fungal and nocardial infection, precise knowledge of the extent of the infection at diagnosis, and the response of all sites of disease to therapy, will lead to the best therapeutic outcome. A general rule of thumb in the treatment of opportunistic infection in the immunocompromised host is that the best clinical results will be obtained if the clinician continues therapy until all evidence of clinical disease has resolved. This end can best be accomplished with CT guidance.

3. Since dual or sequential pulmonary infection is not uncommon in the immunocompromised host, more than one etiologic agent may be responsible for the disease. In patients who have responded slowly or poorly to what should be appropriate therapy, CT can provide clues that additional diagnostic possibilities should be considered. For example, in AIDS patients with *Pneumocystis* pneumonia, the characteristic CT and radiographic findings reflect the diffuse interstitial and alveolar abnormalities. Since acinar and macronodular opacities are relatively unusual manifestations of *Pneumocystis carinii* pneumonia,[220] their identification in a patient not responding to appropriate therapy should raise the possibility of concomitant Kaposi's sarcoma (see Fig. 7) or infection with other agents (Fig. 9). In particular, the identification of a thick-walled cavitary nodule is highly suggestive of a new or coexisting fungal or bacterial infection in the patient with microbiologically or pathologically confirmed *P. carinii* infection.[7]

4. CT can also help in defining which invasive diagnostic procedure is most likely to yield a diagnosis and where the disease is most likely to be found for successful biopsy.[7] CT can provide precise guidance for needle biopsy[221] or for thoracoscopic or open lung excision in the case of peripheral lung nodules. CT is also the best means of predicting whether bronchoscopy is likely to be the most appropriate diagnostic modality for a particular patient. Thus, in patients with pulmonary nodules, CT demonstration of the feeding bronchus correlates with a 60% diagnostic yield with bronchoscopy, as opposed to a 30% yield if this finding is not present.[222] If CT demonstrates centrally located diffuse opacifications, a bronchoscopic approach is the modality of choice for diagnosis.[223]

5. CT can also narrow the differential diagnosis in the patient with suspected opportunistic infection. Cavitary CT lesions are suggestive of infections with *Nocardia, Cryptococcus,* and *Aspergillus*. Opacified secondary pulmonary lobules in the lung periphery are suggestive of bland pulmonary infarcts and of cavitated septic or hemorrhagic *Aspergillus* infarcts. Peribronchial distribution of CT opacities is suggestive of fluid overload and graft-vs.-host disease. An unusual example of this phenomenon is the capillary leak syndrome associated with interleukin-2 (IL-2) treatment. In these patients, the pulmonary edema and pleural effusions are indistinguishable from the heart failure and fluid overload, but invariably develop within a few hours after institution of IL-2 treatment. Dense[224] regional or lobar consolidation on CT is most suggestive of bacterial pneumonia. Apical cystic CT lesions are suggestive of *Pneumocystis carinii* pneumonia, especially in AIDS patients treated with prophylactic aerosolized pentamidine (see Fig. 8). Lung calcifications on CT may be noted after treatment of *Pneumocystis* with aerolized pentam-

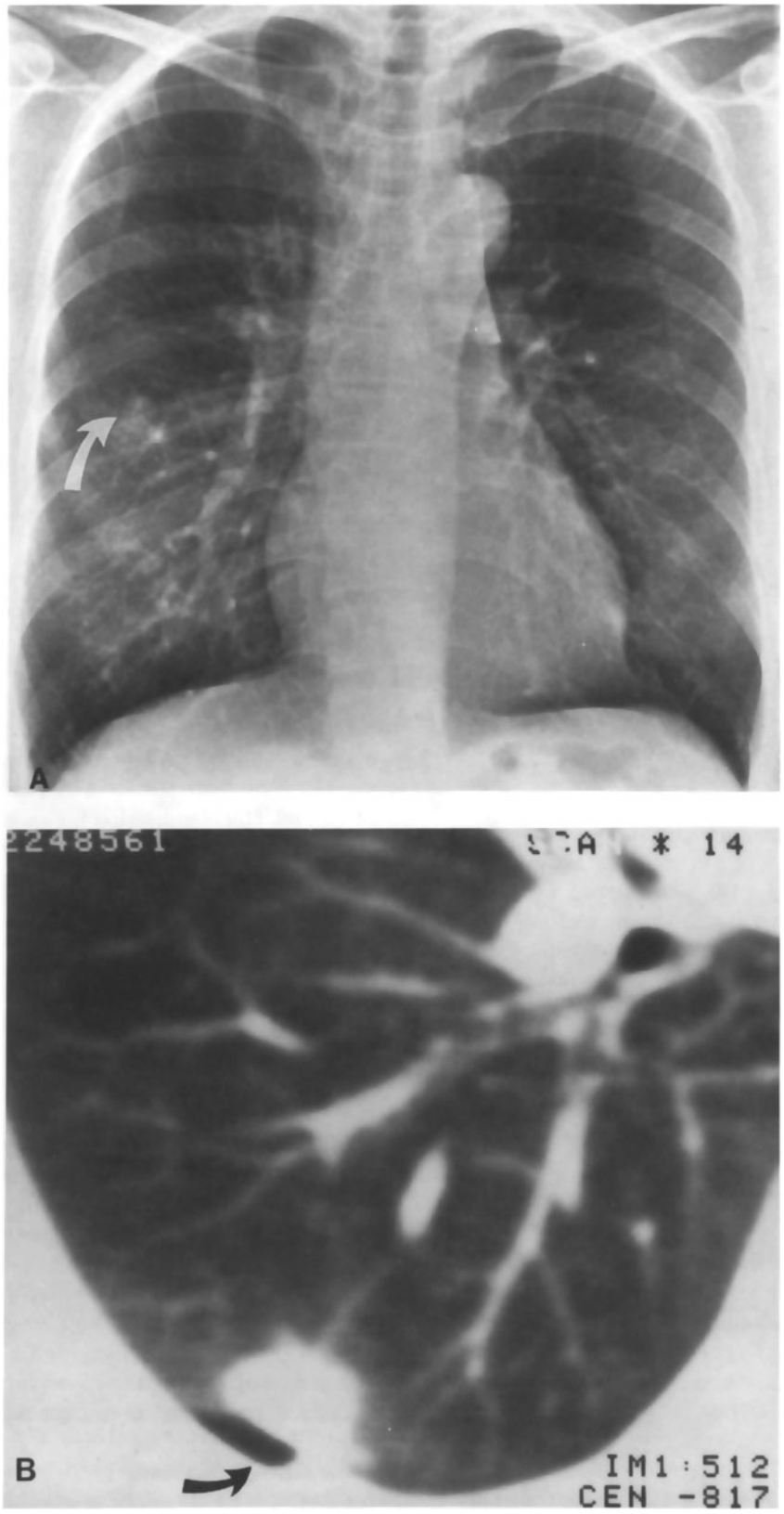

FIGURE 9. Asymptomatic pulmonary cryptococcosis. (A) A subtle, small, nodular opacity is suggested in the right mid-lung zone of a renal transplant patient. (B) A CT scan confirms a solitary peripheral nodular opacity, subsequently proven by transthoracic needle aspiration biopsy to be due to *C. neoformans* infection.

TABLE 5. Radiologic Findings in Acquired Immunodeficiency Syndrome Patients with Pulmonary Disease of Differing Etiologies[a]

Cause of pulmonary disease	Lung[b]				Hilar and mediastinal lymph nodes		Pleura
	D	MF	F	G/T	Enlarged/CT attenuation	Gallium[c]	Fluid
Pneumocystis carinii	+++	++	+	+++/0	0/	0	0
Mycobacteria	+	++	++	++/0	+++/low	+++	+++
Bacteria	+	+	+++	+/0	0	0	+++
Kaposi's sarcoma	+++	+++	+	0/+	++/high	0	+++
Fungus	+	+++	+++	++/0	++/low	++	+++
Lymphoma		++	++	+/+	++/high	+++	+++
Lymphocytic interstitial pneumonitis	+++			+/	0	0	0
Cytomegalovirus	+++	++	+	+/	0	0	0
Septic emboli		+++	+	+/	0	0	+++

[a]Results are expressed as degrees of positivity.
[b](D) Diffuse; (MF) multifocal; (F) focal; (G/T) gallium/thallium.
[c]Nuclear scans.

idine.[225] High-resolution CT can aid in differentiation between apical lung opacities that are due to *M. tuberculosis* scars and benign apical "cap."[226]

4.2. Radiologic Aspects of Thoracic Disease in Acquired Immunodeficiency Syndrome Patients

The intrathoracic conditions most commonly associated with the AIDS patient include *Pneumocystis carinii* pneumonia, pyogenic bacterial and mycobacterial infection, Kaposi's sarcoma, fungus infection, lymphoma, and lymphocytic interstitial pneumonitis. Other less common AIDS-related conditions include septic and non-septic pulmonary emboli; viral infections, especially CMV; and herpes simplex pneumonia.[7,227] Typical radiologic findings in AIDS patients with these conditions are presented in Table 5.

4.2.1. *Pneumocystis carinii* Pneumonia

Pneumocystis carinii pneumonia (PCP) is by far the most common intrathoracic complication of AIDS. The disease most often presents as diffuse, perihilar, bronchovascular lung opacities, but focal and multifocal opacities also occur. The radiographic findings are often quite subtle in the early stages of the disease and may be overlooked if the AIDS history is unknown or if no prior chest radiographs are available for comparison. About 10–20% of *Pneumocystis* infections are totally occult by conventional radiography.[228] CT is not generally required or employed to make the diagnosis in typical cases. However, when radiographic findings are absent, CT may demonstrate more typical or extensive diffuse ground-glass lung opacities characteristic of PCP. In more chonic *Pneumocystis* infection, or at the conclusion of therapy, CT may show evidence of pulmonary fibrosis and septal lines.[229] Atypical findings of PCP in AIDS patients include focal lung opacities, cavities, miliary nodules, and, very rarely, intrathoracic lymphadenopathy and pleural effusions.[220,230] Radiographic detection of pleural effusion and intrathoracic lymphadenopathy are not characteristic of *Pneumocystis*,[231] but massive pleural effusion[232] and massive lymphadenopathy[233] have been rarely reported. Small pleural effusions and small intrathoracic lymph nodes are more likely to be detected with CT.[234] PCP often presents as apical lung opacities with cysts or cavities in those previously treated with aerosolized pentamidine (see Fig. 8).[235] The cavities and subpleural cysts tend to have thicker walls than true subpleural areas of emphysema.[236,237] Some *Pneumocystis* patients may first present with pneumothorax.[238–240] Rarely, *Pneumocystis* pulmonary lesions have been described to increase off steroids and to decrease if steroids are reapplied.[213] Gallium-67 lung uptake in AIDS-related PCP is usually diffuse and intense, while thallium lung uptake is negative. Calcifications of the abdominal viscera may be seen with CT after treatment for PCP.[233] Although magnetic resonance imaging has not yet established itself as an important diagnostic modality in *Pneumocystis*, higher total T1 and T2 signal has been found in patients with PCP than in normals.[241] In order of frequency, CT images of PCP can show diffuse opacification, patchy opacities with spared regions, and focal peripheral opacities. PCP often heals with pulmonary fibrosis, cystic spaces, and zones of emphysema, especially in the upper lung zones.[215] Radio-

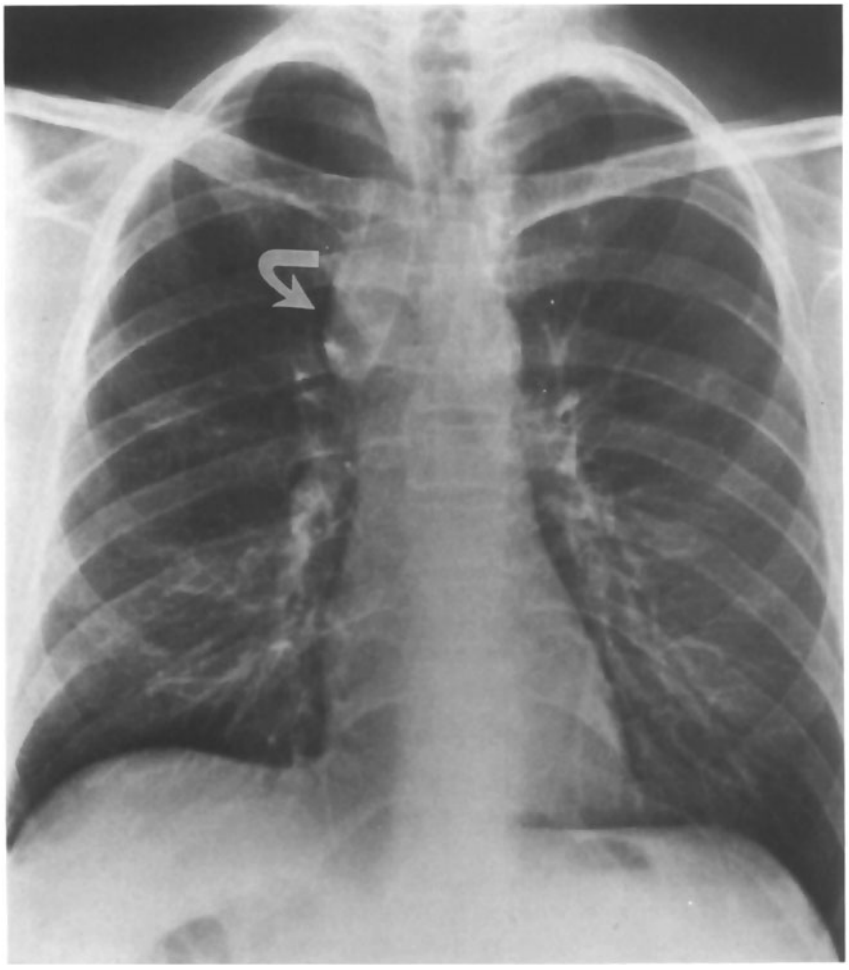

FIGURE 10. Atypical mycobacterial infection. Right-sided mediastinal adenopathy is evident in an AIDS patient with dyspnea, fever, and cough due to *Mycobacterium avium–intracellulare* infection. The adenopathy is also consistent with *M. tuberculosis* and lymphoma. On CT scan, low attenuation centers with enhancing rims of enlarged mediastinal lymph nodes favor mycobacterial infection over lymphoma.

graphic and CT images of CMV pneumonia are indistinguishable from those of *Pneumocystis*.

4.2.2. Mycobacterial Infection

Tuberculosis is an infection of increasing importance in the AIDS patient. In AIDS patients, tuberculosis is most often the result of reactivation of a dormant focus, but the radiologic appearance is more often that of primary tuberculosis. Thus, tuberculosis in AIDS patients more often presents with intrathoracic lymphadenopathy, miliary lung nodules,[242] pleural fluid, and extrapulmonary disease, rather than the apical consolidation and cavitary disease characteristic of reactivation disease.[243,244] Approximately 85% of AIDS patients with tuberculosis have abnormal chest radiographs.[245] Tuberculosis and infection with atypical mycobacteria are by far the most common infectious causes of intrathoracic lymph node enlargement in the AIDS patient (Fig. 10). Hilar and mediastinal lymphadenopathy may be evident on radiography, but CT is significantly more sensitive. Enlarged intrathoracic lymph nodes with low CT attenuation centers and enhancing rims are characteristics of tuberculosis,[246] but are occasionally seen in disseminated fungal infections. The low CT attenuation of tuberculous lymph nodes is different from the higher attenuation of enlarged nodes in Kaposi's sarcoma and lymphoma. Gallium-67 uptake in the lung tends to be more patchy and less intense than in *Pneumocystis*.

Atypical mycobacterial infection of the lungs, especially with *Mycobacterium avium–intracellulare* (MAI), occurs in the AIDS patient, but is much less common than pulmonary infection with *M. tuberculosis,* and tends to occur late in the course of AIDS. MAI infection tends to occur in the AIDS patient with a low CD4 count (<50 cells/mm^3). MAI infection, unlike *M. tuberculosis,* usually has a GI portal of entry and is disseminated by the time it is first detected in the chest. Radiologic findings are not distinguishable from disseminated *M. tuberculosis* infection and include intrathoracic adenopathy and miliary nodules [see Fig. 2 (Section 2.1.2)].[247]

4.2.3. Pyogenic Bacterial Pneumonia

Community-acquired bacterial pneumonia is common in AIDS and is most commonly due to *Streptococcus pneumoniae, Hemophilus influenza,* or mixed organisms. Bacterial pneumonia is similar in AIDS and non-AIDS patients. The lesions are likely to be focal, consolidative, cavitary, and associated with pleural fluid. However, bacterial pneumonia may present with regional or even diffuse interstitial-appearing opacities not unlike PCP.[248] Under appropriate therapy, bacterial infections are much more likely to clear within 3 weeks than is PCP. In contrast to PCP, ^{67}Ga uptake in the lung is less likely to be positive in bacterial pneumonia.

4.2.4. Kaposi's Sarcoma

Kaposi's sarcoma involves the lung in about one fifth of AIDS patients with skin lesions. The lesions tend to be diffuse interstitial or airspace opacities and associated with small peribronchial nodular opacities.[249] The peribronchovascular lung lesions are often associated with subpleural nodules that are particularly well seen on CT (see Fig. 7).[250] The lesions can simulate lymphatic spread of tumor. Asymptomatic lung lesions of Kaposi's sarcoma are often found at postmortem examination in AIDS patients with normal chest radiographs.[251] Hilar lymph node enlargement, and pleural effusions, are common accompaniments of lung lesions. When the mucosa of the tracheobronchial tree is involved, atelectasis may develop.[252] The lymph nodes harboring Kaposi's sarcoma tend to take up ^{201}Tl.[253] When AIDS patients with Kaposi's sarcoma of the skin develop diffuse lung opacities, ^{67}Ga scanning can be helpful in differentiating between PCP and Kaposi's sarcoma of the lung. The lung lesions of Kaposi's sarcoma do not take up ^{67}Ga, while PCP shows avid uptake of this isotope.[219]

4.2.5. Fungus Infection

The most common fungal agent invading the lungs of the AIDS patient (other than *P. carinii,* which is now classified as a fungus) is *Cryptococcus neoformans* (see Fig. 9). Other fungi that commonly affect the AIDS patient include *Aspergillus* species, *Histoplasma capsulatum, Candida albicans,* and *Coccidioides immitis.* In a substantial minority of patients (about 25%), disseminated fungal infection is first discovered in the lung, especially when CT is employed.[254] In *Cryptococcus* infection, chest radiographs usually are negative or show focal disease, with or without cavitation.[255] Diffuse lung disease is often found in patients with *H. capsulatum* infection. *Aspergillus* species tend to cause lung infection late in the course of AIDS and are not as common in AIDS as in the non-AIDS immunocompromised patient. Fungal infections may show consolidations, nodules, cavities, cavities with halos, and pleural effusions. In AIDS patients, *Aspergillus* infections produce varied imaging findings, including upper lobe cavities similar to tuberculosis, pleural-based lung nodules and infarcts, and diffuse infiltrates.[256]

4.2.6. Lymphoma

A small but significant proportion of AIDS patients develop B-cell or other non-Hodgkin's lymphoma in the CNS and abdominal viscera. A fraction of these lymphomas involve the lung at initial presentation. The lesions tend to occur in the lung parenchyma in association with pleural fluid.[257] Lymphoma causes enlargement of mediastinal and hilar lymph nodes in a minority of cases.[228,258] Lung involvement and pleural effusions are more common in AIDS-related lymphomas than in non-AIDS lymphomas. CT is useful in detecting the solitary or multifocal solid lung masses of AIDS-related lymphoma of the lung.[259] Lymphoma may present as a pulmonary mass, mediastinal/hilar adenopathy, pleural effusion, or a chest wall mass. Nuclear scanning is said to differentiate among pulmonary infection, lymphoma, and Kaposi's sarcoma.[253] In infection, the 3-hr delayed ^{201}Tl scan is negative while the ^{67}Ga scan is positive in the lungs. In lymphoma of the lung, both ^{201}Tl and ^{67}Ga scans are positive. In Kaposi's sarcoma, the ^{201}Tl scan is positive while the ^{67}Ga scan is negative. Lymph nodes uptake of ^{67}Ga is avid in mycobacterial infection and lymphoma.[260] Lymphoma is one of several causes of intrathoracic lymph node enlargement in the AIDS patient. Potential causes of lymphadenopathy in the AIDS patient include follicular hyperplasia, non-Hodgkin's lymphoma, mycobacterial infection, Kaposi's sarcoma, metastatic cancer, multiple infectious agents, and drug-induced disease (e.g., that due to trimethoprim–sulfamethoxazole).[261] By far the most common cause of radiologically identifiable lymph node enlargement in the AIDS patient is tuberculosis. High CT attenuation of enlarged lymph nodes in AIDS is suggestive of Kaposi's sarcoma. Low CT attenuation of enlarged lymph nodes is more often associated with mycobacterial infection.[262]

4.2.7. Lymphocytic Interstitial Pneumonitis

Lymphocytic interstitial pneumonitis is often found in pediatric patients with AIDS. The lung lesions tend to be nonspecific linear interstitial opacities admixed with patchy air-space consolidation.[263] In contradistinction to PCP, ^{67}Ga lung uptake in the lung is mild or negative in AIDS-related lymphocytic interstitial pneumonia.[219,260]

4.2.8. Other AIDS-Related Conditions

Septic and nonseptic pulmonary emboli usually present as multifocal or focal nodular opacities, often with cavitation and pleural effusions (see Fig. 6). The role of CMV recovered from the lungs of AIDS patients with clinical pneumonia is controversial.[7,227] It is not certain that the herpes-type viruses are of etiological importance, rather than just coexisters with more serious causes of lung disease. These viruses are usually associated with diffuse interstitial or consolidative lung opacities (both in AIDS patients and in non-AIDS patients, in whom the viruses can more clearly be shown to be the cause of the lung disease). ^{67}Ga scans may show slight lung uptake.[260]

5. Specific Diagnosis

The effective therapy of the febrile pneumonitis syndrome in immunocompromised patients requires rapid and precise diagnosis. Although the diagnostic clues discussed thus far may greatly limit the differential diagnostic possibilities, the specific diagnosis should be sought whenever possible. An aggressive approach to diagnosis will limit drug toxicity and the risk of potentially lethal superinfection without exposing the patient to potentially inadequate therapy. Not surprisingly, several studies have shown that the rapidity with which the diagnosis is made has a major impact in determining the outcome of therapy, whether one is dealing with a noninfectious disease, a conventional bacterial infection, or invasive fungal or nocardial disease.[1–3,97,112,144,263] Therefore, great emphasis must now be placed on the techniques available for making a precise diagnosis: immunologic studies, conventional examination of expectorated or induced sputum specimens, and a variety of invasive procedures designed to sample either lower respiratory tract secretions or lung tissue or both. Indeed, it is largely the skill of the clinician in utilizing the specific diagnostic techniques available that will determine the rate of survival in immunocompromised patients with the febrile pneumonitis syndrome.

As we discuss this aggressive approach to diagnosis, we must also emphasize that the clinician must constantly keep in mind both the risks and the benefits that are involved. The critical question that must be asked before undertaking any invasive procedure in this patient population is what is the likelihood that this procedure will result in a major change in therapy and prolongation of patient survival. Thus, invasive procedures are rarely indicated in patients with advanced leukemia, AIDS, or metastatic cancer. On the other hand, an aggressive approach for precise diagnosis is clearly indicated in organ transplant recipients, patients with treatable Hodgkin's disease or other forms of cancer with a reasonable expectation of a meaningful response to therapy, and patients with such conditions as collagen vascular disease or inflammatory bowel disease being treated with immunosuppressive therapy. In addition to the ethical considerations involved in this distinction between the two groups of patients, the practical matter is that the diagnostic yield of invasive procedures is much higher in the second group of patients. In the poor-prognosis patients, even open lung biopsy may not lead to any diagnosis in as many as 20% of patients, and in others, the findings may include diagnoses such as hemorrhage, tumor, and bronchiolitis obliterans that do not lead to effective therapy. Therefore, risk–benefit analysis must be a careful part of the clinician's diagnostic approach to the febrile pneumonitis syndrome in the immunocompromised patient.[1–3,5,10]

5.1. Immunologic Techniques for Specific Diagnosis

Measurement of antibody and delayed hypersensitivity skin test responsiveness to microbial antigens are time-honored techniques for diagnosing invasive infection. However, such methods have limited applicability when caring for immunosuppressed patients with the febrile pneumonitis syndrome, for several reasons:

1. Even under the best of circumstances in the normal host, there is a delay between the onset of infection and the development of a measurable immune response. In the immunocompromised patient, such responses may be further delayed or totally abrogated. To wait for the development of such a response can interfere greatly with the need and desire to arrive at a rapid diagnosis. For example, we have cared for a liver transplant patient who contracted HIV infection at the time of transplantation (prior to the availability of HIV testing), but who did not develop a positive HIV antibody test until more than $2\frac{1}{2}$ years later, at which time he already had overt AIDS.[264]

In contrast to the lack of sensitivity of the antibody response in diagnosing clinical disease, a variety of antibody measurements are helpful in predicting the risk of disease if exposed: Thus, a negative test for circulating antibody to *Toxoplasma gondii* is very useful in ruling out the possibility of encephalitis due to this organism in AIDS patients, as well as in predicting susceptibility to systemic toxoplasmosis and the need for prophylaxis in a recipient of a cardiac allograft from a seropositive donor. Similarly, a negative antibody test for varicella–zoster virus in an immunocompromised individual delineates an individual very susceptible to disseminated visceral

infection on exposure to this virus. Finally, the attack rate for clinical disease due to CMV in transplant patients can be predicted by knowing the antibody status of the donor and recipient (see Chapters 23 and 24).

2. Since many of the opportunistic infections that cause life-threatening disease in the compromised host cause asymptomatic subclinical infection in the normal population, the presence of a positive result may have little meaning. The classic examples of this phenomenon are the many attempts to make the diagnosis of invasive candidiasis or aspergillosis on the basis of the presence of precipitating or agglutinating antibodies directed against these organisms. It is now clear that because of the failure of development of such antibodies in many compromised patients and because of their presence in many normals, these tests are of limited diagnostic value.[265–267]

3. Appropriate serologic or skin tests are not available for many of the disease processes under consideration.

Therefore, the effectiveness of such traditional immunologic techniques for diagnosis has been disappointing. Even in the situation in which it has been most reliable, diagnosing HIV infection by testing for the presence of antibodies, a positive test does not make a diagnosis of AIDS. This next step requires further information, such as CD4 lymphocyte count and history of opportunistic infection or Kaposi's sarcoma. Antibody testing has been useful in patients with histories of possible exposure to *Coccidioides immitis* or *Histoplasma capsulatum,* in whom the demonstration of elevated or rising titers of complement-fixing antibody is an excellent clue to the presence of active infection with these agents [see Illustrative Case 3 (Section 2.1.2)].[268]

5.2. Sputum Examination

The usual clinical approach to the diagnosis of pneumonia is based on the Gram's stain and cultural examination of expectorated sputum specimens. It should be emphasized that strict criteria should be employed with viewing the Gram's stain of an expectorated sputum specimen before trusting the validity of the specimen: few squamous epithelial cells (<10 per low-power field) and many polymorphonuclear leukocytes (>25 per low-power field). If such criteria are not met, the validity of the specimen is in question. For a variety of reasons, such an approach is often of little diagnostic value in the compromised patient. First, many of these patients, particularly those with significant leukopenia, fail to produce sputum.[6,12,13,269–272] Second, the upper respiratory tract of many of these patients is frequently colonized with a large number of potential pathogens, particularly gram-negative bacilli and fungi. Expectorated sputum specimens will therefore be contaminated by these potential pathogens, and differentiation between organisms truly invading the lung and those that colonize the pharynx may be quite difficult. Third, certain organisms that commonly cause pneumonia in this population, particularly the fungi, rarely shed sufficient organisms into the sputum to permit diagnosis by cultural or microscopic examination. Finally, the noninfectious causes of pulmonary infiltrates will not be diagnosed by examination of expectorated sputum specimens. Therefore, although the clinician should always initiate the diagnostic evaluation of the patient with possible pneumonia by an examination of an expectorated sputum exam, more invasive diagnostic procedures are usually necessary.

Because of the increasing number of AIDS patients presenting with possible PCP, and the need for noninvasive tests for diagnosis, increased attention has been focused in recent years on the examination of induced sputum. Provided skilled respiratory therapists are carrying out the sputum-induction procedure, and equally skilled microbiologists are evaluating the material obtained, the diagnostic yield can be high. Thus, in AIDS patients, approximately two thirds of *Pneumocystis* pneumonias can be diagnosed following staining with Giemsa and other conventional stains. When immunofluorescent staining utilizing a monoclonal antibody specific for *P. carinii* is used, sensitivity and specificity of greater than 90% can be obtained. One caution must be noted, however. Because the organism burden is far greater in AIDS patients with *Pneumocystis* pneumonia than in such other immunocompromised patients as transplant or lymphoma patients with this infection, the sensitivity of this procedure is considerably less (at least 25% less in our experience) in these other patient groups.[273–276]

With the increased ability to carry out induced-sputum examinations, many centers are looking to utilize this procedure in the diagnosis of other forms of pneumonia, particularly those due to bacteria and fungi. Although precise data regarding sensitivity and specificity for other infections in different patient populations are not currently available, there is general agreement that examination of an induced-sputum specimen is an improvement over conventional expectorated-sputum examination. Indeed, it has largely replaced transtracheal aspiration in the initial evaluation of patients with pneumonia of unclear cause. Problems with the transtracheal approach have included the following: hemorrhage, cervical cellulitis, and oropharyngeal contamination (particularly in nonexpert hands).[5,277] This having been said, however, it is fair to say that in the hands of an experienced operator, transtracheal aspiration can be particularly useful in the evaluation of the occasional patient

with possible bacterial infection—particularly anaerobic bacterial infection—provided the following guidelines are followed:

1. There are three absolute contraindications to transtracheal aspiration: (a) an uncooperative patient, (b) a patient with anatomic characteristics (such as an obese person, a child, or one who has undergone surgery or radiation therapy of the neck) that make the procedure technically difficult, and (c) those with uncorrectable bleeding diatheses.
2. In the process of anesthetizing the area over the cricothyroid membrane where the lavage needle and catheter will be inserted, a small 25-gauge needle is employed both to deliver the local anesthesia and to delineate the track that the larger needle will follow.
3. In neutropenic patients, broad-spectrum antibacterial therapy is initiated immediately after the procedure and continued for a minimum of 48 hr post-procedure.[2,3,278,279]

5.3. Invasive Diagnostic Techniques

If the diagnosis has not been made by sputum examination, a more invasive procedure in which direct sampling of lower respiratory secretions, pulmonary tissue, or both may be accomplished is then required. The choice of procedure is dependent on several factors: the patient's degree of illness, the rate of progression of the disease, the type of imaging finding, and the expertise and experience of personnel at the institution. If the presumed pneumonitis and the degree of hypoxia are progressing rapidly, the definitive diagnostic procedure—the open lung biopsy—should be carried out immediately. This urgency is particularly true when the radiographic pattern of infiltrate is diffuse or multifocal. Despite the need for general anesthesia, thoracotomy, and a postoperative chest tube, it is remarkable how well this procedure is tolerated, especially if the treatable process is identified. If the pulmonary process is progressing at a more desultory pace, progressive hypoxia is not an immediate problem, and the clinical problem is more of a diagnostic dilemma than a therapeutic emergency, then less invasive techniques can be attempted, with the open lung biopsy held in reserve if these techniques fail.[3,5,277]

5.3.1. Bronchoscopic Diagnostic Techniques

Fiberoptic bronchoscopy has become a cornerstone of invasive diagnostic studies in the immunocompromised host because it provides opportunities for bronchoalveolar lavage, transbronchial biopsy, bronchial brushing, and inspection of the anatomy of the tracheobronchial tree. Two cautions should be emphasized, however, regarding bronchoscopy in this susceptible patient population. First, even uncomplicated bronchoalveolar lavage will cause a fall in oxygen saturation of 5–10% during and immediately after the procedure, a decline that can be clinically significant in terms of the subsequent need for assisted ventilation.[280] Second, particularly in the elderly debilitated patient, too much local anesthesia from the procedure will leave the patient with an impaired gag reflex that is inadequate to protect the airway from aspiration pneumonia. In addition, contamination by the bactericidal anesthetic agents of the diagnostic material obtained can lower the diagnostic yield.[281–283]

Fiberoptic bronchoscopy, and the ancillary procedures it makes possible, is the diagnostic procedure of choice in the immunocompromised patient with diffuse lung disease. Bronchoalveolar lavage by itself, which has the lowest rate of complications of any of the bronchoscopic procedures, is particularly useful in diagnosing *P. carinii* infection and pulmonary hemorrhage (>95% sensitivity in experienced hands) and is moderately effective in diagnosing cryptococcal pneumonia in the AIDS patient. In the transplant patient, the diagnostic yield of lavage for isolated cryptococcal nodules is far less (<20%). Because of success in diagnosing PCP, bronchoalveolar lavage has become the diagnostic procedure of choice in AIDS patients with diffuse pulmonary opacities. Additional information regarding the prognosis of an AIDS patient with *Pneumocystis* can be obtained by analyzing the bronchoalveolar lavage fluid for the presence of neutrophils. If present, they predict a much poorer outcome of therapy. In diagnosing *Pneumocystis,* transbronchial biopsy and bronchial brushing add significantly to the complication rate without improving the diagnostic yield. Therefore, in AIDS patients, biopsy procedures are usually restricted to patients with focal disease suggesting malignancy or with invasive fungal infection such as aspergillosis.[284–287]

In contrast, bronchoalveolar lavage is of little value in the diagnosis of pulmonary infiltrates in neutropenic leukemic patients. It has a very low yield in diagnosing invasive pulmonary aspergillosis and a high rate of false-positive bacterial isolations due to contamination from the upper airway. Bronchoalveolar lavage will also fail to diagnose more than 50% of malignancies and drug-induced pulmonary processes. An additional problem in the neutropenic patient is the potential for life-threatening bacteremia and postbronchoscopy pneumonia with any bronchoscopic procedure. In order to avoid these problems, we routinely begin broad-spectrum intravenous antimicrobial therapy with ceftazadime or imipenem, with or without vancomycin (depending on cul-

tures of the upper airway), as soon as adequate specimens are obtained in the neutropenic patient. Such antibiotics are continued for 48 hr after the procedure unless some untoward event has occurred that requires further antibiotic therapy.[3,288–291]

Transbronchial biopsy is particularly useful in the diagnosis of allograft rejection in lung transplant recipients, leukemic infiltrates, radiation- and drug-induced pneumonitis, various forms of interstitial pneumonitis, and some viral infections.[1,5,8,10] Tumor invasion is often missed, however, as the biopsy forceps tends to slide off the tumor. Transbronchial needle aspiration through the bronchoscope, utilizing an 18-gauge needle, has been reported to increase the diagnostic yield, providing valuable tissue for histologic examination from paratracheal, peribronchial, and carinal areas without a significant increase in complications.[292]

The yield from transbronchial biopsy is clearly operator-dependent. At many centers, including our own, there has been increasing concern regarding the quality of the biopsy material obtained, particularly in non-AIDS patients. Because of this concern, there has been a revival of interest in an older procedure—transpleural lung biopsy via the thoracoscope. This procedure appears to be particularly useful in the diagnosis of patients with diffuse interstitial pulmonary disease or with focal, pleural-based disease in the periphery of the lung. Although an artificial pneumothorax is induced to carry out the procedure and a chest tube is needed for 1–3 days postprocedure, it may be carried out under local anesthesia and appears to be well tolerated, even in bone marrow transplant patients.[293–296] Thus, Dijkman et al.[293] reported 100% success in the diagnosis of acute pulmonary disease in 26 immunocompromised patients with acute, diffuse pulmonary disease and 90% success among 63 nonimmunocompromised patients with acute, diffuse pulmonary disease and 90% success among 63 nonimmunocompromised patients. They report that in their hands, better diagnostic material was obtained and that the procedure was better tolerated than fiberoptic bronchoscopy, especially in hypoxic patients. We have had a similar positive experience in more than 30 non-AIDS immunocompromised patients.

Bronchial brushing has become less popular in recent years, primarily because it adds little to bronchoalveolar lavage in the evaluation of the AIDS patient. There is still considerable interest, however, in utilizing protected catheters (telescoped plugged catheters) to sample the lower respiratory flora without contamination from the oropharynx. Utilizing this approach and quantitative microbiology, there is some evidence that a finding of more than 10^3 colony-forming units of a particular bacterial species is associated with invasive disease. At many centers, however, there is as yet a significant false-positive and false-negative rate, and the use of protected catheters should therefore be regarded as a research procedure at present.[284,285,297–299]

5.3.2. Percutaneous Needle Biopsies of the Lung

The diagnostic procedure of choice for focal lung disease is some form of percutaneous, transthoracic needle biopsy technique (just as the diagnostic procedure of choice for diffuse lung infiltrates involves either bronchoscopic or thoracoscopic approaches). This is not to say that focal lung disease cannot, on occasion, be diagnosed by bronchoscopic biopsies, but that the diagnostic yield of needle biopsy is greater for focal diseases, and the procedure is usually less uncomfortable for the patient.[5]

Percutaneous, transthoracic needle aspiration biopsy was first described in 1883. Since then, extensive experience has been obtained, particularly in recent years during which high-resolution fluoroscopy and CT guidance of the biopsy procedure have greatly improved both the diagnostic yield and the safety of the procedure.[300–302] The procedures employed can be divided into two general categories: modern small-gauge needle aspiration procedures that provide material for microbiologic and cytologic examination and older cutting-needle biopsy techniques aimed at providing tissue for histologic as well as cultural analysis. Some investigators have been successful in obtaining tissue core samples with fine, circumferentially beveled aspiration needles.[303]

Aspiration-needle biopsy is the most widely used procedure for the diagnosis of focal pulmonary processes in the immunocompromised host, particularly when infection is the primary consideration.[304] Percutaneous needle aspiration is particularly well suited for diagnosing focal peripheral lung lesions, e.g., those due to *Nocardia*, fungi, or tuberculosis.[305] A sensitivity greater than 80% has been noted for infection and greater than 90% for malignancy. At our institution, we have successfully diagnosed more than 90% of fungal or nocardial infections occurring in immunosuppressed patients approached in this manner and regard this procedure as the one of choice for such peripherally placed, focal pulmonary lesions not diagnosed by induced-sputum examination. The diagnostic yield is particularly high if cavitation is present in the lesion. In contrast, the diagnostic yield of this procedure in patients with diffuse lung disease is quite low, and transthoracic needle aspiration should not be carried out in such individuals.[300,301]

The rate of hemorrhage, in patients with adequate coagulation factors (e.g., platelet count $>75{,}000/mm^3$ prior to and for at least 24 hr postprocedure, and normal prothrombin and partial thromboplastin times), follow-

ing needle aspiration is related to the size of the needle employed. Thus, with an 18-gauge needle, an 8.4% occurrence rate of moderate hemoptysis was reported. With 22- and 23-gauge thin-wall needles, the incidence of hemoptysis postprocedure was less than 1%. Such complications as air embolism, implantation of malignant cells into the needle tract, spread of tumor or infection into the pleural space, and bleeding into the chest wall, although reported, are quite rare.[300,301]

The major complication of percutaneous needle aspiration of the lung is pneumothorax, with reported rates of 5–57% (20–25% being an average figure). In most series, approximately half of these individuals have required chest tube insertion. Both the incidence of pneumothorax and the requirement for a chest tube appear to be particularly great in individuals with chronic obstructive pulmonary disease, the FEV_1 being the best predictor of risk.[300,301,306] Moore et al.[307] have appropriately emphasized that careful attention to certain precautions can decrease the requirement for chest tube placement to approximately 1%. These precautions include the following: a single pleural puncture at biopsy, placement of the patient such that the puncture site is down for a period of at least 1 hr or until air leakage has stopped, and restriction of coughing, talking, and activity for this time period. With these precautions, chest tube insertion was required in only 0.4% of 262 patients biopsied. Using Moore's precautions, approximately 89% of postbiopsy pneumothoraces are visible immediately postprocedure, while 9% appear 1 hr postprocedure, and only 1–2% of pneumothoraces appear for the first time 4 hr or more postprocedure. None of the late-appearing pneumothoraces required chest tube insertion.[306,307]

The cutting-needle biopsy technique is of historic interest. Turbine-powered trephine biopsy technique yielded excellent specimens for diagnosis, but was associated with an unacceptably high rate of major complications, including death from hemorrhage or air embolism, and has now been abandoned. Similar difficulties were encountered when percutaneous lung biopsies were carried out with a modified Vim–Silverman cutting needle, and cutting-needle biopsy procedures fell out of favor.[308,309] In the last few years, in order to get tissue for histologic examination, there has been a resurgence of interest in this technique, in large part made possible by the better control provided by CT guidance. If cutting-needle biopsies are to be safely used, certain guidelines must be strictly followed: (1) the patient must be cooperative, (2) coagulation studies should be essentially normal, (3) only abnormalities directly abutting a pleural edge should be biopsied, and (4) the needle should not remain within the lung parenchyma for more than 10 sec if tearing of the lung and pleura is to be avoided. Utilizing these guidelines, overall accuracy rates of greater than 95% have been reported, with a pneumothorax rate of approximately 5%—a higher diagnostic yield and a complication rate comparable to that achieved with needle aspiration techniques.[310,311]

5.3.3. Open Lung Biopsy

The definitive diagnostic procedure in the immunocompromised patient with the febrile pneumonitis syndrome remains open lung biopsy, which should be seriously considered if arterial hypoxemia is intensifying, the pulmonary infiltrates are spreading rapidly, and the patient has a hopeful prognosis from his underlying disease. Despite the need for general anesthesia, thoracotomy, and a postoperative chest tube, the procedure is remarkably well tolerated, especially in those patients in whom a treatable disorder is identified. A specific diagnosis is made in approximately 80% of immunosuppressed patients who come to open lung biopsy. The undiagnosed cases probably represent instances of unrecognized pulmonary drug toxicity, the effects of antecedent antimicrobial therapy in modifying the disease process, or even some new form of pulmonary infection (the examples of *Legionella pneumophila* and *L. micdadei,* both of which had their greatest impact on immunosuppressed patients, come readily to mind in this regard). There is a false-negative rate with open lung biopsy of less than 5%—these instances presumably being related to sampling error or inappropriate handling of specimens.[312–318]

A more important question is how frequently the knowledge obtained results in meaningful therapy. The answer to this question is clearly different for different patient populations. Thus, there is now general consensus that open lung biopsy is rarely indicated in patients with AIDS or in febrile neutropenic patients with acute leukemia. In contrast, in patients with Hodgkin's disease, organ transplant patients, or other immunosuppressed patients whose life expectancies from their underlying conditions can be measured in years, it is very clear that when the febrile pneumonitis syndrome develops, open lung biopsy can provide life-saving information. In these latter individuals, open lung biopsy should be carried out if rapid clinical deterioration is occurring as outlined above, or if less invasive diagnostic procedures have failed to yield a diagnosis.[312–318]

The final issue in need of discussion is the question of the circumstances under which empiric therapy can be carried out without an invasive diagnostic procedure. In our experience, the following are the most common situations in which empiric therapy is necessary: (1) far-advanced AIDS, relapsing acute myelogenous leukemia, and other advanced malignancies that limit life expectancy because of the severity of the underlying illness; (2)

leukemia prior to therapy, since there is an exceedingly low probability of opportunistic infection and antibacterial therapy has a high probability of success; (3) the presence of either an uncorrectable bleeding diathesis or such impaired pulmonary function that invasive diagnostic techniques would not be tolerated; and (4) patient refusal of invasive diagnostic studies. In such patients, the choice of empiric therapy is made on the basis of the indirect clues outlined previously: the epidemiologic and clinical setting, the nature of the immune defect(s) present, the pace of the pulmonary process, and the radiographic pattern.

6. Superinfection

Implicit in this review, and in most published reports concerning the febrile pneumonitis syndrome in the immunocompromised patient, is that a single etiology is responsible for the disease syndrome. That this is not always the case is shown in Table 1 (Section 2), in which 10% of the subjects, particularly the cancer patients, were shown to have mixed infections. Particular combinations of agents that are likely to be present together are CMV with *P. carinii,* gram-negative, or fungal infection; *Nocardia* and *Aspergillus; Cryptococcus* and *Nocardia; Cryptococcus* and *P. carinii;* mycobacterial and fungal infection; and radiation pneumonitis with gram-negative bacillary infection.[3,5]

Even more important is the occurrence of superinfection. For example, in one series of renal transplant patients, it was noted that pulmonary superinfection accounted for 81% of the fatalities.[2] Superinfection appears to be most common in the following situations: following an intense environmental exposure within the hospital to *Aspergillus* species or such gram-negative bacilli as *Pseudomonas aeruginosa,* the previously injured lung being particularly susceptible to environmental hazards; patients who are intubated; patients on high-dose corticosteroids; severely neutropenic patients; and those with pulmonary infarcts or severe chemical injury from aspiration.[1–6,8]

The pathogens responsible for superinfection are somewhat different from those responsible for primary infection. Virtually all the instances of bacterial superinfection are due to gram-negative bacilli. Two organisms that rarely produce primary pulmonary infection—herpes simplex virus and *Candida* species—are not uncommon causes of superinfection, as are *Aspergillus fumigatus* and *Torulopsis glabrata*—again, particularly in the intubated patient.[2,6]

The clinician should be particularly alert to the possibility of superinfection in the following circumstances: in the patient who has shown an initial clinical response to therapy in terms of temperature curve, arterial blood gases, well-being, leukocyte count, and sputum production, but who now shows deterioration in one or more of these parameters; in any patient with significant leukopenia who continues to receive high-dose corticosteroid therapy; and in the patient with progressive deterioration despite apparently effective treatment. In any of these instances, aggressive diagnostic techniques should be again undertaken. At postmortem examination in too many patients, the primary cause of fever and pneumonitis is no longer present, but instead, multiple superinfecting and microorganisms can be demonstrated. Earlier recognition and better prevention are both necessary in dealing with this unsolved problem complicating the febrile pneumonitis syndrome in the compromised host.[1–6,8]

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