Pulmonary Complications in Cancer Patients

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Introduction
The respiratory system is a common site for complications due to cancer and cancer therapy. Several factors can lead to pulmonary complications. Immunosuppression caused by the underlying disease or the cancer therapy can lead to infectious disease. In addition, the lungs contain an enormous capillary bed through which flows the entire venous circulation, making it a frequent site of metastasis and pulmonary emboli. Finally, the pulmonary capillary bed is uniquely sensitive to side effects of chemotherapy and radiation therapy, which often lead to respiratory symptoms. This article reviews the presentation, diagnosis, and therapy of common infectious and noninfectious disorders of the pulmonary system that occur in cancer patients.

Approach to the Diagnosis of Pulmonary Complications
Immunosuppression is defined as a relative or absolute defect in antigen processing or effector cell function. Clinically, it is defined by the susceptibility of certain populations to specific types of infections. Immunosuppression caused by the disease or by the treatment can cause qualitative and quantitative immunologic defects. Certain general immunologic defects are associated with specific infectious organisms, and recognition of an immunologic defect can help in the prediction of the infectious agent (Table 1). Besides immunologic defects, other factors, such as environmental exposure, travel history, iatrogenic procedures, recent hospitalization, and/or antibiotic therapy, must be taken into account in determining the infectious agent.

Review of the radiologic pattern of infiltration also helps focus the differential diagnosis on a subset of likely etiologic agents. A distinction is often made between processes involving a single lobe or segment (localized) and those involving multiple lobes bilaterally (diffuse). The presence of a localized infiltrate with an appropriate clinical history suggests the diagnosis of a bacterial pneumonia. Diffuse infiltrates suggest either infection, especially Pneumocystis and cytomegalovirus (CMV) pneumonia, or noninfectious etiologies, such as drug toxicity and lymphangitic spread of tumor. The presence of infiltrates, cavitation, nodules, adenopathy, or pleural effusions can help focus attention on certain disorders (Table 2).

Pulmonary symptoms in cancer patients with normal chest radiographs also need further evaluation. Tests that are more sensitive than the chest radiograph to detect pulmonary disease include mea-
The seriousness and tempo of an illness are also helpful in determining whether there is time to wait for a response to empiric therapy or whether an invasive procedure should be performed immediately.

For the very ill cancer patient with pulmonary disease, often the goal is to achieve a specific etiologic diagnosis quickly and safely. Adequate samples of lower respiratory tract secretions and/or lung tissue are usually required for pathologic examination, microbial stains, and cultures. Table 3 lists the invasive procedures available for diagnosing pulmonary infiltrates in cancer patients along with an outline of specific etiologic yields and complication rates. Most procedures have a significant false-negative rate, further complicating the decision making, and in some cases even at autopsy a specific etiologic diagnosis cannot be made.

It is important to note that survival is often not affected by making a specific pulmonary diagnosis. Studies do show, however, that morbidity is lessened by making a definitive diagnosis. Thus, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy (if safe) is usually performed as the initial invasive procedure. In general video-assisted thoracic surgery has been shown to be a safe and effective method of obtaining lung tissue with less morbidity when compared with conventional thoracotomy, although no studies have been restricted exclusively to immunocompromised hosts (Table 3).
### Table 2
Radiographic Appearance Associated with Common Pulmonary Disorders in Cancer Patients

| Radiographic Appearance | Pulmonary Disorders |
|-------------------------|---------------------|
| Localized infiltrates   | Pneumonia           |
|                         | Bacterial           |
|                         | Mycobacterial       |
|                         | Fungal              |
|                         | Cancer - lung       |
|                         | Radiation pneumonitis|
|                         | Pulmonary infarct   |
| Diffuse infiltrates     | Pneumocystis carinii pneumonia |
|                         | Viral pneumonia     |
|                         | Cardiogenic and noncardiogenic pulmonary edema |
|                         | Metastatic disease  |
|                         | Drug toxicity       |
|                         | Nonspecific pneumonitis |
| Hilar and/or mediastinal adenopathy | Tuberculosis and atypical mycobacterial pneumonia |
|                         | Pathogenic fungal pneumonia (histoplasmosis, coccidiosis) |
|                         | Lymphomas           |
|                         | Solid tumors (lung, breast, head and neck, germ cell, melanoma) |
|                         | Drugs (methotrexate) |
| Cavitation              | Bacterial pneumonia (gram negatives, anearobes, Legionella, Actinomyces, Nocardia) |
|                         | Tuberculosis and atypical mycobacterial pneumonia |
|                         | Septic emboli (bacterial or fungal) |
|                         | Tumors (squamous lung carcinoma) |
| Pleural effusions       | Bacterial pneumonia (parapneumonic or empyema) |
|                         | Tuberculosis        |
|                         | Tumors (lung, breast, ovarian) |
|                         | Congestive heart failure |
|                         | Pericardial disease (left-sided pleural effusion) |
|                         | Pulmonary embolism  |
| Nodules                 | Bacterial pneumonia (Nocardia, Actinomyces, H. influenza) |
|                         | Atypical mycobacterial pneumonia |
|                         | Metastatic cancer   |
|                         | Bronchiolitis obliterans with organizing pneumonia |
Although sputum and serologic examinations are neither sensitive nor specific for most pulmonary diseases, occasionally a definitive diagnosis can be made by these methods. The presence of malignant cells, *Legionella* antigen, or *Pneumocystis carinii* in the sputum is specific but not sensitive for these disorders. The indications for sputum induction for diagnosis of pulmonary disorders in non-HIV immunocompromised patients have not been defined, but sputum induction may have a role in diagnosing *P. carinii* pneumonia and tuberculosis (TB).

The presence of *Cryptococcus* antigen in the serum is highly sensitive and specific for disseminated cryptococcosis but may not be sensitive for pulmonary *Cryptococcus* infection alone. Serologic tests that demonstrate antibodies for *Aspergillus*, * Blastomyces*, and *Histoplasma* are suggestive of active infection, but the sensitivity of these studies is quite low.

More recently, radioimmunoassay for *Histoplasma capsulatum* antigen has been shown to provide a rapid method for diagnosing disseminated histoplasmosis. The antigen can be detected in 50 percent of blood and 90 percent of urine samples from patients with disseminated histoplasmosis. Most of these data come from patients with acquired immunodeficiency syndrome (AIDS). Whether the sensitivity is this high in non-AIDS immunocompromised patients remains unknown.

The diagnosis of invasive aspergillosis usually requires a biopsy of the infected tissue because the organism is ubiquitous and cultures are nonspecific for invasive disease. However, in neutropenic patients (especially with leukemia) who remain febrile on broad-spectrum antibiotics, the presence of the organism in sputum or bronchoscopic specimens may be a reliable guide to make a diagnosis of pulmonary *Aspergillus* infection because these patients are at greatest risk to develop invasive disease.

### Pulmonary Infections in Cancer Patients

#### Bacterial Pneumonias

The type of bacterial pneumonia that develops in a cancer patient depends on several factors, including the underlying immunologic defect, the duration of the immunocompromised state, and whether the infection is community acquired or nosocomial. *Streptococcus pneumoniae* and *Haemophilus influenzae* are seen in cancer patients with B-cell defects. Gram-negative organisms including *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* species are common in neutropenic patients, but the widespread use of effective gram-negative antibiotic regimens has led to a decrease in the incidence of *P. aeruginosa* infections and to an increase in gram-positive infections in this patient population. The major risk factors for the occurrence of bacterial pneumonia in cancer patients besides neutropenia include corticosteroid administration, inadequate pulmonary drainage from obstructing tumor, and decreased cough.

The clinical signs and symptoms of pneumonia may be typical ones, including acute onset of shaking chills, fever, and productive cough, but in the setting of granulocytopenia, patients may present with atypical or absent findings. Sputum production is seen in fewer than 60 percent of neutropenic patients, and when the absolute neutrophil count is less than 1,000 cells/mm³, purulent sputum is seen in less than eight percent of patients.

In cancer patients the most sensitive sign of bacterial pneumonia is fever, which occurs in virtually all patients who have bacterial pneumonia. Although rales and signs of consolidation occur inconsistently, the chest radiograph is abnormal in 93 percent to 97 percent of patients, usually showing localized infiltrates.

The usefulness of sputum examination in the immunocompromised patient
with pneumonia is controversial. If the patient has sputum and a suspected bacterial pneumonia, we usually send it for gram stain and routine culture. The results are used as a guide to antibiotic therapy if the patient is not improving on the initially prescribed regimen.

Bacterial pneumonia in cancer patients can progress rapidly, and the incidence of bacteremia and mortality is high, particularly in patients with absolute neutrophil counts of less than 1,000 cells/mm³.

Empiric broad-spectrum antibiotic coverage should be initiated immediately when the diagnosis of bacterial pneumonia is suspected or more commonly when the neutropenic patient presents with fever and no obvious source. An aminoglycoside with a third-generation cephalosporin or an extended-spectrum penicillin are favored combinations in neutropenic patients. In some studies monotherapy has been shown to be as effective and less toxic than combination antibiotic treatment. However, concern over the emergence of resistant organisms with one drug therapy remains.

Although the optimal duration of antibiotic therapy for neutropenic patients is unknown, a two-week course is usually sufficient if there is rapid clinical improvement and white blood cell recovery. When prolonged neutropenia is present, longer courses might be considered even if the patient is clinically improving. If the neutropenic patient remains febrile or does not improve on broad-spectrum antibiotics, additional maneuvers that must be considered include reevaluation.

Table 3
Results of Invasive Procedures for the Diagnosis of Pulmonary Disorders in Cancer Patients

| Procedure                              | No. of Patients | Specific Diagnosis | Complications (percent) |
|----------------------------------------|-----------------|--------------------|-------------------------|
|                                        | Number | Percent | Pneumothorax | Hemmorhage |
| Bronchoscopy                           | 584    | 265     | 45 | 4.7 | 3.4 |
| Transbronchial biopsy                  | 328    | 98      | 30 | NA | NA |
| Bronchial brushings/washngs            | 327    | 173     | 55 | 0  | 0  |
| Bronchoalveolar lavage                 | 178    | 116     | 65 | 20 | 10 |
| Needle aspirate                        | 334    | 228     | 71 | 10* | 2  |
| Open lung biopsy                       | 12     | 12      | 100| 8† | 0  |
| Video-assisted thoracoscopic surgery    | 5      | 5       | 100| 10 | 0  |

*Includes cancer patients who were further immunocompromised by chemotherapy, radiotherapy, steroids, and/or bone marrow transplantation.

†Unpublished data from experience at Memorial Hospital, includes patients with significant thrombocytopenia (platelet range, 12,000-476,000).

‡Refers to prolonged air leak needing chest tube drainage.
of antibiotic therapy, additional therapy to cover opportunistic infections (especially Aspergillus), and performance of an invasive procedure to make a specific diagnosis.

When a cancer patient who is not neutropenic presents with suspected bacterial pneumonia and is clinically stable, the same guidelines for treatment are used as for the immunocompetent patient.

Although most bacterial pneumonias in immunocompromised patients are thought to be acquired by the respiratory route or the blood, some pneumonias are caused by aspiration. Cancer patients at particular risk for aspiration pneumonia include those with head and neck tumors and those with mucositis due to infection, chemotherapy, and/or radiation therapy.

Less common causes of bacterial pneumonia in cancer patients include Legionella pneumophila, Mycoplasma pneumoniae, Nocardia and Actinomyces species, and Moraxella catarrhalis.

Legionnaires’ disease in the immunocompromised host is often acquired from a nosocomial source. Fever, malaise, and a productive cough are common. Radiographically, the presence of bilateral infiltrates and cavitation is relatively frequent. Culture of the organism from respiratory secretions, blood, tissue, or pleural fluid is the mainstay for diagnosis. Direct fluorescent antibody tests are quicker but have limited sensitivity. Therapy of Legionella requires the use of antibiotics that can kill intracellular organisms. Although erythromycin is the antibiotic of choice, some experts recommend adding rifampin for the duration of therapy, which should be at least three weeks.

Nocardia infection occurs primarily in patients with impairment of cell-mediated immunity, and its presence in respiratory secretions should always be considered diagnostic of disease. At least six to 12 months of therapy is indicated, and parenteral therapy should be continued for at least four to eight weeks. Sulfonamides are the mainstay of therapy. However, if patients cannot tolerate sulfa drugs or they fail treatment, minocycline alone or in combination with cefotaxime has been successful.

Although protection against bacterial pneumonia by vaccination has not been demonstrated in the immunocompromised host, Pneumovax (Merck & Co., Inc.) is recommended, and H. influenzae B vaccine should be considered in patients at risk for this infection (e.g., splenectomized patients, patients with globulin defects, etc). Prophylactic intravenous immune globulin in cancer patients with quantitative or qualitative hypogammaglobulinemia, such as patients with chronic lymphocytic leukemia or myeloma, has decreased the number of episodes of pneumonia and other infections in these patients. The administration of growth factors (specifically granulocyte colony-stimulating factor) to cancer patients who are at risk for morbidity from febrile neutropenia seems to be of greatest benefit if given before neutropenia develops.

**Tuberculosis**

The prevalence of TB is higher in some immunocompromised patients, particularly those with lung cancer, head and neck cancer, and lymphoproliferative disorders, but its overall incidence in non-HIV-positive cancer patients still remains low. In patients with lung and head and neck cancers, TB typically develops early in the course of the neoplastic disease, while in patients with lymphoproliferative disorders, the infection develops when the underlying malignancy is advanced.

In most cancer patients with TB, the disease results from reactivation of a latent infection. However, the severe malnutrition and weight loss that accompany advanced cancer increase the susceptibility to active infection from exogenous sources as well. Diagnosis of TB is often
delayed because fever and constitutional symptoms are commonly attributed to the underlying neoplasm. Chest radiographs can show typical upper lobe cavities, but lower lobe infiltrates, masses, nodules, and a miliary pattern occur more frequently in immunosuppressed patients. Sputum examination should always be attempted although it is less often positive in these patients. When sputum smears are negative for the tubercle bacillus, bronchoscopy should be performed.

Therapy for sensitive TB is similar and as effective in immunocompromised patients as it is in the general population. Because of the increasing incidence of isoniazid-resistant TB, initially a four-drug regimen is recommended: isoniazid, rifampin, ethambutol, and pyrazinamide (for the first two months of therapy). If the organism is sensitive to isoniazid and rifampin, the ethambutol can be stopped and double therapy should be continued for an additional seven to ten months. If there is microbiological resistance to isoniazid or rifampin, treatment with the sensitive drug (i.e., isoniazid or rifampin) and ethambutol should be extended to at least 18 months including 12 months after sputum conversion. Many authorities recommend continuing pyrazinamide as well. There are no good studies on effectiveness of drugs for multiresistant TB. Four or five drugs to which the organism is sensitive should be given. The appropriate duration of treatment is unknown but probably should be continued for two years or more. Whether surgical resection of localized disease has benefit is unknown.

Immunocompromised patients with positive tuberculin reactions should receive 12 months of prophylaxis with isoniazid (300 mg/day). To increase the sensitivity of the tuberculin skin test in cancer patients, it should be performed before immunosuppressive therapy is instituted, and a reaction size of 5 mm of induration is used to define a positive reaction. Bacille Calmette-Guérin, an attenuated strain of Mycobacterium bovis that is given as a live vaccine, is not recommended for TB prophylaxis because disseminated disease and deaths have been reported in immunocompromised patients.

ATYPICAL OR NON-TUBERCULOUS MYCOBACTERIA

Pulmonary infections with non-tuberculous mycobacteria, which are widely distributed in nature, clinically and often radiographically are indistinguishable from TB, but are not contagious. Mycobacterium avium complex (MAC) and Mycobacterium kansasii are the most frequently isolated organisms and occur commonly in patients with lung cancer, head and neck cancer, and hairy cell leukemia. A non-tuberculous mycobacterium called Mycobacterium haemophilum has recently been identified as a pathogen in immunocompromised patients. The organism causes pulmonary and extrapulmonary disease (especially in the skin, lymph nodes, and joints) and has been reported mostly in bone marrow transplant patients and the HIV infected. Eradication of atypical mycobacteria is often difficult and usually requires four to five drugs to which the organism is sensitive for 18 months or longer.

FUNGI

A useful way to consider pulmonary fungal infections in the immunocompromised patient is to separate them on the basis of the patient’s underlying immunologic defects. Patients with neutropenia more commonly develop infections with Aspergillus, Mucor, and Candida species. These organisms are called “opportunistic fungi” because they usually infect only patients with abnormal host defenses. Patients with T-cell defects more often develop infections with Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, and Blastomyces dermatitides. These organisms are called
“pathogenic fungi” because they also infect immunologically normal persons.

Because *Aspergillus* and *Cryptococcus* are major causes of pneumonia in patients with cancer, they will be discussed here. Immunosuppressed patients at risk for invasive pulmonary aspergillosis include those with prolonged neutropenia; those receiving chronic corticosteroids, antibiotic therapy, and/or chemotherapy; and those with a prior history of *Aspergillus* pneumonia.

The clinical features of pulmonary aspergillosis include fever, dyspnea, nonproductive cough, and pleuritic chest pain with or more frequently without a friction rub. Often the only evidence of *Aspergillus* pneumonia is fever with pulmonary infiltrates that do not respond to antibiotics. Massive hemoptysis is a rare complication and tends to occur during the stage of bone marrow recovery and cavity formation. Tracheobronchitis is another form of pulmonary *Aspergillus* infection that occurs in immunocompromised patients. Patients present with wheezing and/or dyspnea, and the chest radiograph can be normal or show lobar atelectasis. *Aspergillus* pneumonia may or may not accompany the airway disease.

Early in the course of *Aspergillus* infection, the chest radiograph may be normal, or it may show a single nodule; multiple nodules; or a large, wedge-shaped, pleural-based lesion that mimics pulmonary infarction. A computed tomographic scan of the chest can show abnormalities weeks before the chest radiograph becomes abnormal.

Because *Aspergillus* infections are difficult to diagnose before death and because they are an important cause of mortality in neutropenic patients, empiric therapy for aspergillosis in the proper setting has become commonplace. *Amphotericin B* is the drug of choice for invasive aspergillosis. Surgical resection should be considered in leukemic patients and bone marrow transplant recipients who, after therapy, have residual disease especially with mycetomas. Liposomal amphotericin B, which can allow higher doses of drug with potentially reduced toxicity, and *itraconazole* appear to be promising drugs for the treatment of *Aspergillus* infection in immunocompromised patients.

Other strategies for treatment of aspergillosis include adding fungus-specific antibodies to liposomes to increase the efficiency of drug targeting and optimize drug delivery to sites most likely to be infected (e.g., aerosol to the lungs). The clearest correlation with survival in patients with invasive aspergillosis is remission of the underlying malignancy and recovery of functioning neutrophils. The role of granulocyte colony-stimulating factors remains uncertain.

Disseminated cryptococcosis is manifested by the occurrence of meningitis and pulmonary involvement, which occurs in up to 50 percent of patients with disseminated infection. Isolated cryptococcal pneumonia is much less frequent. Radiographically, pneumonia usually presents as a single, well-defined mass that ranges from 2 to 10 cm in diameter and mimics primary lung cancer. Cavititation, intrathoracic adenopathy, and pleural effusions are rare in cancer patients. However, they are common in HIV-infected patients. Because the disease is commonly disseminated when it becomes clinically obvious, cerebrospinal fluid, blood, and urine cultures provide excellent sources for diagnosis. Conversely, when the organism is retrieved from respiratory secretions, the patient should be evaluated for disseminated infection, including a lumbar puncture. The latex agglutination test for cryptococcal polysaccharide antigen is useful for diagnosis and should be followed to measure the efficacy of therapy.

*Amphotericin B* is the recommended therapy for cryptococcal infection, and *flucytosine* is synergistic. This combination should be considered in patients with cryptococcal meningitis. In patients
with pulmonary cryptococcosis alone, amphotericin B may be adequate, but there is no agreement as to the dose and duration of therapy. Although its role in the non-AIDS immunocompromised patient is undefined, fluconazole is a promising azole for the treatment of pulmonary cryptococcosis.

**Viruses**

In patients who are immunocompromised, particularly with deficiencies of cellular immunity, severe morbidity and death can occur during primary infection or reactivation of certain viruses. Cytomegalovirus (CMV) is a major cause of morbidity and mortality in allogeneic bone marrow transplant (Allo-BMT) recipients. Interestingly, in recipients of autologous bone marrow and other cancer patients, it rarely causes active disease.

The clinical signs, symptoms, and radiographic findings of CMV pneumonia are nonspecific and often indistinguishable from other common pneumonias. If the organism is cultured from bronchoalveolar lavage, blood, or urine in Allo-BMT recipients, even if asymptomatic, treatment for CMV is usually given. The combination of ganciclovir and intravenous gammaglobulin has been shown in two small, uncontrolled studies of Allo-BMT patients to significantly decrease the mortality from this disease. In our institution with this regimen, the death rate from CMV pneumonia has decreased from 90 percent to 30 percent. Although ganciclovir prophylaxis appears to prevent CMV pneumonia in Allo-BMT recipients, few studies have shown a survival advantage associated with its use.

Varicella-zoster, herpes simplex, respiratory syncytial virus, adenovirus, and influenza virus can occasionally cause pneumonia in patients with cancer. Prevention of influenza A and B involves the use of an inactivated influenza vaccine, and although the immune response in immunocompromised patients is variable, it is recommended that such patients receive vaccination.

**Protozoans**

*P. carinii* pneumonia (PCP) rarely if ever occurs in patients who have normal immune function. In cancer patients, PCP occurs most commonly in patients who have underlying malignancies associated with defects in cell-mediated immunity; who have undergone organ transplantation; or who are receiving immunosuppressive drugs, especially cyclosporine or corticosteroids. A retrospective, 12-year review at Memorial Hospital showed that of the 142 PCP cases found, 47 percent were in patients with hematologic malignancies, 31 percent were in patients with solid tumors, and 18 percent were in bone marrow transplant patients.

Nonproductive cough, shortness of breath, and fever are the typical symptoms of *Pneumocystis* pneumonia. The natural history of untreated PCP is a rapidly progressive involvement of the lungs culminating in death. The typical radiographic appearance of PCP is one of diffuse bilateral symmetric, mixed interstitial, and alveolar infiltrates. Lobar or asymmetric bilateral infiltrates, solitary and multiple nodules, a miliary pattern, upper lobe infiltrates, pneumothoraces, and normal chest radiographs have also been reported.

The diagnosis of PCP is made only by finding the organism in respiratory secretions or body tissues. Although induced sputum has had a high yield in HIV-infected patients, its sensitivity in cancer patients with PCP appears to be
low. Under most circumstances, bronchoscopy is the procedure of choice to provide the diagnosis in cancer patients.

There are two drugs that are highly effective in the treatment of Pneumocystis pneumonia: trimethoprim-sulfamethoxazole (TMP-SMX) and parenteral pentamidine.30 If a patient does not respond to initial anti-PCP therapy, there are no controlled studies indicating the best approach. However, most clinicians switch from TMP-SMX to intravenous pentamidine and vice versa.

Other agents, such as trimetrexate and difluoromethylornithine, have some efficacy against Pneumocystis pneumonia, but major toxicity, especially bone marrow suppression, limits their usefulness in cancer patients. Atovaquone shows some promise in the treatment of HIV-associated PCP with less toxicity but higher relapse rates when compared with conventional agents.

Controlled, randomized trials in HIV-infected patients have shown that the addition of corticosteroids to conventional agents in patients with moderate to severe PCP (defined as an arterial oxygen tension of <70 mm Hg or an alveolar to arterial gradient of >35 mm Hg while on room air) is beneficial. There are no similar trials in cancer patients, and there are no specific criteria for initiating steroid therapy or for dosing. It has been our experience that adding corticosteroids or increasing the dose in cancer patients already receiving chronic steroid therapy may be beneficial, particularly in patients with moderate to severe PCP.

Effective prophylaxis against PCP can be achieved by administering low, intermittent doses of TMP-SMX. One double-strength tablet of TMP-SMX twice a day for three consecutive days a week has a high degree of efficacy in preventing PCP.31 PCP has a mortality rate of up to 50 percent in cancer patients, reinforcing the need for prophylaxis.28 Cancer patients who require prophylaxis include those with defects in cell-mediated immunity and those undergoing Allo-BMT. Consideration of prophylaxis for cancer patients receiving high-dose corticosteroids should also be given.28 Although TMP-SMX is the drug of choice for PCP prophylaxis, the use of aerosolized pentamidine is an effective alternative in cancer patients who are intolerant to TMP-SMX.32 Other alternatives include intravenous pentamidine every two to four weeks or oral daily dapsone. Because efficacy of these alternative agents has been shown in HIV patients, it is assumed they are effective in other immunocompromised patients as well.

Occasionally, other protozoans can cause serious pulmonary disease in cancer patients. Strongyloides stercoralis should be anticipated in patients who have been exposed to Strongyloides infection any time in their lifetime and then develop illness or receive treatment that affects helper T-cell function.33 The diagnosis should be considered in any immunosuppressed patient who comes from an endemic area and develops vague abdominal symptoms of pain, diffuse tenderness, or distention and then develops pneumonia.

Although blood cultures may be positive for one or more bacteria from the gut flora, the diagnosis is made by demonstrating the filariform larvae in sputum or other respiratory tract specimens, especially bronchoalveolar lavage fluid. The larvae may also be found in feces or in cerebrospinal fluid if meningitis occurs. Standard therapy for Strongyloides asis is thiabendazole. The duration of

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**Pulmonary edema is a frequent complication of cancer treatment and may be of cardiogenic or noncardiogenic origin.**

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therapy is usually between 10 and 14 days. However, the optimal treatment time is unknown. If latent or active infection with *Strongyloides* is proven or highly suspected, treatment with thiabendazole should be given before immunosuppression and active disease occurs.

Toxoplasmosis is an uncommon cause of pulmonary infiltrates in immunocompromised patients. The usual setting of toxoplasmosis is cerebrospinal fluid involvement with meningitis. When pulmonary disease occurs, it is usually in patients with HIV infection or organ transplantation.

**Noninfectious Pulmonary Complications in Cancer Patients**

Patients under treatment for cancer are at risk for a wide variety of pulmonary complications. The pulmonologist is frequently called on to evaluate dyspnea in this setting. The differential diagnosis is broad. Besides pulmonary infection the most frequent causes considered are anemia, exacerbation of obstructive airways disease, cancer progression in the lungs, atelectasis from endobronchial tumor or extrinsic compression, pulmonary edema of cardiac or noncardiac origin, pleural effusion, pulmonary emboli, and drug- and radiation-induced pulmonary toxicity. Leukostasis and leukoagglutinin reactions are less common.

Preexisting lung diseases, such as idiopathic pulmonary fibrosis, must also be distinguished from new acute problems. Review of prior radiographs in this setting is mandatory for a full understanding of the patient’s problem. Unrelated diseases, such as hypersensitivity pneumonitis, can occur in cancer patients as well as any other individual. Patients who have anemia due to their cancer or the effects of chemotherapy will frequently complain of exertional dyspnea as the initial symptom. In some cases, erythropoietin therapy can be highly effective in ameliorating these symptoms.

**NEOPLASTIC DISORDERS**

Diagnostic evaluations for noninfectious pulmonary problems often arise as a result of the identification of radiographic abnormalities. Cancer presents in the chest in several characteristic patterns. Metastatic disease most often presents as single or multiple nodules, in a lymphangitic pattern, and/or as a pleural effusion.

Certain types of cancer can form metastatic endobronchial lesions and present with lobar atelectasis or volume loss on the chest radiograph. Breast and colon cancer most frequently form these endobronchial lesions. Renal cell cancer and melanoma can also metastasize endobronchially. Tumor emboli, though rare, can cause dyspnea and hypoxemia with or without infiltrates.

Lymphomas usually present in the chest as mediastinal lymphadenopathy, but parenchymal nodules, infiltrates often with air bronchograms, and/or pleural effusions may also be present. Sarcoid-like granulomas can be associated with lymphoma or other malignancies, such as germ cell tumors, and radiographically can mimic these malignancies.

Chemotherapy for germ cell tumors metastatic to the lungs often leaves residual radiographic abnormalities. Chemotherapy can also cause toxic reactions in the lung, causing new pulmonary symptoms and diffuse infiltrates. Surgical biopsies are frequently necessary to distinguish between fibrosis, toxic lung injury, and residual viable cancer.

Primary lung cancer can present as a mass with or without hilar or mediastinal lymphadenopathy. Obstruction of airways from an endobronchial mass may lead to cough, localized wheezing, or an infiltrate/atelectasis. The bronchoalveolar form usually presents as a parenchymal infiltrate, which mimics a pneumonic process, often showing air bronchograms.

It is notable that for certain cancers (such as breast and colon cancer, germ cell tumors, and sarcomas), surgical resection of single or a limited number of
Pulmonary nodules due to metastatic disease is associated with a survival advantage in highly selected patients who have no other site of disease. Patients with head and neck cancer who present with a solitary nodule have a high likelihood of having a second primary malignancy, such as lung cancer.

PULMONARY EDEMA

Pulmonary edema is a frequent complication of cancer treatment and may be of cardiogenic or noncardiogenic origin. Cardiomyopathy from anthracycline drugs, cyclophosphamide, or high-dose external-beam radiation therapy may not become clinically apparent until volume expansion for subsequent chemotherapy is undertaken or until anemia develops. Heart failure may also present in a more insidious fashion with gradual onset of exertional dyspnea. Acute noncardiogenic pulmonary edema can be associated with specific treatments, such as interleukin-2 therapy, or an acute reaction to mitomycin/vinblastine as outlined below.

Patients undergoing treatment for cancer are susceptible to a wide variety of infections that can lead to adult respiratory distress syndrome. Patients treated with all-trans retinoic acid are at risk for a capillary leak syndrome with interstitial infiltrates that may lead to respiratory failure. Patients, particularly those with acute promyelocytic leukemia who develop this complication from all-trans retinoic acid therapy, may respond favorably to corticosteroids.

Patients with a prior history of external-beam radiation therapy to the chest have an increased incidence of premature coronary artery disease. They may also be at increased risk for the development of valvular disease.

PLEURAL EFFUSION

Symptomatic pleural effusions due to metastatic cancer are usually unilateral, but can be bilateral. They are seen most frequently with lung and breast cancers and lymphoma, but can also be seen with a variety of other cancers, including ovarian cancer and melanoma. A pleural effusion associated with lung cancer does not in itself make the patient unresectable; malignant pleural disease must be documented, although most patients will ultimately prove to be unresectable for cure. The pH of a malignant pleural effusion due to lung cancer has prognostic significance as well. Patients with a malignant pleural effusion of a low pH (<7.30) had a mean survival of two months.

Closed chest tube drainage and sclerosis are often necessary for effective control of recurrent symptomatic malignant effusions.

Patients with a prior history of external-beam radiation therapy to the chest have an increased incidence of premature pleural effusion.
duced changes in the vasculature, and immobility due to complicating illnesses and treatment side effects. Diagnosis and management of pulmonary emboli and deep venous thrombosis are essentially the same as in noncancer patients, except that chronic anticoagulation may have to be continued for a much longer period of time in some patients whose thrombotic diathesis will be ongoing. Cancer patients with documented thromboembolic disease are often warfarin resistant and may require prophylaxis with subcutaneous heparin and/or inferior vena cava filters.

PULMONARY DRUG TOXICITY

Pulmonary drug toxicity from chemo-therapeutic agents can be difficult to diagnose, because there are no absolutely pathognomonic findings. Diagnosis requires integrating the history, physical findings, and radiographic and physiologic abnormalities with the results of any diagnostic studies such as bronchoscopy, which is often needed to rule out opportunistic infection. High-resolution computed tomographic scans are sometimes helpful in demonstrating subtle interstitial disease or small nodules, particularly when signs and symptoms are equivocal. Gallium scans may show diffusely increased uptake in the lungs, even when chest radiographs are normal. Gallium scanning is sensitive for active alveolitis, but is not specific. Although fiberoptic bronchoscopy is helpful in many cases, open lung biopsy is sometimes necessary to make specific diagnoses. Pulmonary function testing, particularly diffusing capacity and rest and exercise arterial blood gases or oximetry, can be useful for screening and distinguishing toxicity from exacerbation of underlying obstructive airways disease.

Bleomycin is the primary example of a chemotherapeutic agent that can cause pulmonary toxicity. The toxicity is dose-related after a total cumulative dose of 400 to 450 units of bleomycin. At lower doses (even <50 units) toxicity sporadically appears at a rate of about four percent. Patients often present with fever, dry cough, dyspnea, bibasilar rales, and reticular-nodular infiltrates, which can progress to diffuse interstitial infiltrates. However, not every patient with toxicity exhibits these findings. Pleural effusions are rare and should be evaluated for other etiologies if present. Bleomycin can also uniquely cause an acute chest pain syndrome.

Bleomycin toxicity has been extensively studied in humans and animal models, and the mechanisms are fairly well understood. Bleomycin causes an injury to pulmonary capillary endothelial cells and type I alveolar epithelial cells that is associated with release of oxidant free radicals and an inflammatory response that causes further tissue damage and triggers fibrosis. Bleomycin also directly upregulates collagen gene transcription and the transcription of genes for pro-fibrotic cytokines such as transforming growth factor-β. Consistent with this pathophysiology, radiation therapy and oxygen toxicity are both synergistic with the bleomycin effects on the lung. It is not known whether there is any safe dose or duration of supplemental oxygen therapy after bleomycin treatment. Thus, every effort must be made to minimize whatever supplemental oxygen is needed to ameliorate hypoxemia of any cause in patients previously treated with bleomycin. Patients with bleomycin toxicity should not receive any further doses of the drug. Symptomatic patients will often respond to systemic corticosteroids in an initial dosage of 1 mg/kg/day. Once a response is established, the dose must be tapered very slowly.

Mitomycin pulmonary toxicity also can occur, particularly in combination regimens with vinca alkaloids and cisplatin when used as neoadjuvant therapy for stage IIIA nonsmall cell lung cancer. Patients present with acute dyspnea, particularly during or shortly after infusion.
of the vinca alkaloid, and this may be accompanied by wheezing and/or noncardiogenic pulmonary edema. Other patients experience a subacute onset of increasing exertional dyspnea. The dyspnea is often accompanied by diffuse interstitial infiltrates, hypoxemia, oxygen desaturation with exercise, and a drop in the diffusing capacity.

The mechanism of injury is not as well understood as with bleomycin, although diffuse injury to the pulmonary vasculature appears to be the primary early event. There are less data available regarding potential synergy with oxygen and radiation pneumonitis. We believe it prudent to try to minimize supplemental oxygen in these patients as well, due to the clinical observation that some of these patients will have a significant worsening of pulmonary function after undergoing general anesthesia for thoracotomy and being exposed to high oxygen tensions.

Most symptomatic patients with mitomycin toxicity will experience some improvement after treatment with corticosteroids. Our practice is to continue steroids for a period of several months, including through surgical procedures. Some patients have successfully recovered from relatively severe physiologic abnormalities. We are currently studying a number of approaches for early detection and treatment of mitomycin toxicity, including monitoring connective tissue antigens in the serum. Prophylaxis for pulmonary toxicity with pharmacologic agents is another potential approach under study.

Pulmonary toxicity from cyclophosphamide alone is rare, but it may contribute to the damage that occurs in combination with other agents.

Carmustine, particularly in the high doses used in the treatment of glioblastomas, causes bland chronic pulmonary fibrosis without much inflammation that may manifest itself clinically up to 20 years after treatment. The fibrosis has a unique pattern with upper lung zone predominance. Most studies show increased risk of pulmonary fibrosis after the cumulative total dose reaches 1,400 mg/m². Once pulmonary fibrosis develops, response to corticosteroids is poor. A more recent and widespread use of carmustine is in the adjuvant treatment of breast cancer or relapsed lymphoma with high-dose chemotherapy and autologous bone marrow or stem cell transplants. Lung injury in this setting is relatively common and is usually responsive to steroids, although patients with prior mediastinal irradiation for lymphoma may be more sensitive to lower doses (600 mg/m²) and have a worse outcome.

Methotrexate toxicity may present as acute pleuritis with fevers or as noncardiogenic pulmonary edema. The pulmonary edema can occur in patients only receiving intrathecal drug administration. The chest x-ray usually shows bilateral interstitial infiltrates, but sometimes appears nodular or shows an alveolar pattern. Pleural effusion may be present. The mechanism probably involves a hypersensitivity response in the lung. Clinical response to steroids is usually good. There is less experience with edatrexate, but the toxicity is similar.

Taxol and taxotere can produce acute bronchospasm, which is an allergic response to the vehicle. The symptoms

Most symptomatic patients with mitomycin toxicity will experience some improvement after treatment with corticosteroids.
usually respond to aerosolized bronchodilators. Prophylaxis with steroids and cimetidine is usually effective. These drugs also produce a generalized edema-forming state, which can be associated with pleural effusion.

It is worth stating that cancer patients being treated with high doses of steroids for pulmonary toxicity are at risk for PCP, and we believe they should receive Pneumocystis prophylaxis, preferably with TMP-SMX three times a week if the patient does not have a history of hypersensitivity.

**RADIATION PNEUMONITIS**

External-beam radiation used in the treatment of lung cancer, lymphoma, and breast cancer can cause pneumonitis if a large enough dose is used. Most doses of lung irradiation are calculated to give an incidence of less than five percent for symptomatic radiation pneumonitis. Typically, radiation pneumonitis presents one to four months after the completion of treatment. The usual symptoms are nonproductive cough, low-grade fever, and gradual onset of exertional dyspnea. Chest radiographs typically show patchy infiltrates, which may have a nonanatomic border corresponding to the edge of the radiation port. However, infiltrates outside the radiation port or in the contralateral lung can be seen. Pleural effusions if present are usually small and are coincident with the acute pneumonitis. Some patients will progress to acute respiratory failure, which may be fatal, or chronic fibrosis, which appears nine to 12 months postirradiation. The mechanism is thought to be initiated by damage to the pulmonary capillary bed, followed by an inflammatory repair process that sometimes leads to fibrosis. Oxygen and chemotherapeutic agents may be synergistic in this process. Our practice is to treat symptomatic patients with systemic corticosteroids and to taper them slowly over months, similar to drug toxicity.

**BONE MARROW TRANSPLANTATION**

Bone marrow transplantation has important, specific, noninfectious pulmonary complications, including diffuse pulmonary hemorrhage, the idiopathic pneumonia syndrome, and obstructive airways disease. Acute pulmonary edema sometimes occurs in the immediate post-transplant period, particularly in patients who received prior treatment with anthracyclines, high-dose cyclophosphamide, and/or chest irradiation. Adult respiratory distress syndrome can accompany infection in this setting as well. Adult respiratory distress syndrome may also be due, in part, to the effects of the pretransplant conditioning regimen on the pulmonary vasculature and to the systemic release of cytokines due to acute graft-versus-host disease. Noncardiogenic pulmonary edema may also be associated with hepatic veno-occlusive disease, another important complication of bone marrow transplantation.

**DIFFUSE PULMONARY HEMORRHAGE**

Patients with acute promyelocytic leukemia are at risk for disseminated intravascular coagulation, which may lead to pulmonary hemorrhage. Pulmonary hemorrhage is most often seen in autologous bone marrow transplant patients, particularly those with previous high-dose radiation therapy for local bulky disease in the chest. Chest exam usually reveals coarse crackles. Chest x-ray shows patchy or diffuse alveolar infiltrates. Bronchoalveolar lavage fluid in this disorder has a classic diagnostic appearance of increasing bloodiness in sequential aliquots. Macrophages can be shown to contain hemosiderin if stained appropriately. Because hemoptysis is unusual with diffuse pulmonary hemorrhage, bronchoscopy is usually necessary to make the diagnosis and to help rule out infection as the underlying cause of the hemorrhage. The etiology is unknown, but prior subclinical inflammation induced by previous
treatment and conditioning for bone marrow transplantation may play a role. Once patients develop respiratory failure on this basis, recovery is unlikely, although responses to high-dose steroids have been anecdotally reported.52

IDIOPATHIC PNEUMONIA SYNDROME

The post-bone marrow transplant idiopathic pneumonia syndrome, which usually presents with cough and diffuse pulmonary infiltrates, must be distinguished from opportunistic infections, particularly CMV, in the allogeneic transplant patient. A recent NIH consensus conference53 defined this syndrome as evidence of widespread alveolar injury with signs and symptoms of pneumonia, multilobar infiltrates, and evidence of abnormal pulmonary physiology. In addition, active pulmonary infection must be ruled out by performing bronchoalveolar lavage and/or open lung biopsy. The etiology is also unknown and the subject of active current research. One possibility is that prior lung damage from conditioning regimens for bone marrow transplant may be magnified by the effects of chronic graft-versus-host disease54 or other immunopathologic phenomena. A subset of patients with this diagnosis will respond to systemic steroid treatment, but overall the prognosis is poor.52

OBLITERATIVE BRONCHIOLITIS AND OBSTRUCTIVE AIRWAYS DISEASE

For reasons that are unclear, obstructive airways disease frequently develops after allogeneic bone marrow transplantation.55 Most of these patients have mild pulmonary function abnormalities, including modest reductions in both spirometric and diffusing capacity measurements, which tend to subsequently remain stable. A minority of patients develop more severe airways obstruction that may be accompanied by cough, wheezing, and/or dyspnea. Pathologically, many of these patients demonstrate bronchiolitis obliterans. This process may be related to chronic graft-versus-host disease in the lung. Bronchiolitis obliterans may progress rapidly and be refractory to therapy, resulting in hypercapnea and death. However, fever and the presence of pulmonary infiltrates should suggest infectious causes of bronchiolitis, which may be treatable if diagnosed early. Some patients may have bronchiolitis obliterans with organizing pneumonia,56 also known as cryptogenic organizing pneumonia, a completely different steroid-responsive clinicopathologic entity than bronchiolitis obliterans (despite the similar names).

BRONCHIOLITIS OBLITERANS WITH ORGANIZING PNEUMONIA

Idiopathic bronchiolitis obliterans with organizing pneumonia may also occur in cancer patients who have not received bone marrow transplants. Because bronchiolitis obliterans with organizing pneumonia carries a good prognosis if treated promptly with steroids, a high index of suspicion should be maintained in patients with patchy alveolar infiltrates and no infectious diagnosis. The classic description of bronchiolitis obliterans with organizing pneumonia is bilateral symmetric airspace disease, but asymmetric disease frequently occurs. CT scans often demonstrate a peripheral, pleural-based pattern with air bronchograms. Occasionally, only a solitary focal pneumonia is seen. Some patients may only have an interstitial reticular-nodular pattern without radiographic evidence of airspace disease. Open lung biopsy is usually necessary to make the diagnosis, although at times bronchoscopy with transbronchial biopsy is diagnostic.

Additional Treatment Modalities

In selected patients who develop end-stage lung disease as a complication of
cancer treatment, lung transplant may be an option. Primary care physicians should also be aware that the use of systemic or inhaled opioid medications can be very effective in relieving the dyspnea experienced by patients with end-stage cancer in the lungs.

Summary
Pulmonary complications of cancer and cancer therapy represent a broad spectrum of disease. Early diagnosis and treatment are essential to achieve an optimal outcome.

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