

## Chapter 12

# Pneumonia in the Cancer Patient

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**Abstract** Lower respiratory tract infections result in unacceptably high mortality among cancer patients. Pneumonias cause death in this population both directly through impairment of gas exchange and progression to system infection/sepsis, as well as indirectly by precluding delivery of necessary, antineoplastic therapies. Malignancy and treatment-related impairments of host immune responses and the emergence of multidrug-resistant organisms associated with recurrent exposures to hospital environments may not only enhance the risks of mortality, but also exacerbate the difficulty of diagnosing pneumonia in the cancer setting. As a consequence of disordered inflammatory responses, the typical clinical observations of pneumonia, including purulent respiratory secretions and early radiographic findings, may be inapparent or absent. A comprehensive review of etiology, clinical presentation, diagnosis, and management of pulmonary infections is presented in this chapter.

**Keywords** Pneumonia • MRSA • Fungal disease • CMV • Pneumococcus • Drug resistance • Immune defects

Lower respiratory tract infections result in unacceptably high mortality among cancer patients. Pneumonias cause death in this population both directly through impairment of gas exchange and progression to system infection/sepsis, as well as indirectly by precluding delivery of necessary, antineoplastic therapies [1–3]. Malignancy and treatment-related impairments of host immune responses and the emergence of multidrug-resistant (MDR) organisms associated with recurrent exposures to hospital environments may not only enhance the risks of mortality, but also exacerbate the difficulty of diagnosing pneumonia in the cancer setting. As a consequence

of disordered inflammatory responses, the typical clinical observations of pneumonia, including purulent respiratory secretions and early radiographic findings, may be inapparent or absent. Adding to this diagnostic challenge is the frequent colonization of the upper airway with microorganisms that do not contribute to disease, rendering the diagnosis of pneumonia by conventional culture techniques difficult. Conversely, sterile respiratory tract cultures do not exclude an infectious etiology, particularly in the setting of recent exposure to broad-spectrum antibiotics.

Susceptibility to pneumonia in the cancer patient is not only conditioned by the type and degree of immune suppression, but also by its duration. Multiple immune defects may coexist among patients with cancer, which adds to the conundrum and spectrum of opportunistic infections. Immune defects, including compromised acellular and cellular (alveolar macrophages, mast cells, neutrophils) innate and/or altered adaptive immune function, leading to either inadequate immunoglobulin or defective T-cell mediated defenses may promote the development of specific types of pneumonia. In addition, treatment-induced disruption of the respiratory mucosa and ciliary dysfunction may result in inadequate clearance of airway secretions, enhancing the likelihood of pneumonia. Hence, the individual patient's predilection for pneumonia in the cancer setting is best understood by examining the effect of malignancy and its treatment on specific host immune defenses (Table 12.1). Because the immune defect is often mixed, careful attention to clinical and radiographic features and recognition of nosocomial versus community-acquired sources of the infection are critical to making the diagnosis and guiding empiric antimicrobial therapy [4]. Delays in appropriate antimicrobial therapy increase the risk of secondary complications and infection-associated deaths, especially in severely immunosuppressed individuals. Therefore, it is common practice to initiate empiric and/or preemptive antimicrobial therapy in patients in whom the suspicion of infection is high. An approach to the diagnosis and treatment of cancer-related pneumonias based on the specific defects in the major arms of host immunity and broad categories of infection source is emphasized in

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**Table 12.1** Infections causing pneumonia in cancer patients based on the underlying immune defect

Immune defect	Bacteria	Fungi	Parasites	Viruses
Granulocytopenia	<i>Staphylococcus aureus</i>	<i>Aspergillus fumigatus</i> ; non- <i>fumigatus</i> <i>Aspergillus</i>		Herpes simplex virus I and II
	<i>Streptococcus pneumoniae</i>	Non- <i>Aspergillus</i> hyalohyphomycosis such as <i>Pseudallescheria boydii</i> , <i>Fusarium solani</i>		Varicella-zoster virus
	<i>Streptococcus</i> species			
	<i>Pseudomonas aeruginosa</i>	<i>Mucorales</i> (zygomycoses)		
	Enterobacteriaceae <i>Escherichia coli</i> <i>Klebsiella</i> species <i>Stenotrophomonas maltophilia</i>	Dematiaceous (Black) fungi such as <i>Alternaria</i> , <i>Bipolaris</i> , <i>Curvularia</i> , <i>Scedosporium apiospermum</i> , <i>S. prolificans</i>		
	<i>Acinetobacter</i> species			
Cell-mediated immune system Dysfunction	<i>Nocardia asteroides</i> complex <i>Salmonella</i> species <i>Rhodococcus equi</i> <i>R. bronchialis</i> <i>Listeria monocytogenes</i> <i>Mycobacterium tuberculosis</i> Nontuberculous mycobacteria	<i>Aspergillus</i> and non- <i>Aspergillus</i> filamentous molds <i>Pneumocystis jiroveci</i> ( <i>P. carini</i> ) <i>Cryptococcus neoformans</i> Endemic mycoses due to <i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i> , <i>Blastomyces dermatitidis</i>	<i>Toxoplasma gondii</i> <i>Microsporidium</i> spp. <i>Strongyloides stercoralis</i>	Cytomegalovirus Respiratory viruses Influenza A and Influenza B Parainfluenza type-3 Respiratory syncytial virus Adenovirus Varicella-zoster virus HHV-6 SARS-associated coronavirus Paramyxovirus Hantavirus VZV Echovirus
Humoral immune Dysfunction	<i>S. pneumoniae</i> <i>Haemophilus influenzae</i>			Enterovirus
Splenectomy	<i>Neisseria meningitidis</i> <i>Capnocytophaga canimorsus</i> <i>Campylobacter</i>			
Mixed defects	<i>S. pneumoniae</i> <i>S. aureus</i> <i>H. influenzae</i> <i>K. pneumoniae</i> <i>P. aeruginosa</i> <i>Acinetobacter</i> spp.  <i>Enterobacter</i> spp. <i>S. maltophilia</i> <i>N. asteroides</i> complex <i>L. monocytogenes</i> <i>Legionella</i> spp.	<i>P. jiroveci</i> ( <i>P. carini</i> ) <i>Aspergillus</i> spp. <i>Candida</i> spp. <i>C. neoformans</i> <i>Mucorales</i> (zygomycoses) Endemic mycoses (severe systemic dissemination)	<i>T. gondii</i> <i>S. stercoralis</i>	Respiratory viruses Influenza Parainfluenza Respiratory syncytial virus Adenovirus VZV

Note. Patients with mixed immune defects includes, recipients of allogeneic hematopoietic stem cell transplant; acute or chronic GVHD; myelodysplastic syndrome; adult T-cell leukemia lymphoma; antineoplastic agents like cyclophosphamide and fludarabine  
VZV is rarely associated with systemic dissemination in patients with humoral immune defects, or even those with mixed immune dysfunctions

*S. stercoralis* may lead to serious, life-threatening hyperinfection syndrome in patients with marked cellular immune defects

HHV-6 Human herpesvirus-6

the early part of this section, followed by a more detailed discussion of selected pathogens that may cause fulminant infection in the cancer patient.

## Specific Immune Defects

Disruption of local airway defense mechanisms often increases vulnerability to pneumonia among cancer patients. Breach of the respiratory epithelial barrier function and altered mucociliary clearance of secretions may occur as a result of cancer therapy, both through cell-specific injury and through generalized mucositis. Medical devices, such as nasogastric and endotracheal tubes, hinder coordinated glottic activities and mucociliary function and act as conduits for chronic colonization of pathogenic organisms [5]. Numerous defects of local innate defenses are also described following chemotherapy, including derangements of chemotaxis, phagocytosis, and killing by alveolar macrophages and resident mast cells. Respiratory epithelial cells tend to maintain their capacity for elaboration of inflammatory mediators following exposure to pathogens, despite cytotoxic chemotherapy [6, 7]. Yet, they are the primary interface with lower respiratory tract pathogens and are often susceptible to direct injury by MDR pathogens, due to the unique exposures of the cancer patients, as described further below. Further, concurrent alterations in systemic defense mechanisms, such as impairment of the circulating leukocytes of the innate immune system, are exceedingly common.

Neutrophils are exquisitely sensitive to the cytotoxic effects of chemotherapy, which may induce an agranulocytosis by direct myelotoxicity, as well as functional neutropenia by interfering with the phagocytic and chemotactic activity of these cells [8]. In addition, neutrophil dysfunction resulting from radiation therapy, corticosteroid administration and common cancer-related disorders, such as hypovolemia, prolonged hypoxemia, acidosis, and poorly controlled hyperglycemia, is a frequent problem. Severe neutropenia, defined as an absolute neutrophil count of  $\leq 500$  cells/ $\mu\text{L}$ , is associated with refractory lung infections caused by bacterial and fungal organisms [9]. In addition, the rapidity of onset of neutropenia and delay in neutrophil recovery play a role in the infection severity. More than 10% of patients with febrile neutropenia present with pulmonary infiltrates and infection remains the most frequent cause of radiographic abnormalities in these patients. The absence of consolidated infiltrates on chest radiographs does not exclude an evolving occult pneumonia, particularly in the setting of profound neutropenia ( $<100$  cells/ $\mu\text{L}$ ).

Severe pneumonias, including *de novo* infections and exacerbation of chronic lung infections, also arise in the

setting of neutropenia. Gram-negative bacilli (GNB) including Enterobacteriaceae (*Klebsiella*, *Escherichia coli*, *Enterobacter*, *Citrobacter*, *Serratia*) and *Proteus* spp., [10] are the predominant source of pneumonias associated with neutropenic fever. MDR Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta-lactamase-producing Enterobacteriaceae are also frequently cultured in the setting of neutropenic pneumonia. The incidence of pulmonary infections caused by Gram-positive bacteria (*S. aureus*, *Streptococcus* spp., including *Streptococcus pneumoniae*) has decreased over the past three decades, while Gram-negative pneumonias, particularly those caused by *Pseudomonas* spp., have become an increasing source of life-threatening, necrotizing lung infection (Fig. 12.1) [11]. Other nonfermentative Gram-negative bacteria (NF-GNB) such as *Stenotrophomonas maltophilia* [12–15], *Achromobacter*, and *Alcaligenes* species have also increased in the recent years and often lead to difficult-to-treat infections [14, 16]. As is the case in almost all other populations, aspiration of infected material remains the predominant mechanism of entry for lower respiratory tract infection among cancer patients. However, hematogenous dissemination represents a uniquely common source of pneumonia among cancer patients, and bacteremia in febrile neutropenic patients may not present with an obvious primary site of origin. Initial antimicrobial therapy for febrile neutropenia in patients with pulmonary infiltrates should be broad in spectrum and provide antimicrobial activity against drug-resistant strains of *S. aureus* and *Pseudomonas aeruginosa*. Early deescalation therapy may be attempted in patients who have demonstrated prompt clinical response and in whom granulocyte recovery has occurred or is expected to occur in the near future, especially if a pathogen has been identified. Deescalation should be undertaken with caution in high-risk patients with poor clinical response to antimicrobial therapy;



**Fig. 12.1** *Pseudomonas* lung abscess in a patient with acute myelogenous leukemia awaiting bone marrow transplantation

persistent, severe, and/or long-standing granulocytopenia; or patients continuing on systemic immunosuppressive therapy.

In addition to neutropenia, cytotoxic antineoplastic therapies and hematologic malignancies may cause severe depression of humoral and cell-mediated adaptive immunity, resulting in inadequate immunoglobulin production and/or a variety of defective T and B cell-mediated defects. For example, immunoglobulin dyscrasias associated with hypogammaglobulinemia and defects in opsonization owing to asplenia are frequent among patients with certain types of lymphoreticular malignancies, such as multiple myeloma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia. Hypocomplementemia associated with asplenia may lead to unchecked proliferation of encapsulated organisms that require opsonization with complement ( $C_3$ ,  $C_5$ ) for elimination. Furthermore, defects in antibody-dependent lymphocyte cytolytic activity may allow fulminant parasitic infections. Reduced T cell numbers and activity is a frequent finding among patients with Hodgkin's disease, hairy cell leukemia, adult T-cell leukemia, lymphocytic leukemia, and graft-versus-host disease (GVHD). In addition, viral illnesses, antineoplastic agents, and other immunosuppressive drugs (e.g., fludarabine, IL-2 inhibitors, antithymocyte globulins, calcineurin inhibitors, tacrolimus, or glucocorticosteroids) may depress cellular immunity by inducing profound lymphopenia and/or interrupting activated T-cell inflammatory signal transduction pathways. Patients with cellular immune dysfunction are at increased risk of infection due to intracellular organisms such as *Listeria monocytogenes*, *Salmonella* spp., *Legionella* spp., *Pneumocystis jirovecii*, and *Toxoplasma gondii*, invasive pulmonary mycoses, and opportunistic viruses due to human cytomegalovirus, human herpesvirus-6 (HHV-6), and varicella-zoster virus. Thus, virtually every component of normal host immunity may be affected in an untoward manner by cancer or its treatment. The severe and oftentimes protracted immune suppression that follows encourages the development of unusual and intractable infections. Specific pathogens causing pneumonia that are commonly associated with depression of particular immune defects are listed in Table 12.1.

**Community-Acquired Pneumonia (CAP).** CAP, as defined by the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS), refers to the radiographic and clinical development of pneumonia in patients who have not been hospitalized or resided in a nursing home for 14 or more days prior to the onset of symptoms and who do not meet criteria for HCAP [4]. The distinction of CAP from nosocomial pneumonia remains important, as it allows prediction of likely pathogens and permits prognostic estimations based on epidemiologic descriptions of the underlying cause. Consequently, this distinction provides a framework for decisions regarding the diagnostic evaluation and empiric

antimicrobial therapy. Cancer patients are frequently exposed to the healthcare setting, both as inpatients and outpatients. Thus, pneumonia in the cancer patient is most often defined as hospital-acquired pneumonia (HAP) or health-care-associated pneumonia (HCAP), rather than CAP.

The etiologic spectrum of bacterial pathogens causing CAP among those cancer patients with mild-to-moderate immunosuppression is similar to that of patients with no cancer history. However, a clinically insignificant microbial inoculum in the general population may cause severe infection among patients with underlying malignancy. *S. pneumoniae* remains the most commonly identified pathogen and the most frequent cause of lethal CAP [4]. Superinfection with MDR organisms is an emerging problem that complicates the management of CAP. *S. aureus*, nontypeable *Haemophilus influenzae*, *Pseudomonas* spp., and other GNB may also cause life-threatening CAP. Recently, other NF-GNB such as *Stenotrophomonas*, *Burkholderia*, *Chryseobacterium*, *Achromobacter*, and *Alcaligenes* species have been increasingly recognized as etiologic agents in both CAP and nosocomial infections [16, 17]. *S. pyogenes*, *Neisseria meningitidis*, and *Moraxella catarrhalis* also cause CAP less frequently. The incidence of CAP associated with the atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp. varies widely with patient age and geographic location. Viral pneumonias, most commonly influenza, parainfluenza, and adenoviral infections, are sources of CAP, which may cause severe pneumonias in the cancer setting.

The diagnosis of CAP is based on recovery of the likely pathogen from an otherwise sterile source (blood, urine, pleural fluid), isolation of a noncommensal organism in respiratory secretions, or positive results of selected serologic tests. Although the utility of Gram staining and culture of expectorated sputum in the diagnosis of pneumonia has been debated for years, carefully procured sputum specimens with cytologic confirmation of a lower respiratory source appear to be diagnostically useful, particularly if obtained before the initiation of antimicrobial therapy. Early and accurate diagnoses are critical to a successful outcome, although treatment should not be withheld while diagnostic interventions are undertaken. Antimicrobial selections are best based on knowledge of the infecting pathogen, if available, pneumonia severity, underlying immune status, and the presence of comorbid conditions [18, 19].

**Hospital-Acquired Pneumonia.** Lung infections that occur more than 48 h after hospital admission in patients without antecedent clinical symptoms or radiographic findings suggestive of pneumonia are referred to as HAP. HAP is a common complication in patients receiving treatment for cancer. Recently, the ATS and IDSA recognized HCAP as a distinct entity within the spectrum of HAP and ventilator-associated pneumonia (VAP) [20]. HCAP includes patients hospitalized in an acute care hospital for 2 or more days

within 90 days of the current infection, patients treated in a hospital or hemodialysis clinic within 30 days of the pneumonia diagnosis, nursing home, or long-term care facility residents, and recipients of intravenous antibiotics, chemotherapy, or wound care within 30 days of the current infection. HAP, HCAP, and VAP comprise the majority of pneumonias in the cancer setting. The spectrum of pathogens in HCAP closely resembles late-onset HAP and VAP, particularly among elderly patients [21]. Thus, guidelines for the management of HCAP generally overlap with HAP and VAP. In the nonimmunosuppressed solid-organ cancer patient, HAP is most often seen in the intensive care units (ICUs). In fact, admission to the ICU increases the risk of pneumonia in these patients by nearly 20-fold. As many as 80% of ICU-related HAPs occur among patients receiving ventilatory support and the effect of VAP in ICU length of stay, ventilator days, and hospital length of stay is well documented [22].

The etiologic spectrum of microbial pathogens causing HAP among low-risk solid-organ cancer patients with no recent antibiotic exposure is similar as that seen in the general population. *H. influenzae*, *S. pneumoniae*, *S. aureus*, and Enterobacteriaceae are frequently encountered. MRSA may cause refractory HAP, especially among patients with prior community-acquired MRSA colonization, antibiotic exposure, advanced age, and/or prolonged ventilatory support. Protracted mechanical ventilation and recent antibiotic administration are also associated with increased rates of HAP caused by *P. aeruginosa*, *Acinetobacter baumannii*-complex, *Enterobacter* spp., and emerging strains of MDR NF-GNB such as *S. maltophilia*, *Burkholderia cepacia* complex, and *Alcaligenes (Achromobacter)* species, which may be difficult to treat. Mortality rates associated with HAP due to MRSA or *P. aeruginosa* are disproportionately higher than those caused by other nosocomial bacterial pathogens [22].

Severe neutropenia remains an independent predictor of HAP due to NF-GNB. Invasive fungal disease in the severely neutropenic patients with absolute neutrophil counts of <150 cells/L are difficult to treat with antimicrobial therapy alone. Aerosolized antifungals and immune stimulants may also be considered in this context.

Polymicrobial isolates and MDR pathogens are more common among patients with HAP, particularly when it occurs as a late complication during hospitalization. Because of the frequency with which multiple organisms are identified on a single respiratory sample, recent evidence-based guidelines advocate the use of quantitative or semiquantitative lower respiratory tract cultures obtained either bronchoscopically or noninvasively as part of the initial evaluation of the patients with suspected HAP, VAP, or HCAP [20].

Empiric antibiotic selections for HAP that develop within 7 days of admission should target *S. pneumoniae*, *S. aureus* (including MRSA), *Streptococcus* spp., *H. influenzae*, and Enterobacteriaceae. Patients with late HAP (occurring >1 week

after hospitalization) should receive empiric antimicrobial therapy that includes coverage for MDR-GNB. The scope of alternative antimicrobial choices in patients with refractory or slow-to-respond hospital- and/or ventilator-acquired pneumonia (VAP) should be based on institution-dependent susceptibility profiles.

*Pneumonias Caused by Aspiration and Bronchial Obstruction.* Aspiration of orogastric contents and mechanical obstruction of the airways may create a favorable milieu for pneumonia caused by microaerophilic or anaerobic bacteria (e.g., *Peptostreptococcus* spp.). A variety of factors, such as abnormal swallow function, altered cough reflex, impaired mucociliary clearance, altered mental status, use of sedating medications, chemotherapy-induced mucositis, supine positioning, gastroparesis, mechanical ventilation, and nasogastric tube feeding all contribute to the increased predilection for aspiration in the cancer setting. Pneumonia associated with large-volume aspiration of gastric contents typically occurs as a late finding. The acidic gastric contents act as a poor medium for bacterial growth. Thus, the initial clinical syndrome following aspiration of gastric contents arises from the direct caustic effect of the acidic aspirate on the cells of the alveolar-capillary interface (i.e., chemical pneumonitis). Pneumonia due to superimposed bacterial infection, if it occurs, presents as a later finding. ARDS, respiratory failure, and death may rapidly follow. Aspiration of oral contents, by contrast, results from inhalation of nonsterile oropharyngeal material. The clinical presentation is often insidious and the diagnosis is commonly inferred based on a compatible patient risk profile coupled with radiographic evidence of pneumonia. Chest radiographs may show areas of geographic abnormalities that correlate with the patient's position at the time of aspiration. For example, aspiration that occurs while the patient is in the upright position typically localizes to the basilar segments of the lower lobes, whereas the superior segments of the lower lobes and posterior segments of the upper lobes are more frequently affected following aspiration that occurs in the supine position. The major pathogens underlying nosocomial versus community-acquired aspiration pneumonias differ, and in a substantial portion of patients, a microbiologic diagnosis may not be established due to the limited yield of conventional anaerobic cultures. If necessary, such cultures may be best obtained bronchoscopically using a protected specimen brush or other protected strategy.

The management of patients with significant lung injury associated with the aspiration of gastric contents includes aggressive supportive care. Upper airway suctioning, pulmonary toilet, and if necessary, positive pressure ventilation comprise the mainstays of therapy. There is no clearly established role for corticosteroids in this setting, though the practice of prescribing moderate- to high-dose prednisolone is not uncommon. Early and aggressive antimicrobial therapy

is recommended for patients with pneumonia secondary to aspiration of oropharyngeal contents. Antimicrobial selections should be tailored to the immune status of the patient and setting in which the aspiration occurred (community vs. nosocomial), but in general should be broad in spectrum and target Gram-negative organisms with or without anaerobic coverage. Anaerobic coverage should be considered for patients with periodontal disease, putrid sputum, or evidence of necrotizing pneumonia [23].

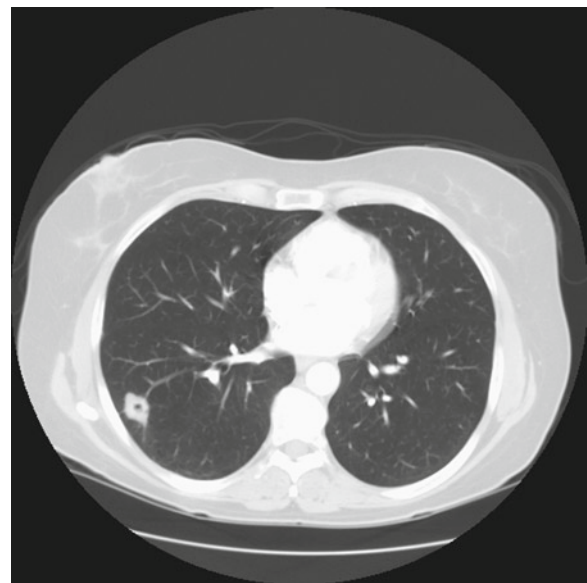
Solid tumors involving the lung may cause obstruction of the airways, atelectasis, and postobstructive pneumonia. Airway obstruction in this setting may be due to endobronchial tumor or an extraluminal mass that results in extrinsic compression of conducting airways. The associated pneumonias tend to be polymicrobial in nature (GNB, staphylococci, anaerobes) and may require relief of the obstruction to achieve adequate antimicrobial effects, even if appropriate antibiotics are selected. This is often most rapidly achieved through interventional bronchoscopic techniques such as tumor debulking by laser, electrocautery, or argon plasma coagulation with or without stent placement. Endobronchial brachytherapy or cryotherapy can be applied bronchoscopically as well, often with excellent results, but the time to effect is generally longer than with the formed strategies. Chemoradiation therapy can be similarly effective in relieving some obstructions, but the effect of these therapies is also delayed relative to bronchoscopic debulking.

*Other Sources of Pneumonia.* The lungs may also become infected via septic emboli arising from suppurative endovascular bacterial, and rarely, fungal infections. Infected intravascular septic deep venous thrombi are increasingly recognized as a potential source of infection in patients with cancer. The radiographic pattern in these patients is distinctive and includes multicentric, pleomorphic lung nodules, with asymmetric, relatively small, thick-walled cavities. In general, this appearance is distinct from the nonspecific infiltrates associated with hematogenous dissemination of distant site infections, as discussed previously.

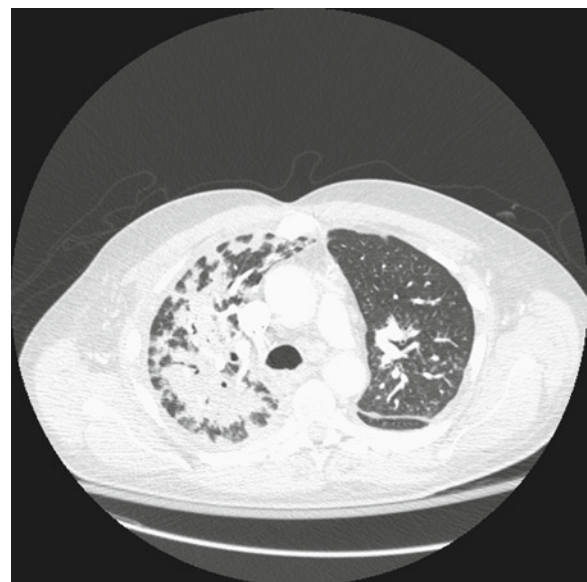
## Specific Pathogens

*Nocardiosis.* *Nocardia asteroides* complex, including *N. asteroides sensu stricto* and *N. farcinica*, accounts for nearly 90% of *Nocardia* infections, both in cancer patients and the general population. Risk factors for *Nocardia* pneumonia include profound deficiencies of cellular immunity, prolonged use of high-dose systemic corticosteroids, especially in the treatment of chronic lung diseases, [24] and the presence of GVHD. Although the latter two risk factors are often seen together (i.e., steroid treatment for GVHD), each appears to independently increase risk. Nodular pulmonary

infiltrates are common radiographic findings, although reticulonodular or diffuse infiltrates are occasionally described. Solitary nodules associated with irregular, thick-walled cavities that mimic invasive pulmonary aspergillosis, histoplasmosis, necrotizing cancer, or chronic bacterial lung abscess have also been reported (Figs. 12.2 and 12.3). Indolent *Nocardia* pneumonia is clinically indistinguishable from other actinomycetes infections and from pneumonias caused by pulmonary eumycetes infections. Severely immunosuppressed cancer patients with refractory leukemia or allogeneic hematopoietic stem cell transplant (HSCT) may



**Fig. 12.2** Histoplasmosis in a patient with lung cancer



**Fig. 12.3** *Nocardia abscessus* right lung infection in patient with lung cancer

present with pulmonary nocardiosis, a rapidly progressive, often multifocal form of *Nocardia*. Spontaneous pneumothorax and hemoptysis are widely reported presentations among immunocompromised patients (Fig. 12.3). Concomitant brain involvement is common, and preemptive evaluation is recommended to diagnose asymptomatic brain abscess in the setting of pulmonary disease. Trimethoprim-sulfamethoxazole (10–12 mg/kg daily) is effective against many *Nocardia* spp. Retrospective studies suggest improved outcomes when appropriate therapy is given for an extended period of time (6–12 months) [25]. Yet, despite antimicrobial therapy, pulmonary nocardiosis carries a high mortality in high-risk cancer patients [24]. Pulmonary actinomycosis typically presents in a very similar manner to nocardiosis, though sulfur granules are described more typically in samples from the former and infections classically cross tissue planes; pulmonary infection oftentimes involves the adjoining pleura and may erode through the chest wall. However, isolation of Actinomycetes from the respiratory tract should be evaluated critically, as in most patients their presence represents oropharyngeal contamination.

**Tuberculous.** *Mycobacterium tuberculosis* is a rare cause of pulmonary infection in the developed world, but is still occasionally found in severely immunosuppressed cancer patients and in foreign-born individuals receiving cancer care in nonendemic regions of the world [26]. Patients with Hodgkin's disease and cancers of the head and neck, lung, and breast are considered at highest risk. Most pulmonary tuberculous infections in oncology centers in the United States are caused by reactivation of a remotely acquired latent infection. Pulmonary tuberculous may present as an insidious pneumonia that is difficult to distinguish from actinomycetes and eumycetes infection. Patients with impaired T-cell response may develop rapidly progressive tuberculous that follows a virulent bacterial infection. Systemic corticosteroid therapy is an independent predictor both of tuberculous reactivation and of a suboptimal response to combination antimicrobial therapy. Hence, once the diagnosis of tuberculous is established, every effort should be made to discontinue steroid therapy [26]. Just as observed in HIV-infected patients who initiate therapy with highly active antiretroviral therapy and demonstrate clinical worsening of their tuberculous pneumonia (i.e., immune reconstitution syndrome), tuberculous-related lung disease in cancer or stem cell transplant patients may infrequently worsen as patients' immune functions recover. Nonetheless, minimizing immune suppression is essential to clearing the mycobacteria.

**Nontuberculous Mycobacteriosis (NTM).** Pulmonary NTM is classically caused by *M. avium-intracellulare* complex and other slow-growing mycobacteria. These opportunistic pathogens can lead to chronic, indolent lung infections. In the United States, the rapidly growing mycobacteria (particularly *M. abscessus* and less frequently *M. fortuitum*, *M. smegmatis*,

and *M. goodii*) have emerged as less frequent causes of NTM infections. The diagnosis of pulmonary NTM remains a challenge as identification of these mycobacteria in respiratory culture samples may result from colonization of the respiratory tract or environmental contamination. Causality is suggested by identification of NTM in sterile lower respiratory tract samples coupled with nonspecific clinical features, such as chronic nonproductive cough and exertional dyspnea. The cough may occasionally become productive, indicating underlying bronchiectasis. Fever, night sweats, weight loss, pleuritic chest pain, and pleural effusions are seldom seen. Radiographic features include upper lobe predominant nonspecific nodular lesions and small, thin-walled cavities. Chest CT findings demonstrating the characteristic "tree-in-bud" appearance may also be seen in patients with chronic infection. The so-called Lady Windermere syndrome, characterized by relapsing or refractory pulmonary NTM due to slow-growing mycobacteria, may be seen in patients with defects in endogenous interferon-gamma activity [27]. NTM pulmonary infections are usually insidious, although rapidly progressive disease has been seen in patients with profound defects in helper T-cells. Treatment should include at least two antimicrobial agents to which the *Mycobacterium* is susceptible, including rifampin, and should be given for 12–24 months. *M. kansasii* is antigenically similar to *M. tuberculosis* and causes lung disease that is clinically and radiographically indistinguishable from pulmonary tuberculous. Endemic areas for *M. kansasii* infections in the US include the urban Southeast and Midwestern States. Due to associated architectural derangements and possibly because of impaired phagocytosis by alveolar macrophages, pneumoconioses are well-established predisposing conditions for NTM infection. Prolonged therapy (12–24 months) with rifampin plus one or two other susceptible antimicrobials is recommended.

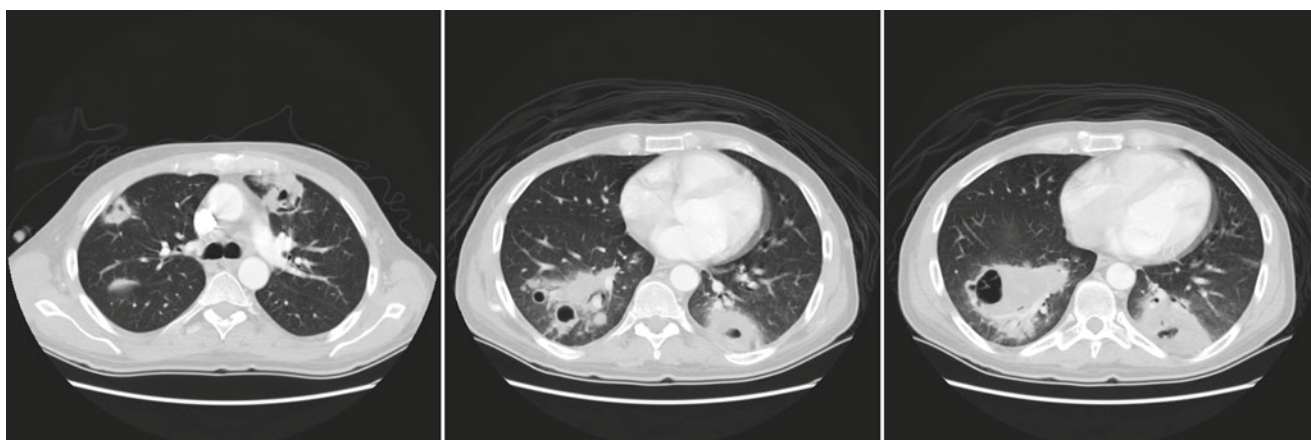
**Pneumocystis.** *P. jiroveci* infections are primarily seen in patients with marked CD4 lymphocytopenia [28]. In most cancer patients, *Pneumocystis* pneumonia presents as a slowly progressive infection accompanied by nonproductive cough, exertional dyspnea, and hypoxemia, although an acute, rapidly progressive form that rapidly progresses to respiratory failure has been reported. CT evidence of perihilar infiltrates may be mistaken for pneumonitis caused by common acquired viral infections (RSV, influenza, parainfluenza type 3) or CMV during the early phase of the infection. Bronchoalveolar lavage typically has a high diagnostic yield, though lung biopsy is occasionally needed, as cancer patients typically have lower fungal burden than do HIV-infected patients. High-dose trimethoprim-sulfamethoxazole given for 21 days is the treatment of choice. Adjuvant systemic corticosteroids should be administered to most patients with severe hypoxemia. Oral atovaquone and parenteral pentamidine may be given to patients who are intolerant to sulfa-containing regimens.

**Invasive Pulmonary Mycosis.** Invasive pulmonary aspergillosis is the most common fungal pneumonia in cancer patients. Risk factors for invasive pulmonary aspergillosis include prolonged (>1 week) and severe (<100 cells/ $\mu$ L) neutropenia, refractory leukemia, allogeneic HSCT, GVHD immunosuppressive therapy, and high-dose systemic corticosteroid therapy [29, 30]. *Aspergillus fumigatus* is most prominent in this group, although amphotericin B-resistant *A. terreus* has recently emerged as the second most frequent *Aspergillus* spp. in cancer patients [31]. The near-exponential rise in pulmonary invasive fungal infections due to non-*Aspergillus* molds such as *Fusarium*, *Pseudallescheria boydii*, and *Scedosporium* spp. and the dematiaceous (black) molds that are often not susceptible to conventional antifungal agents poses a serious challenge in the selection of effective empiric and preemptive therapy. Fever, cough, and dyspnea, when present, suggest lung infection. Hemoptysis is not uncommon chest imaging studies are frequently nonspecific, though CT scans may reveal a highly suggestive “halo sign” or “crescent sign.” In most cases of pulmonary mycosis, the only radiographic findings at the time of presentation are peripheral, pleural-based lung nodules, sometimes with thick-walled regular or irregular cavities (Fig. 12.4) [32]. Alveolar hemorrhage may occasionally herald an invasive pulmonary fungal infection.

A decline in the incidence of endemic mycoses, such as pulmonary histoplasmosis, blastomycosis, and coccidioidomycosis, as well as *Cryptococcus neoformans* infections, has been reported. This has largely been attributed to effective prophylaxis with fluconazole in immunosuppressed cancer patients. The incidence of Zygomycosis, on the other hand, has increased in recent years. This is likely related to the increased utilization of the recently available antifungal agent, voriconazole, with a concomitant decline in the use of

amphotericin B. *Zygomycetes* organisms typically show a high level of susceptibility to amphotericin B. With the decreased utilization of this agent, rates of fungal infections at our institution caused by zygomycosis, invasive aspergillosis, and *Fusarium* species during the years 2002–2004 were 0.095/1,000, 0.302/1,000, and 0.073/1,000 patient-days, respectively [33].

The definitive diagnosis of pulmonary invasive fungal infection requires demonstration of fungal hyphae within the involved lung tissue. Therefore, the clinical diagnosis is often made by inference, as thrombocytopenia and coagulopathies often render biopsies unsafe. It is important to note that the isolation of molds in patients from peripheral or central venous blood samples may not indicate disseminated mycosis, even in severely immunosuppressed allogeneic HSCT recipients [34]. Similarly, isolation of fungi in respiratory samples may misrepresent the etiology of underlying pulmonary infiltrates. Therefore, the current consensus for invasive fungal infections diagnosis includes: (a) evaluation of host’s predisposing factors such as prolonged granulocytopenia, high-risk HSCT, GVHD, immunosuppressive therapy; (b) clinical features (less often seen in cancer and stem cell transplant recipients); (c) radiographic features; and (d) isolation of pathogenic fungus from sterile respiratory sites. The measurement of fungal antigens such as serum galactomannan levels may be helpful in the detection of pulmonary mycosis. In a recent study of HSCT recipients, serum galactomannan levels were diagnostic in >85% of patients. The diagnostic utility of this test, however, was markedly compromised in the setting of antifungal therapy [35]. Newer diagnostic tests, including fungal DNA amplification in sterile samples, are currently under investigation and need clinical validation before routine use is recommended.



**Fig. 12.4** Invasive *Aspergillus fumigatus* and *Rhizopus* multicentric cavitory pneumonia during graft-versus-host disease (GVHD) following donor lymphocyte infection in a patient with chronic lymphocytic leukemia

and allogeneic hematopoietic stem cell transplantation; Postfungal pneumonia course was complicated by recurrent *Pseudomonas* and *Stenotrophomonas maltophilia* secondary lung infection



The treatment of pulmonary mycosis has improved considerably in the past ~10 years. The availability of voriconazole as primary therapy for invasive pulmonary aspergillosis [36] and caspofungin for salvage therapy of refractory invasive aspergillosis [37] is a promising addition to the antifungal armamentarium. Antifungal combinations may be prescribed for high-risk cancer patients and HSCT recipients with invasive mycosis. Due to the lack of prospective randomized trials, there is no consensus in recommending preferred antifungal combinations. A preliminary study using various antifungal combinations hinted modest superiority of caspofungin plus voriconazole in HSCT recipients with invasive fungal infections [38]. Reconstitution of the immune system, including recovery of severe granulocytopenia, remains the critical determinant in promoting resolution of invasive fungal infections. Donor granulocyte transfusions and adjuvant recombinant T<sub>H</sub>1 cytokines need prospective evaluation, although the results of preliminary observational studies among high-risk allogeneic HSCT recipients with disseminated mycosis appear promising [39].

**Viruses.** Human cytomegalovirus pneumonia is the most frequent cause of opportunistic viral complications in cancer patients with defective cellular immunity. Pulmonary Varicella-zoster virus and HHV-6 lung infections are difficult to distinguish from CMV pneumonitis. Seasonal respiratory viruses (RSV, Influenza A and B, Parainfluenza type 3, and Adenovirus) also cause serious lower respiratory tract infections in immunosuppressed cancer patients. Fever and non-productive cough are prominent nonspecific features. In patients with extensive lung involvement, dyspnea may appear early in the course of infection. Viral antigen detection in nasal washes, tracheal aspirates, and bronchial specimens is most frequently used in determining active viral replication. Chest CT scans may show ground glass infiltrates, despite normal conventional chest radiographs. A normal chest CT scan in high-risk HSCT recipients with suspected viral pneumonitis excludes the possibility of infection in >95% of cases. The presence of CMV viremia is another helpful indicator in determining the etiology of a pulmonary process. The isolation of CMV antigen from lower respiratory tract secretions may not, however, necessarily indicate pulmonary infection, as patients with cellular immune defects may have intermittent low-level viral replication and shed virus without developing end-organ disease. Ganciclovir or foscarnet are commonly prescribed for systemic CMV and HHV-6 infections. Antiviral combinations with adjuvant immunoglobulin (IVIG) therapy are associated with variable results and presently not recommended for routine use. Human metapneumovirus (hMPV) has been recently recognized as a serious pulmonary pathogen. The spectrum of hMPV disease may range from mild upper respiratory tract infection to serious disseminated infection leading to respiratory failure and encephalitis. Ribavirin has been

used successfully and intravenous ribavirin may be considered for patients with life-threatening hMPV disease [40].

**Miscellaneous.** Pulmonary *T. gondii* and *L. monocytogenes* infections can lead to serious, often life-threatening, complications in patients with profound cellular immune dysfunction and disease characteristics are described in detail elsewhere [41, 42].

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