Diagnostic Approach to Life-Threatening Pulmonary Infiltrates

10

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Introduction

Diagnosis of pulmonary disease is typically based upon consideration of presenting symptoms, physical examination, and pulmonary function testing in combination with classification of radiographic features, to guide diagnostic tests and initiate empiric treatment. When diagnostic efforts and/or empiric treatment fails, thoracic surgeons have traditionally been called upon to perform surgical biopsy of the lung to aid in the diagnosis of indeterminate, life-threatening pulmonary disease. Such biopsy has been requested specifically in the case of diffuse lung disease among patients receiving treatment for solid-organ or hematologic cancers, particularly when symptoms of respiratory failure progress and when noninvasive diagnostic tests and empiric treatments fail to halt progression. In such circumstances, radiologists, pulmonologists, and thoracic surgeons may be consulted and asked to provide tissue specimens that will allow rapid, accurate diagnosis leading to specific treatment. It is imperative that biopsy take place before respiratory failure supervenes [1], and that the specimens provided to clinical laboratories, pathologists, and microbiologists are comprehensive and properly preserved.

Background and General Considerations

In his review of the subject, Grant attributed priority for pulmonary biopsy, using open thoracotomy in the diagnosis of diffuse lung disease, to Klassen of Columbus, Ohio, circa 1949 [2].

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© Springer International Publishing Switzerland 2017
Y. Fong et al. (eds.), *Surgical Emergencies in the Cancer Patient*,
DOI 10.1007/978-3-319-44025-5_10

By 1971 however, Klassen concluded that

> There is a diminishing need for surgical biopsy of pulmonary lesions as we apply modern diagnostic procedures as a cooperative effort of the internist, radiologist and pathologist. Most patients with diffuse pulmonary disease can have an accurate diagnosis made without a direct biopsy of the lung. When this cannot be established in a relatively short time, thoracotomy and biopsy should be carried out without hesitation. [3]

This statement is as cogent today as it was 46 years ago, but from the perspective of the thoracic surgeon, consults on patients during and following treatment of solid-organ and hematopoietic neoplasms in whom it was early recognized that "virtually any infectious agent can cause pulmonary disease in any immunocompromised host" [4] are increasingly complex. In such patients, the ratio of risk to benefit is often substantial. For a successful outcome, the biopsy must provide definitive identification of a specific etiology. That disease, in turn, must be amenable to successful treatment. Finally, intervention will prove futile if the patient's cancer recurs or progresses.

Differential diagnosis is expansive and sometimes bewildering. The cancer patient is also subject to a wide range of diffuse lung diseases unrelated to infection or malignancy [5, 6]. Lung infiltrates or nodules may represent progression or spread of the primary (or new) neoplasm to the lungs [7, 8]. There are literally thousands of drugs and drug combinations used in the treatment of cancer, and new agents and combinations are added on a frequent basis. Many of these agents have inherent lung toxicity, and most impair the immune response, fostering infection with a wide spectrum of organisms that are seldom, if ever, pathogenic in healthy individuals [9]. These considerations are further amplified in patients who undergo stem-cell transplantation. Profound and prolonged immunosuppression allows an even broader range of infectious pathogens and adds lung damage secondary to other mechanisms (e.g., diffuse alveolar hemorrhage, radiation pneumonitis, and graft-versus-host disease [GVHD]) [10]. Adding further complexity, the entities in the expanded differential diagnosis list are addressed using a plethora of new diagnostic methods which, in their turn, have morphed over time. The risk of individual infectious organisms has also changed in response to the adoption of new prophylactic regimens [11–14].

Time can be of the essence. If the patient's condition is stable and anesthesia with single-lung ventilation is possible, minimally invasive methods (VATS) foster more comfortable and rapid patient recovery. Accordingly, biopsy is optimally performed early, before progressive loss of pulmonary function prohibits single-lung anesthesia and increases the risk of postoperative complications, including the requirement for ventilator support or even death.

Psychological factors may also prove difficult to manage. Patients are often young and have endured multiple, prolonged, and highly stressful treatment regimens and may have experienced distressing complications. Malignant disease may have recurred following initial treatment or salvage regimens. Patients managed with hematopoietic stem-cell transplantation (HSCT) may be subject to manifestations of GVHD. Patients, family members, and primary physicians are frequently frustrated, frightened, and desperate when faced with recurring complications of treatment and deteriorating health status. In such circumstances sympathy may overwhelm sober clinical judgement. Will biopsy provide a meaningful chance of treatment to alleviate suffering or prolong life? The oncologist, patient, or family may desire to continue diagnostic and therapy options even when potential benefit appears minimal. Should surgical biopsy be performed when the patient has little or no chance of survival?

In selected circumstances, e.g., localized fungal infection, second primary lung cancer, or limited lung metastasis, the surgeon must be prepared not just to biopsy, but to try to resect all detectable disease, adding a potential curative benefit [15, 16].

For all of these reasons, it has become increasingly difficult for the busy thoracic surgeon to stay current. There are no formal published guidelines established for management of these situations [17]. There is no randomized controlled study addressing the issue. Results of published series are inconsistent and recommendations vary [18–20].

The surgeon must rely heavily on colleagues in hematology-oncology, pulmonary medicine, infectious disease, radiology, and pathology for guidance and support. It is imperative that such consultation take place before frank discussion of potential risks and benefits with the patient and family and subsequent surgical biopsy. In the case of a major divergence of professional opinion or if the family demands, consultation with a multispecialty ethics committee may be in order.

In order to craft a chapter that will assist surgeons to make the difficult decision as to whether and when surgical biopsy is indicated, decide upon the optimal technique for the biopsy, and ensure that collection of tissue and microbiological specimens is sufficiently comprehensive to allow definitive diagnosis, a group of clinicians and scientists with long and extensive experience in the treatment of solid and hematological malignancies has crafted a coherent, evidence-based diagnostic algorithm for management of the difficult problem of life-threatening diffuse lung disease in the cancer patient. Experience in the management of more than 10,000 patients undergoing HSCT uniquely qualifies them to do so [21]. Their opinions are supplemented by a review of the literature.

We approach this task with humility, in the clear understanding that the advice provided in this chapter may rapidly become obsolete.

Clinical Presentation

The clinical presentation of pulmonary problems does not vary significantly between an oncologic patient, a hematologic patient, and an HSCT patient. The most common presentations the pulmonologist sees in these patient populations are shortness of breath, wheeze, cough, sputum production, and hemoptysis. The differential diagnosis, on the other hand, can vary greatly.

Differential Diagnosis

In a cancer patient presenting with shortness of breath, the differential diagnosis includes obstruction of the central airway secondary to intraluminal tumor or extrinsic compression, lymphangitic spread, a reaction to either chemotherapy or radiation therapy, or infection. Pulmonary edema, emboli, or tumor emboli can also present as shortness of breath in the oncologic patient, as well as pleural and pericardial effusions.

Infections are especially common after treatment with chemotherapy agents that cause neutropenia. Patients treated with prolonged steroids may be more prone to *Pneumocystis* pneumonias.

When an asymptomatic or a symptomatic patient shows radiographic pulmonary infiltrates the primary consideration is whether it is caused by infection.

Differential Diagnosis of Pulmonary Infiltrates in Cancer Patients

Infections

Bacterial

The most common Gram-positive bacteria that cause pulmonary infections in the cancer patient are *Staphylococcus aureus* (including methicillin-resistant *S. aureus* or MRSA), Group A, B, and G streptococci, anaerobic streptococci, *Streptococcus pneumonia*, and enterococci (including vancomycin-resistant enterococci or VRE). Gram-negative causes include *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter* spp., *Enterobacter* spp., *Klebsiella pneumonia* and *K. oxytoca*, *Stenotrophomonas maltophilia*, and anaerobic bacteria (*Bacteroides* spp., *Porphyromonas* spp., *Prevotella melaninogenica*, *Fusobacterium* spp., anaerobic Gram-positive cocci). Other bacteria, including *Mycobacterium chelonae*, *M. abscessus*, *M. fortuitum*, *M. avium* complex, *M. gordonae*, *M. bovis*, and *M. marinum*, *Nocardia* spp., *Legionella* spp., *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* can also cause pulmonary infection in immunocompromised patients.

Fungal

The most common causes of fungal pneumonias in the severely immunocompromised patient, i.e., those with hematologic malignancies (HM) or

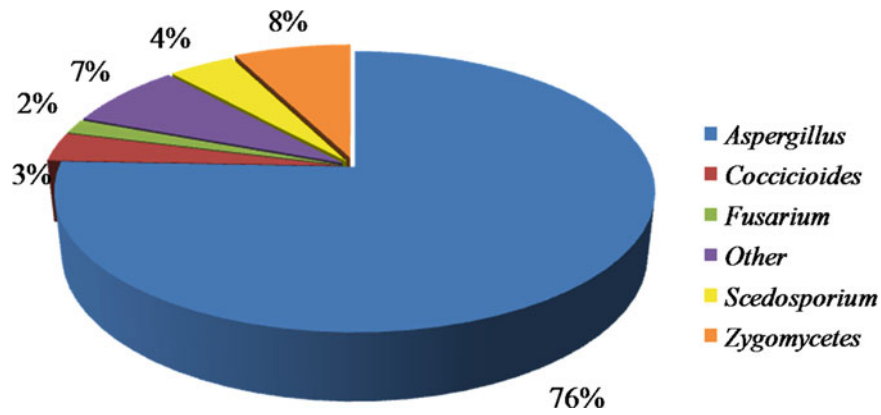

Fig. 10.1 The incidence of invasive mold infections (IMI) in HCT patients at City of Hope between 2003 and 2007 was 5.3 % (119 IMI per 2261 HCST)

hematopoietic cell transplant (HSCT) recipients, are the molds. The most common of these is *Aspergillus* spp., primarily *Aspergillus fumigatus*. The *Aspergillus* spp. are followed in frequency by the *Mucorales* spp., *Fusarium* spp., and *Scedosporium* spp. (Fig. 10.1). Before trimethoprim-sulfamethoxazole (TMP/SMT) prophylaxis became a standard of care in HSCT, *Pneumocystis jiroveci* was one of the most common fungal pneumonias. *Candida* spp., while a common cause of mucous membrane infection and candidemia, rarely cause pulmonary infection, except for the rare pulmonary septic embolus caused by *Candida* spp. Finally, the endemic fungi can cause severe pulmonary infection and disseminated disease: *Coccidiodes immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*.

Viral

The most common causes of viral pneumonias in the most severely immunocompromised cancer patient, the HSCT recipient, are the herpes viruses. These include cytomegalovirus (CMV), herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), and human herpes virus 6 (HHV6). All of these viruses share a number of characteristics including universal exposure/infection before adulthood, latency, and reactivation during immunosuppression. Other viruses that can cause pneumonia are the respiratory viruses including influenza A and B, respiratory syncytial virus (RSV), parainfluenza virus (PIV), metapneumovirus (MPV), and adenovirus.

Parasitic

Toxoplasma gondii can cause pulmonary lesions, but is uncommon since TMP/SMT has been used as prophylaxis. *Strongyloides stercoralis* can cause a disseminated form of pulmonary hyperinfection which is usually lethal.

Clinical Presentation

The presentation of immunocompromised cancer patients with pneumonia is quite varied. The cancer patient with pneumonia or pulmonary nodules may be afebrile and without any signs of infection, but may also be febrile, with productive cough, dyspnea on exertion, pleuritic chest pain, and hemoptysis. Patients may present in septic shock with multiorgan system failure if the causative organism disseminates via the bloodstream.

Certain symptoms are more specific to certain infections. The classic presentation of a patient with invasive pulmonary mold (e.g., aspergillosis, mucormycosis) infection is cough, fever, pleuritic chest pain, and hemoptysis, but alternatively, such patients may be afebrile and asymptomatic.

Although bronchitis is the most common cause of hemoptysis, bleeding can also be caused by tumor invading the airway, necrotic cavitary lesions, pulmonary embolism, or thrombocytopenia. Major hemoptysis can lead to shortness of breath, and if not treated quickly, total airway obstruction, asphyxia, and death. Pulmonary fibrosis, as a reaction to chemotherapy, can cause shortness of breath; the best known example is bleomycin toxicity. Wheezing can be due to partial airway obstruction, heart failure secondary to fluid overload, reactive airway disease as a result of chemotherapy, or pneumonitis secondary to immunosuppression. Cough can be due to infection, hemoptysis, or reaction to treatment. Cough can also be caused by obstruction by endobronchial tumor, pneumonia, or bronchitis secondary to neutropenia following chemotherapy or radiation. Bronchorrhea (cough productive of copious amounts of thin mucous) is sometimes encountered in patients with mucinous adenocarcinoma. Cough secondary to bronchiectasis is usually seen in patients with slowly growing tumors (neuroendocrine tumors) that obstruct a lobar orifice, but is uncommon in most rapidly growing lung cancers. Chest pain can present due to tumor invasion or metastasis to chest wall, pulmonary embolism, pleural or pericardial effusion, and infection (pneumonia with parapneumonic effusion and empyema).

In non-transplant HM patients, shortness of breath can be due to infection, airway obstruction (usually in lymphoma), pneumonitis from chemotherapy, radiation or other treatment, or ARDS secondary to sepsis. More uncommon mechanisms include hyperleukocytosis and leukostasis causing sluggish flow through the lungs. Treatment for hyperleukocytosis can lead to tumor lysis syndrome that can also result in dyspnea secondary to capillary leak syndrome and fluid overload. Certain HM (e.g., acute myelogenous leukemia) can cause hypercoagulation and pulmonary emboli. Other pathophysiologic mechanisms that can combine in causing respiratory failure in hematology patients include DIC and thrombocytopenia with alveolar hemorrhage and hemoptysis. Thrombocytopenia secondary to chemotherapy alone (without DIC) can cause hemoptysis and diffuse alveolar hemorrhage. Prolonged neutropenia can lead to infection with invasive molds, which, in turn, frequently result in hemoptysis, especially in combination with thrombocytopenia.

Differential diagnosis assumes further complexity following HSCT. Shortness of breath and hemoptysis can be due to diffuse alveolar hemorrhage (DAH) either as a result of previous treatment, conditioning regimens, or thrombocytopenia. Most commonly dyspnea is caused by infection. Transplant patients with prolonged (>21 days) neutropenia are especially susceptible to fungal infections and may present with high fever, dyspnea, and occasionally hemoptysis. *Pneumocystis jiroveci* is often seen when steroids are tapered during treatment of GVHD.

When an infectious organism cannot be isolated with sputum culture, bronchoscopy, or invasive biopsy, a number of noninfectious causes must be considered (Table 10.1).

Dyspnea can result from pulmonary fibrosis secondary to chemotherapy. A few examples from a long list of agents that may cause such fibrosis are busulfan, and chlorambucil. Pulmonary fibrosis can also result from radiation received as treatment of lymphoma or as part of conditioning regimens for HSCT. GVHD can also present with shortness of breath. DAH can present as subtle shortness of breath which can become severe if not recognized. Hemoptysis is seen with DAH but the amount is usually not great. If massive hemoptysis is seen in the transplant patient one must seriously consider fungal infection as the cause. Thrombocytopenia alone, in the absence of other disease, can lead to hemoptysis. DIC as a result of

Table 10.1 Noninfectious lung disease [58, 59]

Pulmonary edema
Damage due to chemotherapy or radiation
Diffuse alveolar hemorrhage (DAH) [60]
Adult respiratory distress syndrome (ARDS)
Bronchiolitis obliterans obstructive pneumonia (BOOP) [61]
Cytolytic thrombi
Idiopathic pneumonitis syndrome [62, 63]
Graft-versus-host disease (GVHD) [64]
Second malignant neoplasms [65, 66]

infection or secondary to the hematologic malignancy itself can cause hemoptysis. Cough in the HCT patient is often due to infection but can also be due to GVHD or pneumonitis caused by chemotherapeutic agents and/or radiation pneumonitis. Wheezing in the transplant patient may be due to reactive airway disease from chemotherapy or GVHD.

Diagnostic Workup

The workup for the clinical presentations described above should always start with a comprehensive history and physical followed by a chest X-ray or CT of the chest. The CT scan can be done without contrast unless evaluation of the mediastinum is necessary. If shortness of breath, cough, or wheezing is being evaluated in a non-emergent setting, pulmonary function testing with and without bronchodilators is indicated.

Radiologic Findings

Infections

The radiologic findings of pneumonia in cancer patients can be quite varied [22]. Although radiologists can assist clinicians in differential diagnosis, specific etiological diagnosis is difficult [23]. The radiologist can however assist the clinician to narrow down the differential diagnosis by combining radiologic and clinical factors [24]. Classically, viral pneumonias demonstrate bilateral, diffuse, and interstitial infiltrates, while bacterial pneumonias present with more localized, lobular, and segmental infiltrates or consolidations [25]. Invasive pulmonary mold infections usually present as multiple nodular, pleural-based consolidations (reflecting pulmonary infarction secondary to obstruction of peripheral pulmonary arteries by fungal hyphae) (Fig. 10.2).

The classic early lesion is the "halo sign" where a consolidation is surrounded by a "halo" of hemorrhage [26]. A later lesion evolves into a "crescent sign" lesion that represents early peripheral necrosis, with separation of necrotic lung away from the wall of the cavity (Fig. 10.3).

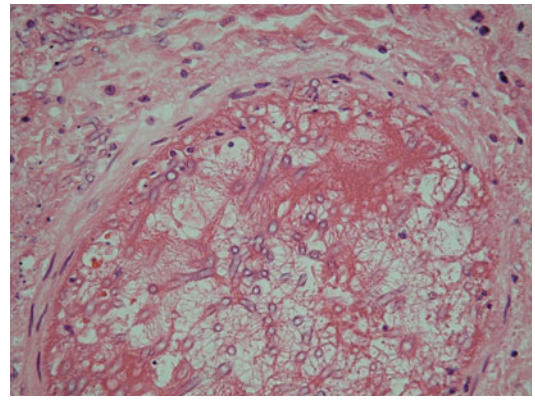

Fig. 10.2 Invasive *Aspergillus* invading and occluding a branch pulmonary artery

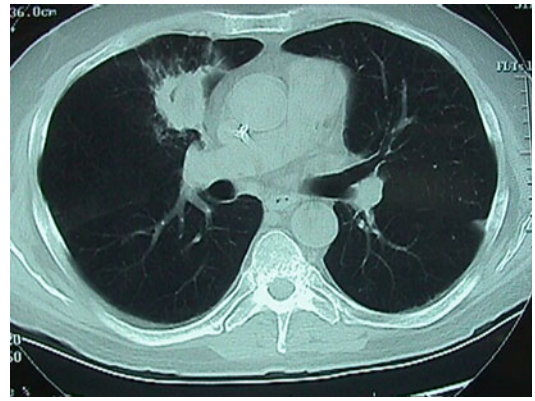

Fig. 10.3 Crescent sign and mucormycosis in a 55-year-old male status post-HSCT for multiple myeloma. The patient was on high-dose steroids for GVHD and developed fever, chest pain, and hemoptysis. Bronchoscopy yielded fungal organisms with broad irregularly branching hyphae. The patient was treated with liposomal amphotericin and fluconazole

Classic radiologic findings are not always present. When pathognomonic findings of invasive pulmonary mold infection are found, CT scans of the sinuses and brain should be ordered since these are other sites to which molds frequently spread.

A review of radiographic findings in patients with diffuse lung disease not being treated for cancer is outside the scope of this chapter [27].

Diagnostic Tests

Approach

Pulmonary complications in BMT patients present an enormous problem, as 40–60 % of HSCT patients develop this complication and 90 % of deaths following HCST are caused by respiratory complications [28].

The first and most important determination to be made in the approach to diagnosis of pulmonary infiltrates in the cancer patient is that of urgency. Urgency is determined primarily by the degree of the immunosuppression. At the top of the list of immunocompromised patients and those at highest risk for devastating opportunistic infection and diseases of the lungs with the highest mortality rates are those patients with HM suffering from prolonged neutropenia due to chemotherapy, particularly in the case of HM, and patients during and after HSCT. Patients with solid organ cancers, whether undergoing short courses of chemotherapy or not, are less immunosuppressed and, therefore, at lower risk for rapidly progressive, devastating pulmonary infection or disease. Immune-compromised patients form the primary focus of our approach below.

When a severely immunosuppressed patient presents with respiratory symptoms (e.g., cough, shortness of breath) a chest radiograph (CXR) is usually ordered. It can be argued that a chest CT scan should be performed because of the lower sensitivity of CXR. The nature of the pulmonary infiltrates can be helpful in making a diagnosis, for example, the halo and crescent signs referenced above.

Initial Testing Prior to Invasive Diagnostic Procedures (See "Approach" Below)

The following tests should be drawn immediately upon presentation of a cancer patient, especially patients with HM or HSCT recipients, with suspected pneumonia: (1) blood cultures; (2) sputum for (a) culture (Gram stain) and sensitivity testing, (b) AFB stains and culture × 3, and (c) fungal culture and KOH examination; (3) nasopharyngeal washings for respiratory virus PCR; (4) serum/plasma testing for (a) Aspergillus galactomannan EIA, (b) 1,3 β-D-glucan, and (c) cryptococcal antigen; (d) *Coccidioides immitis* antibodies; (e) *Histoplasma capsulatum* antigen (also in urine); and (f) Quantiferon Tb gold assay.

Empiric Therapy

At this stage of the workup empiric therapy for infectious diseases and other noninfectious diseases should be initiated, and should continue, with appropriate modifications, based on test results, throughout each stage of the diagnostic workup (Table 10.2).

When a cancer patient presents with radiographic pulmonary infiltrates, a number of factors will determine which antibiotics should be administered. For example, neutropenic febrile patients with pneumonia should be started on empiric cefepime. In addition, if the patient is a known carrier of MRSA, vancomycin should be added. If the patient acquired the pneumonia as an outpatient, coverage of community-acquired pneumonia with azithromycin should be added. If the patient is suspected of having aspirated, anaerobic coverage should be added or, alternatively, piperacillin/tazobactam can be substituted for the cefepime. In the high-risk patient, i.e., the neutropenic patient with HM or the HSCT recipient with GVHD, a broad-spectrum anti-mold agent, i.e., isavuconazonium or an amphotericin B lipid formulation, should be initiated empirically.

Bronchoscopy with Lavage

Because even pathognomonic radiographic findings are not 100 % specific, regardless of the type of lesions or infiltrates present, the patient should proceed to bronchoscopy with bronchial lavage [29]. Prior to bronchoscopy, certain serologies and tests should be performed (see above).

In the oncologic patient with a low platelet count, bronchoscopy with lavage will often yield an etiologic diagnosis leading to change in treatment,

Table 10.2 Specific therapy for infectious and noninfectious disease

Infectious diseases
Bacterial
S. aureus
MRSA—vancomycin
MSSA—nafcillin
Group A, B, C, G streptococci—penicillin G
VRE—linezolid, quinupristin/dalfopristin, daptomycin
P. aeruginosa—ceftazidime, cefepime, levofloxacin, ciprofloxacin, piperacillin/tazobactam, or meropenem (depending on sensitivity testing) + aminoglycoside (tobramycin or amikacin)
Acinetobacter spp., *Enterobacter* spp.—(same as for *P. aeruginosa*—depends upon sensitivity)
Extended-spectrum beta-lactamase (ESBL)—carbapenem (meropenem, imipenem)
Carbapenem-resistant Enterobacteriaceae (CRE)—colistin + (meropenem or imipenem)
Stenotrophomonas maltophilia—trimethoprim/sulfamethoxazole or ticarcillin/clavulanate
Nocardia spp.—TMP-SMX + imipenem ± aminoglycoside; linezolid, minocycline
Mycobacteria
M. avium-intracellulare complex—clarithromycin, ethambutol, and rifabutin
M. abscessus, M. chelonae—clarithromycin + amikacin + cefoxitin (+ surgical excision)
M. fortuitum—amikacin + cefoxitin + probenecid
M. gordonae—rifampin + ethambutol + kanamycin (or ciprofloxacin)
M. kansasii—isoniazid + rifampin + ethambutol
M. marinum—clarithromycin or minocycline or doxycycline
M. bovis—isoniazid + rifampin + ethambutol
M. tuberculosis—isoniazid + rifampin + ethambutol + pyrazinamide
Fungal
Aspergillus spp.—Voriconazole, isavuconazonium, amphotericin B lipid formulations
Mucorales—isavuconazole, amphotericin B formulations
Fusarium spp.—voriconazole, amphotericin B lipid formulations, isavuconazole
Scedosporium spp.—voriconazole, isavuconazole, amphotericin B formulations
Cryptococcus sp.—amphotericin B lipid formulations + 5FC or fluconazole
Coccidioides immitis—amphotericin B lipid formulations
Histoplasma capsulatum—amphotericin B lipid formulations
Pneumocystis jiroveci—TMP/SMX
Viral
Cytomegalovirus (CMV)—ganciclovir (or foscarnet) + IVIG
Herpes simplex virus 1 and 2—acyclovir or foscarnet
Varicella zoster virus—acyclovir
HHV6—ganciclovir or foscarnet
Adenovirus—cidofovir
Influenza A and B—oseltamivir or zanamivir
Respiratory syncytial virus (RSV)—ribavirin aerosolized has been recommended by some
Parasitic
Strongyloides stercoralis—ivermectin or albendazole

clinical response, and survival (Fig. 10.4) [30–33]. The bronchoalveolar lavage (BAL) fluid specimen should be sent to cytology and microbiology (see Table 10.3).

If the initial bronchoscopy and lavage are nondiagnostic, then the next step should be to decide the best way to obtain a biopsy specimen for pathologic and microbiologic studies. Repeat bronchoscopy and BAL have a low yield [34]. Although transbronchial lung biopsy (TBLBx) has been shown to supplement diagnosis by BAL, because HSCT patients typically have low platelet counts and accordingly higher risk of hemoptysis and pneumothorax, TBLBx is seldom utilized today [35, 36].

CT-Guided Biopsy

If the prior workup (including cytologic examination) and culture of the BAL fluid do not result in a diagnosis, one may proceed to percutaneous

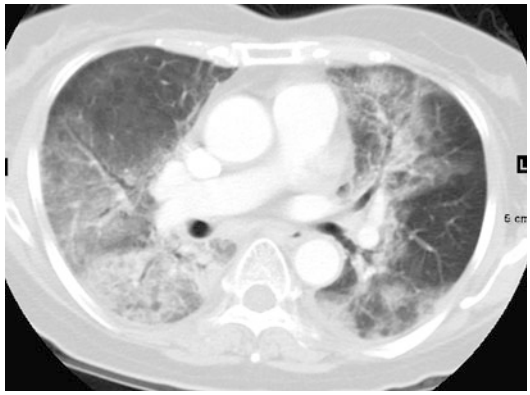

Fig. 10.4 Non-small-cell lung cancer patient post-chemoradiation therapy with diffuse infiltrate and progressive shortness of breath, consistent with radiation pneumonitis. Bronchoscopy revealed colonization with Candida and bacteria. Delayed culture growth grew out Mycobacterium tuberculosis

Table 10.3 Testing of bronchoscopic alveolar lavage (BAL) fluid

Culture (+ Gram stain) and sensitivity testing
AFB culture and smears
Fungal culture and KOH examination
Aspergillus galactomannan EIA
Mucor PCR
Respiratory viruses PCR panel
Pneumocystis jiroveci PCR
Legionella culture
Universal PCR (if all else negative)
Cytology—H&E stain, GMS stain, AFB stain [67]

biopsy of a lung nodule or focal infiltrate. Yield is lower for diffuse infiltrates [37–39].

"Fine-needle" biopsy with single 22-gauge needles has largely been replaced by a coaxial needle biopsy approach. Typically an 18-gauge coaxial guide needle is placed percutaneously into the target area under CT guidance. Then a 20-gauge spring-powered needle is inserted through the 18-gauge needle to obtain 3–5 core samples for pathology and microbiology. This has the advantage of obtaining much better samples and generally requires one puncture of the pleura, and it also eliminates delays for making cytology smears to evaluate for adequacy of the sample. This is most often done under light sedation and local anesthesia. After the needle is removed, a rapid CT scan survey of the chest is done to evaluate for early pneumothorax, significant bleeding, and air embolization (a rare but potentially devastating complication, especially if not recognized before the patient is allowed to get off the CT table). A follow-up inspiration-expiration CXR is generally obtained 2 h after the procedure to check for delayed pneumothorax or bleeding. If all is stable, the patient can then be discharged home with post-procedure instructions.

Thoracoscopic Lung Biopsy

Finally, if there is no diagnosis forthcoming after sputum cultures, bronchoscopy, BAL, and//or CT-guided biopsy, surgical lung biopsy for both diagnostic and possibly therapeutic reasons may be indicated [40, 41]. None of the prior studies are sufficiently sensitive to exclude infectious disease [42]. Additionally, if the patient is deteriorating rapidly, recourse to surgical biopsy may need to precede bronchoscopy or needle biopsy [43, 44].

Surgical biopsy may be performed thoracoscopically (VATS) or via limited thoracotomy.

Most published material on surgical lung biopsy is from series of patients with nonmalignant disease. Ooi et al. found that VATS diagnostic biopsy had a low perioperative mortality (1.8 %) and morbidity (9 %) [45]. 100 % of the patients ($n = 55$) who underwent VATS biopsy had sufficient diagnostic tissue obtained and a median hospital stay of only 2 days. Importantly, this group found that a difference between preoperative clinico-radiological and final histological diagnosis sufficient to change prognosis and definitive management was made in 27.1 % of patients. Kreider and colleagues found that complications in patients who underwent VATS diagnostic biopsy were higher in those who were dependent on oxygen and those who have pulmonary hypertension [46]. Utz et al. found that a DLCO of <35 % predicted and a diagnosis of idiopathic usual interstitial pneumonia were predictors of mortality as well [47]. Preoperative ventilator dependence and an immunocompromised status were the only predictors of mortality

in Lettieri's analysis [48]. Unfortunately, many patients who have life-threatening pulmonary infiltrates will have one or more of the above risk factors and thus worse survival. Those who are acutely ill or are in a late stage of the disease have decreased pulmonary compliance and decreased DLCO and a limited ability to tolerate general anesthesia, particularly with single-lung ventilation. Such patients may require open lung biopsy through a mini-thoracotomy [49].

For many surgeons, open lung biopsy is only performed when VATS is impossible (e.g., extensive adhesions) or if patients are too compromised to tolerate one-lung ventilation. Risks and potential benefits must be carefully weighed when sick patients are being evaluated for surgical biopsy.

Utz and colleagues found that open lung biopsy was associated with mortality in the range of 16–20 % in patients with suspected diffuse interstitial lung disease. Morbidity and mortality associated with surgical lung biopsy may be due to progression of disease or secondary to the surgery itself, which may trigger an exacerbation of the disease. It is imperative that risks of respiratory decline, prolonged ventilation, need for tracheostomy, and even death are discussed with patients and their families before undergoing surgical biopsy, especially if patients have an oxygen requirement, are nonambulatory, or possess other significant comorbidities.

Although some have argued against open lung biopsy in patients receiving ventilator support, in carefully selected patients surgical biopsy may be beneficial. Wong conducted a meta-analysis of 14 series involving more than 500 patients and reported that therapeutic changes ensued in 78 % with 29 % procedure-related complications and mortality of 54 %. Most common diagnoses were fibrosis/pneumonitis and viral pneumonia [50].

Results of surgical lung biopsy (SLB) in immunosuppressed patients have been reported in a limited number of series. Snyder reported the experience at the University of Minnesota with SLB following HSCT in children from 1975 to 1986. A specific diagnosis was obtained in 60 %, but mortality at 30 days was 45 % [51]. Wang et al. performed 35 SLB following HSCT and reported findings leading to change in therapy in 63 % and clinical improvement in 46 %. Findings included idiopathic interstitial pneumonitis (40 %), CMV (20 %), and miliary tuberculosis (9 %). Patients with respiratory failure or GVHD had a worse prognosis [52]. Hayes-Jordan of St. Judes Children's Hospital reported on 19 SLB among pediatric patients following HSCT and failed diagnosis by BAL. There were six infections, five cases of BOOP, four interstitial pneumonias, and other specific diagnoses, with change in treatment in 90 % of patients and improved outcome in 47 %. Mortality was 47 %. No patient with a surgical complication or ventilator status survived [53]. Qualter et al. reported on 16 patients with SLB following failed attempt at diagnosis with BAL in 193 HSCT recipients. 94 % of SLB provided an etiologic diagnosis. The probability of 2-year overall survival was 17.5 % for patients who underwent biopsy [54].

Operative Technique

General anesthesia is induced and either a bronchial blocker or a dual-lumen tube is placed to achieve one-lung ventilation. If both sides are equally diseased, then the right side is generally chosen for biopsy. The patient is placed in the lateral decubitus position with the operative side up. A camera port is placed in the eighth intercostal space in line with the mid to posterior axillary line. A small utility incision is made typically in the fifth interspace more anteriorly and is the site where thoracoscopic instruments enter the chest. The thoracic space is explored and typically two small wedge resections of two distinct disease sites are performed with endoscopic stapler. Thicker lung parenchyma will require thicker staple loads. Biopsies are taken of the upper and the lower lobe along the major fissure. If there is an obvious abnormality within the lung, pleura, or diaphragm, consideration of further biopsy is imperative. Because the differential diagnosis is so broad, it is imperative that the surgeon not omit important studies. Comprehensive informa-

tion on this topic is provided in the section on pathologic workup below.

A chest tube is typically left in place through the camera port. Frequently the tube can be maintained on water seal overnight and removed on the following morning if there is no air leak or persistent drainage. Pleural effusions should be drained and sent for culture and cytology as well. If effusion is recurrent, consideration of placement of an indwelling pleural catheter is reasonable.

When open biopsy is necessary, a small posterolateral incision can be made in the fifth intercostal space and the procedure performed as above.

Although some have questioned the appropriateness of surgical biopsy, it may represent the last and only chance of appropriate diagnosis in patients with life-threatening infiltrates. Although morbidity and mortality can be sizable in sick patients who undergo SLB, in many patients the procedure alters management and offers a chance of cure. Specific potential benefits include identification of occult infection not detected by endoscopic or needle biopsy methods and diagnosis of various noninfectious lung diseases. Although it must be understood that the long-term results of treatment of such entities as BOOP, GVHD, and idiopathic pneumonia syndrome are poor, biopsy results provide an accurate diagnosis to allow assessment of new treatments [55].

Biopsy with Combined Resection of Localized Lung Disease [16]

In cases where lesions are nodular in character, various methods have been described to allow precise identification of the location of the nodule during thoracoscopic resection. Where nodular or cavitary lesions are multiple and limited in scope, and might represent separate lung cancer, lung metastasis, local recurrence of lymphoma, lung abscess, mycobacterial cavity, fungus ball, or invasive mold infection, consideration of resection of all identifiable disease may mandate open thoracotomy with wedge and/or anatomic segmental or lobar resections.

Table 10.4 Testing of biopsy tissue (from CT-guided lung biopsy and thoracoscopic open lung biopsy)

Pathology (H&E, GMS, and AFB stains)
Culture (+ Gram stain) and sensitivity
Fungal culture and KOH examination
AFB culture and stains
Viral culture and PCR
Universal PCR (if all else negative)

Pathologic Evaluation

The pathologic diagnosis of pulmonary infiltrates in patients with and without cancer can be very challenging. The differential is usually extensive and includes infectious organisms (many of which are unusual and rarely seen in immunocompetent patients), reactive processes related to cancer therapy, and recurrence of malignancy. Obtaining the appropriate tissue sample is critical and it is equally important that the clinician communicates to the laboratory/pathologist the pertinent clinical information, radiographic findings, and working differential diagnosis so that interpretation and testing on the specimen are expeditious and meaningful (Table 10.4).

Table 10.5 lists lung specimen types that are commonly used to evaluate pulmonary processes and general information on the fixation as well as handling. Guidelines for handling and reporting pulmonary specimens have been published [56]. In specific settings, the successful identification of the underlying pathologic process will depend on the pulmonary physician's ability to target the diagnostic area of the lesion. In general, the more invasive procedures yield more specific diagnosis.

When recurrent lymphoma or leukemia is suspected, flow cytometry studies can be useful particularly on fluid specimens such as pleural fluids or BAL. The specimen is sent fresh to the pathology lab with instructions to use a portion for flow cytometry. If the specimen is sufficiently cellular, routine analysis is then also done. CT-guided percutaneous lung biopsies have a high diagnostic yield for documenting recurrent malignancy as well as identification of specific infections (Figs. 10.5 and 10.6) [57].

Table 10.5 Specimen types and utility in identifying common etiologies of pulmonary infiltrates in cancer patients

Specimen type	Handling/fixation	Applications
Bronchial washings/ brushings	Collect specimens in sterile containers. Best sent to the laboratory fresh for microbiologic testing as well as cytologic smears and cytospins. The brush can be cut off and placed in a vial of sterile saline.	Useful for identification of some pathogens (fungus, *Pneumocystis*, and some viruses) as well as malignant cells. Rapid GMS stain can be performed to identify fungal elements.
Pleural fluids	Collect specimens in sterile container. High-protein fluids such as pleural fluid may be refrigerated up to 24 h with reasonable cell preservation.	Most useful for identification of metastatic malignancy.
Bronchoalveolar lavage (BAL)	Usually BAL fluid sent to lab without fixation in a sterile container. Refrigerate if not immediately processed. Order appropriate microbiology testing to be done under sterile conditions before processing for cytology examination.	Most useful for identification of specific infectious agents (especially fungi, *Pneumocystis*, and some viruses). Special stains such as GMS can be easily performed as a rapid procedure for identification of fungi and *Pneumocystis*. Also good for establishment of malignancy but it can be difficult to distinguish atypical reactive processes (especially radiation atypia and some chemotherapy reactions) from malignancy.
Fine-needle aspirations	Ideally performed with cytology personnel preparing air-dried or alcohol-fixed smears for immediate evaluation of adequacy. If no cytology is available at the bedside, several smears should be made and air-dried. If there is additional material it can be fixed in neutral-buffered formalin for a cell block.	FNA is very helpful in assessment of localized lesions if they are accessible, particularly in establishment of recurrent malignancy.
Endobronchial biopsy	If infection is suspected, a separate tissue biopsy should be sent to microbiology for culture. In most cases the tissue for histologic examination should be immediately fixed in neutral-buffered formalin. Avoid exposure to air (drying artifact) and do not send on gauze or mesh material as tissue damage is likely.	All of these specimens are useful for identification of specific etiologies for pulmonary infiltrates such as malignancy or pneumonia, but also for nonspecific diagnosis as "diffuse alveolar damage, interstitial fibrosis, and hemorrhage.
Transbronchial biopsy		
Transthoracic core biopsy		
Wedge resections	The specimen is usually sent fresh for microbiology studies and a frozen section can be performed if indicated. The remainder is formalin fixed for routine histologic processing.	

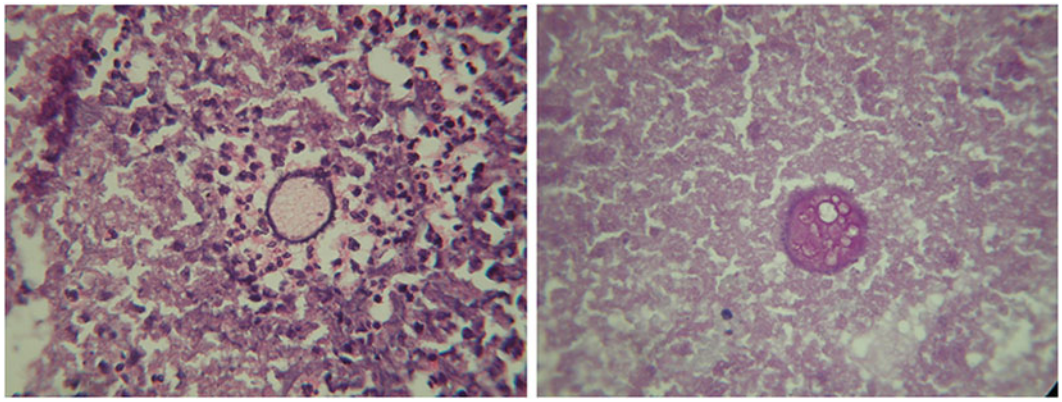

Fig. 10.5 Coccidioidomycosis spherule

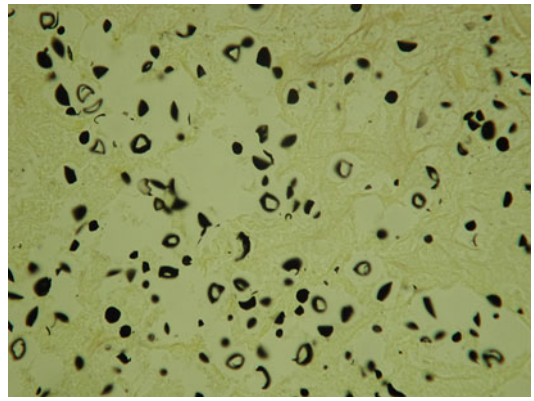

Fig. 10.6 Cryptococcus organisms in a surgical lung biopsy

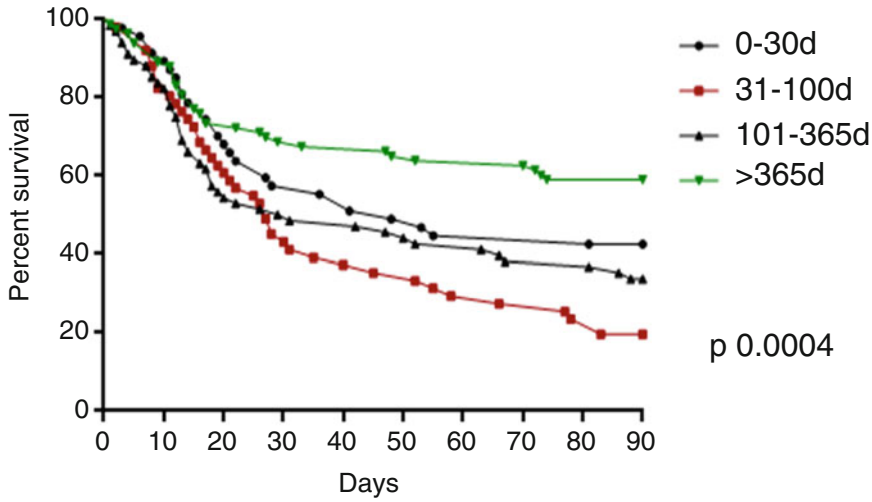

Fig. 10.7 Survival and time of onset of invasive mold infection after HCST

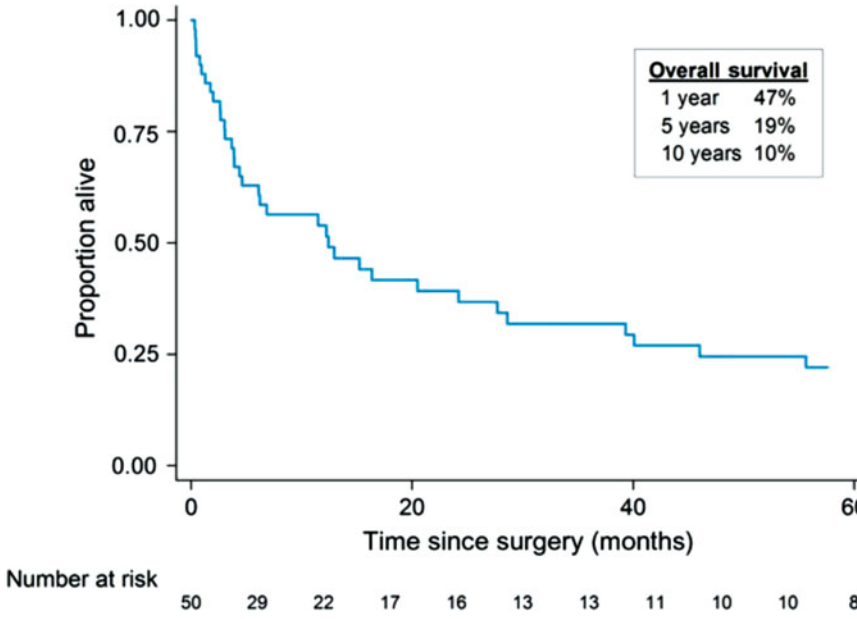

Fig. 10.8 Survival after surgical resection of invasive mold infection

Results

We have published our results in the surgical resection of 50 patients with presumed invasive mold infection (IMI) in immunocompromised patients (Fig. 10.7) [16]. Although there was substantial morbidity and 30-day mortality (12%), and while the majority of patients died from recurrent malignancy or recurrent fungal infection, 19% of patients survived longer than 5 years (Fig. 10.8).

Conclusion

When the surgeon is asked to provide lung biopsy in the workup and/or treatment of patients with life-threatening lung disease in immunosuppressed patients during or following treatment of hematologic and solid cancers with chemotherapy or HSCT, it is important that consultation with colleagues from multiple disciplines take place. While time pressure favors biopsy as soon as possible, unnecessary biopsy can be avoided by ensuring that all reasonable nonsurgical modalities have been tried. Moving forward to minimally invasive surgical biopsy with reasonable dispatch before deteriorating lung function forces open biopsy is clearly in the patient's best interest.

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