

What Has Been Learned from Postmortem Studies?

20

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20.1 Introduction

Infectious and noninfectious pulmonary complications occur in 30–60% of patients with hematological malignancy and recipients of hematopoietic stem cell transplantation (HSCT) and are associated with significant morbidity and mortality [1]. In allogeneic HSCT patients who develop respiratory failure requiring mechanical ventilation, the intensive care unit (ICU) and hospital mortality rates often exceed 80% and 85%, respectively [2–5]. The factors that contribute to the development of pulmonary complications in these patients include immunologic defects due to the underlying disease and its treatment, conditioning regimens, development of graft-versus-host disease (GVHD), and the type of HSCT [2, 6, 7]. The spectrum of pulmonary complications in patients with hematological malignancy and HSCT recipients is changing because of recent advances in antineoplastic therapies, such as the use of monoclonal antibodies and other targeted agents, increased application of HSCT for older patients, widespread use of prophylactic antibiotics and novel antimicrobial agents, and advances in supportive care [8].

Prompt investigation and diagnosis of pulmonary complications in patients with hematological malignancies are essential to improving patient survival. Unfortunately, despite the technological advances in diagnostic testing and imaging modalities, obtaining an accurate clinical diagnosis in these patients remains difficult and at times is made only at the time of the postmortem autopsy examination. Autopsy rates in cancer patients are much lower (13–34%) as compared to general medical and surgical patients (53–64%) [7–9]. This probably reflects the unwillingness on the

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Table 20.1 Pulmonary findings on postmortem studies in patients with hematologic malignancy including HSCT recipients

Infectious	Non-infectious
Fungal	Diffuse alveolar damage
Invasive pulmonary aspergillosis	Diffuse alveolar hemorrhage
Candida	Lymphoma/leukemia
bronchopneumonia	Pulmonary thromboembolism
Zygomycetes	Bronchiolitis obliterans
<i>Trichosporon</i> spp.	organizing pneumonia
<i>Fusarium</i> spp.	Bronchiolitis obliterans
<i>Chaetomium</i> spp.	Pulmonary veno-occlusive disease
<i>Pneumocystis jiroveci</i> pneumonia	Pulmonary alveolar proteinosis
Bacterial	
Vancomycin-resistant enterococci	
<i>Legionella</i> spp.	
<i>Stenotrophomonas maltophilia</i>	
<i>Staphylococcus epidermidis</i>	
<i>Staphylococcus aureus</i>	
<i>Streptococcus pneumoniae</i>	
<i>Pseudomonas aeruginosa</i>	
<i>Serratia</i> spp.	
Other gram-negative bacilli and streptococcus spp.	
Viral	
Cytomegalovirus	
Herpes simplex virus	
Respiratory syncytial virus	
Measles virus	
Parasitic	
Toxoplasmosis	

part of physicians and family members to subject the cancer patient to the same level of scrutiny applied to other major illnesses in determining the primary and contributory causes of death [9]. Additional concerns include legal issues regarding exposition of physicians' errors and non-reimbursement for postmortem examinations [10].

This chapter will review the infectious and non-infectious pulmonary findings that have been described at autopsy in patients with hematological malignancies, including blood and bone marrow transplant recipients. In addition, we discuss the frequently noted

diagnostic discrepancies between premortem clinical diagnoses and postmortem autopsy findings in these patients. Finally, we highlight the difficulties in diagnosing many of these conditions antemortem and emphasize the important role of the postmortem examination in accurately establishing the cause of death. Table 20.1 lists the infectious and non-infectious pulmonary disorders reported in autopsy studies of patients with hematologic malignancy, including HSCT recipients.

20.2 Infectious Findings

20.2.1 Invasive Fungal Infections

The incidence of invasive fungal infections in patients with hematologic malignancies has increased steadily over the past three decades [11]. This has been attributed to improvements in the prevention or preemptive treatment of bacterial infections and other opportunistic pathogens, particularly *Candida* and cytomegalovirus; increased administration of chemotherapies with profound and prolonged immunosuppressive effects on T-cell function (e.g., purine nucleoside analogs, anti-T-cell immunoglobulin, and monoclonal antibodies); and the growing number of allogeneic and nonmyeloablative transplantation procedures that carry a higher risk for chronic GVHD [12]. Patients with hematologic malignancies, especially in the neutropenic state after aggressive chemotherapy or HSCT and HSCT recipients with GVHD, are particularly susceptible to invasive fungal infections [13]. Approximately 20–50% of patients with hematological malignancies and HSCT recipients have evidence of invasive fungal infections at autopsy [8]. These include invasive aspergillosis and fungal infections due to *Candida* spp., *Zygomycetes* spp., *Trichosporon* spp., *Fusarium* spp., and various *Chaetomium* species.

In neutropenic patients with acute leukemia, the histopathological pattern of invasive pulmonary aspergillosis (IPA) is characterized by scant inflammation, hyphal angioinvasion with a high fungal burden, and extensive coagulative necrosis [12, 14]. In contrast, among HSCT recipients with GVHD, the histopathological findings consist of severe lung inflammation and less abundant *Aspergillus* burden. Several autopsy

studies in HSCT recipients have shown that IPA is frequently not diagnosed antemortem or persistent despite diagnosis by sputum or bronchoalveolar lavage (BAL) cultures or by serum galactomannan assay and treatment with amphotericin B [8, 15–21]. In recent years, treatment of IPA with voriconazole has led to better responses, improved survival rates, and fewer side effects than amphotericin B [22].

Autopsy studies have assisted in describing and confirming the immune reconstitution inflammatory syndrome (IRIS) in patients with IPA who are recovering from the neutropenia [23]. When clinical and radiologic worsening coincides with neutrophil recovery, it is usually assumed that this deterioration is related to progressive aspergillosis, prompting changes in patient management. However, its temporal relation with neutrophil recovery suggests that it may be caused by IRIS. The patients who died during the first month had no evidence of aspergillosis at autopsy. Finally, autopsy studies have proved helpful in documenting the efficacy of systemic antifungal therapy and surgery for IPA [24].

Since the early 1990s, the incidence of invasive candidiasis (candidemia and/or hepatosplenic candidiasis) has continued to decrease due to effective antifungal prophylaxis and empirical treatment of high-risk patients with echinocandins and voriconazole [11]. Mucosal damage is a risk factor for invasive candidiasis among patients receiving antineoplastic therapy. HSCT recipients who received conditioning regimens with total body irradiation and patients treated with chemotherapy regimens containing high-dose cytarabine or an anthracycline have an increased risk of developing invasive disease. In recent years, there has been an increase in bloodstream infections caused by non-albicans *Candida* species such as *Candida glabrata* and *C. krusei*. The diagnosis of invasive candidiasis is difficult to prove due to the lack of specific clinical features and the low sensitivity of blood cultures to isolate *Candida*, especially in patients receiving fluconazole prophylaxis [25].

Difficult-to-treat opportunistic molds, such as *Zygomycetes*, *Trichosporon* spp., and various *Chaetomium* spp., including *C. atrobrunneum*, *C. strumarium*, *C. globosum*, *C. perlucidum*, and *C. cinereus* are being described with increasing frequency on autopsy studies in patients with hematologic malignancies [12, 26–31]. Pulmonary involvement with these mold infections is characterized by tissue necrosis from angioinvasion and subsequent thrombosis. As with many

fungal infections, diagnosis of these infections is often not possible until autopsy. Treatment modalities usually involve lipid-based amphotericin B formulations and surgical debulking or debridement in selected cases [32].

20.2.2 *Pneumocystis Jiroveci* (Formerly *Carinii*) Pneumonia

Pneumocystis jiroveci pneumonia (PCP) remains a serious infection in patients with acute and chronic leukemias, myelodysplastic syndrome, and HSCT recipients [8]. However, diagnosis of PCP is frequently obtained by bronchoalveolar lavage with or without lung biopsy; thus, the diagnosis is made on autopsy in only a minority of cases.

20.2.3 Bacterial Infections

Bacterial pneumonias caused by *Pseudomonas aeruginosa*, *Streptococcus* spp., *Staphylococcus aureus*, *Serratia* spp., and *Legionella pneumophila* have been described on autopsy studies in patients with hematologic malignancy and HSCT recipients [33]. As the majority of these patients commonly receive empiric antimicrobial therapy during the initial diagnostic workup for infection, very few autopsy studies report unusual bacterial infections. A single center autopsy series of 15 patients with hematological malignancies found multidrug-resistant strains such as *Enterococcus faecium* to be very prevalent [34]. Two coagulase-negative *Staphylococcus epidermidis* strains were also noted. A few autopsy case reports have also described lethal pulmonary hemorrhage due to *Stenotrophomonas maltophilia* [35].

20.2.4 Viruses

The incidence of autopsy-proven cytomegalovirus (CMV) pneumonia in patients with hematologic malignancy and HSCT recipients has been decreasing in recent years as a result of improvements in early diagnosis and treatment and more effective preventive strategies [36]. However, it is also possible that the

declining rate of autopsies may account for the decrease in the number of reported CMV pneumonias. Other etiologies of viral pneumonias that have been described in autopsy reports include infection due to herpes simplex virus, respiratory syncytial virus (RSV) [37], and measles virus [38].

20.2.5 Toxoplasmosis

Reactivation of latent Toxoplasmosis is a rare but well-recognized opportunistic infection in immunocompromised patients. Besides encephalitis, the other common presentation with *Toxoplasma gondii* infection is interstitial pneumonitis. Because of its non-specific clinical and radiological presentation and its lethal outcome, toxoplasmosis is often misdiagnosed and only revealed at autopsy [39]. Toxoplasmic pneumonitis follows the same pathogenetic mechanism, but occurs less frequently than either toxoplasmic encephalitis or other opportunistic pneumonias, such as PCP. Diagnosis is based upon a high degree of clinical suspicion and demonstration of *T. gondii* in BAL fluid and/or lung biopsy specimens. Widely disseminated necrotic areas with numerous cysts of *Toxoplasma gondii* are commonly reported in autopsy cases.

20.3 Noninfectious Pulmonary Findings

Noninfectious pulmonary complications account for up to 70% of autopsy findings in patients with hematologic malignancies, particularly in HSCT recipients. The most common complications are diffuse alveolar damage (DAD) and diffuse alveolar hemorrhage (DAH) [8].

20.3.1 Diffuse Alveolar Damage

Diffuse alveolar damage (DAD) is a nonspecific finding at autopsy often in association with various infectious and noninfectious etiologies, such as shock, aspiration, alveolar hemorrhage, peri-engraftment respiratory distress syndrome, drug toxicity, and radiation therapy. It is characterized by the presence of alveolar injury and the absence of active lower respiratory tract infection.

DAD has been reported at autopsy in 63.5% of patients with treated leukemia and lymphoma and close to 50% among HSCT patients [7, 8]. Infections as the cause of DAD are identified on autopsy in only a third of HSCT patients, while approximately 20% have DAH. In over 50% of patients with DAD, no etiology is determined, and these patients are considered as having idiopathic pneumonia syndrome (IPS). It is possible that empirically treated previous infections could have caused the histological changes noted in patients classified as having IPS. Only one third of the cases of DAD are diagnosed antemortem [8]. Given that almost half of the cases of DAD may be secondary to IPS, the role of corticosteroids may need to be furthered studied.

20.3.2 Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a clinical syndrome characterized by the acute onset of alveolar infiltrates, bloody bronchoalveolar lavage, and hypoxemia in the absence of infection [1, 40]. The incidence of DAH ranges from 1–5% to 3–7% in autologous and allogeneic HSCT recipients, respectively [41–43]. A few case reports have been described in patients with acute leukemia more commonly in association with chemotherapy [44–46]. DAH has also been described in patients undergoing an umbilical cord HSCT [47, 48]. The majority of patients with DAH develop severe respiratory failure with high mortality rates. Vascular damage and inflammation from chemotherapy and radiation therapy used in the conditioning regimen and immune-mediated events including GVHD have been implicated in the pathogenesis of DAH [41, 43, 49]. Wojno et al. reported that 41% of 37 allogeneic HSCT patients who underwent autopsies had extensive pulmonary hemorrhage, which was thought to have led to severe respiratory failure and death [49]. These patients were subdivided into those with significant acute GVHD and those without. Of the patients with acute GVHD, 59% died of acute respiratory failure secondary to DAH compared with 25% of those without GVHD. Pulmonary hemorrhage was also independently found to be associated with pre-transplant total body irradiation. Although pulmonary and systemic infections cause alveolar damage through similar mechanisms [50], infection-associated alveolar damage has traditionally been excluded from analyses of DAH. Autopsy studies have shown

that pulmonary infections are frequently underdiagnosed in HSCT recipients; thus, patients with alveolar hemorrhage and underlying undetected infections can be misclassified as having DAH [7, 8, 51].

Because inflammation is thought to play a role in the pathogenesis of post HSCT-DAH, high-dose steroids have been used for its treatment, based on anecdotal case reports and small retrospective series [52, 53]. Other treatment modalities that have been used for DAH in HSCT recipients include epsilon aminocaproic acid and recombinant factor VIIa [54, 55]. Unfortunately, the mortality from DAH in HSCT recipients remains high because of misdiagnosis and lack of effective treatments.

20.3.3 Lymphomatous or Leukemic Infiltration

Primary pulmonary lymphomas are very uncommon, especially those arising from bronchus-associated lymphoid tissue (BALT) and have a low mortality. They represent 4% of the extranodal non-Hodgkin's lymphomas (NHLs) and only 0.5% of all primary pulmonary malignant neoplasms and less than 1% of lymphomas. Eighty percent of the cases are low-grade B-cell lymphomas, which are slow growing and respond well to therapy. Autopsy case reports suggest that pulmonary BALT lymphoma can remain restrictive to the thorax for long periods before dissemination, but tend to relapse frequently.

Lymphomatous involvement of the lung is common and occurs in 24% and 38%, respectively, of patients with Hodgkin's lymphomas (HL) and NHL [56]. Typical findings in the lung include peribronchial-perivascular, nodular, alveolar, interstitial, and pleural involvement. Peripheral T-cell lymphomas also involve the lung frequently, 20% at diagnosis and a further 20% during the course of the disease. The nodular pattern is a characteristic of lung infiltration in HL, but no differences could be detected in the subtypes.

Pulmonary parenchymal involvement by multiple myeloma cells is very rare and described on autopsy in few case reports. The antemortem diagnosis of lung involvement by myeloma is difficult to make as infections and alveolar hemorrhage can have the same radiologic features.

Leukemic infiltration of the lungs may occur in 20–30% of hyperleukocytic patients with acute myeloid leukemia (AML). Pulmonary infiltrates are usually microscopic and invariably associated with hyperleukocytosis. There are autopsy case reports of pulmonary leukemia as a cause of pulmonary infiltrates, even in non-hyperleukocytosis AML patients with low blast counts. Radiographically, patients present with an air-space disease with a diffuse interstitial reticular pattern in cases of hyperleukocytosis similar to cases of infectious pneumonia.

Pulmonary leukostasis syndrome involves the occlusion of small blood vessels in the lungs and typically occurs with a WBC count of greater than 100,000 per mL. The increased number of WBCs causes blood viscosity to rise due to the decreased deformability of the abnormal leukocytes, resulting in cell clumping and stasis in the microvasculature, leading to severe hypoxemic respiratory failure. Autopsy studies reveal extensive infiltration by leukemic cells in the pulmonary vasculature; pulmonary infarction with hemorrhage is also noted. [57]

Rarely, lung involvement by intravascular large B-cell lymphoma (IVLBCL) is noted on autopsy [58]. Early diagnosis is difficult as neither computed tomography nor 67-gallium scintigraphy can detect lung involvement. However, 18-fluoro-deoxyglucose positron tomography (FDG-PET) may be a powerful tool for the early diagnosis of IVLBCL with pulmonary involvement [59].

20.3.4 Pulmonary Thromboembolism

Autopsy studies show that pulmonary thromboembolism (PTE) infrequently complicates the course of patients with acute leukemia and severe thrombocytopenia, and HSCT recipients with an incidence rate ranging from 1% to 6.3% [8]. [60] Patients with acute leukemias commonly have clinically silent haemostatic abnormalities, but some may show clinical manifestations, including venous thromboembolism, pulmonary embolism, disseminated intravascular coagulation, and life-threatening thrombohemorrhagic syndrome. The pathogenesis of PTE is complex and multifactorial and may involve tumor cell-derived procoagulant, fibrinolytic or proteolytic factors, and inflammatory cytokines, which affect clotting activation. Chemotherapy and anti-angiogenic drugs also increase the thrombotic risk in patients with

lymphoma, acute leukemia, and multiple myeloma. Infectious complications are another important factor: endotoxins from gram-negative bacteria induce the release of tissue factor (TF), tumor necrosis factor (TNF), and interleukin-1 (IL-1), and gram-positive organisms can release bacterial mucopolysaccharides that directly activate factor XII. Needleman et al. reviewed 80 consecutive autopsies in leukemia patients and found three patients with previously undiagnosed PTE, all of whom had been severely thrombocytopenic. However, *Candida* forms were abundant in the thromboemboli in all three patients, with some containing septate hyphal forms consistent with *Mucor* or aspergillosis. No vessel wall invasion or necrosis was noted, and fungus was not shown to be present in pulmonary vessels in segments of the lung not involved with thromboembolism [60]. Leukemic patients may also be affected by other prothrombotic factors, including hyperleukocytosis, increased TF expression and activation, and the prothrombotic properties of therapeutic agents, such as all-trans retinoic acid and L-asparaginase, which can induce thrombosis involving multiple organs. A higher index of suspicion may lead to the diagnosis, but the signs and symptoms of PTE in patients with hematologic malignancy are variable and nonspecific as with PTE in other populations.

20.3.5 Bronchiolitis Obliterans with Organizing Pneumonia and Bronchiolitis Obliterans

The majority of patients with hematological malignancies who develop organizing pneumonia (BOOP) have been exposed to various chemotherapeutic agents, including cytarabine and anthracyclines as well as radiation therapy. [61, 62] In one autopsy series, Sharma et al. reported on 71 patients who had undergone HSCT, of whom 3% had BO and 1% had BOOP [8]. Unusual histological variants have also been described, including a case report of acute fibrinous and organizing pneumonia following HSCT in a patient with AML [63] characterized by prominent intraalveolar fibrin deposition and organizing pneumonia. The radiographic presentation revealed patchy consolidation in the lower lobes and a diffuse miliary pattern. Clinically, these cases can have subacute presentations similar to cryptogenic organizing pneumonia or have

more rapid progression with clinical features similar to ARDS. BOOP and BO are rare autopsy findings, which may be because infections are being treated aggressively, and often patients not responding to antibiotics and with no clinical evidence of infections are given a trial of corticosteroids.

Yokoi et al. reported bronchiolitis obliterans (BO) on autopsy in 8 of 81 patients who underwent allogeneic BMT with AML or ALL. All patients received conditioning regimens with total body irradiation and cyclophosphamide with or without busulfan or cytosine arabinoside. Immunosuppressive therapies were administered to all patients after BMT, including methotrexate with or without cyclosporine. The onset of respiratory symptoms was 110–430 days after BMT, and the symptoms were non-productive cough, dyspnea, fever, chest pain, and pneumothorax. Seven patients died of progressive respiratory failure and one of relapsed leukemia. Coexistent infections included *CMV*, *varicella zoster*, *Mycobacterium tuberculosis*, and *Aspergillus* [21]. Paz et al. also described two patients who underwent autologous BMT for lymphoma and developed rapidly progressive respiratory insufficiency on post-transplant day 90 and 273. Despite aggressive immunosuppressive therapy, both patients died of respiratory failure. Autopsy studies revealed histological evidence of bronchiolitis obliterans [64].

20.3.6 Pulmonary Veno-occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension that is characterized histopathologically by intimal proliferation and fibrosis of the pulmonary venules and small veins leading to progressive vascular obstruction [65]. The etiology of PVOD remains unclear. It has been reported as an unusual complication of both myeloablative allogeneic, autologous and cord HSCT, suggesting that it might be regimen-related toxicity [65–70]. Surgical lung biopsy provides definitive diagnosis [71]. PVOD carries a poor prognosis, with most reported patients experiencing progressive disease and death within 2 years of diagnosis [72]. Autopsy findings reveal intimal fibrosis of most of the pulmonary veins, with no significant intraluminal thrombi or arterial changes [69]. Treatment

recommendations are anecdotal. Steroids and heparin have been reported to possibly improve outcomes [66].

20.3.7 Pulmonary Alveolar Proteinosis

Autopsy studies in patients with hematologic malignancy (particularly with myelodysplastic syndrome) and following HSCT have revealed rare cases of secondary pulmonary alveolar proteinosis (PAP) characterized by intra-alveolar accumulation of surfactant components and cellular debris, with minimal interstitial inflammation or fibrosis [73–75]. Secondary PAP is frequently noted among patients with hematologic malignancies who develop fungal infection, especially pulmonary aspergillosis. KL-6 protein is produced by type II alveolar pneumocytes and can be helpful in establishing an early diagnosis of PAP [74, 76]. The standard therapy for PAP with hematological malignancy has not yet been firmly established. The administration of GM-CSF has been suggested to activate the alveolar macrophages and increase the rate of surfactant clearance [73]. Case reports indicate that the prognosis of PAP with leukemia is very poor because of the high frequency of superinfections in the affected alveoli [73, 75].

20.4 Discrepancies Between Clinical and Postmortem Autopsy Findings

Several autopsy series have reported diagnostic discrepancies between premortem clinical diagnosis and postmortem autopsy findings ranging from 5% to 64% in patients with hematologic malignancy and HSCT recipients (Table 20.2) [15, 77–83]. The Goldman criteria are commonly used to categorize discrepancies between clinical and pathological diagnoses or causes of death [84]. Class I discrepancies are defined as missed major diagnoses with potential adverse impact on survival and would have changed management. Class II discrepancies are missed major diagnoses with no potential impact on survival and that would have not changed therapy. Class III discrepancies are defined as missed minor diagnoses related to terminal disease, but not related to the cause of death, and Class IV are other missed minor diagnoses.

Gerain et al. reported a 59% major discrepancy rate in 34 cancer patients who were admitted to a medical oncological ICU over an 11-month period. [77] The majority of major discrepancies were due to complications of the cancer itself or its treatment (such as non-cardiogenic pulmonary edema, acute hemorrhage, and pulmonary embolism) rather than infection. Pastores et al. reported a major missed diagnosis rate of 26% in 86 autopsies performed on cancer patients who died in a medical-surgical ICU [78]. Of the 86 patients, 25 (40%) had undergone HSCT, 18 (29%) had either leukemias or lymphomas, 19 (31%) had solid tumors, and 24 (28%) were surgical cancer patients. Among the patients with discrepancies 54% had class I discrepancies, 32% had class II discrepancies, and 14% had both class I and class II discrepancies. Of the 22 discordant cases, 6 had hematological malignancies and 4 underwent HSCT. Opportunistic infections due to viral, fungal, bacterial, and parasitic organisms and cardiac complications were the most common class I discrepancies. The majority of Class II discrepancies were accounted for by cardiopulmonary complications due to pulmonary embolism and thrombotic endocarditis. The study was limited by the retrospective study design and selection bias that may have occurred as physicians and family members of patients with premortem diagnostic uncertainty would have been more likely to pursue an autopsy. Xavier et al. reported a class I discrepancy rate of 31.3% in 118 autopsies of patients with hematological malignancies or severe aplastic anemia [79]. The most common diagnoses causing these discrepancies were hematological disease, pneumonia, and gastrointestinal hemorrhage. Class I discrepancies were more common in elderly patients (>64 years) and in patients who had not received previous specific treatment for the hematological malignancy, had not been treated with bone marrow or peripheral blood HSCT, or had not been treated in a specialized hematology unit. Seftel et al. reported a discrepancy rate of 64% (34% major, 30% minor) in 48 autopsies of patients who underwent HSCT (blood and bone marrow) [82]. Infectious complications, including pulmonary aspergillosis, candidiasis, and infective endocarditis, accounted for the majority of the major discrepancies. Hoffmeister et al. found a 26% discrepancy rate (4% major, 23% minor) in 111 autopsies of patients who had undergone HSCT [83]. In contrast, Al Saidi et al. found a

Table 20.2 List of selected studies describing discrepancies between premortem and postmortem autopsy diagnoses in patients with hematologic malignancy including HSCT recipients

Al-Saidi et al. 2002 <i>N</i> =28		Seftel et al. (2007) <i>n</i> =48	
Class I <i>n</i> =1 (3.5%)	Systemic aspergillosis (1)	Class I (<i>n</i> =16) (34%)	Candidiasis
Class II <i>n</i> =2 (7.1%)	Severe GVHD (1)		Pulmonary aspergillosis
	Hemorrhagic cecal perforation (1)		Infective endocarditis
Class III <i>n</i> =6 (21.4%)	Non infective endocarditis (1)		Adenovirus, with no GVHD
	Spinal cord demyelination (1)		Adenovirus hepatitis
	CMV pneumonitis (1)		Relapse of myelodysplasia
	Bacterial infections (3)		Acetaminophen overdose
Class IV <i>n</i> =1 (3.5%)	Coagulase-negative staphylococcus catheter infection (1)		Sepsis with multi-organ failure
			Disseminated Aspergillosis
			Gut perforation
			Pneumonia
			<i>Candida</i> pneumonia
			Myelodysplasia relapse
			CMV adrenalitis; no lymphoma
			Typhlitis relapse leukemia
			Pulmonary lymphoma
			Radiation pneumonia
Pastores et al. 2007 <i>N</i> =86		Class II (<i>n</i> =14) (30%)	Cerebral and pulmonary aspergillosis
Class I discrepancies <i>n</i> =15 (17.4%)	Opportunistic infections <i>n</i> =10		Pneumonia; cerebral hemorrhage
	VRE pneumonia		Diffuse alveolar damage
	Legionella pneumonia		Congenital absence of kidney
	PCP pneumonia		No pneumonia
	Invasive aspergillosis		No pneumonia; renal abscess
	<i>Candida</i> empyema		No pneumonia; subarachnoid hemorrhage
	Varicella-zoster meningoencephalitis		No pneumonia; cerebellar hemorrhage
	HSV esophagitis		Hemochromatosis and diffuse alveolar damage
	CMV pneumonia		Idiopathic hepatitis
	Disseminated necrotizing toxoplasmosis		Normal colon
	Cardiac complications <i>n</i> =5		Pulmonary fibrosis
	Ischemic cardiomyopathy (2)		Sepsis
	Thrombotic endocarditis (2)		Cholestatic liver disease
	Congestive heart failure (1)		
Class II discrepancies <i>n</i> =10 (11.6%)	Opportunistic infections <i>n</i> =3	Xavier et al. (2005) <i>n</i> =544	
	Candidemia	Class I (8.6%)	Hematological disease – 15
	VRE meningitis		Pneumonia – 5
	CMV proctitis		
	Cardiopulmonary complications <i>n</i> =7		
	Pulmonary embolism (4)		
	Thrombotic endocarditis (2)		
	Pulmonary hemorrhage (1)		

Table 20.2 (continued)

	Gastrointestinal hemorrhage, – 3
	Congestive heart failure – 2
	Acute pancreatitis – 2
	Pulmonary embolism – 2
	Invasive pulmonary aspergillosis – 2
	Pulmonary edema – 2
Class II (8.4%)	Pneumonia – 9
	Hematological disease – 5
	Invasive pulmonary aspergillosis – 5
	Pulmonary hemorrhage – 4
	Other forms of aspergillosis – 2
	Pulmonary candidiasis – 2
Class III (18.7%)	Hemosiderosis – 17
	Secondary malignant neoplasm of kidney and renal pelvis – 9
	Pleural effusion in conditions classified elsewhere – 9
	Secondary malignant neoplasm of other unspecified digestive organ – 5
	Pulmonary hemorrhage – 4
Class IV (20.2%)	Pulmonary hemorrhage – 14
	Pulmonary edema – 8
	Gastrointestinal hemorrhage – 7
	Nontraumatic intracerebral hemorrhage – 6
	Pleural effusion in conditions classified elsewhere – 6
	Secondary malignant lung neoplasm – 5
	Chronic tubulo-interstitial nephritis – 5

The Goldman classification of diagnostic discrepancies was applied. Major discrepancies included two categories (class I referred to missed diagnoses that would have led to a change in management with possible increased survival or cure; class II referred to major missed diagnoses that would not have impacted survival because no treatment was available, treatment was given even though the diagnoses was unknown, or the patient refused further treatment). Minor discrepancies included two categories (class III referred to missed minor diagnoses related to the terminal disease process but not directly related to the cause of death, and class IV referred to missed minor diagnoses that did not contribute to the cause of death but ultimately may have been significant had the patient survived the major illness)

significant concordance between the clinical and postmortem diagnoses in 28 critically ill HSCT patients [15]. Ten (36%) of the twenty eight patients had discrepancies uncovered on autopsy; only two discrepancies would have influenced patient management, and none would have altered patient outcome. Most of the unexpected diagnoses were infections, and the rest included non-infective endocarditis, GVHD, and gastrointestinal and neurologic diagnoses. The authors concluded that clinical diagnosis alone might be appropriate for withdrawal of care decision-making in these patients.

20.5 Summary

Infectious and noninfectious pulmonary diseases are commonly found on postmortem autopsy studies in patients with hematological malignancy and HSCT recipients. Despite the technological advances in diagnostic testing and imaging modalities, obtaining an accurate clinical diagnosis remains difficult and is often not possible until autopsy. Major diagnostic discrepancies between clinical premortem diagnoses and postmortem autopsy findings have been reported in patients with hematologic malignancy. The most common missed diagnoses are due to opportunistic infections and cardiopulmonary complications. These findings underscore the importance of enhanced surveillance, monitoring, and treatment of infections and cardiopulmonary disorders in these patients. Autopsies remain important in determining an accurate cause of death and for improved understanding of diagnostic deficiencies, as well as for medical education and quality assurance.

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