Pulmonary Complications of Leukemia

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The leukemias are a diverse group of disorders. The natural history and management of the acute and chronic leukemias are distinctly different. Several different pulmonary complications are common in patients with any of the leukemias. These are dependent upon multiple factors, including the type of leukemia, the nature and time course of treatment, and the presence or absence of significant neutropenia or thrombocytopenia. Tenholder and Hooper found that 98 percent of leukemic patients who came to autopsy had pulmonary complications. The true incidence of pulmonary complications in leukemia is difficult to assess because most series reported are selected for patients with specific pulmonary problems or particular leukemias. Moreover, the incidence varies over a wide range, depending upon whether symptoms, chest radiographs, pulmonary function tests, or autopsy findings alone are used as the index of disease.

Pulmonary conditions that must be considered in the differential diagnosis of the immunocompromised host, such as the patient with leukemia, are listed in Table 1. Many of the pulmonary abnormalities are not due to the leukemia itself, but are caused by the patient’s immunocompromised status, medications, or a complicating medical illness. All of the conditions listed in Table 1 should be considered during evaluation of these patients in order to narrow the differential diagnosis as much as possible and to avoid unnecessary invasive diagnostic procedures.

In Tenholder and Hooper’s review of the records of 139 patients with leukemia at the Walter Reed Army Medical Center to determine the etiology of associated pulmonary infiltrates, in 84 instances of parenchymal infiltrates for which a cause was found, only 10 were attributed conclusively to leukemic cell infiltration of the parenchyma. Other causes included infection by bacterial and other opportunistic organisms, hemorrhage, leukemic and lymphomatous involvement, leukostasis, leukemic cell lysis pneumonopath, hyperleukocytic reaction, alveolar proteinosis, adverse drug reactions, and other processes including congestive heart failure (Table 2). These will be discussed. The unique spectrum of pulmonary problems in bone marrow transplant patients will not be discussed here. This review summarizes the major causes of pulmonary complications in leukemia.

Infection

Infection with bacteria and opportunistic organisms is responsible for the majority of pulmonary infiltrates in leukemic patients. Sixty to 75 percent of reported deaths in leukemia are due to infection. In Tenholder and Hooper’s series of 68 patients with pulmonary infiltrates, 82 percent of focal and 35 percent of diffuse infiltrates had infectious causes. Common bacterial pathogens were responsible for most of the focal infiltrates, whereas opportunistic organisms accounted

Table 1—Categories of Pulmonary Disease in the Immunocompromised Host

| Recurrence of the underlying disease process involving the lungs (leukemic infiltrates, unusual complications of leukemia, lymphoma, carcinoma, and lymphoid interstitial pneumonia in human immunodeficiency virus infection) |
| Opportunistic infection |
| Opportunistic neoplasm |
| Drug-induced pulmonary reaction |
| “Unrelated” disease process (cardiogenic pulmonary edema and community-acquired pneumonia) |
| Nonspecific fibrosis |
| Unusual complications of the disease or therapy (pulmonary alveolar proteinosis; pulmonary veno-occlusive disease) |
| Combinations of two or more of the above |

Table 2—Causes of Pulmonary Disease in Patients With Leukemia

| Infection |
| Hemorrhage |
| Leukemia and lymphomatous involvement |
| Leukostasis |
| Leukemic cell lysis |
| Hyperleukocytic reaction |
| Alveolar proteinosis |
| Adverse drug reactions |
| Opportunistic neoplasms |

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for most of the diffuse infectious abnormalities. Clearly, diffuse infections may begin as focal infiltrates, but the significant disparity between opportunistic and nonopportunistic organisms and their associated type of pulmonary infiltrate permits the clinician to offer a more reasonable differential diagnosis.

Several studies have described the microbial causes of infection in patients with leukemia. Baldacci and associates\textsuperscript{5} reported 193 cases of infection in acute leukemic patients in a general hospital setting, almost half of which were located in the respiratory tract. Sixty percent of these were due to \textit{Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa}, and \textit{Staphylococcus aureus}. Fungi (Candida, Mucorales, Aspergillus), viruses (CMV, HSV), and protozoans (Pneumocystis) are less common pathogens.\textsuperscript{5,6}

Granulocytopenia is a major predisposing factor for infections. A direct correlation has been demonstrated between the absolute neutrophil count and the incidence of infection. With counts below 1,000 cells/µl there is a steady increase in incidence, below 500 cells/µl there is a marked increase in incidence, and below 100 cells/µl Gram-negative bacteremias and other fatal infections increase further.\textsuperscript{7,8} A rapidly decreasing granulocyte count and damage to the respiratory mucosa and cilia are particularly harmful consequences of chemotherapy which also increase the likelihood of infection.

In addition, the duration of granulocytopenia can determine the probability of infection, and it is of particular importance in the development and subsequent course of invasive pulmonary aspergillosis (IPA) in leukemic patients.\textsuperscript{9,10} In a study of patients with biopsy-proven IPA, Gerson and others\textsuperscript{11} found granulocytopenia to be the single most important factor in the development of the disease, with an incidence approaching 50 percent if granulocytopenia persisted for three weeks or more. Also, recovery from granulocytopenia after chemotherapy has been shown to worsen the course of IPA, with the development of pulmonary cavitation and frequent episodes of hemoptysis.\textsuperscript{12,13}

In childhood leukemia, viruses are thought to be more important as respiratory pathogens and are major causes of morbidity from respiratory tract infections, especially in acute lymphatic leukemia. A wide spectrum of viruses is involved in these infections.\textsuperscript{14,15}

In hairy-cell leukemia, infectious complications secondary to granulocytopenia, defects in cell-mediated immunity, and monocytopenia are the primary causes of morbidity and mortality.\textsuperscript{16,17} Infectious causes of pneumonitis include Gram-negative bacteria, Gram-positive bacteria, fungal infections, and atypical mycobacterial infections.\textsuperscript{18} Opportunistic granulomatous infections, including blastomycosis and coccidioidomycosis, may also occur.\textsuperscript{19} Disseminated atypical mycobacterial infections, with \textit{Mycobacterium kansasii} and \textit{M avium-intracellulare} being the most common, are characterized by fever, chills, and pulmonary infiltrates. They are probably due to impaired cell-mediated immunity and monocytopenia. These infections were reported in 9 of 186 patients in one series.\textsuperscript{20} Prior to effective chemotherapeutic approaches, patients with hairy-cell leukemia but no infectious complications had been found to live significantly longer than patients with infections.\textsuperscript{16} However, interferon-α recombinant and Pentostatin (2′-deoxycoformycin) are distinctly changing the natural history of the disease and its infectious toxicities.\textsuperscript{21,22}

![Chest roentgenogram of a patient with acute myelomonocytic leukemia (AMML) and pulmonary hemorrhage. B. Massive pulmonary hemorrhage in a 67-year-old man with acute lymphocytic leukemia associated with a low platelet count secondary to chemotherapy (hematoxylin-eosin, original magnification, × 64).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21620/ on 04/27/2017)
HEMORRHAGE

Alveolar hemorrhage is often found at autopsy in patients with leukemia.\(^1\),\(^2\),\(^3\),\(^4\) It is frequently related to other pulmonary pathologic conditions, particularly pneumonia from invasive aspergillosis, which generally involves blood vessels.\(^5\),\(^6\) Alveolar hemorrhage is usually not suspected or diagnosed before death because hemoptysis occurs in less than one-fourth of patients in this setting. The chest roentgenogram may show a well-localized infiltrate(s), a pneumonic pattern, or a diffuse infiltrate (Fig 1 A). Unless it is massive (Fig 1 B), the pathologist may sometimes assume the hemorrhage seen microscopically is an artifact induced by transbronchoscopic or open lung biopsy. Bodey and co-workers\(^5\) found some degree of pulmonary hemorrhage in 54 percent of 50 autopsied cases of acute leukemia. In 12 percent of these, the bleeding was severe enough to compromise pulmonary function, but hemoptysis was absent in all of these patients and in none of them was the diagnosis of pulmonary hemorrhage made prior to death. In almost all documented cases, a platelet count of less than 50,000 cells/\(\mu\)l is present\(^5\),\(^6\),\(^7\) and usually it is below 20,000 cells/\(\mu\)l. Associated fever and roentgenographic findings may mimic infection and mask a diagnosis of occult pulmonary hemorrhage, but, as stated above, an aggressive search for invasive aspergillosis as the cause of hemorrhage must be undertaken, especially if the platelet count is greater than 20,000/\(\mu\)l.

Tenholder and Hooper\(^1\) noted that alveolar hemorrhage was the most common cause of noninfectious pulmonary infiltrates (11 percent of focal and 78 percent of diffuse infiltrates). Contributing pulmonary problems were excluded in these patients. Other series suggest that de novo pulmonary hemorrhage is a less common cause of infiltrates, with an incidence of 3 to 8 percent in immunocompromised patients.\(^7\),\(^8\),\(^9\) A possibly effective quantitative measurement of pulmonary hemorrhage is the macrophage hemosiderin content determined through bronchoalveolar lavage.\(^10\) Alveolar hemorrhage is a disorder of exclusion.

LEUKEMIC AND LYMPHOMATOUS INVOLVEMENT

Pulmonary leukemic cell infiltrates are found at autopsy in 31 to 66 percent of patients who die of leukemia,\(^11\),\(^12\),\(^13\) but symptomatic pulmonary disease due to the leukemic cell infiltrates themselves is uncommon (Fig 2). Leukemic involvement may be parenchymal (both focal and diffuse), pleural, peribronchial, or endobronchial (Fig 3A and B).\(^14\),\(^15\) CLL may convert from a low-grade histologic picture to an aggressive intermediate or high-grade non-Hodgkin's lymphoma, Richter's transformation.\(^16\) This is characterized by rapid clinical deterioration, fever, progressive adenopathy, hepatosplenomegaly, and involvement of extranodal sites, including the lung. This process may occur in patients who have had no previous chemotherapy.\(^17\),\(^18\) The disease may be peribronchial,\(^17\) pleural,\(^17\),\(^19\) mediastinal,\(^17\) and endobronchial.\(^19\),\(^20\) The prognosis is poor in these patients, but long-term remissions have been reported in patients who were treated aggressively with anthracycline-based chemotherapy programs.\(^21\)

LEYKOSTASIS, LEUKEMIC CELL LYSIS, AND HYPERLYMPHOCYTIC REACTION

There are three unusual pulmonary complications
unique to leukemia: leukostasis, leukemic cell lysis pneumonopathy, and hyperleukocytic reaction (Table 2).

Patients with acute respiratory failure due to increased leukocyte or blast cell counts are common. In an autopsy review of 206 patients with acute nonlymphocytic leukemia or chronic myelogenous leukemia, McKee and Collins discovered pulmonary vascular “leukostasis” or small vessel infiltration and occlusion by leukemic cell aggregates in all patients with a leukocyte count greater than 200,000/μl.

Myers and associates described a second type of reaction in a group of patients with acute nonlymphocytic leukemia and leukocyte counts of greater than 200,000/μl, 70 to 90 percent blasts, and acute respiratory failure. Each became severely hypoxemic, developing diffuse pulmonary infiltrates within 48 hours after chemotherapy was initiated, with three dying from respiratory failure despite ventilatory support. This phenomenon was termed “leukemic cell lysis pneumonopathy.” Tissue specimens from these patients demonstrated congestion and distention of pulmonary arterioles, capillaries, and venules by leukocytes and blast cell aggregates, with associated small infarctions, perivascular hemorrhage, and interstitial edema. This leukostasis causes local tissue damage and hypoxemia as a result of vascular obstruction and oxygen consumption by blast cells, with the injury being perpetuated by toxic and thromboplastic substances released by these cells as a result of chemotherapy. The lack of deformability of myeloblastic leukemic cells has been substantiated; it is further postulated that chemotherapy may alter the leukemic cell membrane and thus promote aggregation.

The observation that pulmonary symptoms worsen after chemotherapy in patients with high blast cell counts has led to a similar description of leukemic cell lysis pneumonopathy by Tryka and co-workers. In this study, pulmonary symptoms, fever, and infiltrates developed in five patients with myeloblastic leukemia within four days of the cell count nadir. Each had an open-lung biopsy demonstrating diffuse alveolar damage, and all recovered without specific therapy.

A third but similar condition, by a different mechanism, has been observed by Vernant and co-workers in 25 leukemic patients with acute respiratory distress; all had a leukocyte count greater than 245,000/μl and 35 to 80 percent blasts, with a rapid increase in the leukocyte count and number of blasts over several days. In five of these patients who died, pathologic specimens revealed pulmonary leukostasis with the characteristic accumulation of blast cells in arterioles and capillaries, associated microhemorrhages, and alveolar edema. In addition to the leukostatic mechanisms of injury proposed above, it was also noted that a rapid rise to a “hyperleukocytic” state correlated with acute respiratory distress; however, patients with chronic leukemia and a slow rate of increase in their leukocyte counts did not show the same respiratory symptoms, presumably as a consequence of microcirculatory adaptation. Cottner and associates described the same hyperleukocytic reaction occurring in the cerebral vasculature as commonly as in the lung, accounting for the somnolence and confusion associated with this acute respiratory distress.

It must be remembered, however, that conditions of extreme leukocytosis or thrombocytosis may cause falsely low PaO₂ values on peripheral blood gas analysis. This phenomenon of pseudohypoxia is presumably a result of increased oxygen consumption by
these numerous cells. This may lead to an incorrect diagnosis of hypoxemia, particularly if there is a delay between sampling and analysis of the peripheral blood specimen.

Alveolar Proteinosis

PAP must also be included in the differential diagnosis of pulmonary infiltrates in leukemic patients. An association has been made between hematologic malignancies, an increased incidence of PAP, and coexistent opportunistic pneumonias. In a review of 260 cases of PAP reported to date, Bedrossian and co-workers found 22 patients (8.5 percent) with various hematologic disorders, including nine with leukemia. All had alveolar infiltrates and concurrent infections by opportunistic fungi (Candida species, Aspergillus, Mucorales) or bacteria, particularly Nocardia species. Prakash and associates described a similar group of 5 patients of 34 reviewed (15 percent), in whom hematologic malignancies, asymmetric bilateral alveolar-interstitial infiltrates, and "secondary PAP" were present. Several of these had coexisting infections at open-lung biopsy.

Based on the in vitro evidence from Golde et al that defective alveolar macrophage antimicrobial and chemotactic function is a major feature of PAP, Bedrossian et al and Prakash et al suggested that the macrophage dysfunction characteristic of leukemias may promote PAP. Excessive proliferation and desquamation of type II pneumocytes derived from the circulating pool of leukemic monocytes results in accumulation of intracellular substances and phospholipoproteins in the alveoli. Defective macrophages are unable to phagocytize the increased load of debris, and additional macrophages are not recruited because of errors in chemotaxis, causing further filling of the alveoli with proteinaceous substances. Chemotherapeutic agents may inflict further damage to these functions. Thus, the altered cell-mediated immunity in leukemia, manifested by impaired macrophage function, predisposes the patient not only to recurrent opportunistic pulmonary infections, but also to PAP.

Adverse Drug Reactions

Adverse drug reactions affecting the lung can mimic opportunistic infection, pulmonary edema, and leukemic infiltration and must always be considered in the differential diagnosis of pulmonary infiltrates in patients with leukemia who are undergoing treatment with chemotherapeutic agents.

The onset of drug-induced pulmonary disease can be insidious, subacute, or chronic—the last especially with busulfan. Most drug-induced pulmonary disease is associated with fever, but not necessarily a daily fever. It is rarely associated with shaking chills or night sweats. Fever may precede the onset of symptoms of nonproductive cough, dyspnea, and chest roentgenogram abnormality. It is a disease of exclusion. Even though histologic specimens may show some atypia of the type II pneumocyte as well as other cells characteristic of drug effect, this finding is not diagnostic. A diagnosis of drug-induced pulmonary disease requires that the patient be taking a drug known to cause this and have histologic features consistent with drug effect and the exclusion of other causes. It is important to consider a diagnosis of pulmonary drug effect because it is frequently fatal, even after the responsible drug has been stopped and after intervention with corticosteroids. Several acute drug-induced pulmonary disease states are frequently confused with ARDS.

Cytosine arabinoside (Ara-C) produces a unique clinicopathologic picture of noncardiogenic pulmonary edema, usually beginning during treatment or within 30 days of treatment completion. The onset of acute dyspnea and fever mimics ARDS and occurs in up to one-fourth of the patients receiving the drug. Hemoptysis may also occur. Chest roentgenograms show a diffuse infiltrate and histologic specimens show minimal parenchymal changes with diffuse intra-alveolar proteinaceous edema fluid. Treatment is supportive with corticosteroids; there is approximately 50 percent mortality.

Busulfan was one of the first drugs recognized to produce an adverse effect on the lungs. A review of 56 cases with an estimated incidence of 6 percent was recently published. The onset is insidious. Parenchymal infiltrates seen on chest roentgenogram may be asymmetric and may mimic idiopathic pulmonary fibrosis as well as other entities such as CMV disease, Pneumocystis pneumonia, and miliary tuberculosis. In the series by Massin and associates, there was an 84 percent mortality with an average onset at 41 months.

There are hundreds of case reports of methotrexate pneumonitis occurring mainly in children being treated for acute lymphatic leukemia. This reaction is predominantly a hypersensitivity reaction in that over half of the cases are associated with eosinophilia and the onset is within a few days to several weeks of initiating the medication. The reaction disappears in a few days of either just discontinuing the drug or adding corticosteroids. In at least one-third of the cases in which tissue is available, granulomas are seen, but tissue eosinophilia is uncommon. An acute and usually fatal pulmonary edema has been reported with intrathecal administration of methotrexate.

Conclusion

Several practical considerations can be derived from this review. Infection is the most common cause of infiltrates, with local infections being more common.
than diffuse. These can be diagnosed effectively by using blood cultures and specimens from sputum, bronchoalveolar lavage, and open-lung biopsy. Pulmonary infiltrates may be attributable to new pulmonary processes, such as cardiogenic pulmonary edema, pulmonary emboli, and chemotherapeutic drug effect, which are unrelated to the underlying leukemia or the patient’s immunocompromised status. These conditions may be reversible with standard treatment. Similarly, the causes of pulmonary infiltrates discussed above, for which the leukemia is responsible, are potentially reversible with chemotherapy. A rapidly increasing leukocyte count, or an absolute leukocyte count greater than 100,000 cells/μL, is clearly an indication for urgent intervention, including rapid hydration, alkalinization of the urine, and administration of allopurinol and hydroxyurea followed by chemotherapy. In these instances it is essential to prepare for possible cell lysis pneumopathy and respiratory distress with available ventilatory assistance.

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