Pulmonary Infiltrates in Leukemia*

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We reviewed the inpatient records of 139 adult patients with leukemia to determine the incidence of opportunistic infections in immunocompromised patients and the pattern of roentgenographic involvement of such infections. There were 98 parenchymal infiltrates identified, including 43 episodes of local disease and 55 episodes of diffuse disease. The causes of the infiltrates were determined from biopsies of tissue and autopsies whenever possible. If roentgenographic resolution after therapy with an antibiotic or diuretic agent was documented, the cause was considered determined; however, this did not identify a specific bacterial or viral agent. Parenchymal infiltrates (17 episodes) appearing in the period before treatment or within 72 hours of initiating therapy were not opportunistic. Local disease during treatment was infectious in 23 (74 percent) of 31 cases and was bacterial in 20 (87 percent) of 23 cases. Opportunistic organisms caused only 13 percent of the local infectious episodes. Diffuse disease was noninfectious in 26 (65 percent) of 40 episodes; while in the 14 episodes of infectious disease identified, 13 (93 percent) were caused by opportunistic organisms. We conclude that procedures for biopsy to document opportunistic infection are of little value in local or diffuse disease before treatment, are of modest value in local disease during treatment, and are of greatest value in diffuse disease during treatment if little clinical evidence for noninfectious causes exists.

The advent of successful transplantation of organs and effective chemotherapy for malignant neoplasms has led to the evolution of a major new clinical problem, infections with opportunistic organisms. Infections with various fungal species, cytomegalovirus, and parasites like Pneumocystis represent a major threat to the immunocompromised patient; and, unfortunately, such infections are difficult to diagnose and treat. Recently, investigators have stressed the need for "early" histologic diagnosis, the safety of major procedures for biopsy, the high diagnostic yield of such procedures, and the cooperative approach of multiple medical disciplines.1,3

Clinical experience at this institution led us to question the validity and application of some of these principles when dealing with pulmonary infections in the immunocompromised host. In particular, the concept of "early" histologic diagnosis is interpreted differently by different disciplines. The safety of major procedures (such as open lung biopsy)

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when applied to very ill patients with thrombocytopenia and leukopenia is also questioned by some of the medical subspecialists.

To help clarify these relationships and establish guidelines for future studies, we studied one subset of immunocompromised hosts, ie, patients with leukemia. We selected this subset because of the frequency of pulmonary complications observed, the severe degree of their immunocompromise, and the significant experience at this institution with this group of patients. Our findings suggest that the roentgenographic pattern and the timing of the appearance of the parenchymal infiltrate help to predict the expected yield from invasive procedures.

Materials and Methods

We reviewed all inpatient records from patients with leukemia who were 18 years of age and older and who were admitted to Walter Reed Army Medical Center, Washington, DC, between June 1, 1973 and April 1, 1978. We examined these records throughout multiple admissions until the patient was discharged from care at this institution or died during treatment. The diagnosis of leukemia was treated in the following manner. Patients with acute myelogenous leukemia, acute myelomonocytic leukemia, and the blastic phase of chronic myelogenous leukemia were considered as acute-phase leukemia. Patients with acute lymphocytic leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia were treated as separate categories. Those leukemias which could not be classified into one of these groups by the attending oncologist were considered as unclassified leukemias.

Evidence of thoracic disease was established by reviewing all reports on chest roentgenograms for abnormalities. For all patients with abnormal chest roentgenograms, we extracted clinical data from physicians' and nurses' notes and from reports from the laboratory and pathology department. Clin-
ical data specifically evaluated included leukopenia, thrombocytopenia, and therapy with antibiotics, steroids, and chemotherapeutic agents. We obtained evidence for infective agents from cultures and histologic reports and noted all sources.

This study classified abnormal chest roentgenograms reported as parenchymal abnormalities according to the time of onset and the radiographic extent of disease. Local roentgenographic disease was defined as an infiltrative process with a lobar or segmental distribution. More than one lobe or segment could be involved. Disease limited to an area less than a lobe or segment was also considered to be local disease. All other parenchymal abnormalities were considered to be diffuse disease, including nodular, reticular, congestive, or alveolar filling patterns. All roentgenograms located were reviewed by two pulmonary physicians, with agreement reached as to local or diffuse involvement prior to determination of the cause of the infiltrate. If the roentgenogram was not available, the radiologists' description of the extent of involvement was used.

We used clinical and pathologic data to define the causes of the infiltrates. A cause was established when it met one of the following criteria: (1) histologic demonstration of the pathologic abnormality obtained by an invasive procedure or an autopsy; or (2) resolution of the infiltrate after specific therapy (ie, antibiotics or diuretics), when such a relationship had been noted by the attending physicians and confirmed on retrospective review. No attempt was made to separate viral and bacterial causes. Bacterial infections were considered etiologically related to the infiltrates when a clinical response to therapy with antibiotics occurred, when multiple cultures of blood and sputum demonstrated a common pathogenic organism, or when demonstrated by open lung biopsy or autopsy. All episodes of infiltrates which could not be defined by one of these criteria were considered unresolved (unknown cause). The only etiologic diagnoses identified on clinical grounds in this study are bacterial pneumonias and congestive heart failure. All other etiologic diagnoses are established by demonstration of the histologic pathologic abnormality.

We determined the yield from invasive procedures in the following manner. We required documentation of invasion of tissue to diagnose aspergillosis or candidiasis. Hemorrhage was diagnosed only when other diagnostic entities were not present (ie, leukemic infiltrates, Candida, Aspergillus). Leukemia was diagnosed when leukemic cells were easily identified out of the vascular space and no specific infectious cause was found. Pulmonary fibrosis and nonspecific inflammation were not considered etiologic diagnoses, even though the negative information may have some value.

At autopsy the lungs had more than one histologic diagnosis on occasion. We recorded the most significant pathologic abnormality, as noted by the pathologist, and applied the same criteria for establishing the etiologic agent of the pulmonary disease as outlined under the method for analyzing the results of procedures. We made no attempt to relate the pharmacologic history or oxygen therapy with the pathologic changes.

**RESULTS**

In the retrospective review period, 139 adult patients with leukemia were admitted to Walter Reed Army Medical Center. There were 101 men and 38 women, with an age range of 18 to 82 years. Sixty-three patients died during therapy at this institution, while the remaining 76 patients were discharged while in remission or returned to referral hospitals for continuing medical care.

Ninety-eight separate instances of parenchymal infiltrates were reported in 87 patients at some time during their course. Fifty-two (37 percent) of the 139 patients had no parenchymal infiltrates throughout their course at Walter Reed Army Medical Center. Twenty-three patients had only non-parenchymal abnormalities (ie, hilar adenopathy, mediastinal widening, or pleural effusion). The episodes of parenchymal infiltrates occurred prior to treatment or within 72 hours of initiating therapy (period designated as pretreatment) in 17 instances and during the course of treatment in 81 instances. The cause of the infiltrates was established in 86 percent (84) of all 98 episodes.

The relationship between the types of leukemia, pulmonary infiltrates, and opportunistic infections can be seen in Table 1. Opportunistic infections are considered to be those caused by fungus, cytomegalovirus, parasitic disease, or mycobacteria. The groups with acute leukemia were responsible for 88 percent (14/18) of the opportunistic infections. Opportunistic organisms were responsible for 8 percent (3/39) of the local infiltrates and for 29 percent (13/45) of the diffuse infiltrates for which a cause could be established with our criteria.

In the period designated as pretreatment, infiltrates occurred on 17 occasions, with the radiographic pattern being that of local disease in 12 instances and that of diffuse disease in five. A cause was defined in 16 episodes (94 percent). The local disease resolved with antibiotic therapy on eight occasions. Pseudomonas and Escherichia coli were each documented on one occasion, while in six episodes the bacterial pathogen remained undefined. Three local infiltrates resolved without treatment, and in one persistent infiltrate a cause could not be ascertained. The infiltrates with a diffuse distribution represented pulmonary edema twice, leukemic infiltrates on two other occasions, and hemorrhage.

**Table 1—Types of Leukemia, Infiltrates, and Opportunistic Infections**

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>No. of Patients</th>
<th>Infiltrates/Opportunistic Infections</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Local</td>
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<tr>
<td>Acute-phase</td>
<td>65</td>
<td>21/1</td>
</tr>
<tr>
<td>Acute lymphocytic</td>
<td>20</td>
<td>10/1</td>
</tr>
<tr>
<td>Chronic myelogenous</td>
<td>18</td>
<td>5/0</td>
</tr>
<tr>
<td>Chronic lymphocytic</td>
<td>26</td>
<td>5/1</td>
</tr>
<tr>
<td>Unclassified</td>
<td>10</td>
<td>2/0</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>43/3</td>
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on one occasion. No opportunistic infections were found in the period of pretreatment.

During the period of treatment, parenchymal infiltrates occurred on 81 separate occasions in 70 patients. The radiographic pattern was that of local disease in 31 instances (38 percent) and that of diffuse disease in 50 instances (62 percent). A cause for the disease process could be established in 90 percent (28) of the 31 episodes of local disease and in 80 percent (40) of the 50 episodes of diffuse disease. The causes of local disease are presented in Table 2. Of the 28 episodes in which the cause could be established, infectious causes accounted for 82 percent (23 episodes); however, an opportunistic organism was the responsible agent in only 11 percent (3/28 episodes).

The causes of the radiographic diffuse disease occurring during treatment are listed in Table 2. In the patients in whom a cause could be determined, noninfectious causes (ie, hemorrhage, leukemia, edema) accounted for 65 percent (26/40), while infectious causes accounted for 35 percent (14/40) of the episodes. Diffuse hemorrhage and leukemic involvement of the lungs accounted for 48 percent (19/40) of these diffuse episodes, while congestive heart failure or volume overload was responsible in an additional 18 percent (7/40). In contrast to the findings in the treated group with local disease, 13 of 14 infections were caused by opportunistic organisms.

Data from postmortem examinations were avail-

<table>
<thead>
<tr>
<th>Total No. of Procedures</th>
<th>Diagnostic Yield*</th>
<th>Serious Complications**</th>
</tr>
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<tbody>
<tr>
<td>Needle biopsy†</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Transbronchial biopsy</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Open lung biopsy</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>6 (24)</td>
</tr>
</tbody>
</table>

*Histologic diagnosis according to criteria.
**Hemorrhage, infection, or other life-threatening event.
†Abandoned in 1973 because of rate of complications.

able in 45 (71 percent) of the 63 patients who died at this institution. Postmortem findings reflected the results in the treated group with diffuse disease, since the majority of the patients who died (43/45 or 96 percent) were under treatment, and 80 percent (36/45) had diffuse pulmonary disease at the time of their death. Abnormal preterminal roentgenograms were present in 44 (98 percent) of the 45 cases undergoing autopsy. Because of these factors, the cause of diffuse disease was confirmed at autopsy in 90 percent (36/40) of the cases.

The procedures performed in these patients to obtain pulmonary tissue varied because of the assortment of personnel caring for patients at a military institution and because of the evolution of techniques for biopsy during the five years of the period under study. The techniques employed, the diagnostic yield of the procedures, and the frequency of serious complications are recorded in Table 3. These complications were related to hemostasis (60 percent; 3/5), infection (20 percent; 1/5), and ventilatory failure (20 percent; 1/5). The complications were the following: in needle biopsy (discontinued in 1973 because of complications), massive hemothorax and major pulmonary hemorrhage; in transbronchial biopsy, mild pulmonary hemorrhage producing respiratory failure; and in open lung biopsy, persistent hemothorax and bacterial sepsis. The population of patients undergoing procedures represented a very ill group. Thrombocytopenia with platelet counts below 15,000/cu mm was present in 72 percent (8/25) of these patients. These patients all received transfusions of platelets on the day of the procedure.

**DISCUSSION**

This study demonstrates some of the clinical features of pulmonary disease in the patient with leukemia. Knowledge and understanding of these clinical events are important in the approach to and the management of these patients.24 The criteria stud-
ied are particularly valuable in identifying situations in which the probability of an opportunistic infection is significant. Since invasive procedures can be associated with significant complications, selection of patients for procedures by these criteria will improve the yield/risk ratio of the procedures employed. As expected, these patients demonstrated that pulmonary infiltrates and opportunistic infections are primarily problems of "acute-phase leukemia" (Table 1). In addition, our findings indicate that noninfectious causes are significant causes of diffuse pulmonary disease. The timing of the appearance of the infiltrates and the radiographic distribution of the disease are important clinical factors and also must be considered when dealing with this problem.

In our experience, pulmonary infiltrates which occur at the time of presentation for treatment or within the first three days of treatment for leukemia are not caused by opportunistic organisms. Infiltrates with local distribution are frequently infectious, but the cause is bacterial and not opportunistic. Infiltrates of diffuse distribution were noninfectious. Previous investigators have also noted that initial febrile illnesses in leukemia are not caused by opportunistic organisms. Although the sample in this group is small, it suggests that procedures for biopsy of local or diffuse infiltrates to document opportunistic organisms would have very low yield.

Infiltrates occurring in patients receiving therapy represent a far greater clinical problem. In our patients receiving therapy, the separation of infiltrates into local or diffuse radiographic distribution defined distinctive etiologic patterns. When local disease appeared during treatment, it was infectious 82 percent (23/28) of the time; however, the infections were primarily bacterial in origin, with only three opportunistic fungi in this group (13 percent [3/23] of all local infections in treated group). Unfortunately, it is difficult to ascertain from previous literature the magnitude of the opportunistic threat experienced by other investigators in this situation. Previous investigators have not specifically defined roentgenographic patterns or clinical episodes of infiltrates. The focus in these reviews has been on autopsies or specific organisms and not on roentgenographic patterns as predictors of the opportunistic threat.

The episodes of diffuse pulmonary infiltrates occurring during treatment were infectious only 35 percent (14/40) of the time. These infectious episodes, in contrast to the group with local disease, were the result of an opportunistic organism 93 percent (13/14) of the time. Previous studies have defined the incidence of opportunistic fungi at autopsy to be 13 to 31 percent. Opportunistic organisms were the cause of pulmonary pathologic abnormalities in 29 percent (13/45) of the autopsies in our study and accounted for 32 percent (13/40) of the episodes of diffuse disease. It is this subgroup (diffuse disease occurring during treatment) which would have the highest diagnostic yield for opportunistic organisms when invasive procedures are employed.

Our study identified a large number of patients with noninfectious pulmonary disease when diffuse disease occurred during treatment (65 percent [26/40] of the episodes). The majority of these episodes were the result of hemorrhage or leukemic infiltration into the lung (Table 2). The difficulty in establishing these diagnoses clinically is widely appreciated. The presence of fever was not useful in distinguishing infectious from noninfectious causes of the infiltrates. Ninety-four percent (82/87) of the patients with infiltrates had fever.

The data demonstrate that noninfectious pulmonary disease is a major problem in these patients and has to be considered when evaluating the risk/yield benefit for invasive procedures. Histologic demonstration was required for the establishment of the noninfectious diagnoses. In fact, the majority of the noninfectious diagnoses were established at the time of autopsy. The only diagnoses established on clinical grounds in this study were those which resolved with specific therapy, such as congestive heart failure and bacterial pneumonia. It can be argued that the criteria we employed for a clinical diagnosis (resolution after therapy) were not rigid enough or that the postmortem diagnoses favored a nonbacterial process because of the difficulty of diagnosing bacterial processes anatomically in patients receiving antibiotics who have leukopenia. While both arguments are pertinent, neither mitigates the findings of this study. Many infiltrates resolve with antibiotic therapy and behave as a bacterial process. At autopsy the major pulmonary pathologic abnormality is frequently of a noninfectious type.

The procedures employed at this institution to obtain tissue for the diagnosis of opportunistic organisms varied, but all are associated with a significant rate of complications (Table 3). This fact stands in contrast to other series of invasive procedures used in immunocompromised patients, where the reported rates of complications have been much lower. It is interesting to note that the rate of complications reported by other authors varies directly with the number of patients in the higher risk subsets of immunocompromised patients, i.e., those with leukemia and those receiving organ
transplants.\textsuperscript{1,2,11-14,17} The population of patients with leukemia in this study who underwent biopsy tended to be very ill, with compromised cardiopulmonary reserve or hemostatic mechanisms. The complications experienced in our patients occurred despite maximum medical support, which suggests that the primary disease process is a significant factor in producing complications, rather than a compromised cardiopulmonary reserve.

The diagnostic yield for the procedures employed appears to be significantly lower than previous studies.\textsuperscript{1,2,11-14,17,18} In our cases the criteria applied are such that only when a specific infectious organism or leukemic infiltration was identified was a yield reported. Diagnostic findings commonly reported by other investigators (such as fibrosis, non-specific inflammation, and interstitial pneumonia) were considered to be nondiagnostic because of the multiple agents responsible for such pulmonary pathologic abnormalities (ie, chemotherapeutic agents, increasing concentrations of inspired oxygen, irradiation, viruses).\textsuperscript{18-20} Five of six patients whose illness was diagnosed died despite therapy. One patient was treated and recovered from infection with Pneumocystis. Thus, the clinical results of establishing a diagnosis of an opportunistic infection were not good. The clinical value of a biopsy where an infectious agent was not found could not be ascertained from this review.

The experience at this institution in patients with leukemia indicates that clinical criteria can be used to identify situations with a significant probability for opportunistic infections and that procedures to obtain pulmonary tissue for the diagnosis of these infections are associated with significant risk. Consequently, guidelines for the use of invasive procedures in leukemia have been developed.

In situations where infiltrates occur prior to or within three days of the onset of chemotherapy, we believe that invasive procedures should be held in reserve to follow therapeutic antibiotic or diuretic trials. Opportunistic infections did not occur in our patients in such situations. When local pulmonary disease occurs during treatment for leukemia, we believe that invasive procedures should be held in reserve. In such situations, bacterial infections occur 10 times more often than do the opportunistic infections. The length of the antibiotic trial and the approach to the patient whose local disease spreads or becomes diffuse must remain a judgment based on the status of the individual patient and the clinical responses to therapy.

Diffuse pulmonary infiltrates occurring during the treatment of leukemia are the result of opportunistic organisms in one-third of the episodes. It is in this subgroup that invasive procedures have the greatest likelihood of demonstrating opportunistic organisms. Since intrapulmonary hemorrhage, leukemic involvement of the lung, and volume overload are major noninfectious causes of diffuse pulmonary disease (Table 2), the yield of invasive procedures for opportunistic organisms is greatest when these diagnoses are clinically unlikely (ie, normal or reasonable hemostatic mechanisms, leukemic remission, and appropriate fluid balance).

Our study suggests that a conservative approach to invasive procedures during the period designated as pretreatment and for local disease during treatment is reasonable. On the other hand, the "early" use of invasive procedures appears most appropriate with diffuse disease during treatment, unless clinical evaluation strongly suggests noninfectious causes. These guidelines are suggested to be of practical value to the clinician in dealing with these problems. Whether or not similar criteria can be established and utilized for other subsets of immunocompromised patients is speculative, but such a possibility seems likely and deserves clinical investigation.

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REFERENCES

12 Leight GS, Michaelis LL. Open lung biopsy for the


