Summary

The charts and autopsy protocols of 51 patients with Hodgkin's disease were reviewed. Thirty-five patients were found to have significant infectious complications during their clinical course. The majority of these problems occurred during the last quarter of illness, when chemotherapy was ineffective. Bacterial infections, especially septicemia, were most frequent although a relatively large number of viral and fungal diseases were found. Single episodes of toxoplasmosis and pneumocystis were also discovered in this series.

Thirty-five of the 51 patients were infected at the time of death; however, infection per se could not be shown to adversely affect survival for the entire group. However, each of the 4 documented infections with cryptococcosis was primarily responsible for the death of the affected patients. Nevertheless, all patients had active Hodgkin's disease at autopsy. No relationship of infection to various forms of therapy or to leukopenia was found for bacterial infections; however, 90% of the patients with fungal disease and 100% of the patients with cytomegalic inclusion disease received corticosteroids.

Introduction

Infections are frequently encountered during the course of patients with neoplastic diseases (5, 6, 22). Changing patterns of bacterial diseases and increasing frequencies of fungal diseases have been reported, particularly in patients with acute leukemias and malignant lymphomas (14, 16, 25). Moreover, infections due to organisms with low pathogenicity for normal human adults have been described (Refs. 8, 9, 16, 17, 25-27).

This report elucidates the frequency, type, and distribution of infections occurring during the course of patients with Hodgkin's disease and examines the role of therapy and extent of disease predisposing to their development. Moreover, the relationship of infection to mortality was investigated.

Materials and Methods

All charts of patients with Hodgkin's disease autopsied at the NIH during the years 1953-64 were reviewed. The number and type of infectious episodes and the relation of these episodes to the course of disease, treatment, and hematologic status were examined. The clinical and autopsy findings were evaluated to determine the cause of death.

An infectious episode was defined as an event of clinical signs and symptoms highly indicative of sepsis (i.e., chills, temperature greater than 38°C, hypotension, pulmonary symptoms, etc.) coupled with microbiologic documentation of bacterial and fungal disease. In only 1 instance, a response to antibiotic therapy was used as supporting evidence. An infection was considered present if there was appropriate histopathologic evidence regardless of the presence or absence of cultural data. A positive heart blood culture was interpreted in light of clinical and histopathologic data.

The diagnosis of herpes zoster or varicella was made on finding typical clinical signs and symptoms alone, whereas the diagnosis of cytomegalic inclusion disease or disseminated herpes simplex was made usually with confirmatory histopathologic material.

Fifty-four charts were reviewed and 51 were found acceptable for this study. Three were not included because of incompleteness. Nineteen patients were female, and 32 were male. The median age at the time of biopsy was 33 years. The median survival from the time of biopsy (diagnosis) was 30 months (Table 1).

These 51 patients were classified as to the stage of disease (2) by the authors according to the clinical data presented in the records (Table 1).

Results

Thirty-eight of the 51 patients surveyed experienced episodes of infection during the course of their neoplastic disease. Three of these 38 patients had infections which were adequately treated and did not recur so that the infection had no role in the ultimate demise of these patients. The remaining 35 patients had infections at autopsy. In 17 of these 35 patients the infections occurred prior to the terminal episode, whereas 18 became infected only during the last 1-10 days of life (Table 2). The median survival for the 2 groups of patients (i.e., those with and without demonstrable infections at postmortem examination) was essentially the same (Table 2). All patients in this study population had active Hodgkin's disease demonstrated by autopsy, and no patient died of infection alone while the disease was in apparent remission. Five patients were considered to have died because of infection (Table 3).

Types of Infection

All infectious episodes were categorized for the 35 patients with infections at post mortem. The total number of infections was 86 and the average number of infections per infected patient was 2.3 (Table 4). Bacterial infections were most common in this group of patients, caused the major portion of morbidity, and
Infectious Complications

**TABLE 1**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>51</td>
</tr>
<tr>
<td>Ratio of females to males</td>
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</tr>
<tr>
<td>Median age in years (range)</td>
<td>33 (6-71)</td>
</tr>
<tr>
<td>Median survival in months (range)</td>
<td>30 (1-135)</td>
</tr>
<tr>
<td>Clinical staging at time of biopsy</td>
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</tr>
<tr>
<td>Stage I</td>
<td>1</td>
</tr>
<tr>
<td>Stage II</td>
<td>25</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
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<td>B</td>
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<td>Stage III</td>
<td>21</td>
</tr>
<tr>
<td>Not defined</td>
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**TABLE 2**

<table>
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</thead>
<tbody>
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<td>No infections (clinical or postmortem)</td>
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<td>32</td>
</tr>
<tr>
<td>Clinical infections, none at postmortem</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Clinical and/or postmortem infection</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Terminal infection only</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Preterminal and terminal</td>
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<td></td>
</tr>
</tbody>
</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>No. of patients</th>
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</thead>
<tbody>
<tr>
<td>Hodgkin's disease alone</td>
<td>16</td>
</tr>
<tr>
<td>Hodgkin's disease and infection</td>
<td>35</td>
</tr>
<tr>
<td>Primarily Hodgkin's disease</td>
<td>30</td>
</tr>
<tr>
<td>Primarily infection</td>
<td>5</td>
</tr>
<tr>
<td>Infections alone</td>
<td>0</td>
</tr>
</tbody>
</table>

were associated most frequently with mortality. Nevertheless, viral, fungal, and rarer types of infections were noted for 30 of the 86 episodes. The distribution of the different types of infections is listed in Table 4. Mixed infections, i.e., bacterial and viral, bacterial and fungal, bacterial and miscellaneous, accounted for nearly 30% of the total number of infectious episodes.

**Bacterial Infections**

Septicemia occurred with surprising frequency in these patients and represented the most common manifestation of bacterial infection. Seventy-five % of these episodes were associated with a known primary site of infection. Table 5 depicts the frequencies of the different kinds of bacterial infections. Hemolytic *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* were the organisms most frequently associated with blood stream invasion (Table 6). These same organisms were responsible for the majority of pneumonias. There was only 1 instance of pneumococcal pneumonia.

Each of the 4 episodes of enteritis was associated with a strain of salmonella organisms. The usual pathogens were encountered in the instances of urinary tract infections and skin abscesses. All of the 3 cases of empyema and most of the cases or urinary tract infection were associated with structural abnormalities related to the underlying Hodgkin's disease (e.g., fistulous communica-
Viral Infections

There were 8 instances of herpes zoster and 1 case of adult varicella in this group of patients (Table 7). These occurrences were not associated with mortality and therefore were not considered in analyzing the survival data. Nevertheless, 4 of the 5 cases of cytomegalic inclusion disease and all of the cases of disseminated herpes simplex were diagnosed only at postmortem examination. One case of cytomegalovirus infection (CID) was discovered by antemortem culture of saliva. Most CID infections were not implicated as major causes of demise; however, each episode of herpes simplex and one of CID were considered significant contributory factors to mortality. All of the patients with CID had coexisting infections. Four of these 5 had inclusions in alveolar cells of the lungs. The presence of these inclusions was considered to be clinically insignificant in producing disease manifestations except in 1 patient who had a hemorrhagic bronchopneumonia.

Fungal Infections

There were 6 cases of disseminated fungal infections and 4 other patients with localized fungal disease (Table 8). Each instance of cryptococcal disease was felt to be the major cause of death.

Miscellaneous Infections

There were single cases of disseminated tuberculosis and toxoplasmosis and pulmonary pneumocystitis encountered in this series of patients. These infections caused major morbidity but were considered not to be the primary cause of death. The case of tuberculous was the only one in this group in which a positive diagnosis was made before death.

Clinical Correlations

Most of the infections occurred relatively late in the disease course. To substantiate this hypothesis, the clinical course was divided into quarters. The terminal period was listed separately from the 4th quarter. The terminal period was defined as that period (1–10 days before death) in which a sudden adverse turn of events occurred leading to the death of the patient. Table 9 shows the relative frequency of infections according to taxonomic group that occurred during the defined intervals. The preponderance of episodes occurred during the 4th quarter and with the terminal period.

Because chemotherapy and steroid therapy have been implicated as predisposing factors to infection (11, 30), the amount and type of therapy administered was charted according to quarters for both the infected and noninfected patients. As can be seen in Chart 1, the proportion of patients receiving radiation therapy and chemotherapy was relatively constant in each quarter for the infected group. On the other hand, the proportion of patients receiving radiation therapy decreased and the proportion receiving chemotherapy increased as the disease progressed for the noninfected group (Chart 2). The proportion of patients receiving steroids increased significantly in the last quarter for both groups.

Leukopenia (granulocytes less than 1000/cu mm) was not a significant contributing factor to infection as only 4 of the 35 infected patients had this degree of leukopenia during the terminal episode whereas 3 of the 16 noninfected patients experienced this degree of leukopenia within the last 10 days of life.

Although the median survival for both the noninfected group and the infected group was similar, life-table analysis (Chart 3) shows that the slope of the probability curve of survival for the infected group was less than that for the noninfected groups after the point of median survival. Because the staging and histology...
**Infectious Complications**

**Chart 1.** Correlation of therapy to the course of the disease in 25 patients with only bacterial infections at postmortem.

**Chart 2.** Correlation of therapy to the course of the disease in 16 patients without infection.

**Chart 3.** Life-table analysis: probability curves.

*Survival:*
- Infected = 35 Patients
- Uninfected = 16 Patients
Albert R. Casazza, Charles P. Duvall, and Paul P. Carbone

of both groups was similar, the difference in slope implies that infection did not affect survival adversely.

The infected category of patients was then separated into 2 subgroups according to survival. Table 10 shows the distribution of the various types of infection in those patients surviving up to the median time and those living longer. Two points are apparent. Of those 19 patients dying with infection after a brief course of Hodgkin's disease, 15 died with only a bacterial infection, whereas those dying after a relatively prolonged illness were prone to have fungal disease as well as bacterial infections. There was only 1 instance of disseminated fungal disease (histoplasmosis) in the 19 patients living 30 months or less, whereas there were 5 instances of disseminated fungal disease in the 16 patients living longer than 30 months. All 4 episodes of cryptococcosis occurred in patients surviving longer than 30 months. The mean survival of these patients so infected was 92 months (median 102 months).

The mean survival of the 5 patients with CID was 27 months (median 30 months). The episodes of toxoplasmosis and pneumocystis occurred in patients with longer survivals.

Discussion

Infection has been recognized as a major cause of morbidity and mortality in patients with hematologic malignancies (14, 25). Bacterial and fungal diseases have been frequently associated with acute leukemia (14, 30), chronic lymphatic leukemia (4, 21), multiple myeloma (10), and lymphomas with hypogammaglobulinemia (31). Herpes zoster, tuberculosis, and fungal diseases, especially cryptococcosis, have been described as common complications of patients with Hodgkin's disease (1, 5, 12, 16, 28). In the present report, 35 of 51 patients were found to have significant clinical infections during their disease course. Bacterial infection occurred as the only infectious complication in 28 instances of this infection were discovered (Refs. 26, 32; C. P. Duvall, unpublished review). Six cases were associated with Hodgkin's disease, and 2 with other types of lymphoma. Although coexistent cytomegalic inclusion disease was found in 8 of the 29 instances, no patient in this present series had both these infections. Although Pneumocystis carinii pneumonia is a frequent cause of morbidity in patients undergoing renal homotransplantation (15), inclusion pneumonitis was felt to be significant in only 1 patient. A preliminary study published elsewhere by the present authors indicates that the salivary gland virus can be recovered from approximately 33% of adult patients with hematologic malignancies. In those patients, as in these, the symptomatology and pathophysiology of this infection are obscure.

In reviewing the cases of adult Pneumocystis carinii infections, 28 instances of this infection were discovered (Refs. 26, 32; C. P. Duvall, unpublished review). Six cases were associated with Hodgkin's disease, and 2 with other types of lymphoma. Although coexistent cytomegalic inclusion disease was found in 8 of the 29 instances, no patient in this present series had both these infections. Although Pneumocystis carinii pneumonitis was not observed in this small group of patients. An unusual association of salmonella infections with Hodgkin's disease has been reported by Heineman et al. (13) and confirmed by this study, as 4 episodes of salmonella enteritis were discovered in this group of patients.

Herpes zoster occurred with an incidence of 16%. This is higher than the range of 3-8% reported elsewhere (5, 28). There was only 1 case of partial alopecia and facial scarring secondary to herpes zoster. The other episodes were self-limited without serious morbidity. One episode of mild varicella was recorded. Two patients with significant herpes simplex infections had severe ulcerative esophagitis. In 1 patient, there was extension to the tongue, larynx, and bronchi, with an extensive herpetic bronchopneumonia. In addition there was associated candida esophagitis and active Toxoplasma gondii subacute necrotizing encephalitis and focal myocarditis. This case has recently been reported in greater detail (7).

Cytomegalic inclusions were found in 10% of cases. The lungs were involved in 4 of the 5 cases. Although cytomegalic inclusion pneumonia is a frequent cause of morbidity in patients undergoing renal homotransplantation (15), inclusion pneumonitis was felt to be significant in only 1 patient. A preliminary study published elsewhere by the present authors indicates that the salivary gland virus can be recovered from approximately 33% of adult patients with hematologic malignancies. In those patients, as in these, the symptomatology and pathophysiology of this infection are obscure.

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Toxoplasmosis must be recognized also as a complicating feature of Hodgkin's disease. The clinical and pathologic findings have been reported in greater detail (7). In this instance, the correct diagnosis was made at postmortem examination; however,
in at least 1 other instance (8), a correct clinical diagnosis was made and effective therapy was given.

Hodgkin's disease has been reported as the type of lymphoma most frequently associated with fungal disease (16). The intrinsic nature of Hodgkin's disease, adrenal corticoid, and chemotherapy have been reported as factors which predispose to and account for the increased incidence of fungal diseases in these patients (11, 16, 17, 29). The 20% incidence noted in this group correlates well with that reported in the literature (19).

Special mention must be made of the cryptococcal infections encountered in this report. Although the cryptococcus organism is a pathogenic organism under usual circumstances, it seems to assume increased virulence when attacking patients with Hodgkin's disease. The resulting disease is usually more widely disseminated (33), and this was corroborated by this study. This infection was considered the primary cause of death in each instance encountered during this study. Two of the 4 patients had substantial doses of amphotericin, while 1 died shortly after diagnosis and 1 case escaped clinical detection. Hutter and Collins, however, have reported good results in treating 16 cases of cryptococcal with amphotericin B (16).

Patients with Hodgkin's disease usually have normal y-globulin levels. However, decreased antibody production, delayed homograft rejection, and impaired delayed hypersensitivity responses are manifestations of the primary immunologic defects encountered in this disease (2, 3, 18). A retrospective report such as this cannot evaluate such features. This study seemed to indicate that the role of radiotherapy, chemotherapy, and steroid therapy in predisposing these patients to infection was relatively minor. The patients who were not infected received relatively more radiotherapy and chemotherapy than those with bacterial infection, whereas both groups received a similar amount of steroids. All the patients with CID and 90% with fungal diseases received steroids during the course of illness.

It is to be noted that patients with structural abnormalities due to the neoplastic disease behaved like those with localized carcinomas and developed multiple infections (20). Almost all infections occurred when the neoplasm was far advanced and no longer responsive to chemotherapy. This is to be contrasted with earlier periods of active disease during which the patients were notably free of infection. Successful management of these infections requires effective antineoplastic chemotherapy, accurate diagnosis, and specific therapy of the infectious complication. If the disseminated neoplastic disease cannot be controlled, the patient usually will either die with the initial infection or with a subsequent episode occurring shortly thereafter. Examination of the skin and lungs, detection of local mechanical defects, and serial blood cultures should provide valuable information for most bacterial infections. Antibiotic therapy when administered in the absence of known etiologic factors must be geared to combat the high incidence of staphylococcal and Gram-negative bacillary disease. Such a program might include methicillin and colistin.

Unexplained clinical deterioration in the absence of proven bacterial disease should alert the physician to the possibility of fungal infections, particularly for those patients with disease duration in excess of 30 months. All but 2 of the fungal infections present in this series involved either the lungs, blood, meninges or a combination of these sites. Amphotericin B despite its considerable nephrotoxicity, remains the agent of choice for treating cryptococcosis, histoplasmosis, candidiasis, and aspergillosis. Nocardia can be treated with sulfonamides (27).

Similarly, establishing the diagnosis in the rare cases of pneumocystis and toxoplasmosis is of more than academic importance as a new agent, pentamidine isothionate, may be effective for the former (23, 24) and sulfonamides are useful for the latter (8). There is no therapy available for disseminated cytomegalic inclusion disease; however, trials of various antiviral agents in animals are in progress, and in vitro trials utilizing tissue culture technics are planned.

References

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Summary of Infectious Complications Occurring in Patients with Hodgkin's Disease

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