

## Infections in Hairy-Cell Leukemia

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In order to determine the nature of infectious complications in hairy-cell leukemia we studied 20 consecutive patients seen at UCLA and analyzed the available literature. The incidence of serious infection in our series was 40%, and pneumonia and septicemia due to *Pseudomonas* and *E. coli* organisms were the leading types of infections. Fungal infections with *Cryptococci* and *Histoplasma* organisms were documented, and a single case of *Pneumocystis carinii* pneumonia was observed. Noninfectious fever occurred in 30% of our patients. There was a clear relationship between fungal disease and corticosteroid therapy, and the overall incidence of in-

fection was correlated with the degree of neutropenia and corticosteroid treatment. No relationship was found between age, duration of disease, or the use of cytotoxic chemotherapy and infectious complications. Of the 13 infectious episodes, 11 occurred in patients prior to splenectomy. Only two episodes were seen in splenectomized patients, both occurring in the immediate postoperative period. We conclude that splenectomy has a beneficial effect in reducing the incidence of infections in hairy-cell leukemia and that corticosteroids should be used cautiously, since they predispose to opportunistic infection in this disease.

**H**AIRY-CELL LEUKEMIA, or leukemic reticuloendotheliosis, is a well-delineated entity characterized clinically by splenomegaly associated with pancytopenia and neoplastic mononuclear cells in the blood and bone marrow.<sup>1-3</sup> Typically, the hairy cell has prominent cytoplasmic projections and contains the tartrate-resistant isozyme 5 of acid phosphatase.<sup>4,5</sup> Although there is controversy regarding the cell line of origin of hairy-cell leukemia,<sup>6,7</sup> most evidence suggests that the disease fits into the spectrum of B lymphocyte malignancies.<sup>8-10</sup> Hairy-cell leukemia usually has a chronic clinical course, and splenectomy has been recommended as the treatment of choice.<sup>2,5</sup>

Published reports suggest that infection is the primary cause of morbidity and mortality in this disease,<sup>2,11</sup> yet there is little information available on the nature or pattern of infections in these patients. We present here data on the infectious episodes of 20 patients with hairy-cell leukemia seen in the UCLA Center for the Health Sciences and an analysis of the literature attempting to correlate the incidence of infections with clinical parameters and therapy.

### CASE REPORTS

#### *Patient 1*

A 53-yr-old Chinese-American male was in good health until January 1974, when he presented with erythema nodosum. A diagnosis of hairy-cell leukemia was based on the findings of

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splenomegaly and pancytopenia with morphologically typical "hairy" cells in the blood and bone marrow showing strong tartrate-resistant acid phosphatase activity. The patient was treated with prednisone, vincristine, and cyclophosphamide. Two months later he was readmitted with a three-day history of dyspnea and fever to 40°C. A left lower-lobe infiltrate was observed on chest x ray, and the patient was treated with carbenicillin, gentamicin, and cefazolin. On the third hospital day there was radiologic evidence of progression of the pulmonary infiltrates, and the arterial pO<sub>2</sub> was 54 mm Hg. A methenamine silver stain of material obtained by trans-tracheal aspirate showed *Pneumocystis carinii*. The patient responded to a 12-day course of pentamidine isethionate (4 mg/day intramuscularly) and was returned home with a regimen of isoniazid prophylaxis for tuberculosis.

In May 1974 the patient reentered the hospital with fatigue and jaundice. The SGOT was 1560 mU/ml, SGPT 2310 mU/ml, total bilirubin 12.6 mg/dl, and alkaline phosphatase 174 mU/ml. An assay for hepatitis B surface antigen (HB<sub>s</sub>Ag) was negative, isoniazid was discontinued, and he was sent home with a diagnosis of viral hepatitis. The patient was treated intermittently with prednisone, and in August 1974 he was admitted again with a 3-day history of chills and fever to 39°C. The white blood cell count was 1100/μl, with 64% neutrophils. The platelet count was 200,000/μl, and the hemoglobin concentration 11.2 g/dl. A chest roentgenogram was normal, and routine cultures were negative. The patient was empirically treated with amikacin and carbenicillin without evidence of clinical response. On the eighth hospital day a spinal fluid examination showed a positive india ink preparation, and *Cryptococcus neoformans* was subsequently isolated by culture. The organism was sensitive to amphotericin B (MIC\* = 1 μg/ml) and 5-fluorocytosine (MIC = 1 μg/ml). The patient initially was treated with amphotericin B and 5-fluorocytosine but the latter drug was subsequently discontinued because of further leukopenia. He received a total of 1.3 g of amphotericin B. A repeat cerebrospinal fluid examination was normal.

In May 1975 the patient underwent splenectomy. He remained asymptomatic and hematologically stable without treatment for 19 mo.

### Patient 3

A 63-yr-old white female was first admitted to UCLA in July 1972 with a 7-mo history of weight loss and weakness. Splenomegaly, marked lymphocytosis, and typical hairy cells in the bone marrow were present. She was treated with various regimens of prednisone, chlorambucil, cyclophosphamide, vincristine, and isoniazid. There were three hospital admissions with episodes of fever for which extensive work-ups failed to show a cause.

In April 1974 she was admitted to the hospital with a 1-day history of fever, chills, and a 2-cm tender perirectal abscess. The white blood count was 3900/μl, with 1% segmented neutrophils. A blood culture taken on admission grew *Pseudomonas aeruginosa*. She was treated with gentamicin and carbenicillin and recovered. The patient was readmitted in October 1974 with a febrile episode of 2 days duration associated with urinary frequency. She was pale, dyspneic, and appeared toxic. The white cell count was 4900/μl, with 99% mononuclear cells. Urine and blood cultures grew *E. coli*. The patient died 3 days later in septic shock despite antibiotic therapy.

### Patient 5

A 37-yr-old white male was admitted to UCLA in November 1966 with a 7-month history of mild epistaxis and low-grade fever. On admission he had a temperature of 38.5°C. Hepatosplenomegaly was noted on physical examination. The white blood cell count was 10,625/μl, with 12% neutrophils. A diagnosis of hairy-cell leukemia was made on the basis of typical cytologic and cytochemical findings. He was treated with prednisone, with subsequent rapid defervescence.

In December 1971 he reentered the hospital with a 5-day history of chills, sweats, and fever to 38.5°C. The white blood cell count was 2300/μl, with 61% polymorphonuclear cells. A chest x ray showed right middle and right lower lobe infiltrates. Blood cultures were negative. *Pasteurella multocida* was recovered from the sputum, and the patient was treated with ampicillin

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\*MIC, minimal inhibitory concentration.

and tetracycline. Because he developed a skin rash, ampicillin was discontinued and erythromycin added. There was complete clinical and radiologic resolution.

### Patient 8

A 57-yr-old white male was first admitted to UCLA in July 1970. Two years previously he had had a febrile episode and was found to be pancytopenic. The peripheral white blood count was 2000/ $\mu$ l, with 10% neutrophils and 90% abnormal cells. Splenomegaly and typical tartrate-resistant acid phosphatase-containing cells in the peripheral blood were present.

Three months before the UCLA admission he had had fever, erythema nodosum, and a positive tuberculin skin test and was treated with isoniazid, streptomycin, and ethambutol without evidence of clinical response. Later, he developed granulomatous lesions of the mouth and palate, and a histoplasma complement fixation titer was positive at 1/32 for the mycelial phase and to 1/128 to the yeast phase. He was treated with amphotericin B and, when admitted to UCLA, was in renal failure in a near-terminal state. Several blood cultures were positive for *Histoplasma capsulatum*. A chest x ray showed widening of the upper mediastinum. He was continued on amphotericin B and underwent hemodialysis. Complications included an episode of uremic pericarditis with tamponade requiring open drainage. The patient finally recovered after receiving a total of 2 g of amphotericin B. The histoplasma complement fixation tests eventually became negative.

The patient has subsequently had chronic urinary tract infections, due to *E. coli*, treated with various courses of antibiotics. In 1972 the patient had an episode of jaundice with a serum SGOT of 1400 units. His serum was HB<sub>s</sub>Ag negative, but he was known to have been transfused with an HB<sub>s</sub>Ag-positive unit of blood.

## RESULTS

Tables 1 and 2 summarize the pertinent data on the UCLA patients with hairy-cell leukemia. For comparative purposes they have been divided into two groups, 12 patients (60%) who did not have a documented episode of infection and 8 patients (40%) who had 13 episodes of serious infections. Documenta-

Table 1. Patients With Infectious Complications

Patient/ Age (yr)/ Sex	Neut ( $\mu$ l)	Cort	Chem	Spl	Time*	Infection			Evolution (Diagnosis to Last Follow-Up)
						Type	Organism	Treatment	
1/53/M	170	+	+	+	Pre	Pneumonia	<i>P. carinii</i>	Pentamidine	Alive (.3 yr)
	207				Pre	Hepatitis	Viral (?)	—	
	704				Pre	Meningitis	<i>C. neoformans</i>	Amphotericin B, 5-fluorocytosine	
2/60/M	330	+	-	+	Post	Septicemia	<i>P. aeruginosa</i>	Cefazolin, gentamicin	Alive (.1 yr)
3/63/F	39	+	+	-	—	Perirectal abscess and septicemia	<i>P. aeruginosa</i>	Carbenicillin, gentamicin	Recovered
	49				—	Urinary tract infection (UTI) and septicemia	<i>E. coli</i>	Carbenicillin, gentamicin	Died (2 yr)
4/54/M	192	+	-	+	Post	Pneumonia and septicemia	<i>P. aeruginosa</i> <i>E. coli</i>	Cephalotin, gentamicin, chloramphenicol	Died (1 yr)
5/37/M	1403	+	-	-	—	Pneumonia	<i>P. multocida</i>	Ampicillin, tetracycline, erythromycin	Alive (.5 yr)
6/50/M	867	+	-	+	Pre	Abscess	<i>S. aureus</i>	Erythromycin	Alive (.1 yr)
7/39/M	2940	-	-	-	—	Pneumonia	<i>S. pneumoniae</i> (?)	Penicillin	Alive (.1 yr)
8/57/M	60	+	-	-	—	Septicemia	<i>H. capsulatum</i>	Amphotericin B	Alive (.6 yr)
	128				—	Chronic UTI	<i>E. coli</i>	Multiple antibiotics	
	208				—	Hepatitis	Viral (?)		

Neut, neutrophils; Cort, corticosteroids; Chem, chemotherapy; Spl, splenectomy.

\*Pre- or postsplenectomy.

**Table 2. Patients Without Infectious Complications**

Patient/ Age (yr)/ Sex	PMN/ $\mu$ l	Corticosteroids	Chemotherapy	Splenectomy	Evolution (Diagnosis to Last Follow-Up)
a/53/M	300	+	+	-	Died (2 yr)
b/43/M	1200	-	-	-	Alive (> 10 yr)
c/43/M	600	+	-	-	Alive (> 2 yr)
d/68/M	6460	+	-	-	Alive (> 1 yr)
e/65/M	160	+	-	+	Alive (> 6 yr)
f/45/M	1600	+	-	+	Alive (> 8 yr)
g/52/F	5332	-	-	+	Alive (> 2 yr)
h/60/M	3240	-	+	-	Alive (> 11 yr)
i/49/M	1530	-	-	+	Alive (> 1 yr)
j/74/M	1870	+	+	-	Died (1 yr [lung tumor])
k/40/F	4000	-	-	-	Alive (> 2 yr)
l/67/M	792	-	-	+	Alive (> 2 yr)

tion of infection required the isolation of an organism except in the case of viral hepatitis. Minor infections included colds and spontaneously resolving skin infections. Although the groups were small, they were roughly comparable for age and sex. The mean age was 51.6 yr in the infected group and 54.9 yr in the noninfected group. The clear male predominance in this disease was confirmed.

Septicemia and pneumonia were the leading causes of infections. Bacteria were responsible for 8 of the 13 episodes. The gram-negative rods *P. aeruginosa* and *E. coli* were the most common bacterial pathogens. Infections with *C. neoformans*, *H. capsulatum*, and *P. carinii* were also documented.

The incidence of infections correlated with the degree of neutropenia. The group of patients with infections had a mean absolute neutrophil count ( $\pm$  SE) of  $561 \pm 227/\mu$ l at or just before the onset of infection, whereas the representative figure for the uninfected group was  $2259 \pm 597/\mu$ l ( $p \leq 0.005$ , *t* test). All but one of the patients with infections were neutropenic ( $< 2000$  granulocytes/ $\mu$ l). Because of possible bias in selecting the representative total neutrophil count in uninfected patients, we repeated the analysis using the total granulocyte count at presentation to UCLA: in those who developed infections the mean neutrophil count was  $408 \pm 137/\mu$ l, compared to  $2408 \pm 338/\mu$ l ( $p < 0.01$ ) for the uninfected group.

The relationship of corticosteroid therapy to infectious complications was also strong. Of the 13 patients treated with steroids, 7 had 12 episodes of serious infection. Among the seven patients not treated with steroids there was one episode of easily controlled pneumococcal pneumonia. There was no evidence that patients treated with steroids had more advanced or severe disease. However, because the majority of the steroid-treated patients were granulocytopenic, the separate influence of steroid therapy on bacterial infection was not definable. Of the total of 13 infectious episodes (six patients), 11 occurred in patients prior to splenectomy. Only two episodes of infection were documented in the splenectomized patients, and both of these occurred in the immediate postoperative period. All patients undergoing splenectomy had a substantial rise in total granulocyte count; none subsequently became infected.

No clear relationship was observed between infections and the use of cytotoxic chemotherapy. The incidence of infections was the same in patients who received chemotherapy (2 of 5 patients) as in those not treated (6 of 15 pa-

**Table 3. Summary of 55 Patients With Infections (Literature)**

Ref	Pn	Sep	UTI	Ab	Hep	Other	Steroids		Chemo-therapy		Splenoctomy		Follow-Up	
							Yes	No	Yes	No	Yes	No	>24 mo	<24 mo
1	9	4	6	1		2	9	5	10	4	2	12	5	8
2	4	1	1		1	4	4	2	4	2	5	1	2	4
3	1	3		1			1	1	1	1	1	2	1	
5		3			2		1		3		1		1	
11	1	1	1			2			1		3		2	1
12						1	1		1				1	
13						1		1		1	1			1
14	6			1	1	1	3	4	4	3	1	6	3	4
15	2						1	1	1	1		2		1
16	1	1				2	1	1		3	3		2	1
17	1								1		1			
18		1					1		1			1	1	
19	1			1		1	1				3		1	1
20	1	1					1		1		1		1	
21	1	1					1	1	2			2	1	
22	1	1	1	1				2		2	1	1	1	1
Totals							25	18	30	17	23	27	22	22

Pn, pneumonia; Sep, septicemia; UTI, urinary tract infection; Ab, abscess; Hep, hepatitis.

tients). Total serum protein and globulins were normal in all patients except one in the noninfected group who had a monoclonal IgM paraprotein.<sup>12</sup>

#### *Analysis of Data Collected from the Literature*

We were able to collect from the literature data on 55 patients with hairy-cell leukemia in whom one or more episodes of infection were reported (Table 3). From the same literature we identified for comparison 34 patients apparently without infection. The published reports were primarily concerned with the hematologic aspects of the disease, and the information about infectious complications was scanty and incomplete. The data are presented for descriptive purposes, since their reliability is not secure.

The mean age in the infected and noninfected group was 52 yr (range 30–80 yr). The overall male predominance was clear, with only 13 women of a total of 71 patients. The sites of infections and the organisms recovered are summarized in Tables 3 and 4. Pneumonia and septicemia were the leading types of infection. Abscesses, apparent viral hepatitis, and disseminated mycoses were also relatively frequent. Bacteria were the common pathogens in these patients, with *P. aeruginosa*, *E. coli*, and *Staphylococcus aureus* occurring in approximately equal proportions. Disseminated fungal infections were well documented. We could find no other report of *P. carinii* infection in hairy-cell leukemia. Clinically diagnosed viral hepatitis was frequent, probably related to blood transfusion.

Information regarding steroid treatment was available (although often incomplete) in 75 patients with and without infection. Of 39 patients who had received steroids, 25 (64%) had had infections, whereas 14 (36%) had not. We were unable to extract a valid figure for the percentage of patients not receiving steroids who had been infected.

Most of the patients reported in the literature were neutropenic. The mean absolute neutrophil count was  $752 \pm 101/\mu\text{l}$  in the “infected” group and

**Table 4. Microorganisms Recovered (Literature)**

Microorganism	No. of Patients
<b>Bacteria (45 patients)</b>	
<i>P. aeruginosa</i>	3
<i>E. coli</i>	3
<i>S. aureus</i>	3
<b>Fungi (6 patients)</b>	
Aspergillosis	2
Candidiasis	2
<i>C. neoformans</i>	1
Mycotic (nonspecified)	1
<b>Virus (7 patients)</b>	
Hepatitis	4
Cytomegalovirus	1
Herpes simplex	4
<b>Mycobacteria (1 patient)</b>	
<i>M. kansasii</i>	1

1132  $\pm$  262/ $\mu$ l in the noninfected patients. These figures are the available data from the reports but may not be representative of the course of each patient. Information concerning splenectomy was available in 51 of the 55 patients in the group with infections. There were 23 splenectomized patients and 28 non-splenectomized patients. Thirty-six patients (70%) had infections without splenectomy or before it was performed. Seventeen splenectomized patients (33%) had infections. One patient had one episode before and another after splenectomy. One patient had disseminated *Mycobacterium kansasii* infection before splenectomy that continued postoperatively.<sup>15</sup>

Combining the infected and the noninfected group, there is a total of 79 patients on whom information was available regarding chemotherapy. Of 49 patients treated with cytotoxic drugs, 30 (61%) had infections, whereas 17 of 30 patients (51%) not receiving chemotherapy had infections.

In order to assess the influence of disease duration on the incidence of infectious complications, the following data were obtained: Of 37 patients followed for 24 mo or more and 39 followed for less than 24 mo there were 22 patients with infections in each group. Of 82 patients collected from the literature, 39 (48%) were still alive at the time they were reported, and 43 had died (52%). Of the 43 patients who had died 33 had infections; of the 39 patients still alive, 23 were in the noninfected group.

#### *Fever of Unknown Origin*

Six of our 20 patients (30%) had one or more episodes of long-lasting fever for which an extensive in-hospital investigation failed to show an infectious cause. Three of these patients were in the group without infections, and three had well-documented infectious episodes later in their courses. All met the criteria of Petersdorf and Beeson for fever of unknown origin,<sup>23</sup> all were neutropenic, and none had been splenectomized. One of the patients (*a*) died with fever, and autopsy investigation failed to demonstrate an infectious etiology. Four of the patients defervesced with corticosteroid therapy.

The literature review provided anecdotal information indicating that fever may occur on a noninfectious basis in patients with hairy-cell leukemia.<sup>5,11,17,22,24</sup>

#### DISCUSSION

There is now an ample literature dealing with the clinical and morphologic aspects of hairy-cell leukemia<sup>1,4,10,11</sup> and the cellular nature of this disease.<sup>6,8,9</sup> Although infectious complications in hairy-cell leukemia are of major clinical and prognostic importance, there is little information available on the nature of these infections and their relationship to treatment. Therefore we analyzed the UCLA experience with 20 patients and extracted data on 89 patients from the literature in order to define the pattern of infections in these patients.

Our series was roughly comparable to those reported in the literature in terms of mean age and male-female ratio (7:1). The overall incidence of infection in our patients was 40%. The largest published experience (111 patients) reported an incidence of infection on presentation of 22%.<sup>25</sup> Other series reported overall infection incidences at 44%,<sup>22</sup> and 58%.<sup>1</sup> Pneumonia and septicemia were the most common types of infection. As in other leukemias and lymphomas, bacteria were the usual microorganisms isolated. There was a clear preponderance of gram-negative rod organisms, with *P. aeruginosa* and *E. coli* as the most important bacterial isolates. There was a curious and unexplained absence of infections by organisms of the *Klebsiella-Serratia-Enterobacter* group. *Aspergillus*, *Candida*, and *Cryptococcus* organisms were the common fungal agents encountered. We described a single patient with disseminated histoplasmosis and one with *P. carinii* pneumonia. The relationship of fungal disease to corticosteroid therapy was clear; all but two of the patients who had fungal disease were receiving corticosteroid therapy.

The absence of reported cases of tuberculosis in hairy-cell leukemia is remarkable, since tuberculosis affects persons in middle life and steroids have been a frequent form of therapy. A number of our patients were tuberculin skin test-positive and several were treated empirically with antituberculous drugs. The only documented case of mycobacteriosis in the literature reviewed was a single patient with disseminated *M. kansasii*.<sup>15</sup> A high incidence of apparently viral hepatitis was found, and it was related in most cases to transfusion therapy. Also, fever may be a noninfectious manifestation of hairy-cell leukemia and can occur in up to 30% of patients.

The infections seen in hairy-cell leukemia fall into two main categories, bacterial infections associated with neutropenia and opportunistic infections characteristic of impaired cell-mediated immunity, related prominently to corticosteroid therapy. While there was a clear association of infections to neutropenia and corticosteroid treatment, the frequency of infections did not relate to the age of the patient, duration of disease, or the use of cytotoxic chemotherapy. With regard to splenectomy, the immediate postoperative period appears to be especially dangerous; however, the frequency of infection was substantially lower in splenectomized patients. Splenectomy usually improved the peripheral neutrophil count; it may obviate the need for corticosteroids, thereby reducing the tendency toward infectious complications. Others have reported that splenectomy improves prognosis and survival.<sup>2,5</sup>

Since corticosteroids are not documentably efficacious in this disease, our results would indicate that they should be used cautiously if at all because they predispose to opportunistic infection.

Since this manuscript was prepared a number of instances of tuberculosis have been observed in patients with hairy-cell leukemia.<sup>26</sup> Marie et al. recently reported seven cases of tuberculosis in 131 patients with hairy-cell leukemia,<sup>27</sup> and Catovsky has seen four cases of tuberculosis in 50 patients with this disease (Catovsky D: personal communication). Tuberculosis appears to be an important infection in patients with hairy-cell leukemia.

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