Splenectomy as Initial Therapy in Twenty-six Patients with Leukemic Reticuloendotheliosis (Hairy Cell Leukemia)\(^1\)

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**ABSTRACT**

Twenty-six of 44 patients with leukemic reticuloendotheliosis, or hairy cell leukemia, underwent splenectomy as the first treatment for their disease from 1 to 72 months after the diagnosis was established. The median presplenectomy peripheral blood counts were: hematocrit, 32%; leukocytes, 2,600/cu mm; and platelets, 63,000/cu mm. One to 4 months postsplenectomy, the median counts were: hematocrit 35%; leukocytes, 5,500/cu mm; and platelets, 247,000/cu mm. Improvement of the blood counts was the main gain resulting from splenectomy in these patients. Forty-two % of the patients achieved a complete response, and 58% achieved a partial response. The median spleen weight at operation was 1200 g, with a range of 250 to 4450 g. Our data suggest that even the minimally enlarged spleens caused a significant amount of sequestration, which can be alleviated by splenectomy. Thirteen patients had presplenectomy infections; three were acutely ill. Splenectomy was performed on these three patients as an emergency operation after failure of conservative therapeutic measures. All three improved and were discharged within 2 weeks. Nine patients had episodes of infection after splenectomy. Five patients died of hairy cell leukemia at a median time of 9 months after splenectomy; four of these had concurrent overwhelming infections as well. The actuarial survival rate for all 26 patients at 5 years was 72%; for complete responders the rate was 86%, and for partial responders the rate was 47%.

Splenectomy is the first treatment for patients with hairy cell leukemia when counts drop significantly (hematocrit, <25%; granulocytes, <500/cu mm; platelets, <50,000/cu mm) or when repeated infections occur. Eliminating the sequestering organ improves the peripheral blood counts. In spite of spleenectomy and improved counts, however, a few patients have progressive disease. It is necessary to identify this subgroup of patients as soon as possible after splenectomy, inasmuch as therapy with single-agent alkylating drugs has been found to be effective.

**INTRODUCTION**

The major clinical features of leukemic reticuloendotheliosis, or HCL\(^3\) are pancytopenia, circulating mononuclear cells with exaggerated cytoplasmic projections, and splenomegaly without significant adenopathy. Since its first description in 1958 (1), many additional studies have confirmed that HCL, although rather rare, is a distinct clinical and pathological entity (5–7, 11). In spite of the fact that HCL is a widely recognized entity, the best mode of treatment for this disease is still uncertain (4). HCL generally has a chronic course, and the main disturbances are those resulting from neutropenia, thrombocytopenia, and anemia. Splenomegaly and hypersplenism play an important role in the development of pancytopenia; however, decreased production of normal elements by the bone marrow, secondary to infiltration of the marrow with hairy cells, is also contributory (3). Splenectomy is one of the commonly used forms of treatment for HCL and is reported to be beneficial for many patients (1, 3–8).

We have analyzed the 26 of 44 patients (59%) with HCL who underwent splenectomy as the first form of treatment to determine the effect of this procedure on the course of disease and survival.

**MATERIALS AND METHODS**

Of the 26 patients studied, one had been treated previously with an alkylating agent but had not been treated for at least 1 year prior to splenectomy. The diagnostic criteria for HCL have been described previously (8). Peripheral blood counts, clinical presentation, symptomatology, infectious episodes, and the pre- as well as postsplenectomy course of the disease were reviewed for each patient. The results of splenectomy were assessed 1 to 4 months after the operation, according to the criteria of Catovsky (4), in 3 categories; (a) CR if Hct increased above 36%, the granulocytes increased above 1000/cu mm, and the platelets increased above 100 x 10\(^3\)/cu mm; (b) PR if this degree of improvement occurred only in one or 2 of the blood elements or, if in all 3, below the stated levels; and (c) no response. Patients were considered to be in the "leukemic" phase if they had a WBC greater than 10 x 10\(^3\)/cu mm, with 50% or more hairy cells.

Survival times were calculated from the date of diagnosis by the actuarial method (10). The closing follow-up date was September 1, 1978.

**RESULTS**

Splenectomy was performed from 1 to 72 months after the diagnosis of HCL had been established. The median time from diagnosis to splenectomy was 3 months. The age range of the splenectomized patients was 24 to 80 years, with a median age of 51.5 years. Five of our patients were above the age of 65 years, and none of them was leukemic at the time of splenectomy. The male (20 patients) to female (6 patients) ratio was 3.3:1.

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\(^1\) Supported in part by the Robert English Fund, The Thomas Moore Fund, The Donald Nathanson Fund, The Hematology Research Foundation, and USPHS Grant CA-14599 from the National Cancer Institute.

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\(^3\) The abbreviations used are: HCL, hairy cell leukemia; CR, complete response; Hct, hematocrit; PR, partial response.

Received December 19, 1978; accepted March 21, 1979.
The immediate reason for splenectomy was unobtainable in one patient; the other 25 patients had low peripheral blood counts. Nine (36%) had pancytopenia (Hct, ≤35%; WBC, ≤4500/cu mm; platelets, ≤150,000/cu mm); 8 (32%) had combined anemia and thrombocytopenia; 6 (24%) had leukopenia and thrombocytopenia; and 2 (8%) had thrombocytopenia alone. In addition to low counts, 13 patients had infections and fever, 2 had overt bleeding (menorrhagia and epistaxis), 2 had significant abdominal discomfort, and one had splenic infarction. Of the 13 febrile patients with infections, 3 were acutely ill, and the splenectomy was performed as an emergency operation after failure of conservative therapeutic measures.

Peripheral blood counts at diagnosis, presplenectomy, and 1 to 4 months postsplenectomy are shown in Table 1. Five of the 26 patients had more than 50% hairy cells in their peripheral leukocytes prior to splenectomy and were considered to be leukemic. Table 2 shows the pre- and postsplenectomy peripheral blood counts of the leukemic compared to the nonleukemic patients.

The median spleen weight at operation was 1200 g, with a range of 250 to 4450 g. Chart 1 illustrates the leucocyte and platelet counts of 23 of the 26 patients pre- and postsplenectomy in relation to spleen weight. In 2 of the 23 patients, the leucocyte count decreased following splenectomy. Three patients were not plotted because blood counts were unavailable. The median spleen weight in the 5 leukemic patients was 2100 g (range, 1700 to 2350 g), compared to a median weight of 1135 g (range, 250 to 4450 g) in the nonleukemic patients. The pre- and postsplenectomy peripheral blood counts of the 23 patients included in Chart 1 according to spleen weight are shown in Table 3.

The results of splenectomy were assessed in 24 patients; 10 achieved CR and 14 achieved PR. The other 2 are still alive at 66 and 159 months after diagnosis, but their responses were not assessed completely because of insufficient postoperative hematological data.

Thirteen patients (50%) had episodes of infection prior to splenectomy. Six had upper or lower respiratory tract infections; 2 were infections with atypical mycobacteria, and one was a Pneumocystis carinii infection. Two patients had septicemia (one with Staphylococcus aureus and one with Diplococcus pneumoniae). Two had fever of unknown origin, and 3 had cellulitis. Nine patients (35%) had episodes of infection after splenectomy was performed; one had cellulitis, 3 had pneumonia, 3 had septicemia (2 with S. aureus, and one with Pseudomonas aeruginosa), one had subacute bacterial endocarditis (with Streptococcus viridans), and one had an abscess.

The actuarial survival rate for all of the 26 splenectomized patients at 5 years since diagnosis is 72%. For those who achieved CR the rate was 86%, and for those with PR the rate was only 47% survival at 5 years (Chart 2). However, when calculated from the time of splenectomy, the actuarial survival rates at 5 years were 70, 82, and 58%, respectively. Five patients died at a median time of 9 months (range, 8 to 38 months) after splenectomy, and at a median time of 14 months (range, 9 to 45 months) after diagnosis. Four of them were in the PR group, and one was in the CR group. In one of these 5 patients, diffuse infiltration of HCL cells in multiple organ systems was the cause of death, whereas the other 4 also had concurrent infections (3 had septicaemia and one had pneumonia). Only one patient had received chemotherapy consisting of chlorambucil, 4 mg each day, for approximately 1 year. Two of these 5 patients were leukemic at the time of splenectomy. Twenty-one patients are alive at 4 to 159 months since the diagnosis of HCL was established. Three of those still alive required chemotherapy with an alkylating agent because of progressive disease. None of the 3 was leukemic at the time of splenectomy; they are the subject of another report. The remaining 18 living patients are currently stable clinically and hematologically at a median time of 19 months since splenectomy, with the following last-recorded median levels: Hct, 41%; WBC, 5,700/cu mm; granulocytes, 960/cu mm; and platelets, 235,000/cu mm.

**DISCUSSION**

We are just beginning to establish a strategy for sequential treatment of patients with HCL (8). Numerous recent reports have pointed out the value of splenectomy in HCL patients (1, 3, 4, 9, 11, 15). However, splenectomy should not be done merely because a diagnosis of HCL has been made. It was recently shown that there is a group of patients, consisting of elderly individuals with moderately enlarged spleens, who frequently require no therapy at all (7). However, old age was not a contraindication to splenectomy in 5 of our patients (ages 65 to 80 years), in whom cytopenias and infections had not been manageable with medical measures. The median time from diagnosis to splenectomy in our 26 patients was 3 months; thus, when splenectomy was indicated, it was done shortly after the diagnosis of HCL had been established. The indications for splenectomy in our HCL patients were peripheral blood cytopenias, mainly leukopenia and thrombocytopenia and less frequently anemia (Table 1). Low peripheral blood counts, especially leukopenia and thrombocytopenia, were mentioned as the most common reason for splenectomy in other studies as well (3, 4, 7, 11, 15). Nine of our patients were pancytopenic (36%), 14 had a decrease in 2 counts (56%), and 2 had only thrombocytopenia (8%). In addition to low peripheral blood counts, 13 of the patients had infections prior to splenectomy; 3 of them were acutely ill and were operated on as an emergency while they were febrile with active infections. The immediate benefits of splenectomy in these 3 patients were a rise in leucocyte and platelet counts and resolution of the fever and infection. All 3 of them are alive and well since splenectomy and have required no chemotherapy.

The main gain due to splenectomy in patients with HCL was the significant improvement in the peripheral blood counts, especially in leukocyte and platelet levels. This is in concordance with the data presented in previous studies (3, 4, 11). Jansen et al. (9) suggest that splenectomy is beneficial in cases in which anemia and thrombocytopenia are not very severe, while Sebahoun et al. (15) state that anemia and thrombocytopenia have no prognostic significance whatsoever. Lewis et al. (13) compared splenic sequestration of RBC with spleen size in patients with lymphoproliferative and myeloproliferative diseases. The spleens were smaller for maximum sequestration in HCL than in chronic lymphocytic leukemia or myeloproliferative diseases. The spleens were smaller for maximum sequestration in HCL than in chronic lymphocytic leukemia or myeloproliferative diseases.

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Table 1

Peripheral blood counts of patients with HCL who underwent splenectomy

<table>
<thead>
<tr>
<th>Blood counts</th>
<th>Hct (%)</th>
<th>Leukocytes (10^3/cu mm)</th>
<th>Platelets (10^3/cu mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Median</td>
<td>No. of patients</td>
</tr>
<tr>
<td>At diagnosis</td>
<td>20-40</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>Presplenectomy</td>
<td>20-42</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>Postsplenectomy</td>
<td>30-44</td>
<td>35</td>
<td>20</td>
</tr>
</tbody>
</table>

* Measured 1 to 4 months after splenectomy.

Table 2

Comparison of peripheral blood counts of 5 leukemic and 21 nonleukemic patients with HCL

<table>
<thead>
<tr>
<th>Blood counts</th>
<th>Hct (%)</th>
<th>Leukocytes (10^3/cu mm)</th>
<th>Granulocytes/cu mm</th>
<th>Platelets (10^3/cu mm)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Range</td>
<td>Median</td>
<td>No. of patients</td>
<td>Range</td>
</tr>
<tr>
<td>Presplenectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemic</td>
<td>20-41</td>
<td>34</td>
<td>6.0-27.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Nonleukemic</td>
<td>20-42</td>
<td>32</td>
<td>0.6-18.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Postspenelectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemic</td>
<td>32-43</td>
<td>35</td>
<td>13.7-35.0</td>
<td>15.9</td>
</tr>
<tr>
<td>Nonleukemic</td>
<td>30-44</td>
<td>36</td>
<td>2.6-12.8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Chart 1. Pre- and postsplenectomy platelet and leukocyte counts in relation to spleen weight of 23 patients with HCL. *, presplenectomy WBC higher than postspenelectomy counts; Splx, splenectomy.

Our findings partially support this observation that there can be maximum sequestration even with minimally enlarged spleens. Median blood counts showed similar changes from pre- to postsplenectomy whether the spleen weighed 750 g or less or 1501 g or more. Except for abdominal discomfort and a somewhat more severe anemia, there was no difference in pathophysiological symptoms between those patients with larger and those with smaller spleens. The statement that the larger the spleen the greater is its contribution to pancytopenia (4) cannot be supported by our results. It is clear (Table 3) that even the smallest spleens caused a fair amount of sequestration, which was unequivocally alleviated by splenectomy. Seven of the 12 patients described by Katayama and Finkel (11) had spleen weights of less than 1500 g which showed the same extent of sequestration of peripheral blood elements as did larger spleens.

The minimal change between median pre- and postsplenectomy leukocyte counts of our patients with spleen weights...
Pre-and postsplenectomy peripheral blood counts in relation to spleen weight in 23 patients with HCL

<table>
<thead>
<tr>
<th>Spleen wt</th>
<th>No. of patients</th>
<th>Range</th>
<th>Median</th>
<th>Hct (%)</th>
<th>Leukocytes (10^9/cu \text{mm})</th>
<th>Platelets (10^9/cu \text{mm})</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
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<tr>
<td>0-750 g</td>
<td>Presplenectomy</td>
<td>6</td>
<td>250-700</td>
<td>620</td>
<td>24-37 34</td>
<td>2.6-7.2 4.8</td>
</tr>
<tr>
<td></td>
<td>Postsplenectomy</td>
<td></td>
<td></td>
<td></td>
<td>35-42 36</td>
<td>2.3</td>
</tr>
<tr>
<td>751-1500 g</td>
<td>Presplenectomy</td>
<td>8</td>
<td>990-1325</td>
<td>1125</td>
<td>20-42 31</td>
<td>1.2-27.7 2.1</td>
</tr>
<tr>
<td></td>
<td>Postsplenectomy</td>
<td></td>
<td></td>
<td></td>
<td>30-40 34</td>
<td>3.9-15.9 4.6</td>
</tr>
<tr>
<td>1501-2250 g</td>
<td>Presplenectomy</td>
<td>5</td>
<td>1700-2100</td>
<td>1940</td>
<td>22-41 32</td>
<td>2.0-14.2 10.0</td>
</tr>
<tr>
<td></td>
<td>Postsplenectomy</td>
<td></td>
<td></td>
<td></td>
<td>34-43 39</td>
<td>5.5-35.0 13.7</td>
</tr>
<tr>
<td>&gt;2250 g</td>
<td>Presplenectomy</td>
<td>4</td>
<td>2265-4450</td>
<td>3065</td>
<td>28-39 29</td>
<td>0.6-6.2 4.0</td>
</tr>
<tr>
<td></td>
<td>Postsplenectomy</td>
<td></td>
<td></td>
<td></td>
<td>32-44 35</td>
<td>3.1-24.5 12.6</td>
</tr>
</tbody>
</table>

Chart 2. Actuarial survival since diagnosis of HCL in 26 patients who underwent splenectomy. Numbers on curves, patients at risk.

Chart 2. Actuarial survival since diagnosis of HCL in 26 patients who underwent splenectomy. Numbers on curves, patients at risk.

Thirteen (50%) of our patients had febrile or infectious episodes, or both, prior to splenectomy. Following splenectomy, only 9 patients (35%) had infections. Five (38%) patients had pre- as well as postsplenectomy infections, and 8 (62%) benefited from the splenectomy in not having postsplenectomy infections. However, 4 of the patients who did not have an infectious episode prior to splenectomy had infections after splenectomy was performed. Our data generally concur with those of Bouza et al. (2) in terms of percentage of infectious episodes in presplenectomy HCL patients; they differ, however, in the incidence of postsplenectomy infections, which is higher in our group. Furthermore, the postsplenectomy infectious episodes in our patients did not occur during the period immediately following splenectomy. We did not observe postsplenectomy infections with atypical mycobacteria or Pn. carinii. Pathogens such as streptococci, staphylococci, and pseudomonas comprised most of the positive isolates in the postsplenectomy infections. The two patients who had presplenectomy infections with atypical mycobacteria were markedly improved due to the combination of antibiotic chemotherapy and splenectomy. Furthermore, we could not find any correlation be-
between the groups of patients classified according to pre- and postsplenectomy infectious episodes and their granulocyte counts, or even their spleen weights.

In spite of splenectomy and subsequent elevation of the absolute median granulocyte counts, a few patients continued to have infections. It was postulated recently that the presence of one or more chemotactic-factor inactivators in the serum of patients with HCL may interfere with the capacity of monocytes to reach the site of inflammation and thus may play a role in the increased susceptibility to infection in these patients (12). It was suggested as well that, in patients with HCL, marrow granulocyte reserve and leukocyte mobilization are impaired and that the neutropenia is due to poor granulocyte production (18). Thus, the susceptibility to infection could reflect an interaction between several immunological defense mechanisms.

The actuarial survival of our 26 splenectomized patients at 5 years since diagnosis was 72% (Chart 2). It is evident that the patients who achieved CR had a better survival rate (86%) than the partial responders had (47%) at 5 years. At 5 years after splenectomy, the survival rates were not significantly changed, except for the partial responders who showed a considerably higher rate (58%).

Four of the 5 deaths occurred in the PR group. These findings are comparable to the results of a recent study by Turner and Kjeldsberg (16) that showed approximately a 65% 5-year survival rate in a group of 26 splenectomized patients with HCL. The survival for their 11 patients who had achieved CR was similar to that of the age-matched normal population (at approximately the 95% level). Their survival rate for partial responders at 5 years was 75%, and that for nonresponders was approximately 50%. Of 135 patients with HCL reviewed by Jansen et al. (9), 24 had splenectomy which led to an actuarial survival of 75% at 4 years after diagnosis, but the difference from their nonsplenectomized patients (55% actuarial survival) was not statistically significant. These data are comparable to the survival of our group of splenectomized patients at 4 years after diagnosis; however, an evaluation of CR, PR, and no response following splenectomy was not done by these authors. Catovsky’s survival data on 26 splenectomized HCL patients (4) are not comparable to ours because his follow-up period was short; however, at 3 years after splenectomy, the survival rate for patients with CR was approximately 50%, and at 2 years, the patients with PR had a 40% survival rate. The actuarial survival at 5 years, of populations of HCL patients who had received various forms of treatment (splenectomy, chemotherapy, etc.), is approximately 50% according to various studies (7, 16) and approximately 40% according to the results of Sebahoun et al. (15).

Five of our patients died at a median time of 9 months after splenectomy. Only 2 of them were above the age of 65 years. Four of them had autopsies, the results of which are described elsewhere in detail (17). None of these patients had immediate postsplenectomy complications which could have been the cause of death. One of the 5 had diffuse infiltration of HCL cells in multiple organ systems, with no evidence of infection, whereas the other 4 concurrently had terminal, overwhelming, intractable infections. One had staphylococcal sepsis; one had Ps. aeruginosa sepsis; the other 2 had negative blood cultures, but the autopsy findings clearly showed severe diffuse septic infection. One patient had 400 granulocytes/cu mm, and the others had adequate numbers of granulocytes. The one patient who died without concurrent infection also did not have a presplenectomy infection in spite of an absolute granulocyte count of 240/cu mm; however, he experienced one infectious episode after splenectomy which cleared completely with antibiotic treatment. Of the other 4 patients who died, 2 had pre- and postsplenectomy infectious episodes, one had only one postsplenectomy infection, and one did not have any evidence of infection except as the terminal event.

When blood counts drop significantly (Hct, <25%; granulocytes, <500/cu mm; platelets, <50,000/cu mm) or when repeated infections occur, splenectomy seems to be the treatment of choice. This procedure benefits the patient by improving peripheral blood counts, especially leukocyte and platelet counts, through eliminating the sequestering organ. In certain patients with very large spleens, splenectomy lessens the anemia by removing the source of sequestration. The massive involvement with tumor cells in the spleen is well documented in HCL (3, 14); thus, splenectomy also results in elimination of a significant amount of tumor burden. The survival of postsplenectomy patients with HCL seems to be better than that of a mixed population of patients with HCL who were treated with various modalities. In spite of splenectomy, several of the patients had progressive disease. It is necessary to identify this subgroup of patients at the earliest time after splenectomy, because effective chemotherapy with single alkylating agents has been found to be effective.4

REFERENCES

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