Response to Splenectomy in 65 Patients With Hairy Cell Leukemia: An Evaluation of Spleen Weight and Bone Marrow Involvement

By Harvey M. Golomb and James W. Vardiman

Sixty-five patients with hairy cell leukemia underwent splenectomy: 27 had a complete remission as defined by a return in WBC, RBC, and platelet counts to a defined level, and 38 had a partial remission with a return of only one or two of these parameters to the defined level. The 5-yr actuarial survival for all patients is 68%; for CR patients it is 76%, and for PR patients 62%. The response to splenectomy did not correlate with the spleen weight. Seventeen patients had a postsplenectomy platelet count of less than 200 x 10^9/liter, and 34 patients had a postsplenectomy platelet count of 200 x 10^9/liter or greater. A presplenectomy bone core biopsy hairy cell index (HCI) was calculated by multiplying the percent marrow cellularity by the percent of hairy cells in the marrow for 51 patients. The difference in the mean HCI between the two platelet response groups is statistically significant ($p < 0.05$). Of the 15 patients with a presplenectomy HCI of 0.7 or greater, 9 (60%) did not have a satisfactory platelet response to splenectomy, whereas of 36 patients with an HCI of 0.7 or less, only 8 (22%) did not have a satisfactory platelet response to splenectomy ($p < 0.01$). The HCI appears to indicate the significance of underproduction of platelets as a result of marrow replacement by hairy cells.

Hairy Cell Leukemia (HCL) is a disease characterized by pancytopenia, circulating mononuclear cells with prominent cytoplasmic projections, and moderate to massive splenomegaly without significant lymphadenopathy. HCL generally has a chronic course, but problems secondary to neutropenia, thrombocytopenia, and/or anemia are frequent. Splenectomy is one of the commonly used forms of treatment for HCL and has been reported to be beneficial for many patients. Although splenomegaly and hypersplenism play an important role in the development of pancytopenia, decreased production of normal elements by the bone marrow, secondary to infiltration of the marrow with hairy cells, can be equally important. Jansen et al. recently stated that it is "crucial to know which factor (bone marrow underproduction versus splenic sequestration) is primarily responsible for the pancytopenia in HCL." Our study was undertaken on patients with hairy cell leukemia who underwent splenectomy in order to try to determine whether or not a relationship between bone marrow underproduction and splenic sequestration existed. An understanding of this relationship and how it affects the response to splenectomy might allow us to establish prognostic parameters that could predict either a complete, and possibly, lasting response or a partial, and possibly, early relapse. Detection of early relapse is important in the subsequent chemotherapeutic management of patients with HCL.

Materials and Methods

From 1974 through 1980, we established the diagnosis of hairy cell leukemia in 101 patients. Seventy-two of these patients underwent splenectomy: 65 patients had adequate presplectomy (within 1 wk) and postsplenectomy (2–12 wk) blood counts as well as a documented spleen weight. The results of spleenometry were assessed 1–3 mo after the operation, according to a modification of the criteria of Catovsky, in three categories: (A) CR if the hematocrit was above 36%, the granulocytes were above 10^9/liter, and the platelets were above 100 x 10^9/liter, (B) PR if this degree of improvement occurred only in 1 or 2 of the blood elements or, if improvement occurred, in all 3 elements, but below the stated levels; and (C) no response. Actuarial survival curves were calculated from the date of diagnosis. Follow-up was completed through July 15, 1981.

Fifty-one of these 65 evaluable splenectomy patients also had a presplectomy bone core biopsy that could be evaluated for cellularity as well as fraction of hairy cells of the total marrow cells. All evaluations were made by a single hematopathologist (J.V.). From several representative fields of the hematoxylin and eosin stained sections of the biopsy, 1000 cells were counted. Normal marrow hematopoietic elements were also tallied. Megakaryocytes were counted per 10 high power fields. The hairy cell index (HCI) was defined as the cellularity of the bone core biopsy (fraction) multiplied by the fraction of hairy cells present in the cellular portion of the bone core biopsy, and expressed as a number from 0 to 1. Statistical analyses were done using chi-square correlation coefficients, and Student’s t-test.

Results

Of the 65 splenectomized patients, 54 were men and 11 were women; they ranged in age from the third through the eighth decades of life. Of these patients, 27 had a CR (23M, 4F; 22 are still alive) and 38 had a PR (31M, 7F; 28 are still alive). There is no statistical difference in the actuarial survival between males and

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females. For all 65 patients, the 5-yr actuarial survival is 68%; for the CR patients, it is 76%, and for the PR patients, it is 62% (Fig. 1). These differences are not statistically significant by the generalized Wilcoxon analysis. Of note is that the survival curves are flat after 50 mo with 12 patients remaining at risk.

Spleen weights ranged from 250–4600 g; 6 patients had a spleen weight of 500 g or less, and only 3 patients had a spleen weight of 3000 g or more. Figure 2(A and B) are graphs of the response in pre- and postsplenectomy platelet and WBC counts against the spleen weight for each patient. The spleen weight does not predict whether or not the platelet (r = −0.015, p = 0.36) or WBC (r = 0.218, p = 0.06) count will return to normal postsplenectomy. The proportion of patients with spleen weights less than 1000 g who do not have a return of their platelets to 200 x 10^9/liter is similar to the proportion of patients with spleen weights between 2000 and 3000 g who also do not have a return of their platelets to 200 x 10^9/liter.

Evaluation of the bone core biopsy for megakaryocytes per 10 high power fields (HPF) revealed no significant differences in numbers between the PR and CR groups of patients, although two-thirds of the PR group had 10 or less/10 HPF, whereas only one-half of the CR group had 10 or less/10 HPF.

The presplenectomy bone marrow biopsy HCI was determined for 51 of the 65 splenectomized patients. Figure 3 shows the HCI displayed as to whether the patient had a return to a platelet count of 200,000/cu mm or not. Although 100 x 10^9/liter was considered the level for consideration of CR, it is still not a normal value. Only four patients did not reach a value of 100 x 10^9/liter; 10 patients did not reach a value of 150 x 10^9/liter. Seventeen patients did not return their platelets to 200 x 10^9/liter, a value at the lower limits of normal. The difference in the mean HCI between the two platelet response groups (<200 x 10^9/liter versus ≥200 x 10^9/liter) is statistically significant (p < 0.05). No statistically significant difference is seen when the platelet cut-off level is 150 x 10^9/liter, and there are too few patients in the low group when the cut-off level is 100 x 10^9/liter to evaluate. Of 26 patients with an HCI of 0.5 or less, 21 (81%) had a satisfactory platelet level (200 x 10^9/liter) after splenectomy; only 13 of 25 patients (52%) with an HCI of greater than 0.5 had a satisfactory platelet level postsplenectomy (p < 0.05). Of the 17 patients who did not have a postsplenectomy platelet count of 200 x 10^9/liter or more, 9 (53%) had an HCI of 0.7 or more. Of the 34 patients who had a postsplenectomy count of 200 x 10^9/liter or greater, only 6 (18%) had an HCI of 0.7 or more (p < 0.01). Thus, of 15 patients with a presplenectomy HCI of 0.7 or greater, 9 (60%) did not have a satisfactory platelet level after splenectomy. The association between a low postsplenectomy platelet count and a high presplenectomy HCI is significant (r = −.417, p = 0.01). Table 1 lists the spleen weight for all 15 patients with a presplenectomy HCI of 0.7 or lower.

![Fig. 1.](image1)

**Fig. 1.** Actuarial survival curves for all 65 postsplenectomy patients as well as the CR and PR subsets.

![Fig. 2.](image2)

**Fig. 2.** (A) Plot of pre- and postsplenectomy (2–12 wk) platelet counts versus spleen weight for 62 patients. Three patients had spleen weights greater than 3000 g; only 1 increased the platelet count to greater than 200 x 10^9/liter postsplenectomy. (B) Plot of pre- and postsplenectomy (2–12 wk) white blood cell counts versus spleen weight for 62 patients. Three patients had spleen weights greater than 3000 g; 2 did not reach a WBC of 5 x 10^9/liter postsplenectomy. Cross-hatched lines represent patients whose white blood cell count was lower postsplenectomy.
greater; there is a tenfold range of weights in the patients with postsplenectomy platelet counts of less than 200 x 10^9/liter. Thus, the spleen weight alone would have been a poor predictor of their lack of response to splenectomy.

There is not a significant difference between the mean HCI of the two groups of patients with postsplenectomy WBC counts of <5000/cu mm or ≥5000/cu mm (p = 0.25), as was evident with the comparison between groups divided by platelet response.

Figure 4 shows the HCI versus the spleen weight for 51 patients. There is no statistically significant correlation between the size of the spleen and the degree of involvement of the bone marrow (r = 0.15, p = 0.15). For example, patients with a spleen weight of 1000 g or less, have HCIs ranging from 0.12 to 0.87, with an even distribution along the scale. The lack of direct association between HCI and spleen weight helps, in part, to explain the observation made in Fig. 2 that there is no direct correlation between spleen weight and response to splenectomy.

**DISCUSSION**

There have been numerous papers published in the last 5 yr that have attempted to look at the response to splenectomy in HCL.2,4,6 Actuarial survival in a multicenter study at 5 yr for a postsplenectomy CR group of 81 patients and a postsplenectomy PR group of 118 patients was approximately 75% and 50%, respectively.6 Their CR group had a significantly longer survival time than their PR group (p < 0.01); our CR group has a better survival, but it is not statistically significant. Some investigators have tried to assess whether the response can be predicted by studying erythrocyte ferrokinetics3 or splenic red cell pooling.7 Catovsky's2 and our earlier work4 suggested that the postsplenectomy response (CR or PR) could predict the subsequent course. We suggest that what was possibly being measured was that the CR patients had splenic sequestration as their major problem and that the PR patients had bone marrow underproduction as their major problem. Although one might expect the size of the spleen to correlate with the degree of sequestration and the subsequent response, our data (Fig. 2 and Table 1) show that there is no significant correlation between spleen weight and degree of response. This clinical observation is supported by the previous observations of Lewis et al.,2 who showed that maximum sequestration in hairy cell leukemia can occur with minimally enlarged spleens.

Evaluation of the degree of bone marrow infiltration by hairy cells could be associated with the bone marrow underproduction and predict the postsplenectomy response. Although Castro-Malaspina et al.13 did not observe any correlation between the apparent degree of infiltration of the bone marrow by hairy cells and the degree of erythropoietic deficiency, our data...
presented in Fig. 3 suggest that the lack of a satisfactory platelet response postsplenectomy is a reflection of the replacement of the bone marrow by hairy cells. Yam et al. believe that bone marrow failure is the most important cause of pancytopenia in HCL, as they observed an impaired granulocyte reserve even after splenectomy.14

Bone marrow replacement with a resultant underproduction problem appears to be an important consideration in predicting the type of response in the platelet count to splenectomy in hairy cell leukemia. Patients with an HCI of 0.7 or greater whose platelets do not increase to $200 \times 10^9$/liter postsplenectomy may require early intervention with low-dose alkylating agent chemotherapy.9,10

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