Splenic Enlargement and Hyperfunction as Indications for Splenectomy in Chronic Leukemia

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The chronic leukemias are associated with significant morbidity from splenic enlargement and hyperfunction. Although some patients with chronic leukemia benefit from splenectomy, the indications for operation are unclear. To identify those patients who benefit most from splenectomy, nine patients with chronic lymphocytic leukemia (CLL) and eight patients with chronic granulocytic leukemia (CGL) who had splenectomy to palliate the symptoms of massive splenic bulk or to improve the hematologic sequelae of splenic hyperfunction were studied. Splenectomy for bulk symptoms provided good palliation of symptoms, but the duration of the benefit was limited by the stage of the disease. Five of eight patients with CGL with bulk symptoms died within 6 months of operation. Splenectomy for hyperfunction was limited to a short-term hematologic response. In three of four patients with CLL who were Coombs positive, the presence of autoantibodies correlated with a recurrent transfusion requirement within 3 months of splenectomy. Thus, the benefit of splenectomy for bulk symptoms must be weighed against the risk of surgery and the patient's limited life expectancy. The benefit of splenectomy for treatment of splenic hyperfunction depends on the stimulus to hyperfunction and may not be beneficial for patients with refractory autoimmune anemias.

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BOTH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) and chronic granulocytic leukemia (CGL) involve the spleen at some time in the disease process. Involvement is usually manifest by splenic enlargement and/or hyperfunction. Massive enlargement of the spleen results from infiltration of neoplastic cells. The bulk of the spleen may cause symptoms such as pain, weight loss, and fatigue. The enlarged spleen may also sequester blood elements, resulting in depressed peripheral blood counts. The other common splenic manifestation of the chronic leukemias is splenic hyperfunction. Autoimmune-induced cytopenias are commonly associated with the chronic leukemias and appear to stimulate hyperphagocytosis of blood elements in the spleen.

Given the complex role of splenic dysfunction in chronic leukemias, it is not surprising that splenectomy has had mixed results in the treatment of splenic complications. One indication for splenectomy is palliation of bulk symptoms. Several reports have shown that splenectomy resolves the bulk symptoms for both CGL[1-3] and CLL[4-6] patients. Unfortunately, the symptoms occur late in the course of the disease, and splenectomy may have little impact on life expectancy.[2,3,7,8] The hematologic indications for splenectomy are also unclear. Most studies report an unpredictable hematologic response to splenectomy.[5,9,10] In most cases, the response to splenectomy was sustained less than 6 months.

To identify the subset of patients who might benefit from splenectomy, we reviewed the clinical course of nine patients with CLL and eight patients with CGL for the first 6 months after splenectomy. In the patients with CLL, a poor hematologic response to splenectomy correlated with the presence of autoantibodies, suggesting that an immune stimulus to splenic hyperfunction was poorly responsive to splenectomy. In contrast, splenic hyperfunction in patients with CLL who were Coombs negative and almost all CGL patients was thought to reflect congestion of the spleen by malignant cells. Although these patients would theoretically benefit from operation, in many cases the response to splenectomy was limited by advanced disease and inadequate bone marrow reserve.

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TABLE 1. *Clinicopathologic Summary of Patients with CLL*

Patient	Indications		Spleen	
	Primary	Secondary	Size (g)	Histopathologic Finding
A	Transfusions	Pain	375	Extramedullary hematopoiesis
B	Transfusions	—	627	Leukemic infiltrate*
C	C1 inhibitor	Angioneurotic edema	2180	Leukemic infiltrate
D	Transfusions	—	740	Leukemic infiltrate
E	Transfusions	—	1925	Leukemic infiltrate
F	Transfusions	Angina	437	Leukemic infiltrate
G	Transfusions	Pain, thrombocytopenia	2310	Leukemic infiltrate
H	Transfusions	Thrombocytopenia	9900	Extensive infiltrate
I	Transfusions	Pain	3650	Extensive infiltrate

* Splenic histopathologic findings revealed infiltration by CLL cells with preservation of the splenic architecture.

Methods

Medical records at the Brigham and Women's Hospital and the Dana-Farber Cancer Institute were examined for patients with chronic leukemia from 1969–1983. Those patients who had splenectomy for any reason were selected for detailed review. The diagnosis of CGL was based on: (1) granulocytic leukocytosis (15,000 μL) with a spectrum of myeloid maturation, (2) low or undetectable leukocyte alkaline phosphatase score, and (3) hypercellular bone marrow with granulocytic hyperplasia. The criteria for the diagnosis of CLL was based on peripheral lymphocytosis, lymphadenopathy, splenomegaly, and hypercellular bone marrow with lymphocytic hyperplasia. Patients with CLL were excluded if the histologic features were suggestive of poorly differentiated lymphocytic lymphoma.

The medical records of all patients were reviewed to characterize the clinical course. Available data included preoperative therapy, indications for operation, intraoperative status, and postoperative course with follow-up therapy. Complete pathologic records were available on all patients. Preoperative bone marrow histopathologic findings with special stains were available in nine patients. Postoperative laboratory values were grouped into the following intervals: 0–1 week, 1–2 weeks, 0.5–2 months, 2–4 months, and 4–8 months. Mean values were calculated for each interval.

Results

CLL Indications for Splenectomy

Nine patients (4 females, 5 males) with CLL had palliative splenectomies. The mean patient age was 66 ± 9 years with a mean duration of disease of 3 years (range: 2–8 years). All patients had previous cytotoxic chemotherapy. Common therapeutic agents were chlorambucil, vincristine, prednisone, and hydroxyurea. Patients A, F, and I received all four agents during the course of their therapy. The indications for splenectomy were a high red cell transfusion requirement (1–3 units per week) in eight patients and a C1 inhibitor deficiency in one patient (Table 1). Patients B, D, E and I were Coombs positive. The spleen in seven of nine patients was palpable 7 ± 6 cm under the costal margin (UCM). All patients except for patient I had palpable hepatomegaly (2.7 ± 1.3 cm UCM). Only patient D had peripheral lymphadenopathy.

CGL Indications for Splenectomy

Eight patients (5 females, 3 males) with CGL had splenectomies. The mean age was 51 ± 17 years with a mean duration of disease of 3 years (range 1–5 years). All patients had cytotoxic chemotherapy before splenectomy. The primary indication for operation in all patients was splenomegaly with associated symptoms of pain, weight loss, and fatigue (Table 2). Clinical splenomegaly was present in five patients (5.4 ± 2.6 cm UCM). In addition to symptomatic splenomegaly, the indication for surgery was thrombocytopenia (<65,000 platelets/μL) in six patients. Six patients were anemic (hemoglobin levels < 12 g/dL) but anemia was an indication for surgery in only one patient. One patient was pancytopenic. Patient Q had atypical gallbladder pain, accounting for her abdominal complaints. She was the only patient with a normal red cell and platelet count before splenectomy (Table 2).

Operative and Postoperative Complications

The splenectomies for patients with CLL were largely uncomplicated. Intraoperative blood loss correlated with the size of the spleen. The estimated blood loss was 1700 ± 707 mL for spleens larger than 3000 g; spleens under 3000 g were associated with a blood loss of 212 ± 223 mL. After operation patient D had deep vein thrombosis and eventually died of sepsis. Patients C and H had hypoxia and hyperventilation with equivocal lung scans; however, both patients recovered without other evidence of pulmonary embolism. There were no intraoperative

TABLE 2. *Clinicopathologic Summary of Patients with CGL*

Patient	Indications		Spleen	
	Primary	Secondary	Size (g)	Histopathologic Findings
J	Bulk symptoms	Anemia	3526	Extensive infiltrate*
K	Bulk symptoms	Pancytopenia	3540	Extensive infiltrate
L	Bulk symptoms	Anemia, thrombocytopenia	2400	Extensive infiltrate
M	Bulk symptoms	Thrombocytopenia	2030	Extensive infiltrate
N	Bulk symptoms	Thrombocytopenia	2325	Extensive infiltrate
O	Bulk symptoms	Thrombocytopenia	2660	Extensive infiltrate
P	Bulk symptoms	Thrombocytopenia	3440	Extensive infiltrate
Q	Bulk symptoms	No abnormality	530	Extensive infiltrate

* Splenic histopathologic findings revealed extensive infiltration of CGL cells.

complications during the splenectomies for patients with CGL. Patient K died of overwhelming pseudomonas sepsis the day after a technically uncomplicated splenectomy. The remainder of the patients had septic complications attributable to their advanced disease.

Histopathologic Features of the Spleen

All patients had some degree of splenomegaly. The spleens of the patients with CLL had variable amounts of diffuse leukemic infiltration, but had preservation of splenic architecture (Table 1). In contrast, all patients with CGL except for patient Q had extensive neoplastic congestion of the spleen with destruction of the splenic architecture. The spleen weight was greater than 200 g in all patients with CGL except for patient Q (Table 2). This patient had a relatively small spleen that was removed because of atypical abdominal pain.

CLL Response to Splenectomy

An excessive red cell transfusion requirement was an indication for splenectomy in all patients with CLL. To assess the response to splenectomy, the hematocrit was examined at regular intervals for the first 6 months after splenectomy. Four patients did not sustain a response to splenectomy and required transfusions within 6 months of splenectomy (Fig. 1). Three of these patients (B, E, F) had documented antierythrocyte antibodies; patient D was Coombs negative. The remaining five patients were Coombs negative and had an excellent response to splenectomy. The best hematologic response was observed in one patient after removal of a 9.9-kg spleen (patient H). Although this patient had pancytopenia, he had a complete response to splenectomy that lasted 4.3 years. Age, duration of disease, previous therapy, transfusion requirement, hematocrit, platelet count, and histologic features of bone marrow were not associated with a hematologic response to splenectomy.

CGL Response to Splenectomy

Almost all patients with CGL who had splenectomy for mechanical symptoms had significant relief after operation. Patient K died of sepsis on the first postoperative day. The platelet counts for all eight CGL patients with CGL were followed for 6 months after operation. Four of eight patients died within 3 months of splenectomy despite an initial increase in platelet counts (Fig. 2). Common risk factors for these patients were: (1) hepatomegaly, (2) hemoglobin levels less than 11 g/dL, (3) severely dysplastic bone marrow, and (4) fever of unknown origin. Except for one patient with hepatosplenomegaly, the remaining four patients did not have any of these four risk factors. The difficulty in identifying high-risk patients with CGL is illustrated by patient J (Fig. 3). Preoperative evaluation revealed hepatosplenomegaly and anemia, but a normal peripheral white blood cell count and platelet

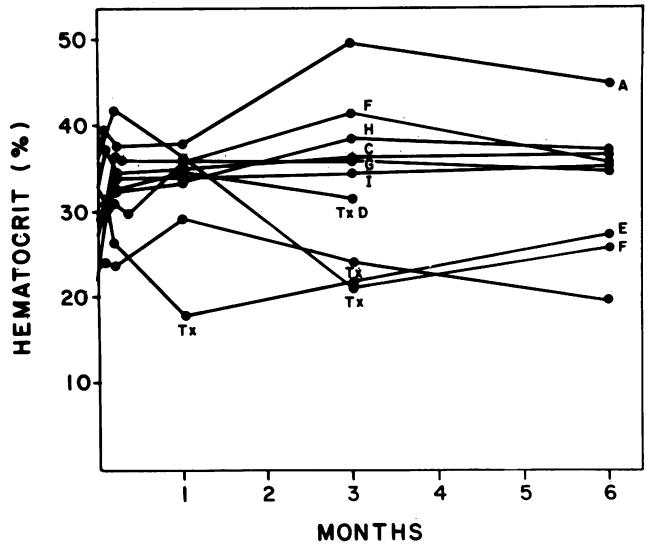

FIG. 1. Serial hematocrit measurements of nine patients with CLL after splenectomy (A–I). The time of recurrent transfusion requirement is shown relative to the time of operation (Tx). Patient D died 3 months after operation from unrelated disease.

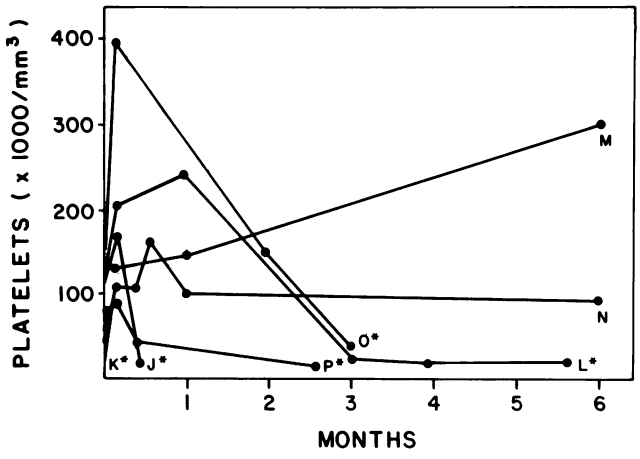

FIG. 2. Serial platelet measurements of eight patients with CGL after splenectomy (I–Q). Asterisks note postoperative deaths within 6 months of splenectomy.

count. The only preoperative indication of blastic transformation was a bone marrow biopsy 7 days before surgery. The histologic findings revealed a severely dysplastic marrow. Despite the suggestion of "accelerated disease," splenectomy was performed. The patient died of fulminant blastic crisis 12 days later (Fig. 3).

Other characteristics of patients with CGL such as age, duration of disease, previous chemotherapy, Philadelphia chromosome, and blast cells in the peripheral blood did not correlate with the response to splenectomy.

Discussion

To identify common characteristics of patients who benefited from operation, we reviewed the medical records of 17 patients with chronic leukemia who had palliative splenectomy. All nine patients with CLL had a short-term hematologic response to splenectomy. The response was sustained less than 6 months in four patients; three of whom had an autoimmune anemia. The remaining patients with CLL and the eight patients with CGL had no evidence of autoimmunity. In the absence of autoantibodies, the splenic enlargement and hyperfunction was most likely secondary to congestion of the spleen with malignant cells. Consistent with previous reports,[1–6] complications associated wtih secondary splenic enlargement, such as bulk symptoms and hematologic depression, were reversed by splenectomy. In our series, the benefit of splenectomy in patients with CGL was limited by the stage of the disease; specifically, by the extent of blastic transformation.

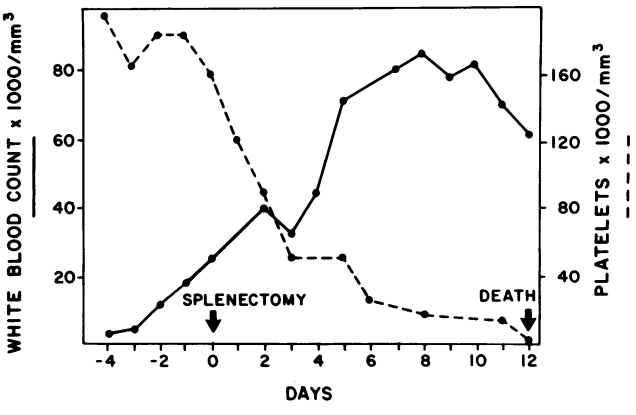

FIG. 3. Pre- and postoperative course of Patient J as reflected by peripheral blood white cell and blast counts. Day 0 identifies the day of splenectomy. The patient died on postoperative day 12 of septic complications of bone marrow failure.

The patients with autoimmune anemia required recurrent transfusions approximately 3 months after splenectomy. This time course may be explained by the phenomenon of work-stimulated hypertrophy of the reticuloendothelial system (RES).[11,12] The spleen can hypertrophy in response to an increased workload as suggested by chronic hemolytic disorders and by the observation that foci of splenic tissue after traumatic laceration can enlarge and function like an intact spleen.[13] Other elements of the RES can also compensate. Kupfer cells of the liver become more proficient in filtering the circulation of splenectomized rats.[11] Postsplenectomy hypertrophy of the RES can occur within weeks[12,13]; a finding consistent with the increased affinity of the liver for ^{99}Tc in one of our patients (scan not shown) and the time course of recurrence in the three patients. Based on these observations, the initial response after splenectomy in our patients indicates a decrease in the filtering capacity of the RES. With the autoimmune stimulus to compensatory hypertrophy, the functional capacity of the RES was restored and the patient developed a recurrent transfusion requirement.

In some cases, splenic enlargement may contribute to an autoimmune response. A spleen-based immune dysregulation is seen in animals with experimental splenomegaly. Rats with chemically induced splenomegaly spontaneously develop polyclonal hypergammaglobulinemia.[12] Similarly, splenomegalic patients with hereditary spherocytosis can demonstrate hypergammaglobulinemia.[14,15] These observations suggest that at least some leukemic patients with autoimmune anemias may benefit from splenectomy. A splenic contribution to autoimmunity may account for the response of a year or more observed in some patients with leukemia who are Coombs positive.[4] It is important to note, however, that our patients with Coombs-positive anemia had severe (2–3 transfusions per week) anemias and had failed immunosuppressive therapy. In such severe cases it is doubtful that splenic enlargement alone can account for the immune perturbation, or that splenectomy will provide long-term benefit.

Splenic hyperfunction in most of the patients with CLL who are Coombs negative and seven patients with CGL appeared to be the result of neoplastic infiltration of the

spleen. Splenic hyperfunction in these patients was a result of organ enlargement and not a consequence of an immune-stimulated hyperfunction. Patients with secondary splenic hyperfunction benefited most from splenectomy. An important qualification is that splenomegaly from infiltrating cells is related to the lineage of the cells and the stage of the disease. In CLL, splenomegaly is an early event that reflects the B-lymphocyte phenotype of most CLL neoplasia. Splenomegaly in these patients need not indicate terminal disease. In contrast, the myeloid cells of CGL infiltrate the spleen as a late event. Secondary splenic hyperfunction in these patients indicates advanced disease, often with extensive bone marrow involvement. Splenectomy exposes the patients to the dangers of diminished bone marrow reserve and postoperative complications.

In the patients with CGL, four high-risk characteristics correlated with terminal disease: (1) hepatosplenomegaly, (2) severely dysplastic bone marrow, (3) anemia (hemoglobin < 11 g/dL) and (4) fever of unkown origin. Although this study comprised a small number of patients, the risk factors are consistent with other reports,[1-3,6,16] and the poor results suggest that splenectomy in these patients will have a limited benefit. At minimum, our results strongly suggest that patients with CGL with advanced disease have a bone marrow biopsy as a routine part of the preoperative evaluation.

If bone marrow failure and end-stage disease can be excluded, splenectomy as a procedure in patients with chronic leukemia is largely uncomplicated.[17,18] Operation clearly benefits patients with bulk symptoms such as splenic pain, weight loss, and fatigue. The future role of splenectomy in patients with chronic leukemia will depend on our ability to discriminate the reason for splenic hyperfunction and further clarify the subset of patients who benefit from splenectomy.

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