Hypothesis: The incidence of primary lymphoma of the spleen in patients with idiopathic splenomegaly is significant.

Design: Retrospective review of all patients referred to a general surgical service for splenectomy.

Setting: A large tertiary care hospital.

Patients: Between 1994 and 2001, 86 nontrauma patients were referred for splenectomy. Of these, 18 had idiopathic splenomegaly despite prior workup with computed tomography, peripheral smear, bone marrow biopsy, and laboratory testing. All patients were symptomatic and displayed varying degrees of cytopenia.

Intervention: All 18 patients underwent open splenectomy for diagnosis and treatment of their cytopenias.

Main Outcome Measure: Incidence of lymphoma in the pathologic specimens.

Results: The mean size of the spleens was 21 cm (range, 14-34 cm) and mean weight was 996 g (range, 320-1840 g). In all 18 patients, the surgical specimen provided a diagnosis. Sarcoïdosis was discovered in 4 patients, and 1 patient had Castleman disease. Six patients with the benign diagnosis of hypersplenism received no further interventions, and the cytopenias resolved in all 6 cases. The remaining patients (39%) were diagnosed with lymphoma. Five had marginal zone lymphoma, and 2 had a more aggressive B-cell lymphoma. Three patients required chemotherapy, but 4 are still in remission since their splenectomies and show no evidence of active disease. The mean follow-up was 20 months.

Conclusions: A high percentage of patients with splenomegaly of unknown etiology will have primary lymphoma of the spleen. Splenectomy is both diagnostic and therapeutic and should be considered for all patients with idiopathic splenomegaly.

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In 1969, Dacie et al described 10 patients with non-tropical idiopathic splenomegaly or “primary hypersplenism” that occurred in isolation without evidence of immune thrombocytopenic purpura, lymphadenopathy, or the B symptoms of lymphoma. He performed a follow-up study in 1978 and found that 4 of the 10 patients developed malignant lymphomas 8 months to 6 years after splenectomy, despite only mild cytological abnormalities in the pathologic specimens. A worldwide review of the literature in 1982 revealed 46 reported cases of splenomegaly of unknown origin, of these, non-Hodgkin lymphoma developed in 9 patients (20%) at 8 to 80 months after splenectomy. The authors named the entity Dacie syndrome and proposed a pathological correlation between isolated idiopathic splenomegaly and the subsequent development of lymphoma.

Since the advent of flow cytometry and immunohistochemistry, it is rare that a patient is labeled with idiopathic splenomegaly after laboratory evaluation, peripheral smear, and bone marrow analysis. Furthermore, the liberal use of computed tomography and magnetic resonance imaging makes discovering intra-abdominal lymphadenopathy easier than ever before and the diagnosis of lymphoma a routine matter. However, despite these advances, splenomegaly without a clear etiology still occurs in 7% to 15% of patients evaluated for possible splenomegaly or hypersplenism. As Dacie et al hypothesized, 2 recent studies have shown that those patients with idiopathic splenomegaly referred for diagnostic splenectomy have occult lymphoma in 43% to 70% of cases. Additionally, the cytopenias from splenomegaly may be the initial manifestation of occult lymphoma in the spleen, a dis-
SUBJECTS AND METHODS

A retrospective study included all patients undergoing splenectomy at a large tertiary care hospital from January 1994 to June 2001. Reviews of the medical records were complemented by direct clinical follow-up during office visits with the patient’s surgeon or hematologist. Records provided information about surgical pathology specimens, bone marrow biopsy results, and laboratory data, which were available for 100% of patients. Information on post-splenectomy treatments and outcomes was obtained. All patients in this series are still alive, and none were lost to follow-up.

ease for which early treatment is vital and may improve survival. However, much of the literature on this subject is more than 30 years old. To determine the incidence and prognosis of primary lymphoma of the spleen in patients with idiopathic splenomegaly in a more recent period, we performed a retrospective study of all patients referred to a general surgery service for splenectomy over 7 years, from 1994 to 2001. Special attention was paid to finding an overexpression of a monoclonal cell line or populations of abnormal lymphocytes in the specimens.

RESULTS

From 1994 to 2001, 86 nontrauma patients were referred to the general surgery service for splenectomy. Of these, 45 (52%) had palpable splenomegaly. The preoperative diagnoses included immune thrombocytopenic purpura in 35 patients (41%), myelodysplasia or leukemia in 15 (17%), lymphoma in 6 (7%), autoimmune hemolytic anemia in 5 (6%), and splenomegaly of unknown etiology in 18 (21%) (Table 1). Thus, 40% of patients (n=18) with palpable splenomegaly did not have a known etiology. These patients are the focus of this study.

The 18 patients without a preoperative diagnosis comprised 9 men and 9 women with a mean age of 56 years (range, 30-83 years). Presenting signs and symptoms included thrombocytopenia (67%), epigastric or left upper quadrant pain (28%), and early satiety (28%). Symptoms had been present for 2 to 6 months (mean, 4 months). All 18 patients had splenomegaly with palpable spleens on physical examination. None of the patients displayed petechiae, purpura, gingival bleeding, or other signs of immune thrombocytopenic purpura. Lymphadenopathy was palpable on physical examination in only 1 patient.

Twelve patients displayed varying degrees of thrombocytopenia (platelet count <150 x 10^3/µL), whereas the remainder had normal platelet counts. Two were anemic (hemoglobin <10 g/dL). Epstein-Barr virus antibody titers were analyzed in 6 patients, and all were negative for IgM antibodies. Angiotensin-converting enzyme levels were checked in 6 patients, with only 1 abnormal value in a patient who did not have sarcoidosis. Antinuclear antibody titers were checked in 5 patients, and all were negative.

In 16 patients, splenomegaly was confirmed by computed tomography, and in 1 patient, splenomegaly was confirmed by magnetic resonance imaging. Imaging studies showed 1 patient with intraperitoneal lymphadenopathy; the remaining patients only displayed isolated splenomegaly.

Preoperative bone marrow biopsies were performed for all patients. Myeloid hyperplasia without evidence of neoplasia was found in 7 patients, normal marrow in 5, nondiagnostic atypical lymphoid aggregates in 5, and non-necrotizing granulomas suspicious for sarcoidosis in 1. All samples were evaluated by an experienced cytopathologist and hematologist.

All splenectomies were performed by the open technique because the mean size of the spleens was 21 cm (range, 14-34 cm) and the mean weight was 996 g (range, 320-1840 g) (Table 2). There were no major and 4 minor complications. One patient developed a wound infection, and a portion of the wound was opened and packed. A second patient with congestive heart failure developed a postoperative atrial fibrillation that was successfully treated. A third patient had a subphrenic fluid collection that was drained under computed tomographic guidance. The final patient had a postoperative ileus. There were no deaths.

In all cases, a diagnosis was provided by the surgical specimen. Sarcoidosis was discovered in 4 patients who were then referred to pulmonologists for medical management; of these patients, 2 were later prescribed prednisone for ongoing symptoms. Six patients with the benign diagnosis of hypersplenism with congestive splenomegaly received no further interventions. The cytopenias from their hypersplenism resolved in all 6 cases (Table 3). One patient was diagnosed with Castleman disease.

The 7 remaining patients (39%) were diagnosed with lymphoma. Five had marginal zone lymphoma, and 2 had a more aggressive B-cell lymphoma. In the 2 latter patients, metastatic disease was discovered in the perisplenic lymph nodes and liver biopsy specimen at the time of surgery; these patients received the cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone chemotherapy regimen. One has done well without a relapse at 17 months. The other patient relapsed and has required 2 further treatment cycles with alternative chemotherapy. Four of the remaining 5 patients who had marginal zone lymphoma had no evidence of metastatic disease or spread outside of the splenic capsule at the time of laparotomy and have required no further treatment. All are still undergoing surveillance without evidence of disease progression at 4, 10, 11, and 30 months, respectively, since their surgery. The final patient with marginal zone lymphoma developed a recurrence in the bone marrow 42 months after her splenectomy and required cyclophosphamide, vincristine, and prednisone chemotherapy, and rituximab monoclonal antibody therapy, but she is still alive 56 months after surgery.

The mean follow-up for the patients in this series is 20 months (range, 1-76 months). Documentation of Haem-
mophilus influenzae, Pneumococcus species, and Meningococcus species immunizations prior to splenectomy could only be found for 14 patients and was unknown for 4. None of the patients have yet developed postsplenectomy sepsis.

This study examined the use of splenectomy to diagnose and treat primary lymphoma of the spleen in patients with idiopathic splenomegaly. Lymphoma that presents with splenomegaly and without peripheral lymphadenopathy occurs in less than 1% of cases. However, several previous reports from centers that treat a lot of patients with hematologic disease have found primary lymphoma of the spleen in patients referred for idiopathic splenomegaly, and these centers promote splenectomy for diagnosis and treatment. Our results confirm these findings with a 39% incidence of primary lymphoma in 18 patients. After surgery, 4 of the 7 patients with marginal zone lymphoma, which is generally considered to have a good prognosis, received only surveillance as no metastatic spread could be documented and are considered to be in remission.

This finding comes at a timely point in medicine when more and more problems once treated with surgery are instead being treated with nonoperative management. It has been proposed that in certain situations, it is appropriate to treat the patient with idiopathic splenomegaly expectantly and defer splenectomy. Based on the data from this study, that course of treatment could potentially delay a lymphoma diagnosis because no prior symptoms or adenopathy were present in these patients and many laboratory tests for other causes of splenomegaly were negative. Kehoe and Straus found that this approach would have missed 13 out of 21 patients with primary lymphoma of the spleen, when the unsuspected diagnosis was confirmed only after splenectomy.

One argument against diagnostic splenectomy has been the high morbidity and mortality associated with removal of massively enlarged spleens. One study from the last decade documented mortality rates of 19% and complication rates as high as 39%, including infection, bleeding, small bowel obstruction, and reoperation. However, another recent report has documented mortality rates of zero. Our series also had a mortality rate of zero and a minor morbidity rate of only 22% (n=4) with no major complications. Therefore, we feel that diagnostic splenectomy, even on massively enlarged spleens, can be done safely with a low complication rate.

Splenectomy provided a diagnosis in 100% of the patients in this series despite previous computed tomography, peripheral smear, bone marrow biopsy, and laboratory testing being nondiagnostic in every patient. Furthermore, 2 patients who were thought to possibly have leukemia based on the bone marrow biopsy specimens actually had marginal zone lymphoma. The chemotherapeutic treatment plans for both patients obviously changed after splenectomy.

In addition to its role as a diagnostic modality, splenectomy cured all patients of their hypersplenic cytopenias. Platelet counts rose dramatically in all thrombocytopenic patients after surgery and remained elevated during follow-up. A similar finding has been reported by Coon, who documented 4 patients with idiopathic splenomegaly who resolved their thrombocytopenias after splenectomy and remained in complete remission for as long as 16 years after surgery.

Although lymphoma is generally considered a systemic disease, 2 variants have been described that tend to be limited, at least initially, to the spleen: splenic lymphoma with circulating villous lymphocytes and marginal zone lymphoma. Both variants have been thoroughly described and usually present with splenomegaly, anemia, and thrombocytopenia. Both are low-grade B-cell non-Hodgkin lymphomas and are histologically indistinguishable from each other. These primary splenic lymphomas are believed to arise from the perifollicular tissue in the spleen and thus would be effectively treated by splenectomy. Marginal zone lymphoma has been shown to be particularly responsive to

### Table 1. Etiology of Splenomegaly in Patients Referred for Splenectomy

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune thrombocytopenic purpura</td>
<td>35 (41)</td>
</tr>
<tr>
<td>Chronic lymphocyte leukemia</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Myelodyplasia, myelofibrosis</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Other leukemia</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hereditary spherocytosis, elliptocytosis</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Total</td>
<td>86 (100)</td>
</tr>
</tbody>
</table>

### Table 2. Pathologic Findings in Splenectomy Specimens

<table>
<thead>
<tr>
<th>Patient No./ Age, y/Sex</th>
<th>Abnormalities</th>
<th>Splenic Weight, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/80/F</td>
<td>Congestive splenomegaly</td>
<td>810</td>
</tr>
<tr>
<td>2/32/F</td>
<td>Sarcoïdosis</td>
<td>320</td>
</tr>
<tr>
<td>3/80/M</td>
<td>B-cell lymphoma</td>
<td>800</td>
</tr>
<tr>
<td>4/30/M</td>
<td>Reactive lymphoid hyperplasia</td>
<td>330</td>
</tr>
<tr>
<td>5/47/F</td>
<td>Congestive splenomegaly</td>
<td>870</td>
</tr>
<tr>
<td>6/52/F</td>
<td>Reactive lymphoid hyperplasia</td>
<td>1600</td>
</tr>
<tr>
<td>7/36/F</td>
<td>Sarcoïdosis</td>
<td>1140</td>
</tr>
<tr>
<td>8/79/M</td>
<td>Congestive splenomegaly</td>
<td>950</td>
</tr>
<tr>
<td>9/49/F</td>
<td>Congestive splenomegaly</td>
<td>950</td>
</tr>
<tr>
<td>10/69/M</td>
<td>B-cell lymphoma</td>
<td>1740</td>
</tr>
<tr>
<td>11/41/M</td>
<td>Sarcoïdosis</td>
<td>760</td>
</tr>
<tr>
<td>12/75/F</td>
<td>Marginal zone lymphoma</td>
<td>1150</td>
</tr>
<tr>
<td>13/62/M</td>
<td>Marginal zone lymphoma</td>
<td>490</td>
</tr>
<tr>
<td>14/36/M</td>
<td>Granulomatous splenitis</td>
<td>890</td>
</tr>
<tr>
<td>15/63/F</td>
<td>Marginal zone lymphoma</td>
<td>1560</td>
</tr>
<tr>
<td>16/24/M</td>
<td>Castleman disease</td>
<td>890</td>
</tr>
<tr>
<td>17/83/M</td>
<td>Marginal zone lymphoma</td>
<td>1840</td>
</tr>
<tr>
<td>18/70/F</td>
<td>Marginal zone lymphoma</td>
<td>850</td>
</tr>
</tbody>
</table>

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In this study, 4 of the 5 patients with marginal zone lymphoma have done very well since surgery and have shown no evidence of recurrence despite having no further treatment with chemotherapy. In fact, splenectomy is considered the most effective therapy for all primary splenic lymphomas and is the treatment of choice for marginal zone lymphoma, which is often isolated to the spleen and tends to have an indolent clinical course.\textsuperscript{15,17}

Whereas some patients with marginal zone lymphoma may remain asymptomatic for years after splenectomy, others will exhibit a slow progression with peripheral lymphadenopathy or bone marrow involvement and may require chemotherapy. Currently, there have been 8 reported cases of patients with marginal zone lymphoma who developed high-grade blastic transformation with an aggressive clinical course leading to death.\textsuperscript{18-20}

Thus, watchful waiting may be an inappropriate option when the etiology of a patient with splenomegaly remains obscure.

In conclusion, a substantial percentage of all patients with idiopathic splenomegaly will have lymphoma. Splenectomy is appropriate not only for diagnosis, but also to treat hypersplenism and restore circulating myelogenous elements to normal levels. This protects patients from requiring transfusions and helps them to tolerate chemotherapy, if necessary, after the neutropenia and anemia have resolved. It also reduces the radiation field. Furthermore, the small percentage of patients with primary splenic or marginal zone lymphoma may be sent into remission by splenectomy alone. Thus, splenectomy plays a major role in the diagnosis and treatment of idiopathic splenomegaly.

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\begin{table}[h!]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Patient No.} & \textbf{WBC, }$\times 10^9/\mu\text{L}$ & \textbf{Hematocrit, %} & \textbf{Platelets, }$\times 10^9/\mu\text{L}$ & \textbf{Follow-up, mo} \\
\hline
\textbf{Preoperation} & & & & \\
1 & 5700 & 32.8 & 166 & 1 \\
2 & 4400 & 40.3 & 108 & 16 \\
3 & 3600 & 27.9 & 51 & 17 \\
4 & 5500 & 49.7 & 50 & 76 \\
5 & 3400 & 28.5 & 151 & 1 \\
6 & 3800 & 33.7 & 85 & 3 \\
7 & 3700 & 31.7 & 256 & 36 \\
8 & 8700 & 32.0 & 228 & 33 \\
9 & 4700 & 35.3 & 540 & 33 \\
10 & 5800 & 22.4 & 123 & 11 \\
11 & 5900 & 41.8 & 118 & 16 \\
12 & 3400 & 35.2 & 145 & 11 \\
13 & 4900 & 37.6 & 105 & 10 \\
14 & 4800 & 47.1 & 128 & 2 \\
15 & 3300 & 33.0 & 108 & 30 \\
16 & 9300 & 45.0 & 454 & 1 \\
17 & 4000 & 45.3 & 81 & 4 \\
18 & 4200 & 35.7 & 110 & 56 \\
\hline
\textbf{Postoperation} & & & & \\
1 & 8100 & 31.3 & 309 & 1 \\
2 & 10 000 & 38.3 & 401 & 16 \\
3 & 16 000 & 36.4 & 270 & 17 \\
4 & 5000 & 43.6 & 361 & 76 \\
5 & 5600 & 33.7 & 420 & 1 \\
6 & 13 600 & 32.8 & 1080 & 3 \\
7 & 8600 & 46.0 & 382 & 36 \\
8 & 7300 & 45.0 & 412 & 33 \\
9 & 10 000 & 35.4 & 575 & 33 \\
10 & 16 000 & 37.7 & 307 & 15 \\
11 & 10 700 & 48.7 & 389 & 16 \\
12 & 9400 & 35.4 & 422 & 16 \\
13 & 13 500 & 39.7 & 278 & 10 \\
14 & 11 800 & 32.3 & 255 & 2 \\
15 & 8400 & 46.2 & 257 & 30 \\
16 & 19 500 & 42.0 & 1053 & 1 \\
17 & 5700 & 37.5 & 259 & 4 \\
18 & 15 600 & 41.2 & 204 & 56 \\
\hline
\end{tabular}
\caption{Myelogenous Response to Splenectomy}
\end{table}

\textsuperscript{*WBC indicates white blood cells.
In this study, Carr et al have made a small but significant contribution to the literature of diseases of the spleen and their surgical management. Over a 7 1/2 year period, 86 consecutive patients with symptomatic splenomegaly were referred to the busy general surgical service of a large urban medical center. Of these patients, 18 (21%), or roughly 2 patients per year, had splenomegaly of unknown etiology, and they are the subject of this review. Two thirds of these patients had palpable spleens. All 18 patients had negative preoperative evaluations, including computed tomography or magnetic resonance imaging, bone marrow biopsies, and serum testing, and all were treated by open splenectomy. There were no operative deaths and minimal (22%) morbidity. The final pathological diagnoses in the 18 patients included: sarcoidosis (n=4), benign hypersplenism (n=6), Castleman disease (n=1), and lymphoma (n=7, 40%). The lymphomas diagnosed in these patients were the marginal zone variant in 5 patients and B-cell lymphoma in 2, both of whom had disseminated disease discovered at laparotomy. Four of the 5 marginal zone lymphoma patients were free of disease without additional treatment with a mean follow-up of 20 months.

The authors make a persuasive argument for operative intervention in patients with undiagnosed splenomegaly rather than careful observation, as is frequently recommended. They corroborate their findings with examples from the literature of other small series of patients in whom diagnoses of malignancy were made only by laparotomy and splenectomy. The authors did not evaluate positron emission tomographic scanning, laparoscopic evaluation or biopsy, or percutaneous biopsy techniques in their preoperative protocol, and surgeons must consider these options before performing splenectomy in all patients with unexplained splenomegaly. The authors also tactily suggest additional evaluation for sarcoidosis, as 22% of these patients were diagnosed by splenectomy.

In conclusion, Carr et al have shown that, after a complete and inconclusive evaluation, the old-fashioned exploration and resection still has a role in the modern management of splenomegaly and may save lives in the process.

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