Long Term Follow-Up after Splenectomy Performed for Immune Thrombocytopenic Purpura (ITP)

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Splenectomy is the only treatment of ITP known to have “curative” effects in a substantial fraction of patients. However, the true long-term outcome is uncertain and controversial because published series have not adjusted for the duration of follow-up. This IRB-approved retrospective study included all patients with ITP who underwent splenectomy between 1988-1993 at three major medical centers and required a minimum postoperative 5-year follow-up. Complete response (CR) was defined as all postsplenectomy platelet counts >150 × 10^9/L without treatment; partial response (PR) as platelet counts ≥50 × 10^9/L without treatment; and failure as platelet counts <50 × 10^9/L or receiving therapy after splenectomy. Seventy-five patients identified with ITP underwent splenectomy from 1988 to 1993. Three patients died prior to 5-year follow-up, and 56 of the 72 patients (78%) were evaluable with follow-up for five years or longer, median 7.5 years. The immediate postoperative complete remission rate was 77%; 57% of patients have remained in prolonged CR. Thirty-seven patients (66%) have not required any therapy after splenectomy. Eight patients had platelet counts >150 × 10^9/L for 4–8.5 years before relapsing; no clear plateau was attained in the remission curve. There was no operative mortality. Ten patients (18%) reported minor postoperative bleeding episodes. No life-threatening infections, significant heart disease, or pulmonary hypertension developed after splenectomy in the 434 patient-years of follow-up. This study helps to define the long-term results of splenectomy for ITP.


Key words: long-term; follow-up; splenectomy; ITP

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by accelerated platelet destruction. Antiplatelet autoantibodies bind to platelets, causing phagocytosis by the mononuclear phagocyte system [1,2]. The approximate incidence is 5–10 per 100,000 persons per year [3]. In affected adults, splenectomy has been considered to be a second-line therapy for ITP in patients who either fail to respond to initial corticosteroids or require continuous treatment to maintain a safe platelet count [2,4,5].

The beneficial effects of splenectomy in successful cases are removal of the sites of antibody-coated platelet destruction and/or antiplatelet antibody production [6,7]. This duality has made prediction of who will respond to splenectomy difficult. Attempts to identify factors that would predict the success of splenectomy have led to conflicting results among published reports [8–17].

Reported response rates to splenectomy have varied from 50% to 80% [2,8–13]. However, the true long-term outcome response rate is not known because follow-up in most studies has been relatively short [10,12–14]. Even in the studies with longer median follow-up, i.e., up to 5–7 years, patients with short follow-up (3 months to 1 year) were included [9,11,15–17] and could not be distinguished from those with longer follow-up.

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There is also very little information describing late complications of splenectomy for ITP other than sepsis. However, in patients with hereditary spherocytosis, there has been speculation that there might be an accelerated occurrence of atherosclerotic events and development of pulmonary hypertension years after splenectomy [18,19]. The purpose of this study was to evaluate the long-term outcome of splenectomy, defining “long-term” as a minimum follow up of 5 years in adults with ITP.

PATIENTS AND METHODS

The study included retrospective analysis of all 75 cases of adults with ITP that underwent splenectomy between 1988 and 1993 in three major medical centers: Cornell University Medical Center in New York; Hadassah Ein-Karem University Hospital in Jerusalem; and The Tel-Aviv Sourasky Medical Center, Israel. Patients were identified via ICD9 and CPT coding. ITP was defined according to the guidelines of the American Society of Hematology [4]. Splenectomy was generally performed when patients did not respond to medical therapy. This study protocol was IRB approved and followed at each of the participating medical centers. Medical records of all patients and their follow-up were sought. Repeated attempts were made to contact all patients via their primary physicians and then directly. Medical information and blood counts were obtained from the patients themselves, their physicians, and/or review of their hospital and outpatient clinic charts. Information received from patients was double checked with medical records, i.e., laboratory reports, physician documentation, or hospital charts.

Criteria for response were defined as follows: complete response (CR), all post-splenectomy platelet counts >150 × 10^9/L without ever receiving treatment after splenectomy; partial response (PR), all other patients with platelet counts >50 × 10^9/L without therapy after splenectomy; failure, platelet counts <50 × 10^9/L or patients who received therapy after splenectomy.

Data Analysis

Statistical analysis was carried out with the Stat-View 4.5 and Prism 3.0 software. Differences were evaluated by the chi-square test. A two-tailed P value of 0.05 or less was considered as statistically significant. Kaplan–Meier analysis was used to estimate remission rates. Patients relapsing between 2 years, i.e., between 4 and 5 years from surgery, were assigned a relapse time of 4.5 years.

RESULTS

Seventy-five patients with ITP were identified who underwent splenectomy between 1988 and 1993 at the three medical centers. Sixteen patients (21%) were lost to 5-year follow-up. Three patients died: two due to malignancy (both approximately 36 months after splenectomy) and one due to pre-existing ischemic heart disease (48 months after surgery). This left 56 of the 75 patients (75%) who had data available for minimum of 5 years after splenectomy. These 56 patients comprised the study group (Table I), and they were followed up to 10.5 years postoperatively with a median of 7.5 years. There were 434 years of patient follow-up after splenectomy in the 56 patients in the study.

In addition to ITP, the medical history of a small number of patients included thyroid disease, connective tissue disease, cancer, and cardiovascular disease (Table I). The median age of the patients at the time of splenectomy was 37 years (range, 15–81). Forty-five of the 56 patients (80%) were women. The median interval from diagnosis to splenectomy was 12 months with a range of 0.5–233 months (Table I). Forty-one of the 56 patients (73%) had platelet counts between 0 and 20 × 10^9/L prior to surgery, and the median nadir platelet count prior to surgery was 14.5 × 10^9/L.

All patients received steroids as initial therapy for ITP. Twenty-seven patients received only steroids prior to splenectomy, while 29 patients received additional medications including immunoglobulins (IVIG) [19 patients], vincristine [10], danazol [8], anti-D [3], cytoxan [2], and imuran [1]. All patients received pneumococcal vaccine prior to the surgery.

The probability of staying in clinical remission (CR+PR) after splenectomy is shown by Kaplan–Meier analysis in Figure 1: 73% of the patients were still in clinical remission 5 years post splenectomy, and 62% were in remission 10 years postoperatively.

These data are divided into CR, PR, and failure in Table II.

Complete Remission (CR) Group

Forty-three of the 56 patients (77%) achieved a complete remission immediately after splenectomy. Thirty-two patients (57% of the total) remained in a prolonged complete remission with a persistently normal platelet count, never having received any postsplenectomy treat-
ment. Eleven patients, 20% of the total and 25% of the complete responders to surgery, relapsed after an initial complete response.

**Partial Remission (PR) Group**

Five (9%) patients achieved a partial remission (PR). All have remained in PR throughout the long-term follow-up maintaining platelet count >50 × 10⁹/L.

**Failure Group**

Nineteen patients (34%) failed splenectomy. In eight patients (14.3%), there was no response to the operation. The other 11 patients initially had a complete response (normal platelet count) and subsequently relapsed. Three patients failed in the first 2 years, two patients relapsed after 4–5 years, three patients after 5–6 years, and three patients between 6 and 8.5 years after splenectomy (Fig. 1).

All 19 patients in the failure group received prednisone after splenectomy, 11 received IVIG, 5 received vincristine, 3 received danazol, 3 received Cytoxan, and 1 received imuran. The eight primary failure patients, who did not have any response to the splenectomy, were also refractory to medical therapy after splenectomy. Of the 11 patients with late failure, 5 responded to steroids.

There were six cases (11%) in which accessory spleens were identified and removed. One was in a primary failure patient, and five were in patients with late failure; of these five patients. Those five patients relapsed 1, 4, 5, and 8 years after splenectomy. The platelet count rose following the removal of the accessory spleens only in the two patients who had normal platelet counts for >4 years after initial splenectomy before relapse.

Young age at splenectomy, defined as ≤37 years, which was the median age, had a trend toward a positive outcome for splenectomy ($P = 0.074$). A good response to splenectomy was not related to the time between diagnosis and splenectomy or to patient gender (Table III). When the failure group patients were subdivided into those who failed to respond immediately and those who responded initially and later relapsed, none of these variables was predictive in either subgroup.

There were no perioperative deaths. Six patients (10%) experienced transient postoperative complications, including infections, subphrenic abscesses, and minor wound hematomas. Hemorrhagic symptoms consisted of ecchymoses and petechiae were noted in 10 patients (18%) in the follow-up period, all but one of which were in the failure group. There were no major or internal hemorrhages. There were no cases of overwhelming post splenectomy infections (OPSI). Two patients suffered from chronic sinusitis after the surgery. One patient unresponsive to surgery was found to have a positive anti-nuclear factor antibody post-operatively, but none developed SLE. Of three patients with ITP in association with connective tissue disease, two failed to respond to splenectomy and one had a PR. Two patients with ITP who had thyroid disease and underwent splenectomy had 2 CR, 1 PR, and 2 failures. Two patients developed cerebrovascular accidents (CVA) after surgery. One was 66 years old at the time of splenectomy and had diabetes mellitus and hyperlipidemia. She was in CR for 4 years, relapsed, and shortly afterward had a CVA. The other had a history of Hodgkin’s disease at age 36. She received chemotherapy and radiation and achieved last-

### Table II. Response to Splenectomy

<table>
<thead>
<tr>
<th>Immediate post-operative</th>
<th>Long-term follow-up</th>
<th>Therapy post-operative</th>
<th>No therapy post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>43 (77%)</td>
<td>32 (57%)</td>
<td>—</td>
</tr>
<tr>
<td>Partial remission</td>
<td>5 (9%)</td>
<td>5 (9%)</td>
<td>—</td>
</tr>
<tr>
<td>Failure</td>
<td>8 (14%)</td>
<td>19 (34%)</td>
<td>19 (34%)</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>56</td>
<td>19 (34%)</td>
</tr>
</tbody>
</table>

### Table III. Outcome After Splenectomy: Influence of Age, Duration of ITP, and Sex

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Response to splenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at splenectomy (years)</td>
<td>CR + PR</td>
</tr>
<tr>
<td>&gt;37 ($n = 29$)</td>
<td>16</td>
</tr>
<tr>
<td>≤37 ($n = 27$)</td>
<td>21</td>
</tr>
<tr>
<td>$\chi^2 3.187; P = 0.074$</td>
<td></td>
</tr>
<tr>
<td>Diagnosis-splenectomy interval (months)</td>
<td>CR + PR</td>
</tr>
<tr>
<td>&gt;12 ($n = 28$)</td>
<td>20</td>
</tr>
<tr>
<td>≤12 ($n = 28$)</td>
<td>17</td>
</tr>
<tr>
<td>$\chi^2 0.717; P = 0.397$</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>CR + PR</td>
</tr>
<tr>
<td>Female ($n = 45$)</td>
<td>28</td>
</tr>
<tr>
<td>Male ($n = 11$)</td>
<td>9</td>
</tr>
<tr>
<td>$\chi^2 1.514; P = 0.218$</td>
<td></td>
</tr>
</tbody>
</table>
ing remission from her Hodgkin’s lymphoma. She underwent splenectomy for ITP at age 42 with primary failure and developed a CVA 3 years after the surgery while maintaining normal platelet counts on steroid therapy. No significant heart disease or pulmonary hypertension developed after the surgery in any of the patients. One patient with coronary artery disease pre-existing splenectomy died 4 years after surgery.

DISCUSSION

Since first introduced more than 50 years ago by Kaznelson [20], splenectomy continues to be the only “curative” treatment for patients with ITP. The immediate postoperative response is in approximately 80–85% of patients [2,11,13,14]. The long-term response rate is less well defined and has been variably estimated to be in the range of 50–80% [8–16]. While there are more than 40 reports of the long-term outcome of splenectomy, only five reports [9,11,15–17] had a median follow-up >5 years. Moreover, all five included patients whose follow-up was as short as 6–12 months; none analyzed the response to splenectomy as a function of time from surgery, and none provided individual patient data. Therefore, the true long-term response rate to splenectomy remains unknown.

The aim of this study was to evaluate the long-term outcome of splenectomy, arbitrarily requiring a minimum follow-up of 5 years. At one center (NYPH) coding for splenectomy in the medical record was only available beginning in 1988 so that only patients who underwent splenectomy from 1988 to 1993 were included. This resulted in the number of patients available for accrual being 75. Only five of the more than 40 published reports included more splenectomized patients [10–14].

Encompassing 56 patients, all of whose follow-up was ≥5 years (median 7.5 years, range 5–10.5 years), 77% of the patients responded immediately after the surgery; 66% of patients achieved a long-term satisfactory response, complete or partial, during the study period not receiving any therapy and always maintaining a platelet count ≥50 × 10^9/L. The Kaplan–Meier probability estimates were similar with a 73% stable remission (platelet count always >50 × 10^9/L, never any need for treatment) at 5 years and 62% at 10 years after surgery. Eight patients (14%) relapsed 4–8.5 years after the operation. The Kaplan–Meier analysis (Fig. 1) indicates that as time from splenectomy increases, the success rate for an excellent response steadily decreases. It is not clear if a plateau was achieved, suggesting a reduction in the rate of relapses.

Despite those late relapses, our study shows long-term sustained remission in 66% of cases, none of whom required any additional treatment. This is a far better outcome than any other treatment modality of ITP. High-dose dexamethasone showed limited and transient response [21], danazol has been used successfully in 40–50% of patients [22], danazol is beneficial in 20–40% of patients [23], and vinca alkaloids showed even lower transient response rate [24]. None induced an unmaintained CR in more than 10% of cases.

One limitation for data interpretation arising from the fact that 16 patients (21%) were lost to follow-up prior to 5 years. Although those 16 patients’ outcome may limit the overall data interpretation, taking into account wide range of outcomes in the missing patients would not substantially change the results reported here. For example, if 13 of the 16 missing patients had a remission, this would result in a 70% sustained response rate whereas if only 5 of the 16 achieved a lasting remission, this would only lower the overall long-term response rate from 66% to 58%. Hence, the long-term response rate at 5–10 years postoperative after splenectomy is 60–70%.

The incidence of an accessory spleen in relapsed patients is 9–22% [9,11,25], as it was in this series (11%). After accessory splenectomy, two patients out of six went into complete remission. As was noted by others [2,26–28] response to accessory splenectomy was only seen in those patients who relapsed ≥4 years after initial splenectomy.

Many studies have attempted to identify prognostic factors for response to splenectomy in patients with ITP without consistent findings among the published reports. In our series, we evaluated the age at splenectomy, time from diagnosis to splenectomy, and sex of the patients. Although none of these factors had a significant association with outcome, there was tendency for younger age to be a positive predictive factor (P = 0.07), as was recently shown by two other reports [29,30]. In our study, due to the long interval between splenectomy and assessment of outcome, the specific details of the preoperative response to steroids or other medical therapy (IVIG) were often unavailable.

Splenectomy caused no surgical mortality or significant morbidity. There was a 10% postoperative morbidity, which included mostly hematoma and infection of the surgical incision, as was seen in other series [8,14]. Our series, which included 434 patient-years post-splenectomy, had no cases of overwhelming post-splenectomy infection (OPSI).

An increased incidence of atherosclerotic events including heart disease, CVA, and pulmonary hypertension have been described after splenectomy, which may be due to abnormal erythrocytes may remaining longer in the circulatory system, initiating platelet activation [18,19,31,32], as well as post-splenectomy thrombocytosis. Recently, Ahn et al. [33] suggested that there was an increased risk of dementia caused by microinfarcts in subsets of ITP patients, especially if potentiated by a rise in the platelet count after splenectomy. Such mechanisms...
may be aggravated in the presence of pre-existing coronary heart disease or hemolytic disorders [18,32]. The low incidence of heart disease in the series reported here is mitigated by both the inclusion of only two males over the age of 50 and the absence of hemolytic disorders. Our series had only 3 patients who developed thrombotic events (1 cardiac and 2 CVA). The possibility of an increased risk of long-term thrombotic complications in patients with ITP requires further evaluation.

In conclusion, splenectomy generally appears to be safe and effective for the treatment of ITP. Prediction of outcome is difficult in individual cases but the immediate response rate was 77%, with 57% of patients staying in prolonged CR and 66% in CR+PR at a median of 7.5 years postoperatively. The information developed here will allow a more informed decision about the risks and benefits of splenectomy in patients with ITP.

REFERENCES


