Splenectomy Is Safe and Effective in Human Immunodeficiency Virus-Related Immune Thrombocytopenia

By Eric Oksenhendler, Philippe Bierling, Sylvie Chevret, Jean-François Delfraissy, Yves Laurian, Jean-Pierre Clauvel, and Maxime Seligmann

Sixty-eight patients, followed in a prospective cohort study of 185 human immunodeficiency virus (HIV)-infected patients with severe immune thrombocytopenia (platelets < 50 × 10^9/L) underwent splenectomy. 2 to 41 months (median: 10 months) after immune thrombocytopenic purpura (ITP) was diagnosed. The mean platelet count increased from 18 × 10^9/L to 223 × 10^9/L with a persistent increase in 52 (82%). It also led to a significant increase of the mean CD4 cell count from 475 × 10^9/L to 725 × 10^9/L within a mean delay of 10 months. In the whole cohort, with a mean follow-up of 63 months (range, 6 to 126), the 5-year estimated rate for progression to acquired immunodeficiency syndrome (AIDS) was 23% (95% confidence interval [CI], 15% to 31%) and the AIDS-free survival was 68% (95% CI, 61% to 77%). To investigate the potential impact of splenectomy, a Cox’s multiple regression model was used; as splenectomy was not randomly assigned, it was incorporated as a time-dependent covariate. After adjustment on the CD4 cell count, no statistically significant differences were observed between the splenectomized and the nonsplenectomized patients: AIDS progression rate (P = 0.23), survival (P = 0.64) and AIDS-free survival (P = 0.72) were not influenced by splenectomy. Splenectomy is both effective and safe in the treatment of severe, refractory ITP associated with HIV infection.

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Immune thrombocytopenic purpura (ITP) is known to be a frequent complication of human immunodeficiency virus (HIV) infection. The mechanisms responsible for platelet destruction are not yet well characterized. HIV itself, some of its antigenic structures, or antibodies to HIV may be directly or indirectly involved. This condition usually occurs at a relatively early stage of HIV infection.

Treatments used in autoimmune thrombocytopenic purpura give poor or transient response. Zidovudine was shown to be effective in more than half of the patients. However, splenectomy is still warrant in patients with persistent, severe, and symptomatic thrombocytopenia. The potential hazards of splenectomy in HIV-infected patients require a long-term follow-up of large series of patients.

Since January 1982, 185 patients with HIV-related severe immune thrombocytopenia were followed in four institutions. Clinical and biologic evaluation were scheduled every 6 months. Long-term follow-up of this cohort study allows evaluation of the possible influence of splenectomy on acquired immunodeficiency syndrome (AIDS) progression rate and survival.

Patients and Methods

Patients. The 68 patients who underwent splenectomy belonged to a prospective cohort study in which 185 patients were enrolled from January 1982 to April 1991. They included 57 males and 11 females (Table I). Initially, the patients were included on the basis of ITP occurring in patients belonging to AIDS risk groups. Retrospective analysis of stored sera confirmed HIV infection in all. None of these patients had full-blown AIDS at inclusion. However, 11 (16%) had symptomatic disease and belonged to Centers for Disease Control (CDC) group IV, 16 patients had persistent generalized lymphadenopathy, and 10 had splenomegaly. Most of the patients had mild immune deficiency status as only five (7%) had a CD4 cell count below 200 × 10^9/L. The mean CD8 cell count was 681 × 10^9/L. Serum p24 antigen was detectable in 9 of 53 (17%).

At inclusion, all patients had a platelet count below 50 × 10^9/L and a normal or increased number of megakaryocytes in an otherwise normal bone marrow (BM) aspiration. Mild hemorrhagic symptoms were observed in the 43 patients with a platelet count below 20 × 10^9/L. Using a direct immunofluorescence assay, platelet IgG were detected in 44 of 58 patients tested (76%) and with an indirect immunofluorescence assay, serum platelet-reactive IgG were detectable in 36 of 60 sera (60%). In 65 cases, splenectomy was proposed to patients who had failed to achieve a persistent response with previous therapy; some of them had experienced a transient response with corticosteroids (19/35), danazol (2/15), high-dose intravenous (IV) polyvalent IgG (36/44), anti-Rh IgG (8/13), or with zidovudine (6/21). For three patients, splenectomy was the first therapy used. Most of the patients received antipneumococcal vaccination and high-dose IV polyvalent IgG in preparation for surgery.

Response to therapy. Response was classified as complete if the platelet count increased above 100 × 10^9/L and partial if above 50 × 10^9/L with a twofold increase in the initial count. Persistence of the response was evaluated after 6 months.

Statistics. Survival analysis was based on the Kaplan-Meier estimate and the logrank test was used for comparisons between the splenectomized and the nonsplenectomized patients. The survival time was calculated from the date of ITP diagnosis. To investigate the potential effect of splenectomy on AIDS-free survival, a Cox’s multiple regression model was used. As splenectomy was not randomly assigned, it was incorporated as a time-dependent covariate.

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Submitted November 2, 1992; accepted February 10, 1993.

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0006-4971/93/8201-0022$0.00/0
### RESULTS

Splenectomy was performed with a mean delay of 13 months (range, 2 to 41) from the diagnosis of ITP. After 2 years, the cumulative probability of splenectomy was 32% (95% CI, 24% to 40%). This population has not been randomly selected and at inclusion in the cohort study, the mean ± SD CD4 cell count was higher (527 ± 264 x 10^9/L) in the 68 patients that were proposed for surgery than in the 117 patients that did not undergo splenectomy (400 ± 274 x 10^9/L), (P < .01; Student’s t-test).

**Response to splenectomy.** The mean platelet count before splenectomy was 18 ± 16 x 10^9/L. The mean peak value of the platelet count after splenectomy was 223 ± 151 x 10^9/L (range, 6 to 776). The initial response was complete in 58 patients and partial in four. At 6 months, six patients had relapsed and the overall persistent response rate was 82%. Late relapses were observed in three patients, 47, 57, and 67 months after surgery. At last evaluation, the mean platelet count was 219 ± 124 x 10^9/L (range, 6 to 669) and eight patients had less than 50 x 10^9/L.

The mean CD4 cell count before splenectomy was 475 ± 301 x 10^9/L and it increased up to 725 ± 612 x 10^9/L after surgery. This significant increment (P = .002, paired Student’s t-test) was caused by a twofold increase in the total lymphocyte count, from 1651 x 10^9/L to 3425 x 10^9/L, whereas the proportion of CD4 cells decreased significantly from 28% ± 11% to 21% ± 10% (P = .04, paired Student’s t-test) within a mean interval of 10 months between the two evaluations. At last evaluation, after a mean delay of 57 months, the mean CD4 cell count had decreased to 551 ± 571 x 10^9/L, and the proportion of CD4 cells to 16% ± 8%.

### Complications

One patient had postoperative portal vein thrombosis. Two patients presented with *Streptococcus pneumoniae* meningitis, respectively, 27 and 41 months after splenectomy. They had not been vaccinated against *S pneumoniae* and they did not take any antibiotic prophylaxis; both of them recovered. Two other patients died of fulminating septic shock, 23 and 26 months after surgery; in one case, *Hemophilus influenzae* septicemia was documented.

**Follow-up and HIV disease progression.** In the whole cohort, the mean follow-up from the diagnosis of ITP was 63 months (range, 6 to 126), 70 months for the 68 splenectomized and 57 for the 117 nonsplenectomized patients (Table 2). At the time of analysis, 16 patients were lost for follow-up (>12 months); 7 of them had been splenectomized. Thirty-six patients of the cohort developed CDC-defined AIDS. The AIDS progression rate from ITP was 23% at 5 years (95% CI, 15% to 31%). Thirty-nine patients have died. In 4, death was related to ITP (2 cases of fatal visceral bleeding in nonsplenectomized patients) or to its therapy (2 cases of fulminant septic shock in splenectomized patients). Twenty-two patients died because of AIDS progression and in 13 other cases, death was not HIV-related. At 5 years, the overall survival was 77% (95% CI, 70% to 84%) and the AIDS-free survival 69% (95% CI, 61% to 77%). A CD4 cell count below 200 x 10^9/L at time of ITP diagnosis appears as the best prognostic indicator for progression to AIDS or death (P < .0001 and P < .0001, respectively).

Survival was then analyzed according to splenectomy, as this treatment might have influenced the natural history of HIV infection. Among the 68 splenectomized patients, 8 developed AIDS and 14 died (Table 2 and Fig 1). Using a time-dependent Cox’s model, splenectomy was associated with a reduction of the AIDS progression rate (P = .01, relative risk: .35) and did not affect survival (P = .41) or AIDS-free survival (P = .46) (Fig 1). However, this apparent favorable predictive value of splenectomy on the AIDS progression rate was explained by the higher initial CD4 cell count in the patients that had been proposed for surgery; indeed, after adjustment on this covariate, splenectomy was no more predictive of reduced AIDS progression rate (P = .23). This adjusted analysis confirmed the absence of influence of splenectomy on survival (P = .64) or AIDS-free survival (P = .72).

### Table 1. Patient Characteristics at ITP Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Splenectomized (n = 68)</th>
<th>Nonsplenectomized (n = 117)</th>
<th>All Patients (n = 185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV drug users</td>
<td>34</td>
<td>49</td>
<td>83</td>
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<td>Homosexual men</td>
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<td>33</td>
<td>52</td>
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<tr>
<td>Hemophiliacs</td>
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<td>15</td>
<td>25</td>
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<tr>
<td>Heterosexual contacts</td>
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<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Blood recipients</td>
<td>2</td>
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<td>10</td>
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<tr>
<td>Unknown risk factor</td>
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<td>4</td>
<td>5</td>
</tr>
<tr>
<td>CDC group IV*</td>
<td>11</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Baseline CD4 cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>527 ± 264</td>
<td>400 ± 274</td>
<td>445 ± 276</td>
</tr>
<tr>
<td>(&lt;200 x 10^9/L)</td>
<td>5</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Positive p24 Ag</td>
<td>9/53</td>
<td>12/95</td>
<td>21/148</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;20 x 10^9/L</td>
<td>43</td>
<td>46</td>
</tr>
</tbody>
</table>

* Symptomatic HIV infection.
† Statistically significant difference between the splenectomized and the nonsplenectomized patients (P = .004, Student’s t-test).

To test the prognostic significance of splenectomy, a likelihood ratio test was used after adjustment on the major baseline prognostic variable (CD4 cell count).

### Table 2. Patients’ Follow-Up From ITP Diagnosis

<table>
<thead>
<tr>
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<tr>
<td>(&lt;10^9/L)</td>
<td>5</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Mean follow-up (mos)</td>
<td>12/95</td>
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<td>211148</td>
</tr>
<tr>
<td>AIDS</td>
<td>8</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>Deaths</td>
<td>14</td>
<td>25</td>
<td>39</td>
</tr>
</tbody>
</table>

* Using a time-dependent Cox’s model, and after adjustment on the baseline CD4 cell count, splenectomy had no influence on AIDS progression rate (P = .23), survival (P = .64), or AIDS-free survival (P = .72).
with mild immune deficiency or/and our reluctance for patients who fail to produce a normal antibody response to "warranted in patients with severe, persistent thrombocytopenia," we recommend splenectomy as an event that could influence the natural history of AIDS or death. However, splenectomy increases the risk of increased immune deficiency led us to avoid steroids as initial therapy. IV polyvalent high dose Ig is effective with a rapid response pattern; it can be used in patients with severe and symptomatic thrombocytopenia, and before surgery or invasive procedures. Repeated infusions or anti-Rh Ig can be used as a maintenance therapy. Zidovudine has emerged as the best first-line therapy. An increase in platelet count over a safe level is obtained in more than half of the patients. Nevertheless, splenectomy is warranted in patients with severe, persistent thrombocytopenia.

Several groups have reported on their experience of splenectomy in patients from different AIDS-risk groups. These gave information on the short-term effectiveness of this therapy and suggested that the response rate ranges from 65% to 100%, associated with a low morbidity. However, long-term follow-up and evaluation of splenectomy as an event that could influence the natural history of HIV infection and especially the progression towards full-blown AIDS or death are not available from the literature. In 1987, Barbui et al had suggested that splenectomy could enhance the risk of AIDS in these patients.

In our experience, patients who were proposed for splenectomy had higher baseline CD4 cell counts than those who were not proposed for surgery. This may reflect either a more severe and resistant thrombocytopenia in patients with mild immune deficiency or/and our reluctance for splenectomy in patients with advanced HIV disease.

With a 5-year follow-up and after adjusting on the CD4 cell count, splenectomy did not influence the progression to AIDS or to death. However, splenectomy increases the risk for severe, sometimes fulminant, sepsis; especially because of encapsulated pathogens such as S pneumoniae. In our series, two patients experienced pneumococcal meningitis and two others died of fulminant septic shock. Although the efficiency of pneumococcal vaccination is uncertain in such patients who fail to produce a normal antibody response to pneumococcal polysaccharide antigen, we recommend both presplenectomy vaccination and postoperative oral antibiotic prophylaxis.

Splenectomy led to a twofold increment of the lymphocyte count and to a significant increase in the absolute CD4 cell count; however, the percentage of CD4 cells still continued to decrease. In these patients, the decisions regarding antiretroviral therapy and especially prophylaxis of opportunistic infections should take these constatations into account and focus on the percentage of CD4 cells.

Therapy is warranted for patients with severe or symptomatic HIV-related ITP. In the cases who fail to respond to medical treatment, splenectomy can be proposed. It is effective in most cases and it does not seem to affect the natural history of HIV infection.

**ACKNOWLEDGMENT**

We thank Dr M.P. Archambeaud, Dr J. Peynet, Dr J.P. Farcat, F. Rocher, M. Legrand, M. Bergere, P. Gallula, M.T. Rannou, and L. Gérard for their support in collecting data, V. Barateau and Dr F. Ferchal for the virological study, and Dr C. Rabian-Herzog for the immunologic study.

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Splenectomy is safe and effective in human immunodeficiency virus-related immune thrombocytopenia [see comments]

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