Hemorrhagic Sequelae of Immune Thrombocytopenic Purpura in Human Immunodeficiency Virus-Infected Hemophiliacs

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Clinical bleeding tendency and tests of immune function were studied prospectively in 11 human immunodeficiency virus (HIV)-infected hemophiliacs with immune thrombocytopenic purpura (ITP) and a platelet count less than 50,000/μL. These 11 patients represented 13% of a well-characterized cohort of 87 HIV+ hemophiliacs. ITP developed a mean 3.5 years after seroconversion, mean platelet count at presentation was 36,000/μL (range, 15,000 to 49,000/μL), and the mean age at seroconversion was 37.1 years. Nine patients (82%) suffered bleeding complications, including four with intracranial hemorrhage, which was fatal in three. At the onset of ITP, five had AIDS and six were asymptomatic. Mean T₄ lymphocyte count at onset of ITP was 126 ± 32/μL (range 5 to 267/μL). Sustained treatment responses occurred with intravenous gammaglobulin (2 of 2), one of whom spontaneously remitted, and with zidovudine (1 of 2), but not with steroids (0 of 6) or danazol (0 of 3). In conclusion, 13% of a cohort of HIV+ hemophiliacs has developed ITP with platelets less than 50,000/μL, a significant proportion of whom (82%) have experienced bleeding complications. It is recommended that treatment for ITP in HIV+ hemophiliacs be instituted once the platelet count falls below 50,000/μL in order to avoid serious hemorrhagic sequelae.

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METHODS

Study population. The study group consisted of a cohort of 87 HIV+ hemophiliacs cared for at the Hemophilia Center of Western Pennsylvania (HCWP, Pittsburgh, PA) as previously described. These patients are seen yearly or semi-yearly at routine clinic visits as part of comprehensive medical care, during which a clinical examination is performed, immunologic testing is accomplished, and symptoms and clinical outcomes are recorded. A total of 11 (13%) patients were found through chart review to have platelet counts below 50,000/μL during the last 10 years. These included 10 with hemophilia A, including 7 severe, FVIII:C less than 0.01 U/mL, and 3 moderate, FVIII:C between 0.01 and 0.04 U/mL, and 1 with severe hemophilia B, FIX:C less than 0.01 U/mL. Three of the hemophilia A patients had inhibitors to factor VIII.

Laboratory data. Antibody to HIV was measured by standard enzyme-linked immunosorbent assay (ELISA) technique using antigen from H9/human T-lymphotropic virus-type III (HTLV-III) cell line (Abbott Laboratories, Chicago, IL) or inactivated whole lymphadenopathy-associated virus (LAV) antigen grown in the CEM-F cell line (Genetic Systems, Seattle, WA). All samples positive by ELISA HIV antibody test were confirmed by Western blot (Abbott or Genetic Systems) by standard technique.

RESULTS

The study group consisted of a cohort of 87 HIV+ hemophiliacs cared for at HCWP, on 84 of whom seroconversion data are available and on all of whom clinical outcomes are known. Thirty (36%) have had platelet counts below 100,000/μL, of whom 11 had platelet counts below 50,000/μL (Table 1). Of these, 11, five (19%) had AIDS, none had AIDS-related complex (ARC), and six (13%) had asymptomatic HIV infection. The mean age at seroconversion in those who developed ITP was 35.2 years (Table 2). In the five with...
AIDS, ITP developed within 6 months of AIDS diagnosis (patients 1 through 5); in the six asymptomatic patients, ITP was not associated with any other known illness or infection. None had end-stage liver disease, although one patient (patient 11) suffered a marked worsening of his chronic transfusion-induced liver disease after he presented with an ITP-related central nervous system (CNS) hemorrhage (see below). Bone marrow aspirates and biopsies were performed in only two patients because of the invasiveness of the procedure, the requirement for blood product with attendant risks, severe factor concentrate shortages, and lack of any other obvious etiology. In the two in whom bone marrow aspirates were performed (patients 7 and 9), adequate megakaryocytes were observed. The mean platelet count at presentation in the 11 patients was 36,000 ± 7,000/µL (range, 15,000 to 49,000/µL). Platelet IgG was elevated in all three in whom it was measured (patients 6, 10, and 11). Although not shown, platelet IgG was also elevated in five of five (in whom it was measured), whose platelet counts ranged from 83,000 to 126,000. The mean time from seroconversion to development of ITP was 50 ± 10 months (range, 24 to 73 months), and the mean T<sub>5</sub> count at onset of ITP was 126 ± 32/µL (range, 5 to 267/µL). Of the eight in whom p24 antigen was measured at the onset of ITP, three (38%) were positive (patients 3, 4, and 9).

Of the 11 patients with ITP, nine (82%) experienced bleeding complications, including four with CNS bleeding (patients 4, 8, 10, and 11), three with an increased frequency and severity of hematomas or hemarthroses (patients 6, 7, and 11), one with hyphema (patient 2), one with recurrent gum bleeding (patient 1), and one with gastrointestinal tract bleeding (patient 11) (Table 2). The mean time interval between detection of thrombocytopenia (platelets less than 50,000/µL) and onset of hemorrhage in the nine experiencing bleeding was 3 months (range, 1 to 8 months). The four with CNS bleeding, none of whom had a history of head trauma, included two with intracerebral hemorrhage (patients 4 and 8) and two with subdural hematomas (patients 10 and 11). Three of the four with CNS bleeding had inhibitors to factor VIII, in one of whom the inhibitor spontaneously remitted with immunodeficiency and development of AIDS (patient 4, see below).<sup>14</sup> Three of the four with CNS hemorrhage died (patients 4, 8, and 11), despite aggressive treatment with factor VIII (or IX) concentrate, steroids, and platelets.

The first of these four patients with CNS hemorrhage (patient 4) was an 18-year-old man with severe hemophilia A (FVIII:C less than 0.01 U/mL) and an inhibitor to factor VIII, which spontaneously remitted with the development of Pneumocystis pneumonia and a diagnosis of AIDS in April, 1987.<sup>14</sup> At that time, the platelet count was 137,000/µL. By September, 1987, the platelet count was 53,000, progressively falling by November, 1987, to 30,000/µL (73 months after seroconversion), associated with slowed mentation and progressive jaundice. Computerized tomographic (CT) scanning revealed a large intracerebral hemorrhage obliterating the right ventricle. Despite high-dose factor VIII concentrate with adequate factor VIII levels and platelet transfusions, he died. An autopsy limited to the brain revealed an intracranial hemorrhage of the right orbital frontal cortex and basal ganglia. Numerous phagocytic nodules and multinucleated giant cells were observed in both cerebral hemispheres.

The second patient (patient 8) was a 22-year-old asymptomatic HIV+ man with severe hemophilia A (FVIII:C less than 0.01 U/mL) who in May, 1986, suffered a spontaneous intracerebral hemorrhage (confirmed by CT scanning) and platelet count of 49,000/µL at 55+ months after seroconversion.<sup>15</sup> Despite craniotomy with evacuation and drainage, he failed to respond neurologically and died 28 hours after admission. Autopsy confirmed a right fronto-temporal subdural hemorrhage and secondary brainstem hemorrhage with resultant severe brain edema and herniations (uncal and cingulate).

The third patient (patient 11) was a 54-year-old asymptomatic HIV+ man with an acquired inhibitor to factor VIII (FVIII:C less than 0.01 U/mL) initially diagnosed in March, 1976. He shortly thereafter was found to be hepatitis B surface antigen-positive (HBSAg+). In December, 1985, 64 months after HIV seroconversion, he was noted to have a platelet count of 45,000/µL. At that time, his liver functions revealed transaminases in the 1.6 to 2.0 times upper limit range. In August, 1986, he developed a right frontal headache, nausea, and lightheadedness; and on presentation at a local emergency room, the platelet count was 10,000/µL. There was no precedent trauma. A CT scan revealed a right subdural hematoma, but despite high-dose steroids, FEIBA (factor eight inhibitor bypassing activity), and intravenous gammaglobulin (IVIG), his mental status deteriorated. Progressive jaundice ensued, and he died 3 days later after cardiorespiratory failure. Autopsy revealed, in addition to the right subdural hematoma, extensive hemorrhage in subcutaneous tissue, subendocardium, and right kidney. Severe micronodular cirrhosis was found, with massive congestive splenomegaly and ascites.

The fourth patient (patient 10) was an asymptomatic HIV+ 34-year-old man with severe hemophilia A (FVIII:C less than 0.01 U/mL) and an acquired inhibitor to factor VIII. He developed ITP with a platelet count of 18,000/µL in November, 1985, 47 months after seroconversion. Despite initial response to steroids and later danazol, the platelet count persistently remained below 40,000/µL, and he suffered frequent and severe hemarthroses and soft tissue hematomas, which persisted even after stopping ibuprofen for painful hemophilic arthropathy. By August, 1986, the platelet count fell to 9,000/µL, and because of continuing symptoms, IVIG was begun and continued on an approximately every 3 to 6 week basis to maintain the platelet count over 50,000/µL. A gradual fall in platelet IgG from 6.2 pg/µL to 1.9 pg/µL over the first 4 months of therapy was
observed. In July, 1988, after the patient allowed more than 8 weeks to pass without IVIG therapy, he began to suffer persistent headaches. A platelet count was 16,000/µL, and a nuclear magnetic resonance scan showed a right subdural hematoma of the frontoparietal area without edema, atrophy, or shift. He denied any trauma. The headaches and subdural hematoma responded to intravenous factor IX concentrate (every 12 hours for approximately 1 week), platelet transfusion, and IVIG. He was the only hemophiliac with HIV-associated ITP and CNS hemorrhage to survive. Because of the inconvenience of the long hours required for continuing IVIG, the patient was switched to zidovudine (azidothymidine; AZT) in July, 1988, beginning at 100 mg every 8 hours and gradually increasing to 200 mg every 6 hours to achieve platelet counts above 50,000/µL; the platelet count was most recently 96,000/µL, and there has been no increased frequency or severity of bleeding.

By treatment (Table 2), none of the six in whom steroids were prescribed had sustained responses (eg, above 50,000/µL once steroids were tapered). None of the three in whom danazol was used had sustained responses, ie, platelet counts greater than 50,000/µL. Azidothymidine has been successful in one patient (patient 10; see above) in maintaining platelet counts above 50,000/µL, at a dose of 200 mg every 6 hours (800 mg). One other patient (patient 7) has been unresponsive after 6 months of AZT therapy, despite escalation to standard dosing, 200 mg every four hours, five times per day (1,000 mg). A third patient (patient 9) is currently on ACTG protocol 036 (AZT versus placebo in asymptomatic hemophiliacs); although we are blinded as to which drug he is on, his platelet count has markedly improved (83,000/µL to 142,000/µL) since initiating the study drug, while his mean cell volume (MCV) has risen from 89 µm³ to 126 µm³.

Of the two patients (patients 6 and 10) treated with long-term IVIG (800 gm/kg; both received Sandoglobulin [Sandoz, East Hanover, NJ] and Gammagard [Cutter, East Brunswick, NJ]), both have had sustained responses (platelet count greater than 50,000/µL) and one (patient 6) has fortunately experienced a complete remission after 10 months of IVIG (November, 1986 to September, 1987). He has received no treatment now for 21 months since his last dose of IVIG, and his current platelet count is 183,000/µL. One patient (patient 11) received IVIG acutely for 5 days (800 mg/kg/d); he showed little response (13,000/µL to 18,000/µL) and died of CNS hemorrhage. One patient (patient 7) showed only minimal rise in platelet count (15,000/µL to 32,000/µL) after five separate treatments with a staphylococcal pattern A immunoadsorption column (Prosorba; Imre, Seattle, WA), and the treatment was stopped because of severe, large bilateral antecubital fossa hematomas resulting from the large bore needles required for access. Current treatment with 1 gm/kg IVIG is underway and thus far has yielded only minimal success (13,000/µL to 22,000/µL).

Listed in Table 3 are the causes of death in both HIV+ and HIV− hemophiliacs (n = 216) followed at HCWP between 1978 and mid-1989 (present). Overall, the leading cause of death has been AIDS, followed by CNS hemorrhage, which before 1984, was the leading cause of death. Of particular interest, while deaths have increased 3.5-fold (from 9 to 32) in the first half (1978 to 1983) to the second half (1984 to 1989) of this time period, deaths attributed to liver disease markedly declined, whereas deaths from CNS hemorrhage continued at the same frequency, with five deaths before and six after 1984. Moreover, while none of the CNS hemorrhages before 1984 occurred in HIV+ or thrombocytopenic hemophiliacs, 50% (3 of 6) of those after 1984 dying from CNS hemorrhage (reported herein) occurred in HIV+, thrombocytopenic hemophiliacs. The remaining three occurred in HIV−, non-thrombocytopenic hemophiliacs.

**DISCUSSION**

Over 10% of this well-characterized group of HIV+ hemophiliacs have developed ITP with platelet counts below 50,000/µL, a figure consistent with the incidence of ITP in other HIV+ high-risk groups. However, in contrast to other high-risk groups, the risk for significant bleeding complications appears to be much greater in HIV+ hemophiliacs with ITP and platelet count less than 50,000/µL: over 80% of this group suffered an increase in the frequency and severity of hemarthroses and hematomas, or hemorrhage into the CNS. Moreover, the mortality from CNS hemorrhage is high. Before AIDS, CNS hemorrhage was the leading cause of death in hemophiliacs, but now has become the second leading cause of death overall in this cohort of both HIV+ and HIV− hemophiliacs, second to AIDS (Table 3). It is of interest, however, that although CNS hemorrhage is no longer the leading cause of death, the number of deaths from CNS hemorrhage remained unchanged between 1978 and 1983 (pre-AIDS) and between 1984 and 1989 (post-AIDS). None of the deaths from CNS hemorrhage before 1984 whereas 66% of the deaths from CNS hemorrhage since 1984 were associated with HIV+ infection. By comparison, deaths from liver disease, previously the second leading cause of death, have markedly decreased over the same time period, presumably because more patients are dying of HIV-related causes before chronic liver disease progresses to end-stage severity. Thus, while the absolute number of deaths from CNS hemorrhage has remained constant, HIV-associated thrombocytopenia (ITP; specifically, with a platelet count greater than 50,000/µL) appears to be an important factor associated with deaths from CNS hemorrhage since AIDS (since 1984). For this reason, we strongly recommend that treatment be instituted in hemophiliacs with ITP, once the platelet count falls below 50,000/µL. This is in contrast with the recommendation for HIV+ non-hemophilic patients with ITP by Ratner that treatment be instituted with bleeding and platelet count less than 20,000/µL. This difference relates to the apparently more common occurrence of bleeding sequelae in HIV+ hemophiliacs with ITP, as compared with HIV+ non-hemophilic risk groups.

The best treatment approach is not clear. Sustained treatment responses with steroids, once tapering begins, were difficult to maintain in hemophiliacs as demonstrated in other high risk groups, and potential immunosuppressive effects are of concern in an HIV+ population. Sustained treatment responses with danazol also appear to be difficult to maintain as observed in other risk groups, and hepatotoxicity is a potential hazard in hemophiliacs who have chronic...
Table 2. Bleeding Tendency and Immune Status in HIV + Hemophiliacs With ITP (platelets < 60,000/μL)

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age at Onset (yr)/Sex</th>
<th>Type Hemophilia</th>
<th>HIV-Related Diagnosis</th>
<th>Platelet Count/μL</th>
<th>HIV-Related Platelet Platelet Count/μL</th>
<th>Duration HIV Infection to ITP (mos)</th>
<th>T_/μL at Onset ITP</th>
<th>p24 Ag at Onset ITP</th>
<th>Bleeding Symptoms</th>
<th>Treatment (Dose)</th>
<th>Platelet Count/μL</th>
<th>Treatment Response</th>
<th>Outcome/Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/M</td>
<td>Hemo A, severe</td>
<td>AIDS</td>
<td>30,000</td>
<td>ND</td>
<td>24</td>
<td>178</td>
<td>ND</td>
<td>Recurrent gum bleeding</td>
<td>Prednisone (unknown) Danazol (unknown)</td>
<td>30,000</td>
<td>54,000</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>32/M</td>
<td>Hemo A, severe</td>
<td>AIDS</td>
<td>48,000</td>
<td>ND</td>
<td>65</td>
<td>6</td>
<td>--</td>
<td>Hyphema</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>D/AIDS</td>
</tr>
<tr>
<td>3</td>
<td>51/M</td>
<td>Hemo A, severe</td>
<td>AIDS</td>
<td>45,000</td>
<td>ND</td>
<td>73</td>
<td>8</td>
<td>--</td>
<td>None</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>D/AIDS</td>
</tr>
<tr>
<td>4</td>
<td>17/M</td>
<td>Hemo A, severe + INH</td>
<td>AIDS</td>
<td>30,000</td>
<td>ND</td>
<td>73</td>
<td>5</td>
<td>--</td>
<td>Intracranial hemorrhage (cerebral cortex)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>D/CNS hemorrhage</td>
</tr>
<tr>
<td>5</td>
<td>80/M</td>
<td>Hemo B, severe</td>
<td>AIDS</td>
<td>15,000</td>
<td>ND</td>
<td>36</td>
<td>ND</td>
<td>ND</td>
<td>Hematuria, melena</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>22/M</td>
<td>Hemo A, severe</td>
<td>ASYM</td>
<td>20,000</td>
<td>5.1</td>
<td>39</td>
<td>168</td>
<td>--</td>
<td>Increased severity, frequency of hematoma and hemarthroses</td>
<td>Prednisone (60 mg daily for 3 wks) IVIG (800 mg/kg every mL)</td>
<td>25,000</td>
<td>106,000</td>
<td>NS</td>
</tr>
<tr>
<td>7</td>
<td>31/M</td>
<td>Hemo A, severe</td>
<td>ASYM</td>
<td>21,000</td>
<td>ND</td>
<td>27</td>
<td>194</td>
<td>--</td>
<td>Increased frequency and severity of hematomas</td>
<td>Prednisone (60 mg daily for 3 wks) Staph A column (5 treatments)</td>
<td>25,000</td>
<td>202,000</td>
<td>NSg</td>
</tr>
<tr>
<td>8</td>
<td>21/M</td>
<td>Hemo A, severe</td>
<td>ASYM</td>
<td>49,000</td>
<td>55+*</td>
<td>ND</td>
<td>ND</td>
<td>--</td>
<td>Intracranial hemorrhage (cerebral cortex)</td>
<td>Prednisone (50 mg daily for 3 wks) 036 (40+ wks)</td>
<td>40,000</td>
<td>114,000</td>
<td>NS</td>
</tr>
<tr>
<td>9</td>
<td>31/M</td>
<td>Hemo A, mild</td>
<td>ASYM</td>
<td>48,000</td>
<td>36+*</td>
<td>91</td>
<td>+</td>
<td>None</td>
<td>None</td>
<td>Prednisone (50 mg daily for 3 wks) 036 (40+ wks)</td>
<td>83,000</td>
<td>142,000</td>
<td>PR</td>
</tr>
<tr>
<td>10</td>
<td>31/M</td>
<td>Hemo A, severe + INH</td>
<td>ASYM</td>
<td>15,000</td>
<td>6.2</td>
<td>47</td>
<td>267</td>
<td>--</td>
<td>Subcutaneous hematoma; increased severity, frequency hematoma/hemarthroses</td>
<td>Prednisone (50 mg daily for 3 wks) Danazol (200 mg 3 times d 3 wks) IVIG (800 mg/kg every mL)</td>
<td>18,000</td>
<td>74,000</td>
<td>NS</td>
</tr>
<tr>
<td>11</td>
<td>54/M</td>
<td>Hemo A, severe + INH</td>
<td>ASYM</td>
<td>45,000</td>
<td>5.3</td>
<td>64</td>
<td>218</td>
<td>--</td>
<td>Subcutaneous hematomas, gastrointestinal bleeding</td>
<td>Decadron (4 mg every 6 hrs for 5 days) IVIG (800 mg/kg/d for 5 days)</td>
<td>10,000</td>
<td>18,000</td>
<td>MR</td>
</tr>
</tbody>
</table>

Abbreviations: INH, inhibitor to factor VIII; C: ASYM, asymptomatic; ND, not done; fg/plt, femtoampliter; platelet (normal ≤ 1.0 fg/plt); D, dead; NS, not sustained; CR, complete response; MR, minimal response; PR, partial response; SR, sustained response. * indicates data of seroconversion unknown; duration of HIV infection calculated based on time from first positive HIV antibody test.

†Possible treatment (other than platelets or factor VIII or IX concentrates) included steroids, danazol, IVIG, staphylococcal A immunoadsorption column (Staph A), AZT, or ACTG protocol 036 (AZT vs. placebo) 036.

‡Complicated by antecubital hematomas.
hepatitis secondary to transmission of hepatitis B and non-A, non-B via chronic blood product exposure. Splenectomy has provided sustained responses in HIV+ patients8-10 but is a less desirable option in hemophiliacs with inhibitors to factor VIII:C in whom the potential risks of perioperative bleeding are significant. Splenectomy for those hemophiliacs without inhibitors remains an option, and while the presence of hemophilia may make surgery more complicated, it is not impossible and may save some patients who might otherwise die of bleeding complications. Unfortunately, in recent years, severe product shortages have markedly curtailed surgical procedures, but recent increases in product availability should alleviate this problem. Finally, the potential postoperative complication of splenectomy, specifically, increased risk for pneumococcal pneumonia, remains a concern, which may be significant in HIV-infected individuals. Intravenous gamma globulin does appear to offer short-lived platelet responses,18,19 but requires at least monthly maintenance treatments, which are unfortunately lengthy (4 to 6 hours) and costly. Treatment of HIV+ patients with ITP with zidovudine (AZT), at least in preliminary studies,10,24 is reported to increase platelet counts, with as small a dose as 500 mg/d. However, most of the reported patients were not bleeding nor did they have hemophilia. Further, how long platelet responses last and the optimal dose of AZT for ITP is not known. The minimum dose of AZT required for a response (platelet count greater than 50,000/μL) in one HIV+ hemophiliac reported in this study was 800 mg/d with suboptimal responses seen at lower doses. Thus, in HIV+ hemophiliacs with ITP and platelets under 50,000/μL, use of AZT may be a reasonable initial approach and if successful, may also be of benefit in slowing progression of HIV disease (as per outcomes of ACTG protocol 019).

The risk of CNS hemorrhage and mortality in ITP appears to be greater in those hemophiliacs with inhibitors to factor VIII (Table 1). Therefore, it would seem prudent in such patients to monitor platelet counts more frequently, with prompt institution of AZT once platelet counts fall below 50,000/μL. Consideration should be given to alternative approaches, ie, porcine factor VIII, activated factor IX, and/or IVIG, if CNS hemorrhage should occur.

Finally, the well-documented problem of chronic liver disease25 in heavily transfused hemophiliacs complicates the evaluation of thrombocytopenia in HIV+ hemophiliacs. However, it is of note that although up to 5% of hemophiliacs before the AIDS epidemic were found to have platelet counts below 150,000/μL,26 these were rarely, if ever, below 50,000/μL. In fact, in no case of CNS bleeding in a large 1985 multi-institutional study of hemophiliacs26 was thrombocytopenia an associated finding. In the cohort from HCWP, reported here, thrombocytopenia below 50,000/μL was not recorded before 1984, despite chronic liver disease in over 90% of highly transfused patients.27 Thus, it is likely that the continued occurrence of cases of CNS hemorrhage in this cohort, at a time of greatly increasing numbers of AIDS-related deaths, may be related to HIV-associated ITP. As the numbers in this study are small, these findings should be replicated in other cohorts of hemophiliacs.

In conclusion, ITP and thrombocytopenia under 50,000/μL in HIV+ hemophiliacs may result in potentially severe morbidity and mortality, including CNS hemorrhage, and intervention is recommended once the platelet count falls below 50,000/μL.

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