Homosexual Men With Thrombocytopenia Have Impaired Reticuloendothelial System Fc Receptor—Specific Clearance

By Bradley S. Bender, Thomas C. Quinn, and Jerry L. Spivak

Classic immune thrombocytopenia purpura (ITP) occurs predominantly in women and is associated with either normal or impaired Fc receptor-mediated clearance of antibody-coated cells. Recently, an increasing incidence of thrombocytopenia has been observed in homosexual men, but whether Fc receptor-mediated clearance of antibody-coated cells is normal or impaired in these men is unknown. To study this question, we measured the in vivo clearance of anti-Rh(D) IgG antibody–sensitized 51Cr-labeled autologous red cells in five homosexual men with thrombocytopenia. The clearance of antibody-coated cells was shorter in the homosexual men compared with five age-matched heterosexual men with clinically normal, healthy, age-matched heterosexual men who were HIV-seronegative. Five homosexual men with thrombocytopenia without an evident cause were studied. Four had antibodies to human immunodeficiency virus, and four had circulating immune complexes as determined by a C1q-binding assay. Two of the men tested also had an increase in platelet-associated IgG. In the four homosexual men with platelet counts of 20,000/μL or less, the clearance halftime of IgG-sensitized red cells was prolonged (mean, 106 minutes; range, 72 to 140 minutes) as compared with the clearance of such cells in five hematologically normal men (mean, 39 minutes; range 30 to 50 minutes; P < .005). One homosexual man with a platelet count of 81,000/μL had a normal clearance halftime (30 minutes). Three patients whose platelet counts increased after corticosteroid therapy were restudied. In all three, the clearance of antibody-coated cells was shortened and returned to normal in the one patient who had achieved a complete remission. No correlation was observed between the presence of platelet-associated IgG or circulating immune complexes and the clearance halftime. These data indicate that severe thrombocytopenia occurring in homosexual men as in some patients with classic ITP is associated with defective in vivo Fc receptor-mediated clearance of antibody-coated cells.

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MATERIALS AND METHODS

Subjects. The subjects were five homosexual men with thrombocytopenia who were otherwise healthy. None of them had recent weight loss, fever, unexplained lymphadenopathy, idiopathic neuropathies, persistent diarrhea, fever, weight loss, and oral thrush have also been linked both epidemiologically and serologically to infection with HIV. Recent reports indicate that the occurrence of thrombocytopenia is increasing among homosexual men, patients with hemophilia, and intravenous drug users— the same groups at highest risk of developing AIDS. Whether the mechanism for thrombocytopenia seen in HIV-positive patients is similar to that for classic immune thrombocytopenia purpura (ITP) is unknown. Classic ITP occurs primarily in women and is associated with either normal or impaired splenic Fc receptor function. Since Fc receptor function is impaired in patients with AIDS, it has been postulated that homosexual men with ITP may also have defective Fc receptor function. To examine this, we studied the rate of clearance from the circulation of 51Cr-labeled, IgG-sensitized autologous erythrocytes in homosexual men with thrombocytopenia before and after therapy.

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Infection with the newly described retrovirus human immunodeficiency virus (HIV) leads to a variety of consequences ranging from asymptomatic carriage to the devastating acquired immunodeficiency syndrome (AIDS). Other illnesses such as unexplained lymphadenopathy, idiopathic neuropathies, persistent diarrhea, fever, weight loss, and oral thrush have also been linked both epidemiologically and serologically to infection with HIV. Whether the occurrence of thrombocytopenia is increasing among homosexual men, patients with hemophilia, and intravenous drug users—the same groups at highest risk of developing AIDS—whether the mechanism for thrombocytopenia seen in HIV-positive patients is similar to that for classic immune thrombocytopenia purpura (ITP) is unknown. Classic ITP occurs primarily in women and is associated with either normal or impaired splenic Fc receptor function. Since Fc receptor function is impaired in patients with AIDS, it has been postulated that homosexual men with ITP may also have defective Fc receptor function. To examine this, we studied the rate of clearance from the circulation of 51Cr-labeled, IgG-sensitized autologous erythrocytes in homosexual men with thrombocytopenia before and after therapy.

Clearance studies. Clearance studies were performed as previously described. In brief, the subjects' erythrocytes were collected, washed with normal saline, and labeled with 51Cr (ICN Pharmaceuticals, Irvine, CA) for 30 minutes at 37°C in a shaking water bath. Afterward, the labeled erythrocytes were injected into a forearm vein. Timed, serial bleedings were performed. Erythrocyte survival was calculated from the clearance halftime of the labeled red cells and defined as the time at which 50% of the labeled cells had been removed from the circulation. Other studies. The presence of circulating immune complexes was detected by a C1q-binding assay. Antiplatelet IgG antibody was assayed by a radiolabeled Coombs' antiglobulin test. Serum antibody to HIV (ELISA assay) was measured with a commercial kit (Litton Bionetics, Charleston, SC) and confirmed by Western blotting.

RESULTS

Clearance studies. Infusion of IgG-sensitized erythrocytes is normally followed by progressive splenic sequestration and destruction. In five hematologically normal and HIV-seronegative men, the mean clearance halftime of IgG-sensitized erythrocytes was 39 minutes (range, 30 to 50 minutes). We have previously determined that Fc receptor–specific clearance is identical in heterosexual and homosexual individuals. Furthermore, only two of nine patients with an AIDS-related illness had a clearance that was outside the normal range. Thus, HIV infection alone does not lead to a defect in Fc receptor–mediated clearance function.
HOMOSEXUAL MEN WITH THROMBOCYTOPENIA

Table 1. Clinical Data on HIV-Positive Patients With Thrombocytopenia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Platelet Count (x10^3/μL)</th>
<th>Platelet-associated IgG*</th>
<th>Immune Complexes†</th>
<th>Fc Receptor Clearance Half-time (min)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td>27</td>
<td>32</td>
<td>42</td>
<td>50</td>
<td>41</td>
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<tr>
<td>HIV</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Direct</td>
<td>8,000</td>
<td>13,000</td>
<td>81,000</td>
<td>20,000</td>
<td>19,000</td>
</tr>
<tr>
<td>Indirect</td>
<td>&lt;1.5</td>
<td>&lt;2.0</td>
<td>7.9</td>
<td>&lt;1.5</td>
<td>ND</td>
</tr>
<tr>
<td>Immune</td>
<td>80%</td>
<td>15%</td>
<td>66%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Complexes</td>
<td>125</td>
<td>72</td>
<td>30</td>
<td>140</td>
<td>87</td>
</tr>
<tr>
<td>Fc Receptor Clearance</td>
<td>188,000</td>
<td>197,000</td>
<td>None</td>
<td>105,000</td>
<td>31,000</td>
</tr>
<tr>
<td>Therapy</td>
<td>Cs</td>
<td>Cs, SPLX</td>
<td>None</td>
<td>Cs</td>
<td>Cs</td>
</tr>
<tr>
<td>Controls</td>
<td>&gt;150,000</td>
<td>&lt;1.5</td>
<td>&lt;2.0</td>
<td>&lt;10%</td>
<td>30-50</td>
</tr>
</tbody>
</table>

Abbreviations: Pt, patient; ND, not determined; Cs, corticosteroids; SPLX, splenectomy.

*Expressed as femtograms per platelet.
†Expressed as the percentage of protein-bound 125I-C1q precipitated from serum.
‡Clearance studies were performed before therapy was initiated in all subjects except patient 4.

Figure 1 depicts the clearance curves of the five homosexual patients with thrombocytopenia. In the four men with platelet counts ≤20,000/μL, the clearance half-time was significantly prolonged (mean, 106 minutes; range, 72 to 140 minutes; P < .005). The one homosexual man with a platelet count of 81,000/μL had a normal clearance. Since reticuloendothelial Fc receptor function can be blocked by circulating immune complexes, the presence of such complexes was examined by a C1q-binding assay. All four patients tested had circulating immune complexes (Table 1), but the greatest amount was present in patient 3 who had the highest platelet count and a normal clearance.

Follow-up studies. Three of the patients (1, 4, and 5) responded to oral administration of corticosteroids with a sustained rise in the platelet count, and one patient (2) required splenectomy for correction of thrombocytopenia; patient 3 has not required any therapy. In follow-up ranging 6 months to 4 years, no patient has developed AIDS or other clinical complications of HIV.

Repeat clearance studies were performed in the three patients who responded to corticosteroid therapy alone. None was receiving therapy at the time of the repeat study. As shown in Table 1 and Fig 2, the clearance half-time returned to normal in patient 1 who achieved a complete remission in spite of the presence of platelet-associated IgG. Patient 4 who had no demonstrable platelet-associated IgG had an improvement in clearance half-time, whereas the clearance half-time of patient 5 who had the least response to corticosteroids was essentially unchanged.

DISCUSSION

Specific membrane receptors on phagocytic cells have been demonstrated to be of functional importance in the recognition, attachment, and ingestion of particulate antigens by the reticuloendothelial system. Recent studies have shown that the functional capacity of reticuloendothelial cells in patients with a variety of immunologic illnesses can be assessed by measuring the in vivo clearance of IgG-sensitized autologous erythrocytes. We have previously reported that splenic Fc receptor–specific clearance is abnormal in patients with AIDS but not in asymptomatic HIV-positive homosexual men or patients with the AIDS-

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Fig 1. Survival of IgG-sensitized 51Cr-labeled autologous erythrocytes. The shaded area is the range of five healthy volunteers, and the individual clearance curves are from the five homosexual patients with thrombocytopenia.

Fig 2. Initial and follow-up Fc receptor clearance half-times in patients 1, 4, and 5. The numbers in parentheses are the patients' blood platelet counts in cells/μL at the time of each clearance study.
related complex, e.g., lymphadenopathy, fever, or weight loss. In this study, we demonstrate that severe thrombocytopenia occurring in HIV-positive homosexual men is also associated with prolonged Fc receptor-mediated clearance. In this regard, the pathophysiology of thrombocytopenia in homosexual men appears similar to some patients with classic ITP. For example, Kelton et al found normal clearances in five patients with ITP but impaired clearance in three others. As in our study, the patients with impaired Fc receptor clearance tended to have the most severe thrombocytopenia. HIV-positive individuals with thrombocytopenia do, however, differ from patients with classic ITP with respect to the presence of immune complexes and a greater degree of platelet-associated IgG.

An impairment of Fc receptor-mediated clearance in the presence of immune-mediated platelet destruction appears paradoxical, and precisely why some patients with classic ITP have a prolonged clearance of IgG-sensitized red cells is unknown. However, some explanations based on the known mechanisms of immune clearance can be offered. First, in some patients with ITP, the liver may be a major site of platelet sequestration, and splenic clearance studies using lightly IgG sensitized and splenic clearance studies using lightly IgG sensitized and Cr-labeled erythrocytes might not accurately reflect the role of the liver. Second, efficient clearance of antibody-coated erythrocytes depends on an intact splenic microcirculation. For example, in rodent malaria, splenic trapping of parasitized erythrocytes induces alterations in the splenic cord microcirculation, thereby causing a delay in clearance function. It is conceivable that trapped, aggregated platelets could also alter the splenic microcirculation, but we are not aware of any experimental evidence to support this contention. Third, phagocytosis is initiated by attachment of IgG-sensitized cells to the macrophage's Fc receptor. It has been suggested that there may be a competition for splenic macrophage Fc receptors between the infused IgG-sensitized red cells and the patient's intrinsically sensitized platelets, particularly if these cells are sensitized with IgM. The treated red cells used in studies such as ours were only lightly coated by IgG, and there may be more efficient or preferential phagocytosis of the patient's IgG- or IgM-coated platelets, thus creating an apparent Fc receptor blockade. Fourth, circulating immune complexes could cause reticuloendothelial blockade, but these are not usually present in classic ITP. Finally, since in some patients with ITP thrombocytopenia is a consequence of impaired platelet production rather than increased platelet destruction, it is possible that impaired Fc receptor-mediated clearance is another disease-related abnormality but not itself responsible for the thrombocytopenia.

Our observations in homosexual men with ITP provide some insight into these issues. First, it is unlikely that enhanced platelet sequestration by the liver was responsible for thrombocytopenia in our patients since their thrombocytopenia was corrected by either corticosteroids or splenectomy. Second, competition with antibody-coated platelets seems unlikely to explain the impaired clearance of sensitized red cells since there was no correlation between the presence or absence of platelet-associated IgG and impaired Fc receptor-mediated clearance. This was true for immune complexes as well; these are not usually present in classic ITP where Fc receptor-mediated clearance can also be impaired. The possibility that impaired Fc receptor-mediated clearance in homosexual men was due to macrophage infection with HIV is also unlikely since in this situation improvement in clearance by corticosteroid therapy or splenectomy would not be expected. The reciprocal relationship between platelet count and Fc receptor-mediated clearance strongly suggests that these are related either as independent manifestations of the same underlying process or as interrelated processes with preferential sequestration of platelets by macrophages. Whether there is a defect in platelet production in homosexual ITP as has been demonstrated in some patients with classic ITP is unknown.

Even though none of our five patients has progressed to AIDS or related conditions, follow-up studies on larger numbers of such patients with ITP over a longer period of time have revealed that AIDS developed in some. Isolated thrombocytopenia may thus represent a particular immunologic consequence of HIV infection, but the potential for progression to AIDS and the occurrence of impaired Fc receptor function in both situations indicates a strong interrelationship.

ACKNOWLEDGMENT

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