Acquired von Willebrand's Disease in the Myeloproliferative Syndrome


An acquired hemorrhagic disorder developed in two patients in association with postsplenectomy thrombocytosis and leukocytosis during the course of the myeloproliferative syndrome. The presence of acquired von Willebrand's disease in these individuals was demonstrated by a decrease or absence of the larger von Willebrand factor (vWF) multimers, alteration of the repeating vWF multimeric "triplet," decreased ristocetin cofactor activity (vWF:RCo), and prolonged bleeding time. The bleeding stopped in both patients after treatment with either 1-deamino-[8-arginine]-vasopressin (DDAVP) or Cohn fraction I. Treatment with thrombocytophoresis and azathioprine or busulfan resulted in reduction of the elevated platelet and white cell counts and was associated with partial correction of the vWF abnormalities and remission of the hemostatic abnormalities. In five additional patients with the myeloproliferative syndrome, but without bleeding symptoms, large multimers of plasma vWF were diminished also. These findings suggest that acquired von Willebrand's disease should be considered when a bleeding diathesis develops during the course of the myeloproliferative syndrome.

THE BLEEDING TIME prolongation seen in association with the myeloproliferative syndrome has been attributed previously to a variety of intrinsic platelet defects. Recently, we have now identified acquired von Willebrand's disease as the apparent cause of an acquired bleeding diathesis that occurred following splenectomy in the course of the myeloproliferative syndrome in two individuals.

Von Willebrand's disease may result from a simple decrease of circulating von Willebrand factor (vWF) protein or from the selective decrease or absence of circulating larger vWF multimers, as is seen in type II variants. Recently, the repeating vWF multimeric unit has been shown to consist of a "triplet" comprising a major central band and at least two satellite bands. In type IIA von Willebrand's disease, not only are the large multimers absent, but remaining multimers are altered in that the relative concentration of the fastest migrating band of the "triplet" is increased. The two patients with bleeding symptoms reported here had an abnormality of vWF reminiscent of that in IIA von Willebrand's disease, with the "triplet" pattern similarly altered and large multimers markedly decreased or absent. A less pronounced decrease of the large vWF multimers was seen in five additional asymptomatic patients with the myeloproliferative syndrome. The bleeding diathesis in the symptomatic patients was successfully treated with 1-deamino-[8-arginine]-vasopressin (DDAVP) or Cohn fraction I. Therefore, acquired von Willebrand's disease should be considered as a treatable cause of bleeding in the myeloproliferative syndrome.

CASE REPORTS

Patient 1 was a 27-year-old male who had the diagnosis of polycythemia vera made in 1977 at the age of 20. There was no history of a bleeding diathesis, and tooth extraction had been performed without excessive bleeding. Therapy with phlebotomy was instituted at that time. Splenectomy was performed in March 1982 because of a lacerated spleen. Platelet count rose from 450,000 to 6,900,000/μL on the sixth postoperative day (Table 1). Severe bleeding at the surgical wound site developed, and the bleeding time was >15 minutes. DDAVP was given, but the response was insufficient for satisfactory hemostasis. Cohn fraction I was then administered and the bleeding stopped. Thrombocytosis and leukocytosis (WBC count, 86,400/μL) were then treated with thrombocytophoresis and busulfan, with a decrease of the platelet count to approximately 1,000,000/μL and the WBC count to 7,800 within a month's time. No further bleeding occurred during a follow-up period of 16 months.

Patient 2 was a 22-year-old woman who had the diagnosis of myeloproliferative syndrome made in 1979 at another institution. A splenectomy was performed at that time. There was no prior history of spontaneous bleeding, bleeding following tooth extractions, or bleeding following an automobile accident that had required surgical intervention. In September 1982, she was seen at the Institut für Experimental Hämatologie und Bluttransfusionswesen der Universität Bonn with severe bleeding following tooth extraction. Platelet count at that time was 2,570,000/μL, the WBC count 23,000/μL, and the bleeding time over 15 minutes. Hemostasis was achieved following administration of DDAVP. However, bleeding recurred the next day and was successfully treated with Cohn fraction I. The patient accepted only intermittent treatment with thrombocytophoresis and azathioprine, resulting in a gradual decline of platelet count to 507,000/μL and WBC count to 10,600/μL in a year's time. There was no recurrence of bleeding symptoms.

Patients 3, 4, 5, 6, and 7 had the diagnosis of myeloproliferative syndrome made prior to study. Patient 6 had bled excessively after tooth extraction, but he and the other patients were asymptomatic at the time that blood samples were obtained. Laboratory data of the asymptomatic patients are shown in Table 2.

MATERIALS AND METHODS

Ristocetin cofactor (vWF:RCo), von Willebrand factor antigen (vWF:Ag; VIIIIR:Ag), factor VIII procoagulant activity (VIIIIC),...
Table 1. Patients With Bleeding Symptoms Related to Absence of Large vWF Multimers

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Date</th>
<th>Platelet Count (per μL)</th>
<th>WBC (per μL)</th>
<th>VIII:C (IU/dL)</th>
<th>vWF:Ag (IU/dL)</th>
<th>vWF:RCo (IU/dL)</th>
<th>Bleeding Time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/21/79</td>
<td>716,000</td>
<td>10,900</td>
<td>61</td>
<td>130</td>
<td>57</td>
<td>6 min</td>
<td>Splenectomy</td>
</tr>
<tr>
<td></td>
<td>3/28/82</td>
<td>450,000</td>
<td></td>
<td></td>
<td>9</td>
<td>35</td>
<td></td>
<td>Bleeding from surgical wound</td>
</tr>
<tr>
<td>4</td>
<td>6/13/82</td>
<td>5,860,000</td>
<td>160</td>
<td>90</td>
<td>190</td>
<td>30</td>
<td></td>
<td>DDAVP response insufficient for hemostasis; Cohn fraction I given, bleeding stopped</td>
</tr>
<tr>
<td>4</td>
<td>6/13/82</td>
<td>5,930,000</td>
<td>130</td>
<td>140</td>
<td>133</td>
<td>1 min, 30 sec</td>
<td></td>
<td>Cohn fraction I given, bleeding stopped</td>
</tr>
<tr>
<td>1</td>
<td>4/14/82</td>
<td>6,900,000</td>
<td></td>
<td></td>
<td></td>
<td>14 &gt; 15 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4/15/82</td>
<td>5,000,000</td>
<td>260</td>
<td>190</td>
<td>35</td>
<td>&gt;15 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9/20/83</td>
<td>1,057,000</td>
<td>86</td>
<td>145</td>
<td>49</td>
<td></td>
<td></td>
<td>Large multimers present but relatively diminished (similar to the patient shown in Fig 3); asymptomatic</td>
</tr>
</tbody>
</table>

Patient 1 was studied prior to the onset of bleeding symptoms and prior to splenectomy. At that time, platelet count was 716,000/μL, and the VIII:C, vWF:Ag, and vWF:RCo were all normal (Table 1). However, the vWF:Ag to vWF:RCo ratio was elevated. Multimeric analysis of vWF was not performed at that time. When seen in April 1982, the platelet count was elevated to 5,860,000/μL, and though the VIII:C and vWF:Ag were normal, the vWF:RCo was significantly decreased. Bleeding time was over 15 minutes. The larger multimers of vWF were absent from plasma, and there was a relative increase in the smallest (most rapidly migrating band) of each vWF triplet (Fig 1). Treatment with DDAVP produced an increase in VIII:C, vWF:Ag, and vWF:RCo, though the latter was not raised to within the normal range. Only a minimal increase in vWF large multimer concentration was evident. These changes were not associated with a correction of hemostasis. Cohn fraction I was then given and the bleeding stopped. Subsequent thrombocytapheresis and busulfan therapy resulted in a reduction of the platelet count to 1,005,000/μL and the WBC count to 7,800/μL. There was an increase in vWF:RCo to normal, a return of large vWF multimers to the circulation, normalization of the triplet pattern, and correction of the bleeding time (Fig 1 and Table 1). Sixteen months later, the platelet count was unchanged, but the WBC count had risen to 19,300/μL. A relative decrease in large multimers was evident, there was some reversion to the abnormal triplet pattern (similar to that of the patient shown in Fig 3), and the vWF:RCo had dropped to borderline levels (Table 1).

Patient 2 was initially diagnosed at another institution where splenectomy was performed. Studies of factor VIII:C or vWF were not available until she presented to the Universität Bonn three years later with severe bleeding following tooth extraction. At that time, the platelet count was 2,570,000/μL, the

Table 2. Patients Without Bleeding Symptoms But With a Relative Decrease in Large vWF Multimers

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Platelet Count (per μL)</th>
<th>WBC (per μL)</th>
<th>VIII:C (IU/dL)</th>
<th>vWF:Ag (IU/dL)</th>
<th>vWF:RCo (IU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1,033,000</td>
<td>11,300</td>
<td>91</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>990,000</td>
<td>12,800</td>
<td>62</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>835,000</td>
<td>12,400</td>
<td>109</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>254,000</td>
<td>37,200</td>
<td>230</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2,000,000</td>
<td>36,400</td>
<td>165</td>
<td>155</td>
<td></td>
</tr>
</tbody>
</table>

*After DDAVP.
ACQUIRED VON WILLEBRAND'S DISEASE

Fig 1. SDS-agarose gel electrophoresis of plasma vWF from patient 1 compared with that from a normal plasma (NP) sample. vWF was identified with 125I-anti-vWF and autoradiography. On the right is the autoradiograph of each gel, and on the left is the densitometric tracing of that gel. The date on which the plasma sample was taken is given for each patient plasma sample and can be correlated with the date given in Table 1. Samples were applied to the top of the gel and the direction of electrophoresis is down. Thus, the largest multimers (highest mol wt) are at the top. For the densitometric tracings, the righthand side corresponds to the top of the gel. Thus, the largest multimers (highest mol wt) are to the right and the smallest to the left. Optical density (OD) is indicated on the left. Each multimer is composed of at least three bands. A typical triplet is indicated by the bracket on the righthand side of each gel, with the corresponding tracing of that triplet indicated by the bracket at the bottom of the densitometric tracing. It can be seen that, on April 13, the largest multimers were not detectable in the resting state. After administration of DDAVP (p DDAVP), a small quantity of larger multimers appeared in the plasma, correlating with increased ristocetin cofactor activity. The triplet pattern was abnormal, with the smallest (fastest migrating) band, rather than the central band, predominating. By May 17, the vWF multimeric pattern was almost normal. Large multimers were now present in plasma and correlated with the return of the ristocetin cofactor activity and bleeding time to normal (Table 1). The triplet pattern was now also normal, with the central band predominating. Sixteen months later, the multimeric structure had deteriorated moderately to resemble that shown in Fig 3, though there was no recurrence of bleeding symptoms.

WBC count 23,000/μL, the vWF:RCo decreased, and the bleeding time was greater than 15 minutes (Table 1). Though VIII:C and vWF:Ag were quantitatively normal, large vWF multimers were markedly decreased, and the individual multimer triplet pattern was altered as in patient 1 (Fig 2). DDAVP partially restored large multimers to the circulation, with a concomitant correction of the bleeding diathesis. When bleeding recurred the next day, it was successfully treated with infusion of Cohn fraction I. Thrombocytapheresis and azathioprine therapy was accepted only intermittently by the patient, and one month later the platelet and WBC counts had decreased only to 1,640,000/μL and 21,500, respectively. Though some correction of the triplet pattern was seen, the large multimers remained decreased. The vWF:RCo was still decreased, the vWF:Ag to vWF:RCo ratio increased, and the bleeding time remained prolonged (Fig 2 and Table 1). A year later, an almost complete correction of the platelet and WBC counts was achieved, and though the vWF:Ag and vWF:RCo were well within the normal range, the large multimers were relatively depleted and the triplet pattern had not returned to normal (similar to the patient shown in Fig 3).

Patients 3 through 7 were studied at the time of routine blood counts. There were no symptoms suggestive of hemostatic abnormalities and the bleeding times were not determined. All had normal levels of VIII:C, vWF:Ag, and vWF:RCo. Multimeric analysis of platelet and plasma vWF from patient 3 is shown in Fig 3. No abnormalities were evident in platelet vWF. However, plasma vWF showed a relative decrease in the largest multimers, and the "triplet" pattern was altered with a relative increase in the fastest moving
band in each. Similar patterns were seen in patients 4, 5, 6, 7, as well as in the most recent samples from patients 1 and 2.

**DISCUSSION**

Von Willebrand factor exists in plasma as a series of multimers ranging in molecular weight (mol wt) from approximately 500,000 to 800,000 to over 14,000,000. The large multimers are the most hemostatically competent and are decreased or absent from plasma in some forms of von Willebrand’s disease. Each multimer consists of a triplet of at least three bands. In normal individuals, the central band predominates, whereas in type IIA von Willebrand’s disease, a relative increase in the smallest (fastest migrating) band has been demonstrated.

All of the patients reported here had abnormalities of vWF multimeric structure, though only two had bleeding symptoms that could be directly related to decreased function of vWF. In these latter two individuals, large multimers were either entirely lacking from their plasmas or were markedly decreased, and the triplet pattern was altered with a relative increase in the most rapidly migrating member of each set. There was a disparity between vWF:Ag concentration (which was normal) and vWF:RCo (which was decreased), a finding typical of type II von Willebrand’s disease.

The five asymptomatic patients with myeloproliferative syndrome all showed a similar, though less pronounced, abnormality of multimeric structure (Fig 3). Large multimers were decreased and the triplet pattern showed a relative increase of the most rapidly migrating band. Platelet vWF, on the other hand, was found to have a pattern indistinguishable from normal.

In all but one of the asymptomatic patients, the vWF:Ag was higher than the vWF:RCo, though both values were within the normal range.

Evidence that the acquired bleeding diathesis demonstrated by both symptomatic patients resulted at least in part from abnormalities of vWF is provided by several observations. First, absence or marked decrease of large multimers has been associated with bleeding in all previously reported cases. In addition, both patients responded to infusion of vWF in the form of Cohn fraction I, with transient correction of hemorrhagic symptoms. DDAVP transiently corrected the multimeric abnormality and the bleeding diathesis in patient 2. Reduction of the platelet and WBC counts by thrombocytapheresis and busulfan therapy in patient 1 was accompanied by the appearance of large multimers in the circulation, normalization of vWF:RCo, correction of the bleeding time, and disappearance of bleeding symptoms. In patient 2, correction of the thrombocytopenia and leukocytosis with thrombocytapheresis and azathioprine was also associated with an increase of circulating large multimers, an increase of vWF:RCo to normal, and a disappearance of the hemorrhagic diathesis.

The cause of acquired von Willebrand’s disease in the two symptomatic patients and the multimeric abnormality in plasma of the asymptomatic patients cannot be known with certainty at this time. It is likely that the von Willebrand factor becomes altered after release into the circulation. This is suggested by the normal multimeric structure of platelet vWF and the transient correction of plasma vWF multimeric structure after treatment of patient 2 with DDAVP. This latter observation indicates that vWF in tissue stores was normal even when plasma vWF multimeric abnormalities were severe. Though reduction in platelet and WBC counts was associated with disappearance of symptoms and improvement of the abnormal multimeric pattern, it is not clear that the vWF abnormalities were directly related to elevated concentrations of either of these formed elements. Abnormalities of multimeric structure (Fig 3) were evident when (a) the platelet count was normal and the WBC count was elevated (patient 6); (b) when the platelet count was elevated and the WBC count was barely above normal (patient 3); or (c) when both counts were almost normal (patient 2, Nov 10, 1983). In any case, these studies suggest that acquired von Willebrand’s disease should be considered when a bleeding tendency occurs during the course of the myeloproliferative syndrome. This is particularly relevant in view of the fact that two agents known to be effective in von Willebrand’s disease (DDAVP and Cohn fraction I) were successfully used to stop bleeding in two patients.
REFERENCES

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