Acquired von Willebrand Syndrome Associated with Hashimoto’s Thyroiditis and Subcutaneous Mucosa-associated Lymphoid Tissue Lymphoma

Takatoshi Koyama¹, Kazumi Fujimoto¹ and Midori Shima²

Abstract

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder with laboratory findings similar to those of congenital von Willebrand disease. We herein report a case of AVWS associated with Hashimoto’s thyroiditis and subcutaneous mucosa-associated lymphoid tissue lymphoma. An IgG autoantibody against von Willebrand factor (VWF) was detected. The antibody bound to VWF but did not inhibit VWF activity. Rapid clearance of VWF seemed to be the cause of AVWS in the present case. VWF-containing concentrates stopped the bleeding. Even if such a complication is rare, for AVWS patients, prompt recognition of the underlying mechanism can save lives.

Key words: acquired von Willebrand syndrome (AVWS), Hashimoto’s thyroiditis, mucosa-associated lymphoid tissue (MALT) lymphoma

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Introduction

Acquired von Willebrand syndrome (AVWS) or acquired von Willebrand disease (AVWD) is a rare bleeding disorder with laboratory findings similar to those of congenital VWD. Unlike the congenital form, AVWS generally occurs in individuals with no personal or family history of a bleeding disorder. AVWS is associated with various underlying conditions (1). Lympho- or myelo-proliferative disorders and cardiovascular disorders are the most common (2, 3). Less commonly, AVWS has also been described in solid tumors and autoimmune disorders. AVWS occurs in each age group but it is most common in the elderly, with a median age of 62 years at the time of diagnosis (2). AVWS is underdiagnosed and sometimes misdiagnosed probably because of its relatively indistinct clinical and laboratory features. There are concerns that these reports may be just the “tip of the iceberg” (4, 5). We herein report a case of AVWS associated with Hashimoto’s thyroiditis and indolent non-Hodgkin lymphoma.

Case Report

A 60-year-old woman was referred to a metropolitan hospital for general malaise, hoarseness, loss of appetite, and gastrointestinal bleeding of unknown origin. She had experienced recurrent epistaxis and gum bleeding for 3 years. She had no personal or family bleeding history. She delivered 4 daughters without excessive bleeding; hemostatic laboratory findings were normal in the 4 pregnancies.

The initial medical evaluation revealed hypothyroidism because of Hashimoto’s chronic thyroiditis (Hashimoto’s thyroiditis or Hashimoto’s disease) (Table). The results of the microsome test (anti-microsomal antibody) and the thyroid test (anti-thyroglobulin antibody) were highly positive with 1:6,400 (normal, <1:100) and 1:102,400 (normal, <1:100), respectively. Thyroid hormone replacement therapy with 100 µg/day of levothyroxine sodium hydrate was started immediately with fast and persistent normalization of thyroid function. She was referred to our hospital because of a prolonged activated partial thromboplastin time (APTT).
Analyses of hemostatic parameters in our hospital (Table) showed a prolonged APTT, reduced plasma levels of factor VIII activity (FVIII:C), VWF antigen (VWF:Ag), and VWF ristocetin cofactor activity (VWF:RCo). VWF:RCo was measured with BC von Willebrand Reagent (Siemens Healthcare Diagnostics, Tokyo, Japan). Large multimers of VWF were absent and medium multimers were markedly reduced (Figure), which is consistent with a type-2A VWD pattern. The immunoglobulin (Ig)G autoantibody against VWF was analyzed by enzyme-linked immunosorbent assay as described previously (6). The value of optical density obtained for anti-IgG and anti-IgM in 1:50 diluted plasma was 0.261 and 0.003, respectively; the positive cut-off value is >0.1. The antibody bound to VWF but did not inhibit VWF:RCo (<0.3 Bethesda U/mL). Three years after the diagnosis of AVWS, she developed a solitary soft-tissue mass on her back. The 40×13×12 mm mass was completely excised. To cease the acute bleeding episodes and prophylaxis during invasive procedures (1), in general, in AVWS, even if bleeding episodes are mainly mild and mucocutaneous, blood transfusion has not yet been necessary. In the present case, the rapid clearance of FVIII/VWF complex due to binding, non-neutralizing autoantibodies to VWF appeared to be the cause of AVWS. Large multimers seemed to be cleared preferentially with the antibodies. While the precise mechanism is not yet clear, a selective removal of the high molecular weight multimers from plasma is frequently observed in AVWS (2). The affinity of the antibody to large multimers may be higher than to small multimers and antibody-bound large multimers may be more easily recognized by Fc receptor-possessing cells in the mononuclear phagocytic system. Even though hemostatic disturbances are generally reversible by hormone replacement treatment (7, 9), the AVWS in the present case has not been reversed after 5 years of euthyroid status, which may be explained by the sustained autoimmune disorders.

**Discussion**

Hemostatic disturbances may be present in patients with Hashimoto’s thyroiditis (the most common thyroid disorder) independent of their thyroid hormone status (7). Hemostatic disturbances include increased plasma levels of VWF, fibrinogen, factors VII and X, and plasminogen activator inhibitor-1 (7, 8). Conversely, AVWS type 1 seems to be the main factor responsible for bleeding diathesis in overt hypothyroidism (9, 10). Different from other types of AVWS, decreased VWF levels in hypothyroidism are generally secondary to a reduction in synthesis and/or secretion. In the present case however, the rapid clearance of FVIII/VWF complex due to binding, non-neutralizing autoantibodies to VWF appeared to be the cause of AVWS. Large multimers seemed to be cleared preferentially with the antibodies. While the precise mechanism is not yet clear, a selective removal of the high molecular weight multimers from plasma is frequently observed in AVWS (2). The affinity of the antibody to large multimers may be higher than to small multimers and antibody-bound large multimers may be more easily recognized by Fc receptor-possessing cells in the mononuclear phagocytic system. Even though hemostatic disturbances are generally reversible by hormone replacement treatment (7, 9), the AVWS in the present case has not been reversed after 5 years of euthyroid status, which may be explained by the sustained autoimmune disorders.

**Table. Hemostatic Parameters and Thyroid Hormones of the Patient**

<table>
<thead>
<tr>
<th>Platelet count ($\times 10^{9}$/L)</th>
<th>Hemoglobin (g/dL)</th>
<th>APTT (s) (cont. 27.7)</th>
<th>PT (%)</th>
<th>FVIII:C (%)</th>
<th>VWF:Ag (%)</th>
<th>VWF:RCo (%)</th>
<th>FT$_4$ (ng/dL)</th>
<th>TSH (μIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) 270</td>
<td>10.9</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>&lt;0.1</td>
<td>216.08</td>
</tr>
<tr>
<td>2) 272</td>
<td>11.5</td>
<td>44.9</td>
<td>90.1</td>
<td>21</td>
<td>10</td>
<td>14</td>
<td>1.1</td>
<td>14.09</td>
</tr>
<tr>
<td>3) 307</td>
<td>10.4</td>
<td>47.7</td>
<td>95.6</td>
<td>13</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>1.22</td>
<td>4.95</td>
</tr>
</tbody>
</table>

1) Results at the time of diagnosis of Hashimoto’s disease.
2) Results at the time of diagnosis of AVWS, 6 months after the diagnosis and treatment of Hashimoto’s disease.
3) Results at 5 years after the diagnosis of AVWS.

n.d.: not determined, PT: prothrombin time, FT$_4$: free thyroxine, TSH: thyroid-stimulating hormone

(1,500 mg QD) to control recurrent gum bleeding. Oral iron replacement therapy has also been necessary to treat iron-deficiency anemia. Her AVWS persists irrespective of the euthyroid state for 5 years after the diagnosis of AVWS.
Lymphoproliferative disorders account for a significant proportion of cases with AVWS in the literature (30%) and in the International Society on Thrombosis and Hemostasis registry (48%) (1, 3). In the present case, AVWS was associated with an autoimmune disease, Hashimoto’s thyroiditis and MALT lymphoma. A similar complication of AVWS with an autoimmune disease, Sjögren’s syndrome and thymic MALT lymphoma, has been reported (11). MALT lymphoma arises in mucosal sites where lymphocytes are not normally present and where MALT is acquired in response to chronic infectious conditions or autoimmune processes, such as Hashimoto’s thyroiditis or Sjögren’s syndrome. Accordingly, patients with Hashimoto’s thyroiditis are at a higher risk of primary thyroid lymphoma than the general population (12). MALT lymphoma and diffuse B cell lymphoma are most common in primary thyroid lymphoma. An association of solitary subcutaneous MALT lymphoma and Hashimoto’s thyroiditis has not been reported, but autoimmune, inflammatory disorders may be related to the co-occurrence of AVWS, Hashimoto’s thyroiditis, and subcutaneous MALT lymphoma in the present case. Unlike systemic lupus erythematosus, autoimmune thyroiditis cannot be treated with steroids. In the present case MALT lymphoma is now in complete remission and the patient is now free from uncontrollable bleeding in her daily life. Therefore, we have not considered treatment with steroids or high-dose intravenous immunoglobulins. But if MALT lymphoma relapses, it may be necessary to consider the induction of immunchemotherapy using anti-CD20 monoclonal antibody rituximab.

For patients with AVWS, prompt recognition of the underlying mechanism can be life-saving. AVWS may become more prevalent and internists are more likely to encounter such patients with this condition in the future.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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References

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