Case Report

An Acquired Factor VIII Inhibitor in a Patient with HIV and HCV: A Case Presentation and Literature Review

S. B. Zeichner, 1 A. Harris, 1 G. Turner, 1 M. Francavilla, 2 and J. Lutzky 3

1 Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, FL 33140, USA
2 Department of Radiology, Mount Sinai Medical Center, Miami Beach, FL 33140, USA
3 Division of Hematology/Oncology, Mount Sinai Medical Center, Miami Beach, FL 33140, USA

Correspondence should be addressed to S. B. Zeichner; simonzeichner@gmail.com

Received 26 July 2013; Accepted 29 August 2013

Academic Editors: R. Herrmann, K. Khair, M.-C. Kyrtsonis, and Y. Matsukawa

Copyright © 2013 S. B. Zeichner et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction. Despite its low incidence, acquired factor VIII inhibitor is the most common autoantibody affecting the clotting cascade. The exact mechanism of acquisition remains unclear, but postpartum patients, those with autoimmune conditions or malignancies, and those with exposure to particular drugs appear most susceptible. There have been several case reports describing acquired FVIII inhibitors in patients receiving interferon alpha for HCV treatment and in patients being treated for HIV. To our knowledge, this is the first case of a patient with HCV and HIV who was not actively receiving treatment for either condition.

Case Presentation. A 57-year-old Caucasian male with a history of HIV and HCV was admitted to our hospital for a several day history of progressively worsening right thigh bruising and generalized weakness. CTA of the abdominal arteries revealed large bilateral retroperitoneal hematomas. Laboratory studies revealed the presence of a high titer FVIII inhibitor.

Conclusion. Our case of a very rare condition highlights the importance of recognizing and understanding the diagnosis of acquired FVIII inhibitor. Laboratory research and clinical data on the role of newer agents are needed in order to better characterize disease pathogenesis, disease associations, genetic markers, and optimal disease management.

1. Introduction

Despite its low incidence of 1.3 to 1.5 patients per million per year [1, 2], acquired factor VIII (FVIII) inhibitor, or acquired hemophilia A, is the most common autoantibody affecting the clotting cascade [3–5]. Incidence increases with age, with a median age of onset of 74 years [2, 6]. The exact mechanism of acquisition remains unclear, and the most common disease associations are idiopathic (64%; [7]), autoimmune conditions (16%; [8–11]), malignancies (12%; [12–17]), pregnancy (8%; [3, 4, 18, 19]), and exposure to particular drugs (5–10%; [5, 20]). The severity of the bleeding, response to treatment, and overall prognosis are heterogeneous with a mortality rate of 8–22% [3, 21, 22].

There have been several case reports describing acquired FVIII inhibitors in patients receiving interferon alpha for hepatitis C virus (HCV) treatment [23–27] and in immune reconstitution inflammatory syndrome (IRIS) in patients being treated for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS; [28–32]). To our knowledge, this is the first case of a patient with HCV and HIV who was not actively receiving treatment for either condition.

2. Case Presentation

A 57-year-old Caucasian male was seen in our emergency department for a several day history of progressively worsening right thigh bruising and generalized weakness. His past medical history was notable for HIV (diagnosed ten years before; not on highly active antiretroviral treatment-HAART), HCV (diagnosed ten years before; never treated), end stage renal disease (etiology unclear; on hemodialysis for the previous five months), non-Hodgkin’s lymphoma (NHL; diagnosed seven years before; underwent treatment with radiation and chemotherapy, rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisonone-R-CHOP; had a complete response and has been in remission ever since),
Figure 1: On admission, computed tomography angiogram (CTA) of the abdominal arteries without the use of intravenous contrast revealed large hyperdense retroperitoneal hematomas expanding both psoas muscles, left more than right, that extend into the iliopsoas muscles, and right quadriceps femoris musculature.

Our presentation of a severe case of a very rare condition brings to light many interesting issues related to the pathogenesis, presentation, diagnosis, and treatment of acquired FVIII.
Table 1: Comparison between a meta-analysis by Delgado et al. [33], a case series by Collins et al. [2], and our patient.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>249</td>
<td>154</td>
<td>1</td>
</tr>
<tr>
<td>Age category (median)</td>
<td>64 (range, 8–93)</td>
<td>78 (range, 2–98)</td>
<td>57</td>
</tr>
<tr>
<td>Sex</td>
<td>Female: 55%</td>
<td>Female: 57.38</td>
<td>Male</td>
</tr>
<tr>
<td>Underlying diagnosis</td>
<td>Malignancy</td>
<td>Autoimmune disorders</td>
<td>Malignancy: 14.7</td>
</tr>
<tr>
<td>FVIII level category at diagnosis (median)</td>
<td>2 IU/dL (range, 0–30)</td>
<td>4 IU/dL (range, &lt;1–12 IU/dL)</td>
<td>&lt;1 IU/dL</td>
</tr>
<tr>
<td>Inhibitor titer at diagnosis (median)</td>
<td>10.0 BU/mL (range, 0.9–32,000)</td>
<td>7.2 BU/mL (range, 1.4–219 BU/mL)</td>
<td>230.4 BU/mL</td>
</tr>
</tbody>
</table>

Table 2: Laboratory values and treatment regimen used during patient’s hospital course.

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Day 7</th>
<th>Day 21</th>
<th>Day 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.2</td>
<td>8.6</td>
<td>10.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>22.3</td>
<td>26.3</td>
<td>31.6</td>
<td>37.9</td>
</tr>
<tr>
<td>Platelet count (/uL)</td>
<td>200 × 10^3</td>
<td>204 × 10^3</td>
<td>130 × 10^3</td>
<td>160 × 10^3</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>65.6</td>
<td>62.4</td>
<td>63.5</td>
<td>44.3</td>
</tr>
<tr>
<td>Factor VIII activity (%)</td>
<td>&lt;0.1</td>
<td>3</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Total pRBCs used</td>
<td>—</td>
<td>15</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>—</td>
<td>(1) Solumedrol 80 mg IV q 8 hrs</td>
<td>(1) Solumedrol 80 mg IV q 8 hrs</td>
<td>(1) Solumedrol 80 mg IV q 8 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Cyclophosphamide 50 mg PO daily</td>
<td>(2) Cyclophosphamide 50 mg PO daily</td>
<td>(2) Cyclophosphamide 50 mg PO daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) Recombinant coagulation factor VIIa 2000 mcg IV BID</td>
<td>(3) Recombinant coagulation factor VIIa 1000 mcg IV TID</td>
<td></td>
</tr>
</tbody>
</table>

3.1. Pathophysiology/Disease Associations. FVIII inhibitors are known to bind to the highly antigenic C2 and A2 domains on FVIII which in turn leads to reduced procoagulant activity [34–36]. The reason for the development of these inhibitors in certain individuals is poorly understood. Mahendra et al. theorized that the presence of certain gene polymorphisms or autoreactive CD4+ T lymphocytes accounts for individual variation [37].

Our case is unique in that our patient had many different possible causes for his acquired FVIII inhibitor. At the time of admission, our patient was taking many different medications, but none of which were started over the previous month, and none of which have been associated with FVIII inhibitors. Drug induction of inhibitors, accounting for 5–10%, has been associated with penicillin, sulfamides, chloramphenicol, methyldopa, depot thioanxthene, phenytoin, interferon, and fludarabine [5, 23, 38]. Our patient was found to have a lupus anticoagulant (LA), in the absence of obvious systemic lupus erythematous (SLE) or rheumatoid arthritis (RA). Both of these disease entities, in addition to other autoimmune conditions, such as Sjogrens’ syndrome (SS), Goodpasture’s syndrome, myasthenia gravis (MG), Graves disease, and autoimmune hemolytic anemia, have been shown to induce inhibitors [3, 13–15]. Although our patient had a normal factor II (prothrombin) level, the presence of LA has been associated with antibodies against prothrombin, in what is known as lupus anticoagulant hyperprothrombinemia syndrome (LAC-HPS; [39–41]).

Our patient was found to have a monoclonal gammopathy of unknown significance (MGUS) with 0.43 grams of IgG Kappa. It is unclear whether this patient had an associated lymphoproliferative disorder, as a bone marrow biopsy was not performed, and whether or not this was related to the patient’s HCV [42]. There was no evidence of recurrent lymphoma in the multiple CT scans performed during his hospital stay. It is also unclear whether this finding was incidental or was playing a larger role in the production of autoantibodies. Several reviews have shown that both solid tumors and hematologic malignancies can cause this phenomenon, with lung and prostate adenocarcinoma and low grade lymphoproliferative diseases being the most common culprits [17–22]. Although there have been several case reports describing patients with HCV who developed acquired FVIII inhibitors, most of these patients were undergoing treatment with interferon, a known immunomodulatory agent [24–28]. Schreiber and Bräu proposed that the presence of autoantibodies to FVIII in HCV was in fact extrahepatic autoimmune manifestations similar to cryoglobulinemia and hepatitis-induced thrombocytopenia [24]. There have been several case reports associating inhibitors...
Figure 2: Repeat computed tomography of the abdomen and pelvis demonstrating hematoma stability. Better seen are mixed-aged bilateral retroperitoneal hematomas in the posterior pararenal spaces displacing both kidneys anteriorly with marked mass effect on peritoneal structures.

3.2. Clinical Features/Diagnosis. As was seen in our patient, the clinical presentation of acquired FVIII is often life threatening and usually involves large, rapidly expanding hematomas, uncontrolled gastrointestinal bleeding, and/or hematuria. Hemarthrosis, as seen with the inherited FVIII deficiency, is rarely seen with an acquired FVIII inhibitor [5]. A classic presentation, in addition to an elevated aPTT, is often diagnostic. However, several other conditions can give an elevated aPTT in the setting of bleeding, including deficiencies or inhibitors of factors VIII, IX, or XI, Von Willebrand disease (VWD), and the iatrogenic use of heparin. The presence of heparin can be assumed with a prolonged thrombin time and a normal reptilase time. In a mixing study, a patient’s plasma is mixed with pooled normal plasma, and the aPTT is measured immediately and two hours afterward. Correction of the aPTT suggests factor deficiency or VWD, whereas an unchanged or minimally corrected aPTT represents the presence of an inhibitor. The Bethesda assay has great utility, as it not only establishes the diagnosis of acquired FVIII inhibitor but also quantifies the titer [43]. In the assay, serial dilutions of patient plasma are incubated in normal patient plasma for two hours; the stronger the inhibitor, the greater the dilution required to allow for factor VIII activity.

3.3. Treatment. Control of bleeding and the elimination of the inhibitor are the primary goals of treatment. The initial treatment is primarily based on the severity of the bleeding and the titer of the inhibitor [38, 44, 45]. Non-life-threatening bleeding with low inhibitor titers can be treated with desmopressin (DDAVP) or high dose human factor VIII concentrate, whereas more substantial bleeding and higher inhibitor titers call for more aggressive measures, including bypassing agents such as activated prothrombin complex concentrate FVIII bypassing agent (FEIBA) and human recombinant factor VIIa (rFVIIa) [46–49]. FEIBA has shown complete response rates of 76% with severe bleeds and 100% with moderate bleeds [47], whereas rFVIIa has shown an overall efficacy of 95% in the first line setting and 80% as salvage therapy [48, 49]. Although there are
no randomized clinical trials demonstrating superiority of a particular regimen, immunosuppressive therapy is the cornerstone for the elimination of factor inhibitors. In a large registry, the most commonly employed regimens were glucocorticoids (G), glucocorticoids plus cyclophosphamide (GC), and glucocorticoids plus rituximab (GR), with complete response (CR) rates of 48%, 70%, and 59%, respectively, with a significantly shorter time to a negative inhibitor and normal FVIII level in the GC group but no difference in overall outcomes [7]. In a large literature review, the CR for GC was significantly greater than for G at 78% and 70%, respectively [50]. Although rituximab was introduced as a potential novel agent for the treatment of acquired FVIII, only anecdotal studies have demonstrated efficacy [7]. Rituximab has therefore been relegated as second-line therapy in such cases. Intravenous immune globulin (IVIG) demonstrated activity in a select group of patients, but responses were highly variable [13, 45, 51]. In treatment-resistant acquired FVIII inhibitors, there was anecdotal evidence for the use of cyclosporine, cladribine, vincristine, and extracorporeal plasmapheresis [52–59].

3.4. Natural History/Prognosis. Although most patients with acquired FVIII are treated with immunosuppressive drugs, there are a significant number of patients who recover spontaneously. Studies cite a spontaneous recovery rate of 36% and 31% at an average duration of 14 and 31 months, respectively [3, 60]. The patient we presented had a long protracted hospital course, requiring numerous transfusions of blood products, before he began clearing the inhibitor and restoring factor VIII activity. His course was not unusual, as patients with low antibody titers (<5 Bethesda units) tend to have remissions within months, whereas those with higher titers may have antibody persistence for years. Low antibody titers and those with pregnancy-associated FVIII inhibitors appear to respond best to treatment and have the lowest relapse rates [2, 42]. The overall relapse rate is estimated at 20%, with 70% of these patients achieving a second remission. The overall prognosis varies, with mortality rates ranging from 8 to 22%, with fatal bleeding (3.2%) being very uncommon [6]. Evidence shows that GC, especially if given to the elderly, is associated with significant adverse effects in 40% of patients, most commonly infection and neutropenia. Meanwhile, G (25%) and GR (37%) are associated with less adverse effects, most commonly infection and diabetes, respectively [7]. The survival rate at 8 months for acquired FVIII inhibitor secondary to all causes is 69%, with those secondary to malignancy having the worst outcomes [7].

4. Conclusion

Our case of a very rare condition highlights the importance of recognizing and understanding the diagnosis of acquired FVIII inhibitor. Laboratory research and clinical data on the role of new agents are needed in order to better characterize disease pathogenesis, disease associations, genetic markers, and optimal disease management. The hope is to one day better identify patients who are at increased risk for the disorder and then personalize treatment regimens in order to improve disease morbidity and mortality.

Conflict of Interests

The authors declare that they have no conflict of interests.

References


Submit your manuscripts at http://www.hindawi.com