Management of Severe Gastrointestinal Bleeding in a Patient with Acquired Von Willebrand Disease Complicating Enteropathic-Associated T-Cell Lymphoma

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Standard Abbreviations
vWD: von Willebrand’s disease
vWF: von Willebrand’s factor
CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone
EATL: enteropathic-associated T-cell lymphoma
DDAVP: desmopressin
Humate-P: pasteurized human anti-hemophilic factor / vWF complex
NHL: non-Hodgkin’s lymphoma

Acquired von Willebrand’s disease (vWD) is a rare bleeding disorder with clinical and laboratory features mimicking the congenital form of the disease. An abnormal bleeding time, decreased levels of both factor VIII and von Willebrand factor (vWF), and moderate to severe mucosal bleeding characterize both forms of the disease. Acquired vWD occurs sporadically with no family history of vWD and usually with no previous coagulopathy. It is often linked with immune system dysfunctions and particularly with clonal hematoproliferative diseases, including Enteropathic-Associated T-cell Lymphomas (EATL). Treatment of acquired vWD is often difficult and requires either correcting the acute bleeding episode or treating the associated condition. This case report supports the use of cyclophosphamide, doxorubicin, vincristine, and prednisone therapy (CHOP) for the rare patient with EATL presenting with persistent, severe gastrointestinal hemorrhage.

CASE REPORT
A 65-year-old man was referred for evaluation and management of intermittent, obscure intestinal bleeding for the previous 5 years. Angiography at an outside hospital revealed bleeding of a portion of the mid-
jejunum and it was resected. An outside pathology report revealed only lymphoid hyperplasia, yet in retrospect and upon subsequent review by our pathologists, the patient’s pathology at that time was consistent with a diagnosis of EATL. Upon referral to our center in April 2002, CT scan and video capsule endoscopy revealed two ulcerated lesions measuring 10 cm and 6 cm in diameter in the proximal jejunum (Figure 1). During preoperative evaluation, the patient had a bleeding time greater than 15 minutes. He had never experienced bleeding problems in the past despite two prior inguinal herniorrhaphies, coronary artery bypass grafting, and a tooth extraction just one year prior. He had a negative family history of bleeding disorders. After correction of the prolonged bleeding time with infusions of pasteurized human antihemophilic factor/vWF complex (Humate-P) and cryoprecipitate, a 30-cm segment of proximal jejunum containing the two lesions was resected. Pathology revealed findings consistent with celiac sprue and EATL (Figure 2). The patient was subsequently diagnosed with acquired vWD secondary to his EATL.

The patient continued to bleed and required aggressive transfusions and vasopressors to maintain hemodynamic stability. Repeated endoscopic and contrast studies, mesenteric angiographies, radionuclide-tagged red blood cell scans and a second laparotomy with intraoperative enteroscopy from mouth to mid-transverse colon also failed to locate a source of the bleeding. Treatment of his acquired vWD with desmopressin (DDAVP), octreotide infusions, additional cryoprecipitate, and Humate-P failed to slow his bleeding. Although the patient’s bleeding stopped for one week after administration of methylprednisolone sodium succinate for treatment of his sprue, he was again re-admitted to the hospital for recurrent massive intestinal bleeding.

CHOP chemotherapy was ultimately administered for treatment of the patient’s lymphoma. After the second cycle of CHOP therapy, the patient’s bleeding stopped. He continued to receive cryoprecipitate, octreotide, and methylprednisolone sodium succinate. At the patient’s request, no further diagnostic tests were ever performed on this patient. After five cycles of CHOP, the patient remained without gastrointestinal bleeding until his death from relapsing lymphoma nearly 15 months later.

**DISCUSSION**

This case report presents the difficult management of severe gastrointestinal bleeding in a patient with acquired vWD complicating celiac disease linked EATL. Although EATL accounts for less than 0.5% of...
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the new cases of Non-Hodgkin’s Lymphoma (NHL) each year, EATL is the most frequent malignancy associated with celiac sprue (1). Furthermore, EATL is the single most common cause of death in celiac sprue (2).

Acquired vWD is a rare complication of an autoimmune or neoplastic disease with only eighty-eight cases documented in the English literature (3). The pathophysiology of EATL associated acquired vWD is not fully understood and can result in ineffective treatment. The more common congenital form of vWD results from defective synthesis of factor VIII. Acquired vWD has normal factor VIII synthesis, but vWF is abnormally rapidly cleared from the circulation. The mechanism most frequently proposed for the rapid clearance of factor VIII from the circulation is the development of anti-vWF antibodies in the patient. In some reported cases, the specific inhibitor was contained in purified IgG fractions of the patient’s sera, whereas in others, the vWF inhibition was mediated by the lymphoma-related monoclonal protein itself (4-6).

A similar but alternative mechanism involves the formation of immune complexes between the vWF protein and mono-specific antibodies produced by tumor cells (7). Finally, another possible mechanism explaining the clearance of vWF in the setting of a clonal proliferative disorder like EATL is that immunoadsorption of vWF onto a malignant clone of cells renders factor VIII incompetent. It has been suggested that an aberrant tumor-cell expression of the platelet vWF receptor glycoprotein Ib (CD42) mediates this adsorption (8).

Understanding the pathophysiology of these two forms of the disease aids in directing the treatment and explains why patients with acquired vWD are refractory to traditional therapies. In congenital vWD, correcting the acute bleeding time often involves replenishing vWF by administration of DDAVP, clotting factor products, vWF/factor VIII complex, or concentrated vWF as was done in our patient. These methods are inadequate for acquired vWD because the substitution products will continue to be rapidly cleared. On the other hand, therapeutic interventions used to treat acquired vWD such as intravenous immunoglobulin or corticosteroids are effective because they suppress the clearance of vWF. Plasma exchange, extra-corporeal factor VIII immuno-adsorption and immuno-suppressive drugs such as azathioprine and cyclophosphamide work in patients with acquired vWF because they suppress the clearance of vWF. If the underlying tumor is discrete, treatment can be effected though surgical resection. The administration of the anti-fibrinolytic agent, tranexamic acid, has also been shown to correct vWF levels in acquired vWD (3).

While clinical and laboratory presentations of the congenital and acquired forms of vWD are similar, the pathophysiologies are different. It was for this reason that traditional therapies were unsuccessful in our patient to treat his bleeding disorder. Unconventional therapeutics like CHOP therapy likely suppressed the EATL cells producing anti-factor VIII antibodies and ultimately resulted in a lasting remission of the patient’s acquired vWD. This case report supports the use of CHOP therapy for the patient with EATL who presents with a bleeding disorder in the absence of a history suggesting congenital or familial bleeding diathesis.

References