

Acquired Hemophilia in Association With Pemphigus Vulgaris; An Uncommon Coexistence: A Case Report



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ABSTRACT

Acquired Hemophilia (AHA) is a relatively rare disease that occurs in patients with no previous family history of hemophilia. The spontaneous development of autoantibodies (IgG1 and IgG4) against factor VIII has been reported as the most probable cause of AHA. AHA has been reported in association with other conditions, including some autoimmune bullous skin diseases, such as bullous pemphigoid, pemphigus vulgaris, and pemphigus foliaceus. To the best of our knowledge, only 21 cases of AHA with skin autoimmune bullous diseases have been reported so far. Herein, we report a 63-year-old male with a previous history of pemphigus vulgaris who developed large ecchymotic areas on his lower abdomen and forearms after the second infusion of rituximab. Based on coagulation factors evaluation, he was diagnosed with AHA. Treatment with factor VII led to the improvement in his coagulation status, but unfortunately, he passed away because of inferior wall myocardial infarction four days later.

Introduction

A

quired Hemophilia (AHA) is a relatively rare disease that occurs in patients with no previous family history of hemophilia. Its incidence is approximately 1.5 per million each year. Although the exact patho-

genesis of this condition is unclear, the spontaneous development of autoantibodies (IgG1 and IgG4) against factor VIII has been reported as the main cause. These antibodies interfere with the coagulant activity of factor VIII that presents with spontaneous hemorrhage into the skin, muscle, and soft tissue [1]. About half of the cases of AHA are associated with autoimmune diseases, pregnancy, malignancy,

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and drug reactions and the remaining 50% are idiopathic [2]. Among autoimmune diseases, some autoimmune bullous skin diseases, including bullous pemphigoid, pemphigus vulgaris and pemphigus foliaceus have been reported in association with AHA [3]. To the best of our knowledge, only 21 cases of AHA with skin autoimmune bullous diseases have been reported so far [4, 5]. Due to the rare nature of this association and the importance of correct recognition of the disease, we report a patient with the previous history of pemphigus vulgaris who developed AHA in the course of the disease.

Case Presentation

A 63-year-old man presented to the emergency room with the complaint of fatigue, weakness, and altered mental status for 2 weeks. He had been diagnosed with pemphigus vulgaris 11 months before based on clinical symptoms, histology findings, and laboratory exams. He had been treated with 1 mg/kg of prednisolone for two weeks at the time of diagnosis. The prednisolone had been gradually tapered and he was receiving 10 mg/day of prednisolone starting four weeks before admission. He had also received two infusions of intravenous Rituximab 375 mg/m² every week for the past two weeks. After the second infusion, which was two weeks before admission, he had developed weakness and fatigue plus altered mental status. On physical examination, he was found with large, painless ecchymosis on the lower abdomen and both forearms (Figures 1A & B) and a crusted erosive nodule on his lower lip

(Figure 2). He was then transferred to the emergency room for further evaluation.

In his previous medical history, he reported poorly controlled diabetes, ischemic heart disease, and angioplasty of two coronary vessels. His lab results were HbA1C of 6.7 mg/dl, fasting blood sugar of 118, and normal arterial blood gas, and his blood chemistry profile was normal.

Investigation of laboratory work revealed markedly prolonged Activated Partial Thromboplastin Time (APTT) of 120.0 s (reference range: 25-36 s) and International Normalized Ratio (INR) of 7.8 (normal range below 1.1), while platelets remained normal at 412/000 μ L (reference range, 145 000-400 000 μ L). Also, hemoglobin had decreased from 12 g/dl to 8.1 g/dl (reference range, 11.3-14.0 g/dl) within two days.

These clinical and laboratory findings were consistent with AHA. A clotting screen revealed factor VIII levels of 0 (reference range, 50%–150%) and positive factor VIII inhibitor assay on Bethesda testing (285 Bethesda with normal range <0.4). These findings confirmed the diagnosis of an AHA.

Computed tomography did not show any evidence of internal malignancy in the brain, trunk, and abdominopelvic area, but demonstrated a large hematoma in the lower abdomen. The patient was treated with oral steroids and infusion of factor VIII for 4 days, which resulted in the correction of his coagulation profile.



Figure 1. Cutaneous presentation of acquired hemophilia

A: Painless ecchymosis on the lower abdomen of the patient with pemphigus vulgaris; and B: Ecchymosis on both forearms.



Figure 2. Crusted erosive nodule on the lower lip consistent with pemphigus vulgaris

However, four days after the correction of the coagulation profile, the patient had a massive inferior wall myocardial infarction and unfortunately passed away. This was due to previous ischemic heart disease and poorly controlled diabetes.

Discussion

Herein, we described a rare case of AHA associated with pemphigus vulgaris, which was also caused by autoantibodies against specific skin proteins, desmoglein 1 and 3. Few cases of this association have been described in the literature but the exact characterization of the autoantibodies has been limited and recognition of additional cases is necessary to have a better understanding of this coexistence.

Pemphigus vulgaris is a chronic autoimmune disease resulting from the production of autoantibodies against desmogleins, which are transmembrane glycoproteins of the cadherin (calcium-dependent cell adhesion molecule) family and are the antigens that have been most extensively studied in pemphigus vulgaris and pemphigus foliaceus. Desmogleins are components of desmosomes, integral structures for cell-to-cell adhesion [6].

AHA is a very rare coagulation deficiency disease caused by the production of anti-factor VIII IgG antibodies. The main clinical presentation of AHA is widespread purpura in the skin and hematomas in soft tissues. If this bleeding occurs in multiple organs, AHA can be life-threatening [1]. Therefore, proper diagnosis and management of AHA are essential.

The diagnosis of AHA is based on clinical presentation and laboratory results, including increased APTT, decreased factor VIII activity, and the existence of fac-

tor VIII inhibitors. These factor VIII inhibitors are mainly composed of the IgG4 subclass [3]. Our patient had laboratory results consistent with AHA. Regarding the association of AHA with internal malignancies, computed tomography was performed for the patient and was negative for any internal malignancy.

Half of the patients with AHA have underlying disorders, including malignant tumors, pregnancy or postpartum, drug reactions, autoimmune disorders, and skin diseases (2-8.3%), such as psoriasis and pemphigus [7]. An association has been demonstrated between autoimmune bullous dermatoses and bullous pemphigoid, linear IgA disease, pemphigus foliaceus, and pemphigus vulgaris. In our patient, AHA and autoimmune bullous dermatosis were associated.

Rare cases of pemphigus vulgaris have been reported with AHA. The main hypothesis of AHA in these patients is the development of autoantibody cross-reactivity between anti-desmoglein 1 and 3 antibodies and FVIII epitopes.

Treatment modalities for AH include activated prothrombin complex concentrate and activated recombinant factor VII. In addition, immunosuppressive therapy is also useful in reducing the production of factor VIII inhibitors, such as prednisolone, cyclophosphamide, and cyclosporine. Rituximab (anti-CD20 monoclonal antibody) has also been tried and reported effective [8].

Although our patient had received rituximab and prednisolone for the treatment of pemphigus vulgaris, he had developed large ecchymosis on his flanks and abdomen and laboratory examination had confirmed the diagnosis of AHA. Also, the infusion of factor VIII led to an improvement in clinical and laboratory findings.

This association between AHA and autoimmune bullous dermatosis must be considered in any sudden drop of hemoglobin or spontaneous bleedings in patients with autoimmune disease. Regarding the documented mortality rate of 8% to 42% [5], early detection and proper management of the patient are crucial.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

Authors' contributions

All authors equally contributed in preparing this article.

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Conflict of interest

The authors declared no conflict of interest.

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