

## A Little Known but Potentially Life-threatening Association of Bullous Pemphigoid and Acquired Hemophilia: Case Report and Review of the Literature

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### Abstract

While bullous pemphigoid has been associated with a number of medical conditions and drugs, the link with acquired hemophilia (AH) has not been widely reported. AH is a rare yet life-threatening autoimmune disorder with an estimated mortality rate ranging from 8-22%. A PubMed search revealed fifteen cases of AH reported in patients with bullous pemphigoid (BP). Here we describe an additional case of BP in a 49-year-old female who later developed AH, and review the evidence behind this association.

**Keywords:** Bullous pemphigoid; Acquired hemophilia; Factor VIII inhibitor; Sulphonamide-induced hypersensitivity

### Introduction

Acquired hemophilia (AH) is a rare yet fatal autoimmune disorder with an estimated mortality ranging from 8-22%. Most common associations with AH are pregnancy (post-partum), autoimmune disease, malignancy, and drugs [1]. Bullous pemphigoid (BP) is the most common blistering disease, with an incidence estimated at 4.3 per 100,000 [2]. To date, only fifteen cases have been reported of AH occurring in patients with BP. The pathophysiologic mechanism is unclear at this time; however, the leading hypothesis is epitope homology between BP and AH. Here we review all previous cases, describe an additional case of BP in a 49-year-old female who later developed AH, and review the evidence behind this association.

### Case

A healthy 49-year-old Latina female developed intense pruritus on the lower legs over several weeks, followed by a worsening bullous rash. She reported a history of taking trimethoprim-sulfamethoxazole for presumed cellulitis 3 weeks prior to developing the rash. Physical exam revealed numerous tense bullae scattered on the trunk and extremities. Initial skin biopsy revealed subepidermal split with mixed inflammation consisting of eosinophils, neutrophils and lymphocytes, but with a negative direct immunofluorescence for IgG, IgM, IgA and C3. Despite this, she was given a presumed diagnosis of BP and started on oral prednisone at 1 mg/kg/day, with minimal response. IVIG therapy was subsequently added. With this combination therapy, the patient's skin greatly improved with near clearance of her bullous lesions, however directly after the patient's second IVIG infusion she acutely developed dysphagia and was admitted to the hospital where she was found to have hematemesis from esophageal erosions. This admission was four months after the initial onset of bullae. Several days after admission, she developed rebound abdominal tenderness. Her CT showed a retroperitoneal hematoma in the right abdominal sidewall extending down to the right pelvis. Her coagulation studies at that time revealed PTT 51.8 seconds (normal: 25-35 seconds), FVIII activity of 2% (normal: 60-150%), and positive FVIII inhibitor at 10 Bethesda units (normal: <1 Bethesda units/ml). She did not use anti-coagulants and had no personal or family history of bleeding disorders.

Despite FVIII infusions at doses of 1000 to 2000 units TID, cyclophosphamide 150 mg daily and varying doses of IV and oral

steroids, her hemoglobin continued dropping, and she required multiple transfusions. Although angiography found no active sites of bleeding, empiric transcatheter embolization of the right inferior epigastric artery was performed.

She was transferred to a tertiary care center given the severity of her disease. Upon arrival, her PTT was 56.4 seconds, FVIII activity of 6.25%, and positive FVIII inhibitor was 17.0 Bethesda units. She was treated with Factor Eight Inhibitor Bypassing Activity (FEIBA), cyclophosphamide, and high-dose corticosteroids for acquired hemophilia. Her skin examination revealed a few small tense blisters on her lower extremities and post-inflammatory changes suggestive of more extensive prior blisters (Figure 1). A skin biopsy performed on perilesional skin showed 3+ linear depositions of IgG and C3 along the basement membrane, consistent with a diagnosis of BP. These clinical and laboratory findings indicated AH in the setting of BP.

She was continued on cyclophosphamide 150 mg daily for 3 more weeks and then weaned to every other week. During this time, she was also treated with daily oral prednisone at 1 mg/kg/day. Her coagulation studies normalized during this time, with PTT 31.8 seconds, Factor VIII activity level 152%, and Factor VIII inhibitor 0 Bethesda units. Skin examination showed some residual BP activity with only a few small (2-4 mm) tense bullae in her lower left leg, as well as post-inflammatory hyperpigmentation in the locations of prior bullae.

### Discussion

BP is the most common blistering disease with an incidence of up to 4.3 per 100,000 based on a United Kingdom cohort study [2].

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Received November 02, 2012; Accepted November 27, 2012; Published December 04, 2012

Citation: Nguyen C, Gordon JS, Chang ALS (2012) A Little Known but Potentially Life-threatening Association of Bullous Pemphigoid and Acquired Hemophilia: Case Report and Review of the Literature. J Clin Exp Dermatol Res S6:003. doi:10.4172/2155-9554.S6-003

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**Figure 1:** Lower extremity of patient shows small intact blister (arrow) in background of post-inflammatory changes indicative of extensive prior bullae. Purpura and petechiae in linear pattern is also seen in areas of scratching, indicative of her coagulation deficiency.

An estimated 20% of cases include involvement of oral mucosa and it is rare to involve the pharynx or larynx [3]. BP is caused by autoantibodies against bullous pemphigoid antigens 1 or 2 of the hemidesmosome (BPAG1 and BPAG2), resulting in subepidermal separation at the dermoepidermal junction. The classic histologic changes are characterized by a subepidermal split associated with a superficial dermal infiltrate containing many eosinophils. While a positive DIF test has been found in 70-80% patients, with C3 and IgG most commonly deposited at the basement membrane, a positive test may only be found after repeated biopsies, as was the case here. While our patient did take trimethoprim-sulfamethoxazole prior to blistering, there are no reports of BP associated with this drug exposure.

Acquired hemophilia is a rare bleeding disorder occurring in 1 to 4 per million each year. It is caused by autoantibodies against FVIII. Commonly reported associations with AH include pregnancy (post-partum) [4], autoimmune disease, malignancy, and drugs. Up to 90% of AH presents with bleeding events that often require transfusion [1]. When associated with erosions of the skin due to BP, there is a potential for bleeding that is difficult to detect, especially if it involves the larynx, pharynx, or in this case, the esophagus.

Since our patient received trimethoprim/sulfamethoxazole before the onset of these conditions, it is worth noting that sulphonamide-induced hypersensitivity is a known cause of AH [5]. Anticonvulsants and antibiotics, particularly penicillin, sulfonamides and chloramphenicol have well-established associations with AH [6]. However, our patient's bullae persisted 6 months after she stopped taking the sulphonamide, and AH did not occur until 4 months after sulphonamide exposure, making it unlikely that it contributed to the development of her BP and subsequent AH.

To date, 15 cases reported of AH in patients with BP have been reported in the literature [5,7-20], but the timing of disease onset between AH and BP has not been delineated. We performed our

own review of the cases, including our current case, and found that BP occurred before AH in 11 cases (ranging 4 weeks to 3 years prior), AH before BP in 2 cases (ranging 4 months to 3 years prior), and simultaneously in 3 cases [5,7-20]. Hence, the clinical diagnosis of BP occurred prior to AH in the majority of cases.

To date, the pathophysiologic mechanism linking the two entities is unclear. One previously reported case demonstrated that a patient with BP possessed an IgG antibody that could recognize a FVIII inhibitor. In that report, investigators were able to show through immunoblotting and immunonephelometric methods the presence of the IgG subclass (IgG4 and IgG1, IgG4 predominantly) inhibitor against the 44KD FVIII: C A2 domain. A second case reported showed no homologous sequences between BP and AH epitopes in a protein database search, however this patient had a background of additional underlying autoimmune diseases [5,16].

In reviewing the treatment response in the prior 15 cases of BP and AH, 7 cases reported BP resolved before the onset of AH, 5 cases reported BP resolved with treatment for AH, and in 3 cases it was unclear if BP resolved with treatment of AH. It is therefore unclear if treating BP (should it appear prior to AH) decreases the risk of subsequent AH development. Once AH develops, it is not unexpected that BP improve with AH treatment because chronic immunosuppression is standard therapy for both diseases.

Our patient did not respond to FVIII infusions but immediately achieved hemostasis with FVIII inhibitor bypassing agent (FEIBA) and immunosuppression using prednisone and cyclophosphamide. While many other immunosuppressant medications are often used to treat BP in place of cyclophosphamide, the goal in our patient was to achieve rapid hemostasis, and cyclophosphamide was chosen based on the recommendations of the hematology service at our hospital for treatment of the acquired hemophilia. The patient was continued on cyclophosphamide at 150 mg daily for 3 weeks and 150 mg every other day for one week. Her prednisone was continued at 60mg daily for 3 weeks. She is currently on a tapering dose of prednisone and continues to do well without any bleeding complications. Her BP significantly improved upon treatment of her AH with only occasional new vesicle formation.

In conclusion, AH in patients with BP is a rarely reported, but potentially life-threatening circumstance given the risk of significant bleeding at sites of epithelial erosion. Future research may shed light on the pathophysiologic link between these two disease entities.

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This article was originally published in a special issue, [Dermatology: Case Reports](#) handled by Editor(s). Dr. Anetta Reszko, Cornell University, USA