CLINICAL CASE

ACQUIRED HEMOPHILIA A IN A PATIENT WITH PEMPHIGUS VULGARIS

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ABSTRACT

Pemphigus vulgaris is a rare autoimmune disorder involving painful blisters and erosions on the skin and mucous membranes caused by antibodies directed against desmoglein 1 and 3. Acquired hemophilia A (AHA) is a relatively rare coagulation disorder caused by the spontaneous presence of anti-factor VIII immunoglobulin G antibodies (IgG1 and IgG4), known to cause spontaneous clinically significant hemorrhages into the skin and soft tissues in patients with no previous known diagnosis of bleeding disorders. This coagulopathy has been described in conjunction with autoimmune bullous skin diseases, malignancies, and drug reactions. Only a few cases of such interaction have been documented, we herein report a case of a 50-year-old woman with a history of pemphigus vulgaris who has developed extensive ecchymosis on her right arm and right calf. A diagnosis of AHA was made considering the modified coagulation tests. Initiation of treatment with factor VIII led to clinical improvement, however, the patient stopped showing up for further follow-ups.

KEYWORDS: *hemophilia A; Acquired hemophilia; pemphigus vulgaris*

INTRODUCTION

Pemphigus vulgaris is an autoimmune disease with antibodies against desmoglein 1 and desmoglein 3, causing blisters and erosions of differing sizes at skin and mucous membranes levels. In the majority of cases, it occurs in middle-aged or elderly people, rarely affecting children [1]. Acquired hemophilia A (AHA) is a rare coagulation disorder, having an incidence of approximately 1 per million every year, arising in patients with no known familial cases of coagulation disorders. The exact pathogenesis is not clearly defined, however, the spontaneous accumulation of antibodies against factor VIII has been described as the main pathogenesis mechanism, leading to life-threatening hemorrhages at the skin and mucosal level [2]. AHA has been associated with malignancy, pregnancy, and autoimmune diseases including autoimmune bullous skin diseases [3]. Taking into consideration the rare occurrence of AHA with an autoimmune bullous skin disease, we report a case of AHA developed in a patient with a known history of pemphigus vulgaris in the course of treatment.

CASE PRESENTATION

A 51-year-old woman diagnosed with pemphigus vulgaris in May 2021 was admitted to the Department of Dermatology on August 2021 due to extensive exacerbation of skin lesions with multiple painful well-demarcated post-bullous erosive lesions with hemorrhagic crusts and oozing erosions on an erythematous base at the level of the scalp, superior and inferior limbs, trunk and mucosal membranes (oral, genital, conjunctival) and sudden emergence of ecchymosis on the right upper and lower limb. The patient affirms the debut of cutaneous lesions in December 2020 with an initial localized cervical lesion, subsequently with extension and aggravation of lesions. She had been treated with corticosteroids (prednisone 40 mg/day) with periods of clinical improvement but with worsening lesions on attempting to reduce the corticosteroid dose. An attempt was made to introduce an immunomodulatory drug (Azathioprine 50mg/day – normal TPMT activity), however, the patient showed a significant decrease in the number of leukocytes in the context of the treatment, leading to the decision of stopping the treatment.

In her previous medical history, she is known for hypothyroidism in treatment with Levothyroxine, chronic venous insufficiency, hypertension, and a severe depressive episode.

Physical examination was normal, except for the skin lesions. On clinical examination of the skin, the patient presented with well-defined post-bullous erosive lesions, mostly covered with hemorrhagic crusts, some converging into plaques and placards, painful, located on the scalp, upper and lower limbs, thorax, and mucous membranes as well as some post bullous hyperpigmented lesions at the level of the trunk and limbs (Figure 1). Besides, the patient was found with a large and painless ecchymosis on the right arm and right calf (Figures 2 and 3).

Routine blood work revealed: leukocytosis with neutrophilia and a prolonged APTT (Table 1). Due to the relatively poor evolution of the disease on corticosteroids, a suspicion of paraneoplastic pemphigus vulgaris was raised and a thoracoabdominal CT scan was performed which ruled out any paraneoplastic origin. A hematological consult was requested and a diagnosis of AHA was made based on the abnormal coagulation labs (APTT=82.3 s, FVIII 1%) for which the patient is prescribed factor eight inhibitor bypassing activity (Feiba 80 UI/kg at 2 days interval). On hematological reevaluation, the patient presents with corrected APTT = 34s, FVIII= 9.8%, and inhibitor titer= 0.5 BU and it is decided to take the patient off Feiba, continuing only with corticosteroid therapy with the recommendation of APTT and FVIII reevaluation after discharge.

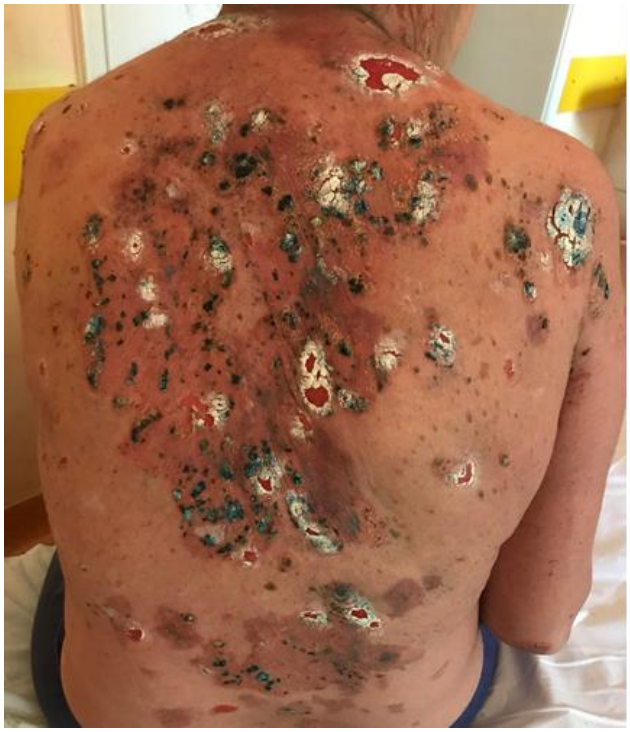

Figure 1 – Post-bullous erosive lesions, mostly covered with hemorrhagic crusts along with post bullous hyperpigmented lesions

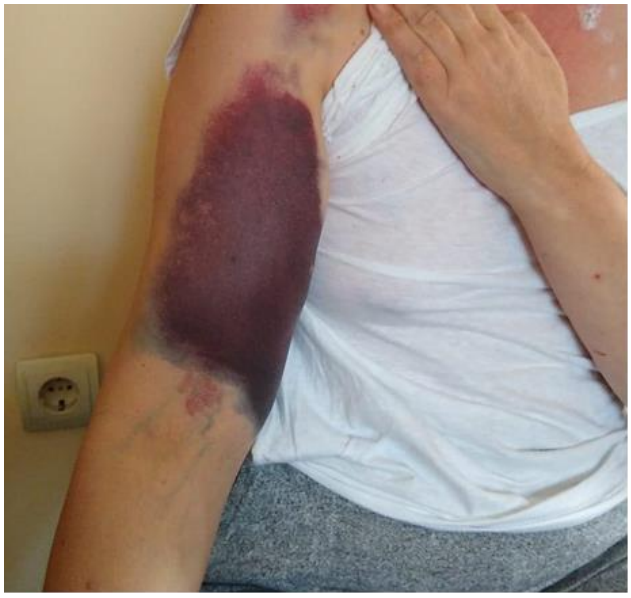

Figure 2 – Painless ecchymosis on the right arm of the patient with pemphigus vulgaris

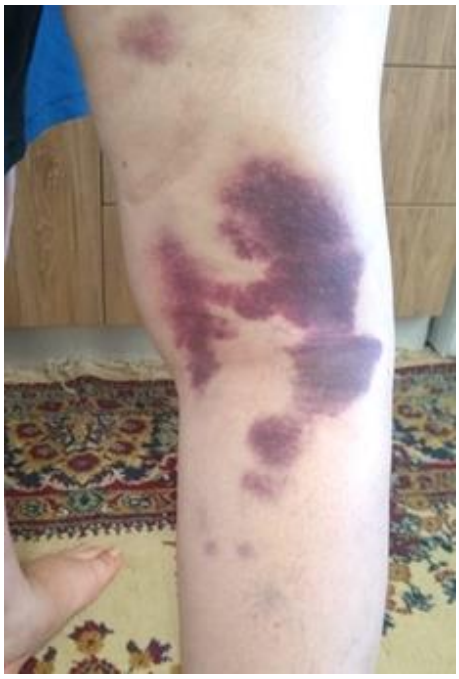

Figure 3 – Ecchymosis on the right calf

The patient initially followed a course iv Dexamethasone 12 mg/day, subsequently followed by oral administration of Dexamethasone with slow dosage tapering. She had also received iv 3rd generation cephalosporin. The systemic treatment was complemented with local therapy with dermatocorticoids and emollients.

On discharge, on top of the Dexamethasone therapy, the patient was prescribed injectable Methotrexate 15 mg/week subcutaneously.

Unfortunately, the patient had not returned to the hospital for further reevaluations and we are not aware of how her disease progressed.

Parameter	Values
VSH 1h	12 mm/1h (0-20)
Fibrinogen	299 mg/dL (238-498mg/dL)
Hemoglobin	11.3 g/dL (11.7-15.9 mg/dL)
Platelets	$321*10^3$ /µl (150-400 /µL)
Neutrophils	$9.95 *10^3$ /µL (2-7)
Leukocytes	$13.47*10^3$ /µL (4.6-10.2)
Creatinine	0.76 mg/dL (0,83)
Urea	52.61 mg/dL (15-50)
ALT	15 U/L (9-52)
AST	17 U/L (14-36)
APTT1(sec)	69.5 (30-40)
PT (sec)	11 (11-13.5)
INR	0.93

Table 1 – Blood works

DISCUSSIONS

Pemphigus vulgaris along with bullous pemphigoid, pemphigus foliaceous, linear IgA bullous dermatosis, and epidermolysis bullosa acquisita have all been reported to be coexisting with AHA, however, this correlation is rare in literature [4-7]. We, therefore, describe a case of pemphigus vulgaris associated with AHA.

Pemphigus vulgaris is a chronic autoimmune bullous dermatosis that leads to the formation of autoantibodies against the desmosomal cadherins desmoglein 1 and desmoglein 3 [8]. Patients with pemphigus vulgaris present with significant morbidity and mortality rates as well as a significant deterioration in the quality of life [9,10].

AHA is a rare coagulation disorder mediated by the production of IgG autoantibodies against factor VIII, impairing its function and leading to spontaneous widespread skin purpura and soft tissue hematomas, frequently being life-threatening [2]. AHA diagnosis is commonly made on the clinical manifestation along with laboratory investigations. The common presentation of AHA is with isolated prolongation of APTT, a reduced F VIII activity, presence of FVIII inhibitors, and normal prothrombin time and fibrinogen concentration. Factor VIII inhibitor is proven by an abnormal APTT correction test; however, the inhibitor titer doesn't correlate with hemorrhage severity [11-13]. In AHA, increased age, multiple comorbidities, underlying malignancy, and high titers of FVIII inhibitor have been correlated with poor prognosis and increased risk of death [14].

Treatment options for AH should be centered on both diminishing the bleeding episodes as well as lowering the inhibitor titer. The main therapeutic approach taking into consideration both pemphigus vulgaris and AHA is oral corticosteroids. Specific treatments for AHA include activated prothrombin complex and activated recombinant factor VII. As in the case of our patient, a bypassing agent (FEIBA or rF7a) may be attempted as the main therapeutic approach, however, in case of failed therapy, a combination of therapies may be effective [15]. Additionally, immunosuppressive agents such as prednisolone, cyclophosphamide, and azathioprine are known to be effective in

reducing FVIII inhibitors production. Successful eradication of FVIII inhibitors has also been documented with the usage of rituximab [16,17]. It has been reported that relapse will occur in around 20% of the patients within 1 week to 14 months after immunotherapy cessation, therefore, follow-up over a long period of time is compulsory in such patients [18]. Unfortunately, our patient failed to present herself for further follow-up.

CONCLUSIONS

In conclusion, diagnosing a patient with AHA may be challenging and should be taken into consideration when a patient with no personal or familial history of bleeding, presents with hemorrhage of recent onset, accompanied by an isolated prolongation of APTT, more so if the patient is known with an autoimmune disease. Early detection and proper management are crucial considering the high morbidity and mortality rates.

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