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A rare case of acquired A haemophilia associated with bullous pemphigoid complicated by cerebral fungal abscesses and multiple opportunistic infections

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Abstract

Acquired A Haemophilia (AHA) is a rare autoimmune disease caused by production of anti VIII factor's antibodies that could cause multiple haemorrhagic manifestations. Usually idiopathic, could be related with other conditions, such as Bullous Pemphigoid (BP), an autoimmune dermatologic disease.

We report a case of a 77-year-old man with a recently diagnosed BP that was admitted to our ward for haemorrhagic diathesis. After the diagnosis of AHA was treated with immunosuppressive therapy, with improvement of the haemorrhagic manifestations but with onset of multiple opportunistic infections, including candidemia with multiple cerebral abscesses, that caused the exitus of the patient.

Immunosuppressive therapy is an effective treatment for both AHA and BP but could cause also opportunistic infections that must be treated promptly. To our knowledge, the onset of fungal abscesses in these patients was never reported before.

Keywords

Acquired A haemophilia; Bullous pemphigoid; Candidiasis; Cerebral abscesses; Fungal abscesses; Opportunistic infections.

Abbreviations

AHA: Acquired A Haemophilia; FVIII: anti VIII factor; aPTT: activated Partial Thromboplastin; BP: Bullous Pemphigoid; CMV: Cytomegalovirus; CPAP: Continuous Positive Airway Pressure; CT: Computed Tomography; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging; PT: Prothrombin Time.

Introduction

Acquired A haemophilia (AHA) is very rare autoimmune disease (incidence 1 person per million/year) caused by the production of anti VIII factor (FVIII) autoantibodies. It is mostly idiopathic, but it can be associated with elderly, pregnancy or neoplastic, infectious or autoimmune diseases. The diagnosis is confirmed by isolate prolongation of aPTT time, reduced levels of FVIII and the detection of anti FVIII antibodies [1]. Bullous pemphigoid (BP) is also an autoimmune bullous disease of the skin caused by production of autoantibodies against proteins (BP230 antigen and BP180 antigen) of hemidesmosomes of dermo-epidermic junctions and seldom could be associated with AHA.

We report a rare case of AHA associated with BP treated with immunosuppressive therapy complicated by several opportunistic infections, including CMV related pneumonia and Candidemia with multiple fungal brain abscesses. To our knowledge, this is the only case of candida related brain abscesses reported in literature in this category of patients.

Case Presentation

A 77-year-old man was admitted to our ward because of severe epistaxis, diarrhea and bleeding skin lesions. In his past medical history, he has a recently diagnosed bullous pemphigoid in treatment with oral prednisone and type 2 diabetes.

The physical examination was unremarkable except for the presence of diffused bullous pemphigoid lesions. Blood exams showed only moderate normocytic anaemia (7.8 g/dL), mild leucocytosis (10.900/μL), prolongation of aPTT ratio (1.4) and increased reactive-C-protein serum levels (3.8 mg/dL). Chest and abdominal X -rays, stool culture and Clostridium Difficile antigen on stool were negative. The patient was treated with blood transfusions and endovenous fluids and he was then admitted to our ward. During hospitalization, the patient showed a haemorrhagic diathesis (melena, epistaxis, haematuria, skin bleeding from the pemphigoid lesions and multiple subcutaneous hematomas) with consequent severe anaemia (Hb up to 6.6 g/dL) requiring further blood transfusions.

The patient underwent an esophagogastroduodenoscopy and colonoscopy which were negative for both active bleeding sites and neoplastic lesions, as well as an unremarkable abdominal ultrasound. Conversely, a video laryngoscopy showed a voluminous oropharyngeal vegetating ulcerated bleeding lesion which was not biopsied because of the poor patient's general conditions.

Blood exams confirmed an isolate prolongation of aPTT ratio with normal prothrombin time and the dosage of single clotting factors showed a reduction of VIII factor with the presence of anti VIII factor's antibodies, configuring the condition of acquired A haemophilia. A treatment with high dose steroid was started endovenously (1 mg/kg methylprednisolone). In addition, a treatment with activated eptacog alpha (Novoseven®) firstly, and then with anti-inhibitor coagulant complex (Feiba®), was administered with improvement in both the haemorrhagic diathesis and the skin bullous lesions.

After 16 days of hospitalization, the patient developed a bilateral interstitial pneumonia sustained

by CMV and requiring high flow oxygen supplementation and CPAP cycles, so that intravenous ganciclovir was started. In addition, analysis of the sputum found positivity for Pneumocystis Jirovecii DNA (along with increment in beta-D-glucan serum levels), so intravenous cotrimoxazole was added. In the next weeks there were a progressive improvement in respiratory exchanges and of clinical conditions. A new video laryngoscopy aimed at identifying the nature of the oropharyngeal lesion was performed, showing complete remission, speculating on a possible localization of bullous pemphigoid.

Unexpectedly, the patient developed confusion along with fluent aphasia. The EEG was negative, but both a brain CT scan and MRI, showed left temporal lesion with perilesional oedema suspicious for cerebral abscess. Haemocultures were sent and a treatment with meropenem and acyclovir was started. At blood test herpes-simplex virus DNA was negative, but levels of beta-D-glucan (>900 ng/L) and galactomannan antigen (6.800) were very high, suggesting the diagnosis of multiple fungal cerebral abscesses, so that a treatment with liposomal amphotericin B was promptly started. However, the patient rapidly worsened, until the exitus two days later. Some days after the death, the haemocultures positivized for Candida Albicans.

Discussion

We report a very complex case of AHA secondary to BP, where treatment of both disease with immunosuppressive therapy led to the onset of several opportunistic infection, mainly fungal, which were fatal to our patient. Indeed, despite high dose steroidal therapy controlled the disease, however infections are frequent adverse events. In our case, despite an accurate diagnostic pattern aimed at identifying the source of infection and at starting an adequate antimicrobic treatment, the rapidly subsequent infections in a long-term hospitalized and fragile patients could have, possibly, caused the exitus.

In literature to our knowledge are described only 32 cases of AHA associated with BP, and large databases of AHA patients report an incidence of BP in AHA around 2.1% [2]. Interestingly, BP is usually diagnosed few months before the onset of AHA, as reported in our case [3]. The pathophysiology of the association between these two diseases is not fully understood, but a cross-reactivity between specific regions of BP's autoantibodies (in particular BP180 collagen XVII domain) and FVIII's epitopes is hypothesized [2]. As suggested by guidelines, our patient was supported with blood transfusions and a treatment for bleeding control with recombinant factor VII activated (Novoseven®) and activated prothrombin complex concentrate (Feiba®), whereas the replacement therapy with recombinant FVIII was avoided due to high antibodies titer [1]. In a minority of patients AHA could cause the death of patients consequent to comorbidities, older age, high antibodies titers (≥20 BU/mL) and opportunistic infections related to immunosuppression, as in our case [3].

Indeed, immunosuppressive therapy could be associated with neutropenia, infections or sepsis, with a mortality up to 4 % [1], as our patient who developed severe multiple infections as CMV and Pneumocistis Jirovecii pneumonia and finally candidemia by Candida Albicans associated with multiple fungal brain abscesses.

In literature only few cases of deaths due to infective complications during immunosuppressive treatment of AHA and BP are reported. Gupta et al. reported the case of a 84-year-old woman who responded well to immunosuppressive treatment with cyclophosphamide and dexamethasone but who died for multiorgan failure in sepsis [4], whereas Zhang et al of a 88-year-old man successfully treated with intravenous methylprednisolone and rituximab but who developed a fatal pneumonia [5].

To our knowledge this is the first case in literature describing an opportunistic infection characterized by multiple fungal abscesses by Candida consequent to candidemia in a patient with AHA and BP treated with immunosuppressive therapy.

In conclusion, AHA associated with BP is a very rare condition and the treatment with immunosuppressive drugs is effective, but it could be related with opportunistic infections that could be life-threatening, as in our patient. Furthermore, it is important to stress that in immunocompromised patients, along with multi-resistant bacterial and viral infections, fungal ones need to be taken into great account and require to be promptly treated to avoid a poor prognosis.

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