

# Localized bullous pemphigoid associated with multiple milia formation - an atypical presentation

Corina Baican, Elisabeta Candrea, Adrian Baican, Alina Vasilovici, Daniela Vornicescu, Sorina Danescu

<sup>1</sup>Department of Dermatology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

**Abstract.** Bullous pemphigoid is an autoimmune blistering disease associated with autoantibodies targeting proteins of the hemidesmosomal anchoring complex. This report describes the first patient with localized pretibial bullous pemphigoid that presents milia associated with the blisters. The levels of autoantibodies to the BP180-NC16A domain were low. However, cutaneous lesions responded only at systemic corticosteroids and immunosuppressive drugs.

**Key Words:** bullous pemphigoid, collagen XVII, autoimmunity, direct immunofluorescence, milia.

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**Corresponding Author:** A. Baican, e-mail: adrianbaican@yahoo.com

## Introduction

Bullous pemphigoid (BP) is an organ-specific autoimmune disease of the skin characterized by autoantibodies against the transmembrane hemidesmosomal antigens BP180/collagen XVII and the intracellular plakin BP230 (Ottens et al 2014). The disease usually occurs in elderly and represents the most common autoimmune blistering disease in Western Europe. The overall incidence of BP ranges from 0.22 to 4.3 new cases/100 000 inhabitants/year. In our country the incidence of BP is 0.25 cases/100 000 inhabitants per year (Baican et al 2010). This lower incidence could be explained by a particular genetic susceptibility, a shorter life expectancy in Romania or an underdiagnosis of BP in patients with atypical variants.

The clinical presentation is polymorphic. The disease usually presents with pruritic, tense bullae of 1-3 cm diameter which may arise on erythematous or apparently normal skin (Bağcı et al 2017). Several generalized or localized atypical variants of BP have also been described, including vesicular, vegetans, papular or nodular lesions without blisters, erythrodermic and toxic epidermal necrolysis-like BP (Bernard et al 2017). Localized pretibial pemphigoid, a rare variant of BP, was reported in approximately 1% of BP patients (Chang et al 1996).

Here, we report a patient with BP limited to the pretibial area showing numerous milia, scarring and cutaneous atrophy.

## Case report

A 60-year-old patient presented with a 5-month evolution of pruritic blisters to the bilateral pretibial legs. His medical history was significant for a cerebral stroke 3 years earlier.

Physical examination revealed tense bullae, erosions, milia, cutaneous atrophy on the pretibial area (Fig. 1a). Mucous surfaces were not involved. The patient was initially treated with topical corticosteroids for 2 months without any improvement. Laboratory tests showed elevated white blood cell at 22,000/ $\mu$ l (normal range: 4,000 - 10,000/ $\mu$ l). The blood chemistry and liver function were normal. Autoantibody testing revealed positive antinuclear antibody (1 :160, nucleolar pattern). Other tests as autoantibodies anti-nRNP/Sm, SS-A, dsDNA, Scl-70 and cardiolipin revealed normal values.

Biopsy of affected skin demonstrated a subepidermal blister, dermal unilocular cyst lined by stratified squamous epithelium and inflammatory infiltrate in the upper dermis (Fig. 2a). Direct immunofluorescence on perilesional skin revealed linear deposition of IgG and C3 at the basement membrane zone (Fig. 2b, Fig. 2c). Indirect immunofluorescence of 1 M NaCl normal human split skin showed that the patient's IgG antibodies reacted with the epidermal side of the split (Fig. 2d). In order to determine the levels of specific anti-BP180 and anti-BP230 autoantibodies, commercially available enzyme-linked immunoassay (ELISA) kits were used (MBL, Japan). ELISA was positive for BP180 (40 U/ml) and BP230 (10 U/ml). The cut-off value for positive levels of anti-BP180 and anti-BP230 autoantibodies was taken as  $\geq 9$  U/ml.

Oral prednisone 30 mg/day with azathioprine 100 mg/day for 2 months suppressed new blister formation. Thereafter, prednisone was tapered gradually and azathioprine was stopped after 3 months. During the follow-up period of 2 years, no recurrence of blisters or milia was detected (Fig. 1b).

The patient signed an informed consent form, that gives permission for the use of medical data and pictures.

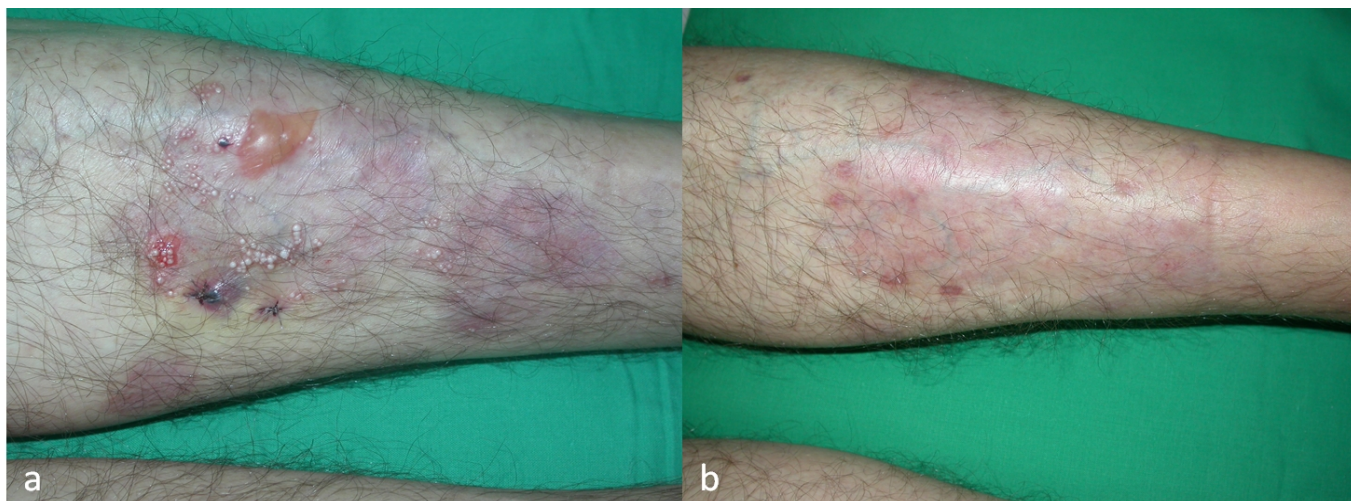


Fig. 1 (a) Tense blister, erosion and multiple milia of the pretibial region. (b) complete regression of the lesions after 3 months of systemic treatment

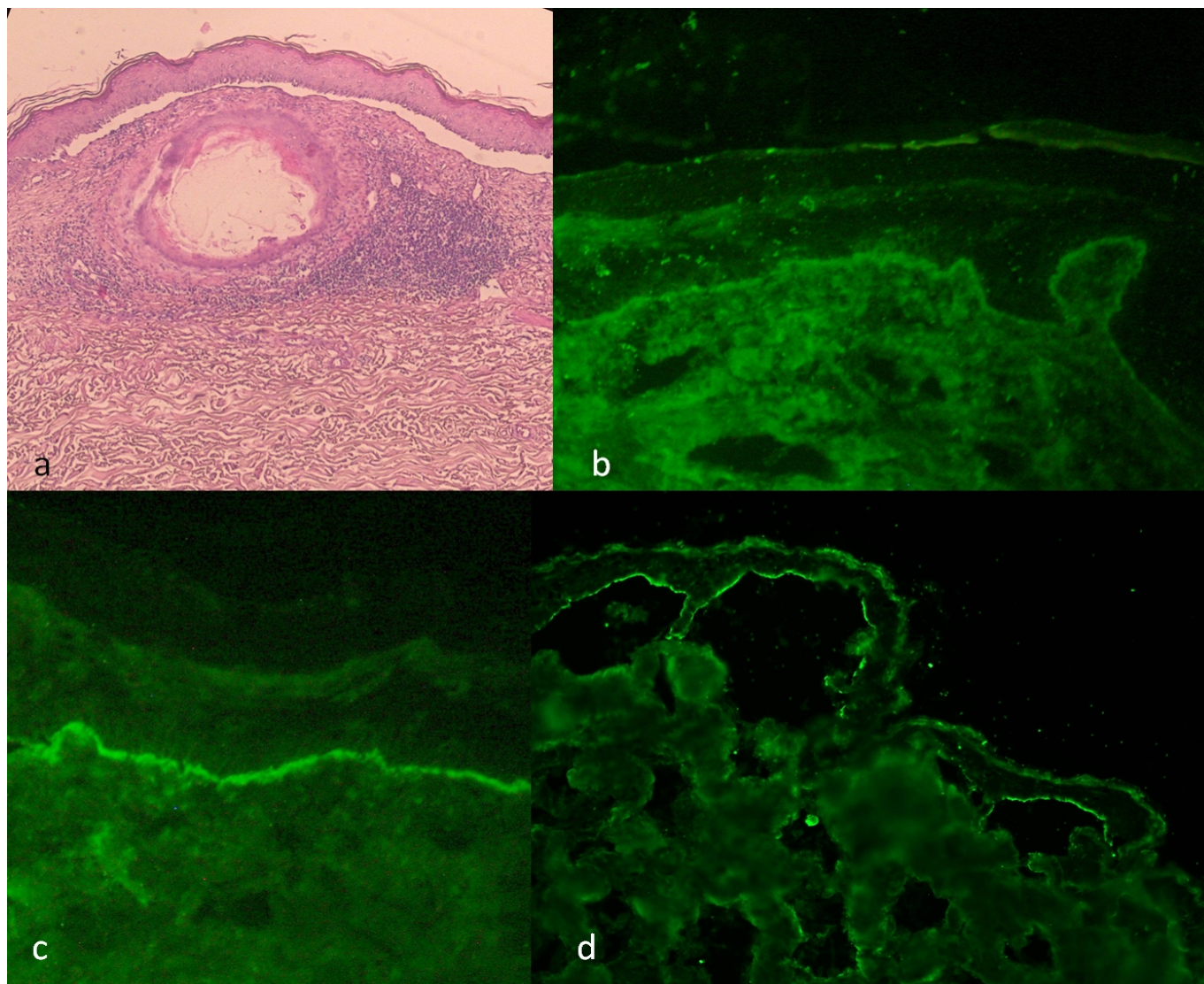


Fig. 2 Skin biopsy reveals: (a) Histopathological features showing subepidermal bulla, dermal unilocular cyst lined by stratified squamous epithelium and inflammatory infiltrate in the upper dermis (H&E x10); Direct immunofluorescence showing linear IgG (b) and C3 (c) deposition at the basement membrane zone. (d) Indirect immunofluorescence of 1 M NaCl-split normal human skin showing IgG reaction to the epidermal side of the cleft.



## Discussion

Coexistence of milia and blisters is a rare feature of BP. The clinical presentation was reminiscent of porphyria cutanea tarda but the patient do not have other hallmarks such as photodistribution of the eruption or scleroderma-like changes. Our patient mimicked also mechanobullous variant of epidermolysis bullous aquisita marked by skin fragility. The differential diagnosis is based on the combination of clinical features, histopathology, direct immunofluorescence, indirect immunofluorescence on 1 M NaCl-split normal human skin and ELISA. Detection of immune deposits on the epidermal side of the blister and circulating autoantibodies targeted against BP180 NC16A and BP230 proteins confirm the diagnosis (Bağci et al 2017).

Milia formation in BP is rare, only several cases have been reported (Ding et al 2017, Kumudhini et al 2018, Tsuruta et al 2013). Milia are small superficial cysts containing keratinous material, enveloped by stratified epithelium. The lesions can arise spontaneously without any known cause or they can be secondary to various processes. Clinical variants of primary milia are congenital, milia en plaque, nodular grouped milia, multiple eruptive milia and nevus depigmentosus with milia. Among secondary milia, there are several variants, including genodermatosis, bullous disease, trauma and medication (Berk et al 2008). The regeneration process of disrupted sweat glands or hair follicles might be involved in milia formation. Recently, Uchida et al. reported a refractory BP case leaving numerous milia during recovery. The occurrence of milia secondary to blisters might have been due to aberrant interaction between the hemidesmosomes and the extracellular matrix components beneath the hemidesmosomes (Uchida et al 2014). However, the mechanism and significance of this rare phenomenon have not been clarified.

There are only few cases of localized pretibial BP reported (Amber et al 2018, Wantz et al 2011, Calcaterra et al 2009, Kakurai et al 2007, Nakatani et al 1998, Borradori et al 1992, Muramatsu et al 1991, Person 1983). None of them developed milia.

The localized forms of BP carry a better prognosis than the generalized forms with a good response to topical therapy. Therefore, topical high potency corticosteroids represent the first-line therapy in the treatment of localized BP. Our patient was treated with oral prednisone and azathioprine in addition to topical corticosteroids, which could not control the skin lesions. A medium dose of systemic corticosteroids, such as prednisone 0.5 mg/kg/day is effective in moderate disease (Joly et al 2002). The association between BP and neurological diseases, like stroke in our patient, might be explain by cross reactivity between BP180 and BP230 isoforms in the skin and brain. Patients with BP are 5 times as likely to have or develop neurological disorders compared to controls, and in the majority of cases this precedes the diagnosis of cutaneous disease, usually by about 5.5 years (Lai et al 2017).

## Conclusions

We herein present, to our knowledge, the first reported case of localized pretibial BP with coexistence of milia and blisters. It remains unclear why some patients develop localized form with milia. The low levels of autoantibodies against BP180 might explain the limited localization of bullous lesions.

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## Authors

Corina Baican - Department of Dermatology, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Clinicilor street, 400006, Cluj-Napoca, Romania, E-mail: cibaican@yahoo.com

Elisabeta Candrea - Department of Dermatology, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Clinicilor street, 400006, Cluj-Napoca, Romania, E-mail: Candrea.Elisabeta@umfcluj.ro

Adrian Baican - Department of Dermatology, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Clinicilor street, 400006, Cluj-Napoca, Romania, E-mail: adrianbaican@yahoo.com

Alina Vasilovici - Department of Dermatology, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Clinicilor street, 400006, Cluj-Napoca, Romania, E-mail: alina\_letca@yahoo.com

Daniela Vornicescu - Department of Dermatology, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Clinicilor street, 400006, Cluj-Napoca, Romania, E-mail: dvornicescu@yahoo.com

Sorina Danescu - Department of Dermatology, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Clinicilor street, 400006, Cluj-Napoca, Romania, E-mail: sorinadanescu@yahoo.com

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