

CASE REPORT

# Bullous Pemphigoid with Lymphocytic Colitis: A Case Report and Short Literature Review

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## ABSTRACT

The association of autoimmune bullous diseases (i.e., bullous pemphigoid, linear IgA disease, mucous membrane pemphigoid and IgA pemphigus) and inflammatory bowel disease, namely ulcerative colitis and Crohn's disease has formerly been reported. However, to our knowledge, we report herein the first case of lymphocytic colitis with concomitant bullous pemphigoid.

**Keywords:** Autoimmune bullous disease; Bullous pemphigoid; Inflammatory bowel disease; Lymphocytic colitis

## INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune bullous disease in elderly patients.

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BP is associated with immunoglobulin (Ig) G tissue-bound and circulating autoantibodies which target hemidesmosomal proteins of the dermal-epidermal junction, named BP 180 (collagen type XVII) and BP 230. The disorder usually presents with generalized tense blisters or crusts, urticarial plaques, and prurigo-like eczematous lesions and is accompanied by severe pruritus [1].

Lymphocytic colitis is an intestinal disorder which manifests as watery diarrhea. As a subset of microscopic colitis the macroscopic aspects of the colon mucosa on endoscopy remain unsuspecting, while histology reveals increased infiltrates of lymphocytes, plasma cells and eosinophils in the epithelium and lamina propria, respectively. The etiology is unknown, but auto-immunity is suggested [2, 3].

Both entities, namely BP and lymphocytic colitis, occurring temporarily concomitant have not been described so far.

## CASE REPORT

A 75-year-old female presented with a recent onset of itchy erythematous plaques with erosions and few blisters particularly on the

flexor side of her arms and proximal thighs, as well as on her abdomen and bottom in the course, on physical examination. The mucosa was not affected. She reported having recurrent episodes of diarrhea for 25 years, ascribing it to a putative and expanded food intolerance. During increased intestinal symptoms in the last 3 months she lost ~6 kg of body weight.

Histopathology revealed subepidermal blisters and eosinophilic infiltrates. The results of commercial available enzyme-linked immunosorbent assay kits (ELISAs) were positive for BP180 NC16A domain (index 44 U/mL, normal <20 U/mL), while being negative for BP230 and type VII collagen. Direct immunofluorescence (IF) microscopy of a perilesional skin biopsy showed strong linear staining of C3 and weaker labeling of IgG at basement membrane zone (BMZ). Indirect IF using human 1 M NaCl-split skin revealed strong binding of C3 solely at the dermal side of the artificial split, while no IgG reactivity was found. Immunoblotting of normal human epidermal extract did not detect further IgG autoantibodies to type VII collagen and p200 antigen. Immunoblotting of concentrated culture supernatant of HaCaT cells did not demonstrate IgG-reactivity with laminine-332, the soluble ectodomain of BP180 (LAD-1) or BP230, respectively. These findings established a diagnosis of BP.

Meanwhile, gastroenterological examinations were performed to clarify the cause of her chronic diarrhea. On endoscopy, the colonic mucosa seemed to be normal, but biopsy samples from various sites of the colon revealed diffuse infiltrates of lymphocytes, while cryptal architecture remained regular (Fig. 1). Unfortunately, no direct or indirect IF for immunoglobulins was performed on colonic epithelium. These findings were diagnostic of lymphocytic colitis.

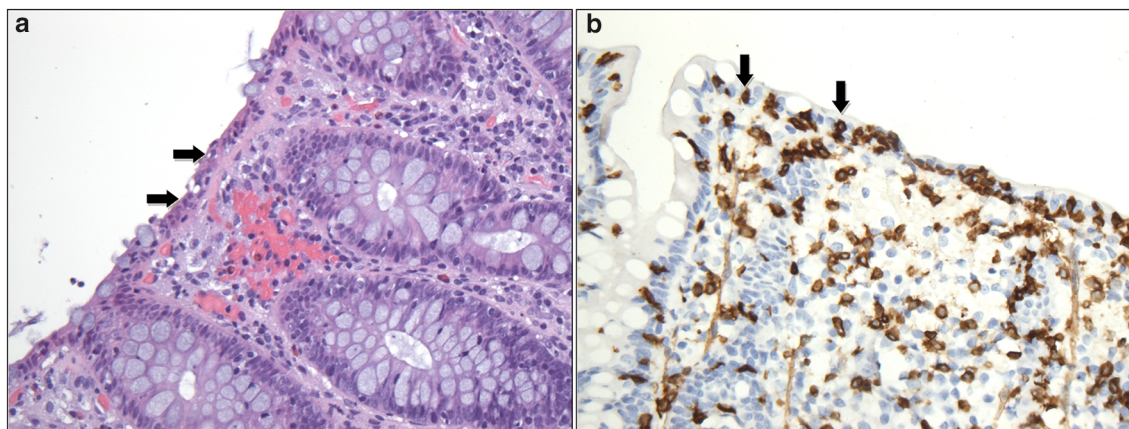
The patient was started on a therapy with low-dose systemic corticosteroid (methylprednisolone, initially 30 mg/day) and high-potency topical corticosteroids. Soon after partial remission was achieved on tempering doses of methylprednisolone, therapy was switched to oral budesonide, which is known to be effective at the side of the inflamed bowel. During the further course of 6 weeks, only a premonitory erythematous plaque on the forearm remained, while the frequency of diarrhea decreased significantly.

Informed consent was obtained from the patient for being included in this case report.

## DISCUSSION

BP in patients with underlying inflammatory bowel disease (IBD) is relatively rare and has especially been reported for ulcerative colitis (UC) and Crohn's disease (CD). Shipmann et al. [4] reported on 19 patients with UC plus BP and two patients having CD and BP in his review of literature. In almost all cases the onset of intestinal symptoms preceded the first skin eruptions for 6 months to 23 years in UC and 1 or 2 years in CD [4]. Of note, the time span between CD and the onset of all bullous skin disease was shorter than for the majority of cases of UC. The association between IBD and autoimmune blistering diseases was overall more common for linear IgA disease (LAD 25 cases) than for BP [4].

In a recent case series, only one patient with UC and concomitant BP was detected, while two had LAD or IgA pemphigus, respectively, and one had mucous membrane pemphigoid (MMP) [6]. To date, only one case of LAD in a 66-year-old female with lymphocytic colitis has been reported [3]. In our case, the subsequent occurrence of BP in preexisting enteropathy



**Fig. 1** Histology of colonic mucosa showing a dense cell infiltrate of lymphocytes (*arrows*) in the epithelium. **a** Hematoxylin and eosin,  $\times 10$ , **b** CD3-staining,  $\times 20$

could certainly be coincidental. However, the rising gut symptoms immediately before the first skin eruption favor the hypothesis that both conditions might be related.

As a possible pathogenetic mechanism for the co-occurrence of IBD and BP, a steadily autoimmune response against the denuded proteins of the inflamed colonic epithelium at the BMZ can be assumed. In the course of months or even years, intra- and inter-molecular epitope-spreading phenomena might occur due to uncovered new protein components, explaining the cross-reactivity of autoantibodies with different exposed antigens. Otherwise, preformed autoantibodies targeting similar or identical structural protein in colonic and skin epithelium can derive from a formerly non-pathogenic antibodies fraction following the same process [5–7].

Firm evidence of a cross-reactivity of autoantibodies between colonic and skin epithelial antigens has been proven in dermatitis herpetiformis, where immune complexes containing IgA and epidermal transglutaminase as well as autoantibodies against endomysium, tissue transglutaminase and epidermal transglutaminase are responsible for clinical signs [8]. Equally, it has been

described in patients with epidermolysis bullosa acquisita, where IgG autoantibodies to type VII collagen react upon IF with colonic BMZ [6]. These autoantibodies could be also detected by ELISA and immunoblot analysis in sera from patients with CD and UC, respectively [7]. Moreover, demonstration of positive IF in the gut in two cases of LAD and CD substantiate this conclusion [4].

Possible antigen proteins expressed likewise in the gut and skin are BP180, desmoglein-1, type VII collagen, and plectin. The latter is co-localized and structural similar to BP230, both linking the hemidesmosome to the cellular cytoskeleton [6, 7].

In our case, indirect IF showed binding of C3 only on the floor of the artificial split. Further indirect IF with IgG and IgA (on monkey esophagus and human 1 M NaCl-split skin) carried out in the stadium of improved symptoms of skin and gut remained negative. The IgG staining by direct IF microscopy and the strong labeling of C3, that could only be weakly induced by IgA autoantibodies, according to the positive ELISA for BP180 NC16A, finally favored a diagnosis of BP. Nevertheless, the role of BP180 antibodies stays unclear in our case, as the NC16A

portion of BP180 would have positive IF at the roof of the artificial split. Yet BP180 spans the lamina lucida of the dermal–epidermal junction and possesses both an intracellular region and an ectodomain with many immunodominant regions, respectively. Possibly, a yet unknown autoantibody is present in our patient or a different epitope of BP180 located at the C-terminus of NC16A, is recognized by the autoimmune response, similar to patients with lichen planus pemphigoides [9].

The incidence of BP in parallel with lymphocytic colitis may be under-reported as the inflammation and damage of colonic tissue is, in contrast to classical IBD like UC and CD, less severe. Thus, auto-immune processes with recognition of autologous antigens and formation of auto-antibodies could require more time. As lymphocytic colitis usually affects patients in their sixth and seventh decade, most patients might not develop both entities lifelong.

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**Compliance with Ethics Guidelines.** Informed consent was obtained from the patient for being included in this case report.

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