Peristomal and Generalized Bullous Pemphigoid in Patients with Underlying Inflammatory Bowel Disease: Is Plectin the Missing Link?

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Abstract
Bullous pemphigoid (BP) is a blistering disorder of the skin and mucosa that may coexist with inflammatory bowel disease (IBD). The authors’ experiences with peristomal and generalized BP in five patients (three with ulcerative colitis [UC] post colostomy surgery and two with Crohn’s disease [CD] post ileostomy surgery, time since surgery 5 to 20 years) is described. The patients presented with peristomal blisters and erosions, subsequently confirmed as BP by skin biopsy. Treatments for the skin disease included potent alcohol-based topical corticosteroids, oral tetracyclines, and oral corticosteroids. In three patients (two with UC, one with CD), the initially localized peristomal disease later became generalized across the skin; these patients were more likely to require systemic immunosuppressive therapy. Because an involvement of plectin, a cytoskeletal protein that attaches skin and mucosal cells to their extracellular matrix, in IBD has been shown, it is possible that this protein forms the missing link between IBD and BP via epitope spreading. The inflammation of IBD exposes plectin, stimulating a secondary immune response that may, in susceptible individuals, cross-react with the skin, provoking BP. Further research into this area could enable clinical testing for plectin auto-antibodies in patient sera, possibly preempting the development of BP and expediting the initiation of early effective treatment.

Keywords: case series, stoma, bullous pemphigoid, plectin, inflammatory bowel diseases

Potential Conflicts of Interest: none disclosed

Bullous pemphigoid (BP) is an autoimmune blistering disease of skin and mucosae, the pathogenesis of which involves the development of auto-antibodies against the proteins BP180 and BP230. Both these proteins are key components of the hemidesmosome, a vital structure within skin cells, responsible for attaching them to the extracellular matrix: BP180 is a transmembrane receptor,1 and BP230 links the hemidesmosome to the cellular cytoskeleton.2 Like BP180 and BP230, plectin is also an important hemidesmosomal protein. It belongs to the same plakin family of cytoskeletal proteins as BP230, sharing great structural similarities and widely expressed in mammalian cells.3

Peristomal BP in patients with underlying inflammatory bowel disease (IBD) has rarely been observed and reported. The authors describe their experience with five patients (two men, three women, with either ulcerative colitis [UC] or Crohn’s disease [CD]) with peristomal BP seen in their combined dermatology-stoma clinic. Their facility is a monthly outpatient clinic staffed by a consultant dermatologist, a trainee dermatologist, and two stoma care nurses, supported by a gastroenterologist and general surgeon if required, serving 20 to 30 tertiary-referral patients, all with resistant peristomal dermatological problems seen in a supraregional dermatology center. Potential mechanisms of association between these two autoimmune diseases are discussed, with particular focus on the phenomenon of epitope spreading. An epitope is the part of an antigen recognized by the immune system; as such, it stimulates the immune response. Epitope spreading is known to occur in autoimmune conditions as a consequence of chronic inflammatory processes.
uncovering new protein components (e.g., epitopes). \(^1\) Existing evidence in the literature of the involvement of plectin in BP is presented, and a role for plectin as an epitope is proposed: the inflammation of IBD exposes plectin within the bowel mucosa, stimulating the production of auto-antibodies against it and, in susceptible individuals, these antibodies cross-react with the skin, subsequently provoking the blisters and erosions that constitute BP.

**Case Report**

Clinical features. Five patients (age range 61 to 87 years) with long-standing IBD (one man and one woman, with CD and ileostomies; one woman, with UC and colostomies) that had necessitated stoma surgery between 5 and 20 years ago presented to the authors’ facility over a period of 15 months. Noteworthy comorbidities included only hypertension in two individuals. No patient was currently receiving, or had received in the 6 months before the onset of blistering, immunosuppressive medications, such as prednisolone or azathioprine, or anti-tumor necrosis factor therapy. All patients had recurrent blisters and erosions on their peristomal skin in the preceding 2 to 9 months that hindered the application of stoma devices (see Figure 1).

Clinically, the differential diagnoses of such lesions include irritant contact dermatitis, allergic contact dermatitis (e.g., to the stoma adhesive or skin cleanser), a blistering skin infection such as bullous impetigo (secondary usually to Staphylococcus aureus or Streptococcus pyogenes), therare skin condition pyoderma gangrenosum in which ulcerations/erosions predominate, cutaneous Crohn’s disease, and BP, the primary blistering disorder of the skin.

In three patients (two with UC, one with CD), the initial peristomal lesions later generalized to involve widespread areas of the skin surface including the trunk and limbs (see Figure 2). This provided a diagnostic clue towards BP, as many of the other blistering skin conditions would not become generalized. However, because of the range of differential diagnosis and their varied treatments, patients had their diagnoses of BP confirmed via skin biopsies approximately 2 months later, taken under local anesthetic (1% lignocaine with 1:200,000 adrenaline injected subcutaneously) from the edge of a blister for hematoxylin and eosin staining, and from peri-lesional skin for direct immunofluorescence. Histological characteristics in all patients included eosinophil-rich subepidermal blisters, with linear IgG and C3 along the basement membrane on direct immunofluorescence.

Treatment. Because topical creams/ointments can cause stomas bags to detach, all patients initially were treated with potent alcohol-based topical corticosteroids, such as fluocinolone acetonide 0.025% (Synalar gel® Bioglan, Malmö, Sweden), to avoid interference with stoma appliance adherence. \(^2\) In two of the UC and one of the CD patients, all of whom had generalized disease, short courses of oral corticosteroids (usually oral prednisolone, 40 mg once daily, tapering over 4 to 6 weeks) were necessary to gain disease control, with long-term oral tetracyclines (such as minocycline 100 mg once/twice daily for 12 to 24 months) as long-term maintenance therapy. These antibiotics are presumed to have efficacy as a result of their anti-inflammatory effects, \(^3\) are usually well-tolerated, and can be continued in the longer-term with fewer side effects than oral immunosuppressants. \(^7\) One Crohn’s disease patient with generalized blisters required a short admission to the dermatology ward to commence treatment with oral prednisolone and potent topical corticosteroids (Dermovate® cream, clobetasol propionate 0.05%, GlaxoSmithKline, Middlesex, UK) applied twice daily to blisters/pre-blistering urticated areas of skin, due to the widespread nature of her blisters. The remaining four patients were successfully managed on an outpatient basis with regular follow-up until disease control was gained before gradual weaning of the oral corticosteroids after 4 to 6 weeks. The patients are now in follow-up with their local practitioners, in addition to an at-least annual review in the dermatology-stoma clinic.

**Key Points**

- The authors observed and describe the care of five patients with either ulcerative colitis or Crohn’s disease who presented with recurrent peristomal blisters and erosions.
- Clinical presentation and biopsy confirmed bullous pemphigoid (BP).
- The authors theorize the incidence of peristomal BP is under-reported, and inflammation of IBD uncovers plectin within the bowel mucosa, triggering a secondary autoimmune response.

**Figure 1.** Erythema, bullae, and erosions surrounding stomal site.
Discussion

IBD and blistering disorders: lessons from IBD and epidermolysis bullosa acquisita. An association is recognized between IBD and an alternative blistering condition known as epidermolysis bullosa acquisita (EBA), which is attributable to autoimmunity to the EBA antigen within type VII collagen. Chen et al demonstrated, by western blot analysis, the presence of type VII collagen in the epithelial basement membrane zone of healthy human colon. These authors also used an enzyme-linked immunoassay to test sera from patients with CD, UC, celiac disease, rheumatoid arthritis, and controls for antibody reactivity against type VII collagen. Reactivity was noted in 13 of 19 patients with CD and four of 31 patients with UC (but not in control subjects, patients with celiac disease, or rheumatoid arthritis). Furthermore, the sera from CD patients also reacted with type VII collagen by immunoblot analysis. These findings led Chen et al to hypothesis that the inflammation originally evoked by CD perturbs the intestinal basement membrane zone such that new antigenic components are exposed, resulting in autoimmunity to type VII collagen. In a similar fashion, the authors propose that in a different subset of patients including the cohort of five patients presented here, autoimmunity to an alternative antigen (rather than type VII collagen) develops, which results in BP rather than EBA.

Proposed mechanisms of association of IBD and BP. Although the phenomenon of Koebnerization (the appearance of skin lesions at site of previous trauma) may explain the appearance of BP blisters surrounding the stomal site, this fails to explain the widespread nature of the skin disease exhibited by a subset of patients. A potential explanation is that cross-reactions occur — ie, antibodies directed against colonic mucosa cross-react with the skin, leading to bullae formation. Chronic irritation from stomal effluent leads to inflammation of peristomal skin that consequently may unmask new antigens in this area; preformed antibodies originally directed against the colonic mucosa then may bind structurally similar protein components within the skin.

Epitope spreading. Expanding this cross-reactivity hypothesis further is the theory of epitope spreading, in which a specific self-reactive immune response develops to new antigenic components — ie, epitopes — distinct from the original disease-inducing antigen. In this fashion, it is proposed that lymphocytes mistaken by target themselves against a previously sequestered secondary epitope uncovered in the gut as a consequence of the chronic tissue inflammation that occurs during IBD. Furthermore, in certain susceptible patients, these lymphocytes cross-react with protein components found within the cutaneous basement membrane, producing peristomal or generalized BP.

BP and concomitant IBD. Although IBD and BP are associated with a variety of other autoimmune disorders, only rarely have they been reported to coexist. However, in those few cases that have been described, the diagnosis of IBD preceded skin involvement, and this was similarly the case for all of the patients discussed here. Furthermore, at least temporary resolution of skin disease has been observed following some cases of colectomy. Taken together, these observations suggest that, in general, the inflammatory process of IBD may be driving the pathogenesis of BP in predisposed individuals.

Potential role of plectin. An interesting question is whether plectin, in the case of BP in certain IBD patients, could be the secondary epitope. Plectin is a widely expressed member of the plakin family of cytoskeletal proteins and, pertinent to this scenario, is present in both skin cells and bowel mucosa. Its mutation already has been shown by immunoelectron microscopy and immunohistochemistry to underlie a rare but severe inherited blistering disease of the skin. Plectin and BP230 share great structural similarity, particularly in their central domains, and both are co-localized to hemidesmosomes. Buisjorgge et al retrospectively investigated 282 patients who presented with subepidermal blistering diseases: immunoblot analysis of patient sera revealed that 11 of these 282 patients had antiplectin antibodies. Nine of these 11 patients had BP, and sera from these individuals also bound other BP antigens — ie, BP180 and BP230. The remaining two patients had an alternative blistering skin diagnosis (linear IgA disease). On further characterization, epitope mapping demonstrated that the auto-antibodies in these 11 individuals were particularly targeted against plectin’s central coiled rod domain, the region also found in BP230. Unfortunately, the authors do not comment on the comorbidities of their patients, so it is not possible to correlate these results with coexistent IBD.

Laffitte et al similarly examined the sera of 16 patients with BP using immunoprecipitation/immunoblot analysis: all 16 immunoprecipitated BP230, but antiplectin antibodies were demonstrated in only one individual (and none of the three control subjects). Their plectin-positive patient was unusual: a 5-month old child with BP.
These results provide supporting evidence that, in at least some perhaps rare subtypes of BP, antiplectin antibodies contribute to cutaneous disease, either by targeting plectin within the cutaneous basement membrane and/or by cross-reacting with the structurally similar BP230. It may be that for individuals with concomitant IBD, higher levels of antiplectin antibodies are generated, and assist in contributing to disease pathogenesis. In addition, although BP may affect any age group, it is predominantly considered to be a disease of the elderly. Yet, those patients with IBD and concomitant BP tend to form a younger subset, suggesting possible dissimilarities in the underlying disease mechanisms. This would be in keeping with the unusually low age of one plectin-positive patient described above.

Conclusion

The association between IBD and the blistering skin disorder EBA is recognized, but reports of peristomal/generalized BP in IBD patients are rare. Five patients with pre-existing IBD who subsequently presented with peristomal erosions and bullae subsequently confirmed as BP are described. Treatments for the skin disease included potent alcohol-based topical corticosteroids, oral tetracyclines, and oral corticosteroids. In three patients (two with UC, one with CD), the initially localized peristomal disease later became generalized across the skin; these patients were more likely to require systemic immunosuppressive therapy. The patients in this case series were inevitably subject to selection bias, because the referral criteria for the author’s clinic exempt IBD sufferers who do not have stomas.

Important differentials of peristomal bullae/erosions to consider include contact dermatitis and EBA, but these can be distinguished by skin biopsy with immunofluorescence studies. The incidence of peristomal BP may be under-reported because localized forms may be misdiagnosed (as an irritant dermatitis in particular), and topical steroid-responsive lesions would not necessarily be biopsied.

Plectin is a hemidesmosomal protein that shares great structural similarity with the BP antigen BP230 and is present in both bowel mucosae and the skin. Antiplectin antibodies have been found in exceptional cases of BP. The authors hypothesize that in some IBD patients, the phenomenon...
of epitope spreading occurs, whereby the inflammation of IBD uncovers plectin within the bowel mucosa, triggering a secondary autoimmune response with the development of antibodies against plectin. In certain susceptible individuals, these antibodies may cross-react either with the plectin within the skin cytoskeleton or with the structurally similarly hemidesmosomal protein BP230 (the target in “normal” cases of BP), causing the blisters and erosions that constitute BP.

Further research into the links between BP and IBD, with particular focus upon the involvement of plectin and the target of antiplectin antibodies — ie, plectin and/or BP230 — is needed. In particular, with the development of a hospital-based method to demonstrate antiplectin antibodies within patient sera in a similar fashion to the detection of capital-based method to demonstrate antiplectin antibodies — ie, plectin and/or par.

Within the skin cytoskeleton or with the structurally similarly hemidesmosomal protein BP230 antibodies, it then may be possible to preempt the development of BP and direct therapies appropriately. Moreover, clinical researchers could explore the development of BP in IBD patients before stoma surgery and, furthermore, potentially correlate skin signs with IBD disease activity.

References