Bullous colon lesions in a patient with bullous pemphigoid

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Bullous pemphigoid (BP) is a subepidermal blistering disease associated with circulating autoantibodies directed against structural components of hemidesmosomes, adhesion complexes promoting epithelial-stromal adhesion in human skin, and other complex epithelia. Two hemidesmosomal proteins, the BP antigen 180 (BP180) and the BP antigen 230 (BP230), have been shown to be the target antigens.1,2 BP230 is a cytoplasmic component of the hemidesmosomal plaque, whereas BP180 is a transmembrane protein with a collagenous extracellular domain. These 2 target antigens are expressed, as assessed by immunofluorescence microscopy by using either specific antisera and/or polyclonal BP patient sera, in stratified and some complex epithelia that ultrastructurally exhibit hemidesmosomes at the epithelial-stromal interface: in the skin; the ocular, buccal, and genital mucosa; the esophagus; and trachea.3 These peculiar tissue distributions of BP230 and BP180 explain the potential in patients with BP for involvement of various mucous membranes and the upper GI tract in addition to the skin.4

BP and linear immunoglobulin (Ig) A bullous dermatosis, a condition that might overlap with BP, have been associated with GI disorders such as ulcerative colitis.5-9 However, the exact pathophysiologic relationship remains unclear because small intestine and colon mucosa do not possess bona fide hemidesmosomes with BP180 and BP230 components.

This is a description of a patient with typical clinical and immunopathologic features of BP who developed severe bullous lesions of the colon reminiscent of BP, and a discussion of the potential pathogenic link between the immune-mediated subepidermal disorder and the bowel disease.

CASE REPORT

A 74-year-old white man presented with a 3-month history of a pruritic bullous eruption. His history included surgery for a prostatic cancer 8 years earlier. He was not taking any medication. Examination revealed tense cutaneous bullae of 4 to 30 mm diameter arising in erythematous skin. These lesions were located predominantly on the flexural aspects of the upper extremities, the lower abdomen, and the anterior and posterior aspects of the thighs (Fig. 1). Some bullae had ruptured, resulting in crusted and eroded areas. Healed lesions exhibited postinflammatory hyperpigmentation. Milia were not observed. The oral mucosa was unaffected, but some bullous lesions were present in the perianal region.

Light microscopy of the skin lesions showed subepidermal bullae containing many eosinophils (Fig. 2). In the
upper and mid dermis there was an inflammatory infiltrate composed predominantly of eosinophils. Direct immunofluorescence studies of perilesional skin demonstrated linear deposits of C3 along the dermoepidermal junction. By indirect immunofluorescence microscopy, circulating IgG antibody was found that bound the epidermal side of 1.0 mol/L sodium chloride-separated normal human skin at a titer of 1:640.10 Immunoblot (IB) studies of keratinocyte extracts disclosed that the patient had circulating autoantibodies directed against a protein of 230 kd, whereas IB studies of dermal extracts were negative.11 By using recombinant fragments of BP230, the patient’s serum was found to contain IgG autoantibodies immunoblotting the COOH-terminus of this protein (residue stretch 1946-2649), but not its NH2-terminal half (residue stretch 1-555 and 663-1293).12 No reactivity was observed against recombinant fragments of BP180 corresponding to its entire extracellular and intracellular domain.13

The patient suddenly experienced rectal bleeding with a decrease in hemoglobin but without any systemic signs of infection. Colonoscopy showed normal rectal mucosa. However, beginning in the sigmoid colon there was mucosal edema with bullae formation resulting in stenosis of the lumen, as well as deep, 1- to 2-cm diameter ulcers with a fibrinous exudate (Fig. 3). The mucosal alterations were more extensive proximal to the splenic flexure; in the

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transverse colon the bullae completely obstructed the lumen, precluding evaluation of the right colon.

Abdominal US (7.5 MHz) showed hypoechogenic wall thickening (wall diameter up to 6.0 mm) of the entire colon with the most pronounced changes in the transverse and descending colon. Nuclear magnetic resonance disclosed an inhomogenous rectal mucosa with thickening but no signs of colonic tumor.

Histopathologic evaluation of biopsy specimens from the sigmoid and descending colon disclosed focal mucosal edema with segmental subepithelial bullae formation and a slight eosinophilic infiltrate (Fig. 4A and B). Scattered erosions and ulcerations were present (Fig. 5). Specific findings were not present for Crohn’s disease, ulcerative colitis, or for eosinophilic, lymphocytic, or collagenous colitis. Moreover, the ulcerations and histologic findings were not thought to be compatible with a diagnosis of pneumatosis cystoides intestinalis. Immunoperoxidase studies on paraffin-embedded tissue demonstrated vascular deposits of IgG, C3, C4, and fibrinogen in the colon mucosa. A search was negative for circulating autoantibodies binding to the basement membrane zone (BMZ) of the colon mucosa by using an immunoperoxidase technique and indirect immunofluorescence or immunoperoxidase staining. Nevertheless, the evolution of the GI manifestations paralleling that of the skin eruption in terms of severity, as well as the histopathologic findings, raised the intriguing possibility that the colonic lesions were pathophysiologically related to BP and not purely coincidental. This hypothesis is strengthened by the fact that other intestinal disorders, including Crohn’s disease, ulcerative colitis, eosinophilic, lymphocytic, or collagenous colitis were excluded on the basis of macro- and/or microscopic features.

Although expression of BP180 was recently demonstrated by polymerase chain reaction by using complementary DNA synthesized from RNA isolated from colon,14 both BP180 and BP230 are not significantly expressed in normal small intestinal and colonic mucosa, as assessed by using either polyclonal BP sera or specific antibodies.15-17 Therefore, even if faint deposits of immunoreactants were not detected in our patient with the techniques used, autoantibodies to BP230 are unlikely to have been relevant pathogenically in the development of the GI lesions. However, in 1 patient with bona fide bullous pemphigoid and adenocarcinoma of the colon, deposits of IgG and C3 at the periphery of the tumor were found, suggesting that the patient had circulating autoantibodies that cross-reacted with antigens expressed by the colon tumor.18

DISCUSSION

The patient described here had a generalized bullous disorder with clinical and immunopathologic features that are characteristic for BP. He had tissue-bound and circulating IgG autoantibodies directed against the epidermal BMZ, that immunoblotted a 230 kd protein, fulfilling the diagnostic criteria for BP. In addition, the patient’s serum was reactive against the COOH-terminal region of BP230 that contains the immunodominant sequences recognized by the majority of BP sera. However, our patient was unusual in that he developed bullous lesions of the colon associated with rectal bleeding. Strikingly, light microscopy of specimens of colonic mucosa showed a histologic picture highly reminiscent of BP with subepithelial bullae formation comparable with the bullae present in the skin biopsy specimen.

Immunoperoxidase studies on paraffin-embedded tissue samples were performed to assess whether the colonic lesions were associated with the presence of specific immunoreactants. These failed to disclose tissue-bound deposits of immunoglobulins or complement components along the colon BMZ. In addition, no circulating autoantibodies to the BMZ of colon mucosa were found by indirect immunofluorescence or immunoperoxidase staining. Nevertheless, the evolution of the GI manifestations paralleling that of the skin eruption in terms of severity, as well as the histopathologic findings, raised the intriguing possibility that the colonic lesions were pathophysiologically related to BP and not purely coincidental. This hypothesis is strengthened by the fact that other intestinal disorders, including Crohn’s disease, ulcerative colitis, eosinophilic, lymphocytic, or collagenous colitis were excluded on the basis of macro- and/or microscopic features.

Figure 5. Photomicrograph of biopsy specimen showing mucosal erosion with focal epithelial regeneration (H&E, orig. mag. x200).
BP, and more frequently linear IgA bullous dermatosis, are known to occur concomitantly with inflammatory bowel diseases, especially ulcerative colitis. In patients with linear IgA bullous dermatosis, a disorder commonly associated with IgA auto-antibodies targeting a 97/120 kd protein, deposits of IgA within the colon mucosa were occasionally detected. Although the specificity of these immunoreactants was not assessed, it is again unlikely that the GI manifestations in these patients resulted from autoantibodies to the same 97/120 kd protein expressed in the skin, because the latter appears to correspond to the shedded extracellular domain of BP180.

It has been speculated that the association of a GI disorder with an immune-mediated subepidermal blistering disorder may be caused by an “epitope spreading phenomenon”—in the context of a distinct immunogenetic profile, inflammation of the colon may expose normally hidden epitopes that stimulate the production of auto-antibodies. This B cell response might recognize “secondary” epitopes within the same protein or distinct molecules that cross-react with antigens in the skin. This epitope-spreading phenomenon is thought to explain the association of Crohn’s disease and ulcerative colitis with epidermolysis bullosa acquisita, a subepidermal bullous disorder associated with autoantibodies to type VII collagen. This protein is the major component of anchoring fibers in human skin and seems also to be expressed in colon mucosa. Bhagat and Das have recently found the existence of common epitopes in colonic, ocular, and joint tissues. This might explain the extracolonic manifestations of ulcerative colitis.

It is conceivable with regard to our patient that either an as yet uncharacterized or a known protein expressed in both the skin and bowel mucosa, such as the α6β4 integrin and plectin (a protein showing high homology with BP230), constituted a potential target antigen for autoantibodies. Demonstration of such reactivity might require more sensitive methods such as combined immunoprecipitation and immunoblotting studies.

REFERENCES