40 Cutaneous manifestations of inflammatory bowel disease

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Introduction
Cutaneous manifestations are common in inflammatory bowel disease (IBD). In one study, the incidence was reported to be as high as 34%. [1] However, some of the early studies included non-specific inflammatory conditions such as urticaria, various maculopapular eruptions, and pigmentary abnormalities, some or all of which may be unrelated to the bowel disease. Other rigorous studies provide a more reasonable estimate of cutaneous involvement in patients with ulcerative colitis (UC) and Crohn’s disease (CD) (9-19%) [2]. Greenstein et al., in an older study of 498 patients with CD, noted that cutaneous manifestations are more common when the large intestine is involved [3].

Mucocutaneous manifestations of IBD may be classified as specific lesions, reactive lesions, and miscellaneous associations (Table 1). For completeness, cutaneous manifestations secondary to malabsorption [4, 5] or treatment may also be considered, but will not be treated in this text. Specific lesions refer to those lesions that are due to direct involvement of the skin by the same disease process that affects the gastrointestinal tract. This includes fissures, fistulas, and metastatic CD [2]. In contrast, reactive lesions do not show the same pathologic features as are found in the gastrointestinal tract, but instead represent a reaction to the underlying IBD. The pathogenesis of reactive lesions remains speculative; most are probably immunologically mediated, some because of cross-antigenicity between the skin and the gut mucosa [6].

In this review only the more common and clinically significant specific and reactive cutaneous manifestations of IBD will be discussed. An attempt will be made to compare and contrast the various entities with regard to their prevalence in either CD or UC; treatment issues will not be considered in this chapter. The reader is referred to various sources [7, 8] for explication of the most current treatments of the entities discussed herein.

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Specific cutaneous lesions of ulcerative colitis and Crohn’s disease
Fissures and fistulas are the most common cutaneous manifestations of IBD, and may even be the presenting complaint in CD. In contrast, they occur infrequently in UC. The most commonly affected site is the perineum, especially the perianal area, although peristomal skin and the abdominal wall may also be affected. In a study of 569 patients...
with CD, perianal fissures and fistulas were found in 36% of patients [9]. Only 25% of those patients with small bowel disease alone had perianal involvement, whereas more than 40% of patients with colonic disease exhibited perianal disease [9]. The perianal fissures and fistulas of IBD are typically multiple and involve the anus circumferentially. Abscesses, undermined ulcers, and skin tags or 'pseudo' skin tags formed by edematous skin are often noted on the perineum. The edema can be so severe as to produce lymphedema [10]. Histologic examination of the perianal inflammatory lesions characteristically shows transmural inflammation with lymphoid aggregates and non-caseating sarcoidal-type granulomas typical of CD. In one series of 29 biopsies, granulomas were identified in 25 [11]. The clinical and histologic findings may help distinguish CD from UC, as perianal disease is rare in UC. Perifistular and peristomal disease is less helpful diagnostically; since once a colostomy has been performed or cutaneous fistulas have developed, the diagnosis of CD is secured.

Oral Crohn’s disease

Examination of the oral cavity allows clinicians to readily observe two of the classic morphologic features of CD: ulceration and cobblestoning. The ulcers are often tiny, herpetiform, occasionally linear, and may resemble ordinary aphthae. They can, of course, become large, undermining and indolent. When linear ulcers or tissues connect and the intervening mucosa is edematous, a 'cobblestone' appearance develops [10].

The oral manifestations of CD tend to vary by location within the mouth. The buccal mucosa appears to be the most common site of cobblestoning, while the gingival and alveolar mucosae often exhibit tiny nodular growths [12]. Linear ulcers are more common in sulci [12]; the lips may become swollen, hardened, or ulcerated, especially at the angles of the mouth [13]. Because of the granulomatous histology the lip changes have been called cheilitis glandularis [14]. It is unclear from previous studies how often granulomatous inflammation of the lip is associated with CD as compared to being associated with Melkerson–Rosenthal syndrome or being idiopathic. Finally, there may even be inflammation and ulceration of the epiglottis and larynx [10].

While nodules or ulcers with granulomatous histology strongly implicate CD, the role of aphthous ulcers is less clear. Some studies [12] have suggested that they are a non-specific finding, while others [10] suggest that they may be the most frequent oral lesions seen in CD. Aphthae, oral lesions, and oral ulcerations have been estimated to occur in between 4% and 20% of CD patients [15, 16]. In the UCEDS study only five of 569 patients (1%) had aphthae at the beginning of the study, but another 23 (4%) developed them during the study even on systemic therapy [17]. These figures are not incompatible with the presence of aphthae in the general population. Although aphthae in CD have not been studied in depth histologically, they do not appear to be granulomatous.

Despite these caveats the presence of aphthae can suggest the diagnosis of CD [16]. If a biopsy shows a granulomatous histology, CD should be the major consideration in the microscopic differential diagnosis. Recurrent aphthae may be the first manifestation of CD; thus a history of their presence may prove useful in the work-up of patients with chronic diarrhea and/or abdominal pain.

Metastatic Crohn’s disease

Metastatic CD refers to nodules, plaques, or ulcerated lesions that demonstrate a granulomatous histology identical to that of the IBD, and that are located in the skin and subcutaneous tissue at sites distant from the gastrointestinal lesions of CD. Metastatic cutaneous CD is rare; studies [18] have
emphasized a flexural distribution, and have shown that metastatic CD may be non-ulcerative and may even mimic erythema nodosum [19, 20].

Metastatic CD can be viewed as still another ‘great imitator’ both clinically and histologically. Cases have been initially diagnosed as factitial dermatitis, intertrigo, severe acne, hidradenitis suppurativa, chronic cellulitis, or erythema nodosum among many other entities [10]. Metastatic CD does not seem to appear in the absence of gastrointestinal CD. Histologically, most patients present with typical sarcoidal granulomas, raising the microscopic differential diagnosis of infection, sarcoid, and a foreign-body reaction. Rarely, cases of metastatic CD may differ histologically. Two patients with erythema nodosum-like lesions showed granulomatous perivasculitis [10].

EN does not appear to be a good marker for CD. In large series of patients with EN, very few have CD [2]. Furthermore, all nodose lesions on the extremities of CD patients are not erythema nodosum. Histologically, in addition to the septal panniculitis of EN, one may see polyarteritis or granulomatous inflammation. Thus, in a CD patient with EN-like lesions clinically, a biopsy of sufficient depth and size to evaluate the subcutaneous fat as well as the dermis is a necessity.

EN is believed to represent the expression of a hyperimmune response and may be seen in association with various disease entities and as a reaction to various drugs (Figs 1 and 2). The possibility of a drug reaction should be considered in all patients with EN, especially those being treated with sulfa derivatives. It is interesting to note that studies have suggested that EN may be the most common extra-colonic manifestation of UC in children [1] and that usually the lesions heal without scarring.

Pyoderma gangrenosum
Pyoderma gangrenosum (PG) usually begins with small papules, plaques, or hemorrhagic blisters that rapidly enlarge and ulcerate with violaceous undermined edges. The lesions may occur anywhere on the skin, but most frequently are located on the lower extremities. Patients may give a history of preceding trauma to the area. Lesions are sterile and are characterized by a dense dermal infiltrate of neutrophils (Figs 3 and 4). PG has been noted in approxi-
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Figure 4. Close-up reveals a predominantly neutrophilic dermatosis surrounding reactive blood vessels without evidence of vasculitis. These histologic findings are typical of any of the various neutrophilic dermatoses, including pyoderma gangrenosum.

Vesiculopustular eruption

A vesiculopustular eruption that can be localized or generalized has been described in some patients with UC [27]. The lesions consist of grouped erythematous vesiculopustules (3–5 mm in size) that sequentially crust and heal, resulting in postinflammatory hyperpigmentation. Some authors consider this entity to be a forme fruste of PG; cases have been reported in which most lesions of a vesiculopustular eruption have resolved while a few lesions developed into typical PG [28, 29]. Histologic examination reveals intraepidermal neutrophilic abscesses with mixed inflammatory dermal infiltrates [27].

Pyoderma vegetans

Pyoderma vegetans has been described in several patients with UC [21, 30]. It initially appears mainly in intertriginous areas with vegetating plaques and vesiculopustules that resolve with postinflammatory hyperpigmentation. Mucosal involvement may also occur (pyostomatitis vegetans). Histologically, the principal features include pseudoeipitheliomatous hyperplasia and intraepidermal abscesses that contain neutrophils and eosinophils. Pyoderma vegetans may also represent a forme fruste of PG (Fig. 3) [21].

Cutaneous vasculitis and polyarteritis nodosa

Cutaneous vasculitis is a rare cutaneous manifestation of IBD [31]. Both leukocytoclastic vasculitis and cutaneous polyarteritis nodosa have been reported. Vasculitis is more commonly associated with UC whereas polyarteritis nodosa has been documented only in association with CD [2].

Necrotizing (leukocytoclastic) vasculitis generally presents as palpable purpura, ulcerations, and, rarely, gangrene [2]. The usual sites of involvement are the legs and anal areas. Mixed cryoglobulinemia may sometimes be demonstrated in these patients. Histologic examination reveals fibrin thrombi and/or fibrinoid necrosis of blood vessel walls with associated leukocytoclasia and extravasated erythrocytes.

Cutaneous polyarteritis nodosa is characterized by tender or painful erythematous nodules which often ulcerate. They are commonly located on the legs but may affect other areas of the body. The lesions can be clinically mistaken for EN, metastatic CD or PG. The biopsy specimen exhibits a necrotizing leukocytoclastic panarteritis that may show...
granulomatous features and often a variable infiltrate of eosinophils. Associated features of cutaneous polyarteritis nodosa include livedo reticularis, peripheral neuropathy, arthralgias, and myalgias; severe systemic involvement does not occur. Cutaneous polyarteritis nodosa usually runs a benign but chronic course that is usually unrelated to the activity of the bowel disease [31, 32]. Cutaneous polyarteritis nodosa usually presents after the diagnosis of CD has been established, but may occur before the diagnosis of IBD [31–34]. Circulating immune complexes have been demonstrated and may contribute to the pathogenesis [33, 34].

**Epidermolysis bullosa acquisita (EBA)**

There appears to be a greater than chance association between EBA and IBD, particularly CD. EBA is an acquired blistering disorder that occurs mainly on the knees, elbows, hands, and feet. It is mediated by antibody deposition and immune activation at the dermo-epidermal junction [34–36]. When it occurs in relation to CD it usually begins many years after the onset of the bowel disease – it may be best considered a long-term complication of CD.

**Other associations**

Reactive eruptions such as erythema multiforme and urticaria may occur in patients with IBD [24]. These may be due in part to a response to the disease or its treatment. An increased incidence of thromboembolic events, clubbing, psoriasis, and vitiligo has also been noted in patients with IBD [24, 37, 38]. Palmar erythema has been associated with CD [10]. A case report of acne fulminans has suggested an association with CD [39]. The association of psoriasis and vitiligo with IBD may be related to HLA linkage rather than a true cause-and-effect relation [24]. Secondary amyloidosis may rarely develop in the setting of chronic inflammatory disorders including CD and UC [2].

**Conclusion**

It is important to become acquainted with the various cutaneous manifestations of IBD because some of them may serve as sentinels of the disease and may actually help to clarify a diagnosis. Approximately one-quarter of all Crohn’s patients will present initially with perianal disease [10], and oral changes may precede intestinal symptoms. The skin conditions which have been reported to precede the development of IBD are listed in Table 4. Moreover, skin disease may help to clarify a diagnosis and aid in the distinction between CD and UC, still a challenging clinical and histopathologic differential diagnosis. Some cutaneous changes are far more common in CD than in UC and vice-versa (Tables 2 and 3). When a patient presents with perioral disease or granulomatous skin disease at multiple sites or the oral cavity, the intestinal disease will invariably be CD. Conversely, the presence of a vesiculopustular eruption, pyoderma vegetans, or even a leukocytoclastic vasculitis favors a diagnosis of UC.

The pathogenesis of the cutaneous aspects of IBD probably reflects the immunologic basis of the intesti-
inal disease. The presence of skin changes suggests that the same factors which elicit and propagate the gut disease are capable of stimulating an abnormal immune response in the skin. Whether or not these responses are the result of crossreacting antigens or the deposition of circulating immune complexes remains unclear. It remains to be seen whether the immunologic/microbiologic advances which promise to unlock the secrets of the etiologies of CD and UC in the near future will similarly shed light on the pathogenesis of the many and varied cutaneous changes which may herald and accompany these diseases.

References