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The Dermatological Manifestations of Inflammatory Bowel Disease: Looks Might be Deceiving!

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Introduction

Inflammatory bowel diseases (IBD) is a poorly understood auto-immune clinical entity that include indeterminate colitis, Crohn's (CD) and ulcerative colitis (UC).

Being a chronic relapsing illness, IBD is a multi-system disorder than can involve the eyes, skin, joints, Liver and kidneys, but mostly characterized by chronic relapsing intestinal inflammation. Although IBD, is a chronic inflammatory disorder of the gut, the manifestations of CD and UC are not limited to the gastrointestinal tract. Extraintestinal manifestations (EIMs) are frequently observed in patients with IBD, with a reported frequency of 6-46% [1]. The skin, musculoskeletal, joints, eyes, and hepato-biliary tract are the organs most affected by EIMs.

Of these, the three most common mucocutaneous manifestations with IBD are erythema nodosum (EN), pyoderma gangrenosum (PG) and aphthous stomatitis [1]. These have a reported incidence of more than 18-20%% [1].

According to the different pathophysiological mechanisms, cutaneous EIMs are divided into the following four "4" categories:

1. Lesions directly related to IBD, with specific skin manifestations with the same histological features as IBD, such as metastatic CD.
2. Shared pathogenesis, with reactive skin manifestations with similar pathophysiological mechanisms to IBD, such as PG, Sweet's syndrome, EN, and aphthous ulcers.
3. Mirror image related skin lesions with IBD-related skin diseases, such as psoriasis, Hidradenitis suppurativa, and atopic dermatitis.
4. Drug induced skin lesions with IBD-treatment-induced skin lesions, such as anti-tumor necrosis factor (TNF)-alpha-induced skin eruptions.

The dermatological manifestations of IBD are extensive and might be difficult to treat, with the various dermatological manifestations can look ugly but might be potentially treatable, these might include: Drug-induced skin eruptions, Metastatic CD to the skin, aphthous ulcerations of the mouth and genitals, Pyoderma Gangrenosum (PD) figure 2, Erythema Nodosum (EN) figure 1, and Hidradenitis Suppurativa figure 3.

Pyoderma gangrenosum (PG) can be classified as a reactive manifestation of IBD because it is an autoinflammatory, dysfunctional innate immune response triggered by common antigens shared by gut bacteria and skin [1]. It occurs in about 1-2 % of patients with IBD [2]. It is more frequently associated with UC, females, and African Americans with a positive UC family history [2]. The goal of treatment for PG is to control inflammation and this is usually achieved by systemic corticosteroids, dapsone, cyclosporine, TNF inhibitors, IL-12/IL-23 inhibitor, IL-1 receptor antagonist, or anti-IL-1β monoclonal antibody [1].

Erythema Nodosum (EN) is an inflammatory disease of subcutaneous nodules. Although the pathogenesis is not known, it is thought that deposition of immune-complexes due to antigen reactions produces TNF-alpha and leads to granuloma formation [3]. IBD has been shown to have a higher risk of EN possibly secondary to the similarities between EN and IBD such as genetics, clinical presentations, and immunological profiles [4].

Hidradenitis suppurativa (HS) is an inflammatory skin disease that affects hair follicles in skin folds. While the pathogenesis of HS is not fully understood, dysregulated immunity is considered a primary role in HS. Studies have shown patients with HS have elevated inflammatory cytokines such as TNF [5]. IL-17 pathway, a factor essential in CD, has also been associated with HS [5].

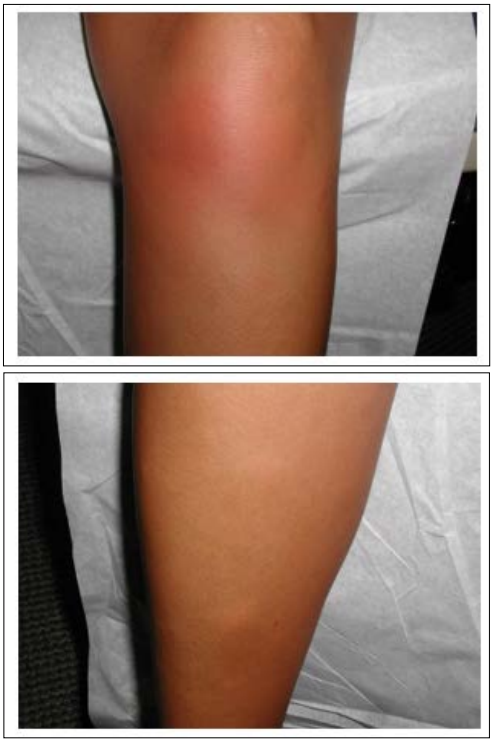

Figure 1: Erythema Nodosum

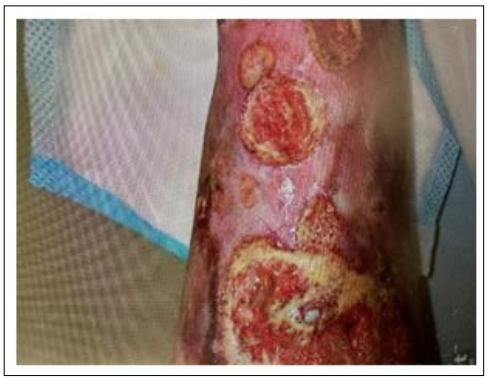

Figure 2: Pyoderma Grangrenosum

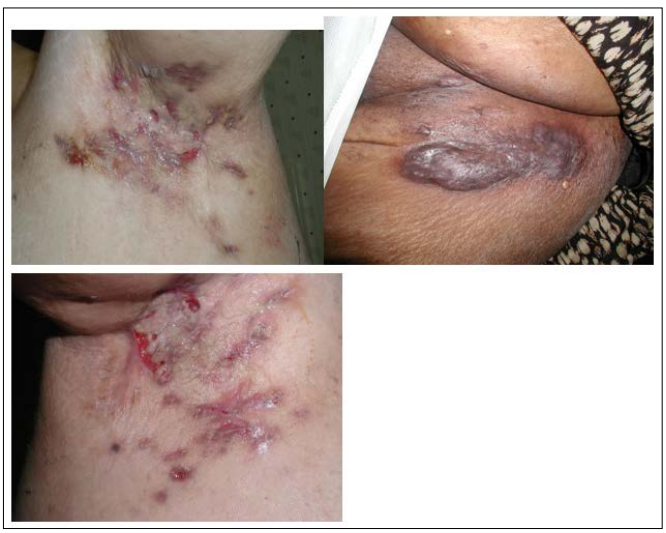

Figure 3: Hidradenitis Suppurativa

Discussion

Although the skin manifestations share many of the pathophysiological changes as IBD, the dermatological manifestations of IBD do not always correlate with the IBD disease activity, with skin lesions occurring before, during, and after IBD. EIMs can occur in 10---20% of IBD patients, with the various IBD skin lesions affecting 1---5% of people with IBD, however, when they happen, there are particularly distressing.

Erythema Nodosum "EN" is considered an auto-immune delayed-type hypersensitivity reaction resulting from exposure to various antigens; however, the pathogenesis is not fully understood. The pathogenic mechanism may involve immune complex deposition in the septal venules of the subcutaneous fat, neutrophil recruitment with resulting reactive oxygen species formation, tumor necrosis factor (TNF)-alpha production, and granuloma formation.

Classically, EN manifests as painful erythematous, usually tender, nonulcerated, immobile nodules on the bilateral shins. The nodules are slightly raised and typically 20 to 30 mm in diameter. Less frequently, lesions can coalesce into plaques or arise on other areas such as the ankles, thighs, arms, buttocks, calves, or face.

The nodules develop over several days and may follow a prodrome of fatigue, fever, malaise, arthralgias, or upper respiratory infection symptoms by one to three weeks. Joint swelling, erythema, or pain may accompany the skin manifestations.

Nodules typically resolve spontaneously without scarring within eight weeks of presentation. Secondary bruising, also known as "erythema contusiformis," often occurs during resolution. Residual hyperpigmentation may take weeks to months to resolve.

On the other hand, Pyoderma Gangrenosum "PG" is a painful skin condition consistent with its categorization as a neutrophilic dermatosis, PG is characterized by neutrophil-predominant infiltrates in the skin. Research has begun to elucidate dysregulation in the innate and adaptive immune response, in addition to genetic factors, in the pathogenesis of PG. Immune dysregulation is a major factor with strong association with IBD. This inflammatory upregulation leads to a proinflammatory state through increased activation of inflammasomes, dysregulation of the innate immune system, and recruitment and activation of neutrophils. PG tissue also has increased expression of pattern recognition receptors (PRRs), JAK2, and STAT1, implicating both adaptive and innate immune response dysfunction. The complement pathway, particularly C5a and its role in neutrophil activation, chemotaxis, and inflammatory signaling, may also contribute to the complex pathogenesis of PG. In addition, Genetic susceptibility also likely contributes to the development of PG. Familial cases of PG have been reported. Mutations of the autoinflammatory genes MEFV, NLRP3, NLRP12, NOD2, and LPIN2 have been demonstrated in PG, PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis) syndrome, and other inflammatory conditions, including familial Mediterranean fever, cryopyrin-associated periodic syndrome, Crohn disease, and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome.

Similar to trauma induced GI mucosal inflammation, the same phenomenon happens in the skin. Pathergy, a term used to describe the induction or exacerbation of PG in sites of incidental or iatrogenic trauma, is frequently mentioned in descriptions of the clinical behavior of PG. However, not all patients with PG exhibit this feature. Data on the proportion of patients with PG who experience pathergy are limited. In a retrospective study of

103 patients with PG, pathergy was documented in the medical records of 31 percent of patients (7). In a series of 166 patients with PG, 25 (15 percent) experienced 33 episodes of postsurgical recurrence or exacerbation of the disease; factors associated with increased risk of pathergy included open surgical procedures, Mohs surgery, and PG present at the time of procedure.

There are four types of Pyoderma Gangrenosum, and those include: Ulcerative (classic) pyoderma gangrenosum, Bullous (atypical) pyoderma gangrenosum, Pustular pyoderma gangrenosum, and Vegetative pyoderma gangrenosum.

Hidradenitis suppurativa (HS) is a chronic, painful, follicular, occlusive disease that affects the folliculopilosebaceous unit mainly, but not exclusively, in intertriginous axillary, groin, perianal, perineal, genital, and inframammary skin. The clinical course is highly variable, ranging from relatively mild disease characterized by the recurrent appearance of papules, pustules, and a few inflammatory nodules to severe cases demonstrating deep, fluctuant abscesses; draining skin tunnels; and severe, rope-like scars.

Numerous interventions exist for the treatment of HS, including topical therapies, oral therapies, biologic therapies, surgery, and laser and light interventions. Disease severity, patient tolerance of specific agents, comorbidities, and treatment cost and availability guide treatment selection.

This particular skin disorder can be particularly annoying because of its location on the buttocks or in the arm pits. HS is a chronic condition, and the pain, drainage, odor, and disfigurement caused by HS profoundly affect quality of life, even when the disease is relatively mild. Feelings of shame may produce self-imposed social isolation and, combined with chronic pain, likely contribute to higher rates of depression and anxiety.

The Interventions for HS target one or more of three major goals which are weirdly similar to IBD goals of therapy:

1. To reduce formation of new inflammatory lesions, skin tunnels, and scarring.
2. To treat existing lesions and reduce associated symptoms (eg, pain, suppuration).
3. To minimize impact on quality of life and associated psychologic morbidity.

Treatment involves the same biological agents as IBD therapy. The severity of HS influences the approach to treatment. Key features used to determine disease severity include the extent of skin involvement and the presence of secondary lesions, including skin tunnels and scarring. Similar to IBD, responses to therapy are indicated by reduced frequency and severity of inflammatory lesions, improvement in symptoms, and improvement in quality of life.

Conclusion

- Extraintestinal manifestations (EIMs) of IBD are common, 10---20% of IBD patients have at least one of these conditions. The most common extraintestinal IBD manifestations are those of the skin or skeleton. Less commonly involved are the eyes and the Liver.
- EIMs could manifest years before gastrointestinal symptoms start, so the clinicians have to keep that fact in mind.
- In short, the dermatological manifestation of IBD can be severe, ugly looking, and deceiving, however, as mentioned in the title of this manuscripts, looks can be deceiving, as all of these lesions are potentially treatable with proper diagnosis and management; that includes but not limited to dietary modifications, corticosteroids, and Immune modulators, and biological therapy. One Should consider longer follow-up for those patients for early detection of IBD [4]. Future further research is needed particularly with development of numerous newer biological therapy agents.

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