ABOUT THE AUTHOR

Abdulhadi Jfri, MD, MSc, FRCPC

Dr. Abdulhadi Jfri holds certification as a Fellow of the Royal College of Physicians of Canada (FRCPC) in dermatology and as a Diplomat of the American Board of Dermatology (DABD). He completed both his Masters' degree in experimental medicine in the department of epidemiology and biostatistics and a five-year dermatology residency at McGill University. He also completed a fellowship in advanced surgical procedures at Icahn School of Medicine at Mount Sinai, New York. Dr. Jfri is currently completing his complex medical dermatology fellowship at Harvard School of Medicine, where he is rotating between Brigham and Women's Hospital and the Dana-Farber Cancer Institute.

APPROACH TO SKIN LESIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES

Introduction

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD). This group of chronic inflammatory diseases has many extra-intestinal manifestations. Skin is the second most common extra-intestinal organ affected after the musculoskeletal system.[1] The prevalence of cutaneous manifestations among IBD patients is estimated to be 15%. Some manifestations are more common in UC while others are in CD.[2] This review provides a practical approach to the cutaneous manifestations among IBD patients to help guide investigation and management when patients with IBD are referred for a dermatology consult. The cutaneous manifestations of IBD are summarized in **Table 1**.

This review divides the cutaneous manifestations of IBD into four major subgroups:

I. Cutaneous extension of the disease:

Metastatic Crohn's disease is an unusual presentation of CD that manifests with non-specific violaceous papules or nodules that can ulcerate anywhere on the body but are most commonly found in intertriginous areas, but can also be seen on the abdomen and the extremities. Such lesions require pathological confirmation showing non-caseating granulomas similar to the underlying CD to make a diagnosis.[3] Peri-anal fistulae are a contiguous extension of CD and can be a presenting manifestation. Other contiguous lesions include knife-cut ulcerations of the inguinal folds that are considered to be the most common presenting cutaneous sign in adults.[4] Genital edema that leads to lymphangiectasias is considered the most common presenting sign in pediatric patients.[5]

II. Nutritional deficiencies:

Patients with IBD often suffer from multiple nutritional deficiencies related to chronic inflammation, dietary restrictions (especially during flares), and surgical resection. These nutritional deficiencies can also result from malabsorption and diarrhea.

The most common nutritional deficiency among IBD patients is the acquired form of acrodermatitis enteropathica due to zinc deficiency. It presents with periorificial and acral scaly erythematous patches and plaques that lead to crusted vesiculobullous erosive psoriasiform and pustular lesions and may be associated with diffuse non-scarring alopecia.

Additional nutritional-related dermatoses may include: pellagra, due to vitamin B3 deficiency, which presents with photosensitivity and photo-distributed hyperpigmentation, sebaceous hyperplasia and stomatitis; scurvy, due to a vitamin C deficiency, which presents with hyperkeratotic papules, twisted corkscrew hairs with perifollicular hemorrhage and inflamed gums that bleed easily; purpura, due to a vitamin K deficiency; stomatitis/glossitis/angular cheilitis from any of the vitamin B deficiencies; and xeroderma (or dry skin and eczematous patches) due to essential fatty acid deficiency.[6,7]

III. Oral manifestations:

Oral findings in IBD are varied and include: aphthous stomatitis (reactive with disease flare up), linear fissures of buccal vestibule, mucosal cobble-stoning (seen with CD and represents coalescing mucosal granulomatous nodules), angular cheilitis, pyostomatitis vegetans (oral pustules and erosions in a snail-track arrangement), pyodermatitis-pyostomatitis vegetans and granulomatous cheilitis or persistent swelling of buccal mucosa which is observed more in patients with CD.[8]

IV. Associations:

Several associated dermatoses that are observed among IBD patients are depicted in **Figure 1** and further described below.

Some of these associated dermatoses tend to correlate with disease activity, while others may occur in well-controlled patients. Erythema nodosum is the most common associated cutaneous lesion in IBD and is seen more often in females with active colitis; it presents as multiple tender erythematous subcutaneous nodules on the extremities, typically on the anterior lower legs.[9] Pyoderma gangrenousm (PG), the second most common cutaneous lesion in IBD, occurs more frequently with UC and does not appear to correlate with disease activity. PG can appear anywhere on the body, but mostly present on the extremities following trauma. Lesions manifest as painful single or multiple violaceous papule/pustules that ulcerate with gun-metal grey undermined borders and which heal with cribriform scars.[9] Another cutaneous association with IBD is hidradenitis suppurativa (HS). In a 2019 meta-analysis and systematic review involving five case-control studies, 2 cross-sectional studies, and 1 cohort study with a total of 93 601 unique participants, analysis demonstrated associations of HS with CD (pooled OR, 2.12; 95% CI, 1.46-3.08) and UC (pooled OR, 1.51; 95% CI, 1.25-1.82). IBD patients tend to have more perianal involvement compared to non-IBD patients with HS.[10]

Neutrophilic dermatoses including Sweets syndrome, which presents with acute fever and painful nodules and plaques on the upper body, usually presents in conjunction with an active flare up of IBD.[11] Bowel-associated dermatosis-arthritis syndrome (BADAS) may also present with papulopustular papules on the extremities, also in the setting of active IBD.[12]

Cutaneous vasculitis is also seen in association with IBD with or without disease activity. This includes cutaneous small vessels vasculitis (CSVV)[13] presenting with palpable purpura evolving into hemorrhagic blisters or cutaneous polyarteritis nodosa (PAN)[14] characterized by purpura, nodules, ulcers, and livedo reticularis.

Mounting evidence suggests an association between EBA and IBDs, such as UC and CD. IBD has been shown to be present in approximately 30% of EBA patients.[15] EBA presents with fragile skin blisters which heal with scarring and milia in areas of friction such as hands, elbows, knees, and ankles.[16] Bullous pemphigoid (BP) has been thought to be drug induced in the setting of IBD due to the use of mesalamine or sulfasalazine. However, a population-based case-control study involving a total of 5,263 BP patients and 21,052 age-, gender-, and hospital visit number-matched controls from the National Health Insurance Research Database of Taiwan (1997-2013) confirmed that the association between UC and IBD treatment was not associated with development of BP. BP presents as tense blisters overlying a preceding or concomitant pruritic urticarial plaque.[17] The prevalence of linear IgA bullous dermatosis (LABD) was found to be 7.1% in patients with UC compared to 0.05% in the general population.[18]

A significant association exists between IBD and psoriasis as shown in a recent meta-analysis that included over 7.7 million patients. Patients with psoriasis had an increased risk of CD (RR, 2.53; 95% CI, 1.65-3.89) and UC (RR, 1.71; 95% CI, 1.55-1.89).[19] Another association which may be medication-induced is the "paradoxical" palmoplantar pustular psoriasis which can be associated with tumour necrosis factor alpha (TNFα) inhibitors. In a review and analysis of 127 case of patients receiving TNFα inhibitors for the treatment of rheumatoid arthritis, ankylosing spondylitis and CD [70 patients on infliximab (55.1%), 35 on etanercept (27.6%), and 22 on adalimumab (17.3%)], there was a documented induction and exacerbation of palmoplantar pustular psoriasis in 40% of these cases, and plaque-type psoriasis in 33.1% of the cases.[20]

Although lichen nitidus is a rare skin condition that presents as skin-coloured asymptomatic flat-topped

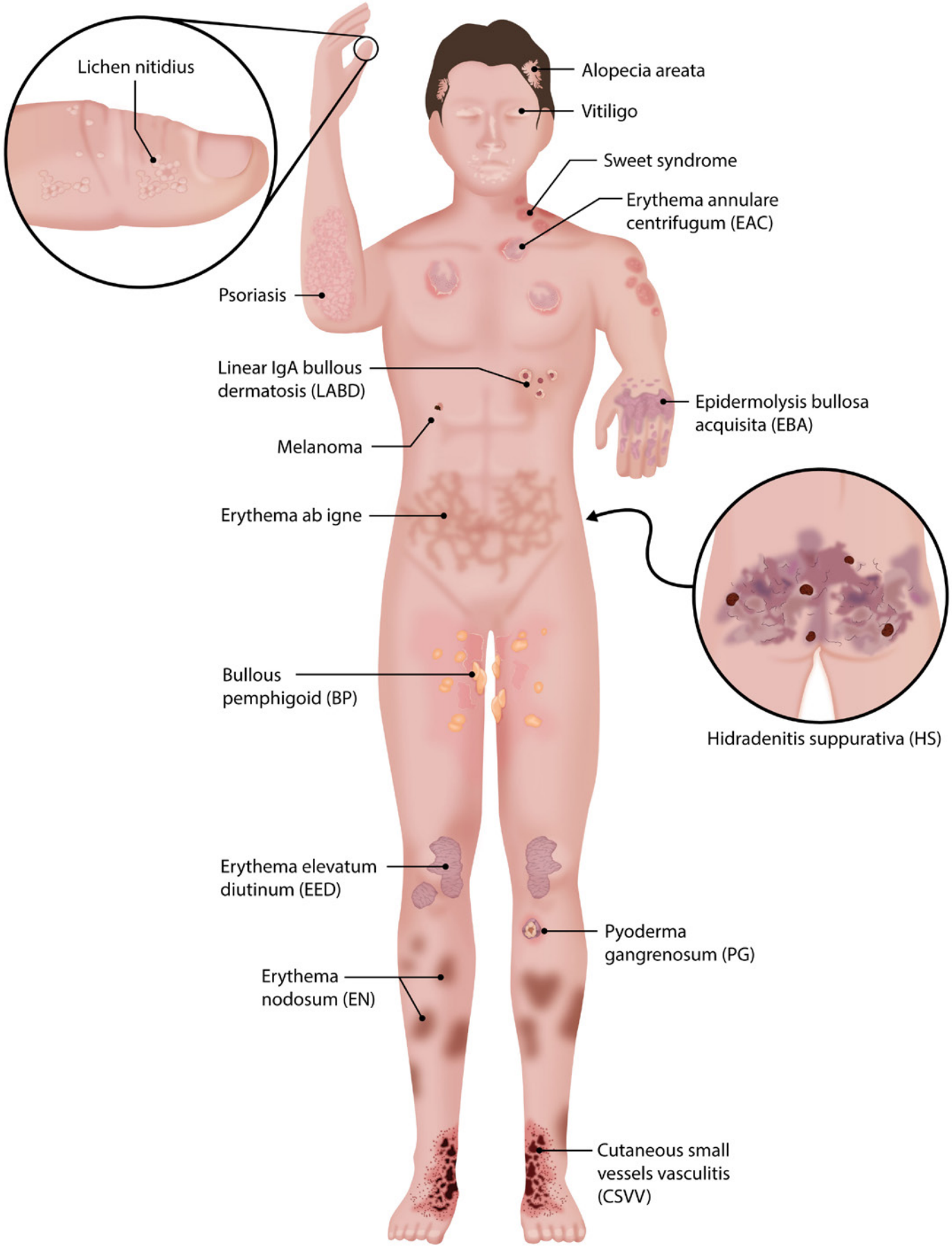

Figure 1: *Associated dermatoses with inflammatory bowel disease (IBD); courtesy of Dr Abdulhadi Jfri, MD*

monomorphic papules, it has also been reported to be associated with CD. This is especially true of the extensive variant.[21] Other associations include erythema annulare centrifugum (EAC), erythema elevatum diutinum (EED), cutaneous lesions of secondary amyloidosis, and coexistence of other autoimmune diseases such as vitiligo. Erythema ab igne, related to repeated use of heating pads to relieve abdominal pain during disease flares, can be seen on various body areas particularly the abdomen.[21]

The prolonged use of immunosuppressive agents, such as azathioprine and prednisone, and biologics can also increase the risk of skin cancers among IBD patients. The risk of nonmelanoma skin cancers (NMSC) increased more than two-fold in patients with IBD who were taking thiopurines (HR 2.28, 95% CI 1.5-3.5).[22] In a meta-analysis comprised of 12 studies involving over 172,000 patients, IBD was associated with a 37% increase in the risk of melanoma (12 studies: RR, 1.37; 95% CI, 1.10-1.70) compared to the general population.[23]

Conclusion

In conclusion, cutaneous findings in patients with IBD have various etiologies, including disease associations, vitamin deficiencies, cutaneous complications, and complications of medical or surgical therapies. The recognition of these clinical cutaneous findings in IBD patients is important for the proper diagnosis and management.

References:

1. *Kethu SR. Extraintestinal manifestations of inflammatory bowel diseases. J Clin Gastroenterol 2006;40:467-475.*
2. *Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol 2011;106:110.*
3. *Burgdorf W. Cutaneous manifestations of Crohn's disease. J Am Acad Dermatol 1981; 5:689.*
4. *Yüksel I, Başar ., Ataseven H, et al. Mucocutaneous manifestations in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(4):546-550. doi:10.1002/ibd.20807*
5. *Palamaras I, Pietropaolo N, Thomson P, Mann S, Robles W, Stevens HP. Metastatic Crohn's disease: a review. J Eur Acad Dermatology Venereol. 2008;22(9):1033-1043. doi:10.1111/j.1468-3083.2008.02741.x*
6. *Sehgal VN, Jain S. Acrodermatits enteropathica. Clin Dermatol. Nov-Dec 2000;18(6):745-8. doi: 10.1016/s0738-081x(00)00150-4.*
7. *Maria O'Sullivan, Colm O'Morain. Nutrition in inflammatory bowel disease. Best Pract Res Clin Gastroenterol. 2006;20(3):561-73. doi: 10.1016/j.bpg.2006.03.001.*
8. *Lankarani KB, Sivandzadeh GR, Hassanpour S. Oral manifestation in inflammatory bowel disease: a review. World J Gastroenterol 2013;19:8571–8579.*
9. *Farhi D, Cosnes J, Zizi N, et al. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. Medicine (Baltimore) 2008; 87:281.*
10. *Wei-Ti Chen, Ching-Chi Chi. Association of Hidradenitis Suppurativa with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. JAMA Dermatol. 2019 Sep; 155(9): 1022-1027*
11. *Travis S, Innes N, Davies MG, et al. Sweet's syndrome: an unusual cutaneous feature of Crohn's disease or ulcerative colitis. The South West Gastroenterology Group. Eur J Gastroenterol Hepatol 1997; 9:715.*
12. *Truchuelo MT, Alcántara J, Vano-Galván S, et al. Bowel-associated dermatosis arthritis syndrome: another cutaneous manifestation of inflammatory intestinal disease. Int J Dermatol 2013; 52:1596.*
13. *Akbulut S, Ozaslan E, Topal F, et al. Ulcerative colitis presenting as leukocytoclastic vasculitis of skin. World J Gastroenterol 2008; 14:2448.*
14. *Chiu G, Rajapakse CN. Cutaneous polyarteritis nodosa and ulcerative colitis. J Rheumatol1991; 18:769.*
15. *Iwata, Hiroaki, et al. "Meta-analysis of the clinical and immunopathological characteristics and treatment outcomes in epidermolysis bullosa acquisita patients." Orphanet journal of rare diseases 13.1 (2018): 1-9.*
16. *Keyal, U.; Liu, Y.; Bhatta, A.K. Dermatologic manifestations of inflammatory bowel disease: A review. Discov. Med. 2018, 25, 225–233.*
17. *Yi-Ju Chen, Chao-Kuei Juan, Yun-Ting Change et al. Association between inflammatory bowel disease and bullous pemphigoid: a population-based case–control study. Sci Rep. 2020; 10: 12727.*
18. *Paige DG, Leonard JN, Wojnarowska F, Fry L. Linear IgA disease and ulcerative colitis. Br J Dermatol. 1997;136:779–782.*
19. *Yun Fu, Cheng-Han Lee, Ching-Chi Chi. Association of Psoriasis With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. JAMA Dermatol. 2018 Dec 1;154(12):1417-1423. doi: 10.1001/jamadermatol.2018.3631.*
20. *Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. J Dermatolog Treat. 2009;20(2):100–108*
21. *Karolyn A Wanat, Rosalie Elenitas, Sam Chacklin et al. Extensive lichen nitidus as a clue to underlying Crohn's disease. J Am Acad Dermatol. 2012 Nov;67(5):e218-20. doi: 10.1016/j.jaad.2012.04.005.*
22. *M P Tighe, R A Morenas, N A Afzal, et al. Erythema ab igne and Crohn's disease. Arch Dis Child. 2008 May;93(5):389. doi: 10.1136/adc.2008.137968.*
23. *Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. Am J Gastroenterol2014; 109:163.*
24. *Singh S, Nagpal SJ, Murad MH, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014; 12:210.*

Cutaneous extension of disease	Nutritional deficiencies	Oral	Associations	Complications of medical treatment	Complications of surgical intervention
Metastatic Crohn's disease **Fistulas:** perianal/ abdominal in CD **Genital lymphedema:** more in pediatrics. **Knife-like cut ulcerations** most common presentation in adults	**Zinc:** acquired acrodermatitis enteropathica **Vit. B3:** pellagra **Vit C:** scurvy **Vit K:** purpura **Iron:** angular cheilitis, atrophic glossitis, brittle hair, koilonychia **Essential fatty acid:** eczematous patches	**Linear fissures of buccal vestibule** **Mucosal cobble-stoning** **Aphthous stomatitis** **Angular cheilitis** **Pyostomatitis vegetans:** / + cutaneous lesions called **pyodermatitis-pyostomatitis vegetans**, **Granulomatous cheilitis:** more with CD.	**Erythema nodosum** **Pyoderma gangrenosum** **Hidradenitis suppurativa** **Sweet syndrome** **Bowel associated dermatitis arthritis syndrome (BADAS)** **Cutaneous small vessels vasculitis (CSVV)** **Cutaneous Polyarteritis nodosa (PAN)** **Epidermolysis bullosa acquisita (EBA): >CD** **Bullous pemphigoid** **Linear IgA bullous dermatosis (LABD)** **Psoriasis** **Erythema annulare centrifugum** **Erythema elevatum diutinum (EED):** CD>UC **Erythema ab igne** **Vitiligo** **Lichen nitidus:** > CD **Secondary amyloidosis** **Skin cancers (NMSC & melanoma)**	**Immunosuppressants:** NMSC **Biologics: TNF-α** Psoriasis Sarcoidosis GA Interstitial granulomatous dermatitis LCV BP SCLE Lichenoid **Ustekinumab (IL12/23 inhibitor):** cellulitis, herpes zoster, lymphomatoid drug eruption, urticaria, injection site reactions, recurrent erythema annulare centrifugum, bullous pemphigoid, erythema multiforme, and eczematous drug eruptions, fixed drug eruption **Tofacitinib (JAK inhibitor):** NMSC (report of aggressive cSCC) Melanoma VZV reactivation Pruritis Acne Aphthous ulcers Drug eruption **Natalizumab (IgG4κ antibody):** Urticaria Melanoma Drug eruption Acquired perforating dermatosis Recurrent HSV **Vedolizumab (IgG1 antibody antagonist of a4b7 integrin):** Injection site reaction	**<u>Peri-stomal:</u>** **Irritant contact dermatitis (ICD):** due to fecal material under occlusion **Allergic contact dermatitis (ACD):** adhesives, rubber and the stoma/ ostomy bags **Koebnerization from trauma** that led to development of existing associated dermatitis such as **psoriasis** or can cause **pathergy** and causes **peristomal pyoderma gangrenosum.** **Cutaneous infection** commonly colonization of yeast and bacteria. **Pseudo-verrucous papules and nodules** mistaken as verrucae.

Table 1: *Cutaneous manifestations of inflammatory bowel diseases (IBD); courtesy of Dr Abdulhadi Jfri, MD*