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Cutaneous manifestations of IBD: Potential role of vedolizumab

Introduction

Knowledge of the pathophysiology of immune-mediated diseases continues to advance. In the past decade there has been a rapid evolution of immune-targeted therapies that have grown in precision. Overlapping immune abnormalities results in overlapping diseases, co-morbidities, and treatments. Dermatologists, gastroenterologists, rheumatologists, respirologists, allergists, and oncologists now share and co-manage more patients who often have more complex issues. Understanding how our therapies impact these immunologically related and often comorbid conditions is necessary to provide comprehensive care. Frequently, the dermatologist makes therapeutic decisions that have a positive impact on numerous comorbidities without exacerbating other conditions. This is especially prevalent in some parts of the country that have long wait times to receive care and a dearth of specialists. Of interest is the idea that as our therapies become even more precise and disease specific, they may no longer have an overlapping therapeutic effect on common comorbidities. For instance, the evolving landscape of inflammatory bowel disease (IBD) treatments, and the increased use and development of gut-specific therapies introduces the question of whether these treatments will have any impact on the incidence and management of extraintestinal manifestations (EIMs) of IBD. The intent of this article is to review the more common and important EIMs of IBD and to explore the available evidence on the impact of vedolizumab, which is a gut-specific medication, on these EIMs.

Extra-intestinal Manifestations (EIMs)

IBD, Crohn's Disease (CD), and ulcerative colitis (UC) can have a broad range of associated EIMS which affect various body systems. Most commonly affected are the joints, skin, and eyes. At least 10% of patients with IBD have mucocutaneous EIMs, which are more common in CD where they have been reported in up to 44% of patients.[1,2] In fact, mucocutaneous manifestations can sometimes be the presenting feature of IBD.[3] Risk factors for mucocutaneous manifestations in CD and UC include female gender, younger age at diagnosis, and eye or joint involvement. Additional risks in CD include a family history of IBD and disease that requires immunomodulatory therapy.[4]

The possible mucocutaneous EIMs of IBD are numerous and it is therefore not feasible to discuss every condition in this review; only the more common and significant mucocutaneous EIMs will be addressed. They are best approached by classification according to pathophysiologic origin, including those that are IBD specific, reactive conditions, associated conditions, nutritional deficiencies, and treatment-related

conditions **(Table 1)**. I aim to highlight those EIMs that mirror gut disease activity and have the potential to be inadvertently treated with gut-specific molecules used to treat the underlying IBD. In addition, EIMs with activity that has a reduced potential to be managed with more precise gut-specific molecules will be highlighted. Considering that nutritional deficiencies are not directly impacted by these immune therapies, they will not be reviewed in any detail.

IBD specific lesions	Reactive conditions	Associated conditions	Nutritional deficiencies	Therapy related lesions
Fissures & fistulas (perianal and peri-stomal	Apthous Ulcers	Finger Clubbing	Acrodermatitis Enteropathica	Alopecia
Metastatic Crohns Disease	Epidermolysis Bullosa Aquisita	Hidradenitis Suppurativa	Glossitis	Drug rash/Drug Hypersensitivity Syndrome
Oral Crohns Disease	Erythema Nodosum	Lichen Planus	Pellagra	Neutrophilic Dermatoses
	Sweet Syndrome	Linear IgA Dermatosis	Phrynoderma	TNF-alpha induced skin changes
	Polyarteritis Nodosa	Palmar Erythema	Scurvy	Toxic Epidermal Necrolysis/Steven's Johnson Syndrome
	Pyoderma Gangrenosum	Psoriasis		
		Vitiligo		

Table 1. Common and important mucocutaneous extraintestinal manifestations ; courtesy of Jennifer Lipson, MD
Abbreviations: IBD, irritable bowel disease; IgA, immunoglobulin A; TNF-alpha, tumour necrosis factor-alpha

IBD-specific mucocutaneous conditions

IBD-specific mucocutaneous conditions affect the skin by the same mechanisms as in the gastrointestinal (GI) tract and share the same pathology, non-caseating granulomas. This category includes metastatic CD, oral CD, and contiguous lesions (perianal ulcers, fissures/fistulas).[2]

Metastatic Crohn's disease (MCD) is an extremely rare entity. Accurate prevalence and incidence data are lacking, and the condition is most likely underdiagnosed due to its varied morphology.[2] MCD typically occurs in well-established GI disease. Skin disease that precedes GI disease is seen more commonly in children and manifests with skin and genital lesions. There does not appear to be an association between MCD activity and GI activity. MCD can have numerous morphologies, including erythematous plaques, nodules, and linear ulcerations occurring more often than pustules, papules, or abscess-like lesions. The most commonly affected site is the genitals; this occurs in two-thirds of children and half of adults with MCD. Consequently, MCD is typically classified as genital and non-genital MCD.[2] Genital MCD may present with genital edema, knife-like fissures, condyloma-like papules, and skin tags which show granulomas on pathology.[2] Vulvar CD occurs as four primary presentations: ulceration,

vulvar swelling, hypertrophic lesions, and chronic suppuration.[5] Non-genital MCD most commonly affects the legs, abdomen, trunk, and intertriginous sites, and rarely occurs on the face. Because MCD is a rare manifestation of CD, treatment reflects anecdotal evidence from case reports and case series, and none of the available treatments are reliably efficacious.[2] Treatments with reported efficacy include intralesional and systemic glucocorticosteroids, oral metronidazole, tumour necrosis factor α (TNFα) inhibitors, azathioprine, methotrexate, cyclosporine, thalidomide, and surgical excision.[2] A recent case report has shown vedolizumab improved a single patient with MCD.[6]

The granulomatous process of CD extends to the oral cavity (known as oral CD) in 8%–9% of patients. This can present as a cobblestone appearance of the mucosa, deep linear ulcers, indurated mucosal skin tags, gingivitis, or swelling of the face, tongue, or lips. The lips are the most common site of swelling and may develop painful vertical fissures. This disease entity is referred to as granulomatous cheilitis **(Figure 1)**.[7] Oral lesions typically respond to treatment of the underlying disease; however, local treatment with topical or intralesional steroids, topical calcineurin inhibitors, topical anesthetic, acetylsalicylic acid, mouth rinses, topical non-steroidal anti-inflammatory paste, and antiseptic washes to prevent infection can also be used. Other treatments used include hydroxychloroquine, colchicine, dapsone, thalidomide, clofazimine, TNFα alpha inhibitors, ustekinumab, infliximab, and surgery.[8,9] A case report of a patient with CD and granulomatous cheilitis refractory to three biologics has shown the condition had resolved with vedolizumab administered concurrently with doxycycline and triamcinolone.[8]

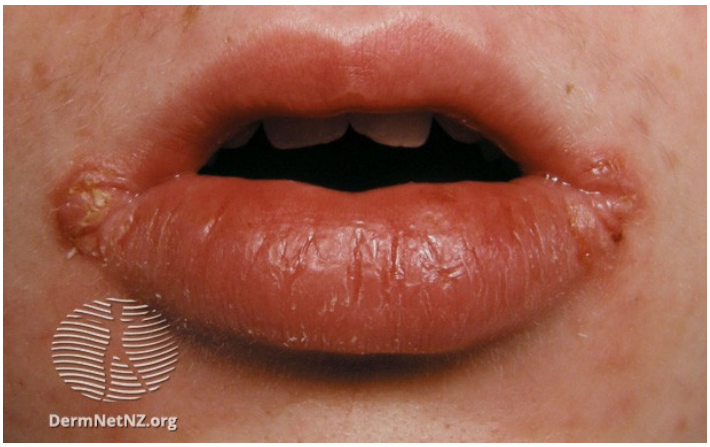

Figure 1. Typical granulomatous cheilitis with lip swelling and fissuring
Photo courtesy of DermNetNZ.org

Controversy exists regarding whether perianal fissures and fistulas should be considered to be EIMs. The European Crohn's and Colitis Organization (ECCO) 2016 guidelines do not consider perianal fissures and fistulas to be EIMs when they occur within the GI tract.[3,10]

Reactive conditions

Reactive conditions are felt to be due to cross antigenicity between skin and the intestinal mucosa and have different pathology from the underlying IBD3. The most common mucocutaneous EIMs in the reactive category are erythema nodosum (EN) affecting approximately 7.4% of patients, pyoderma gangrenosum (PG) affecting approximately 2.3% of patients, and aphthous stomatitis.[10]

EN is an acute inflammatory process of the subcutaneous fat, also known as panniculitis. It presents with a rapid onset of tender, deep, non-ulcerating red to purple-brown bruise-like nodules that are 1 cm-5 cm in size **(Figure 2)**. The most characteristic location of these nodules is the shins,

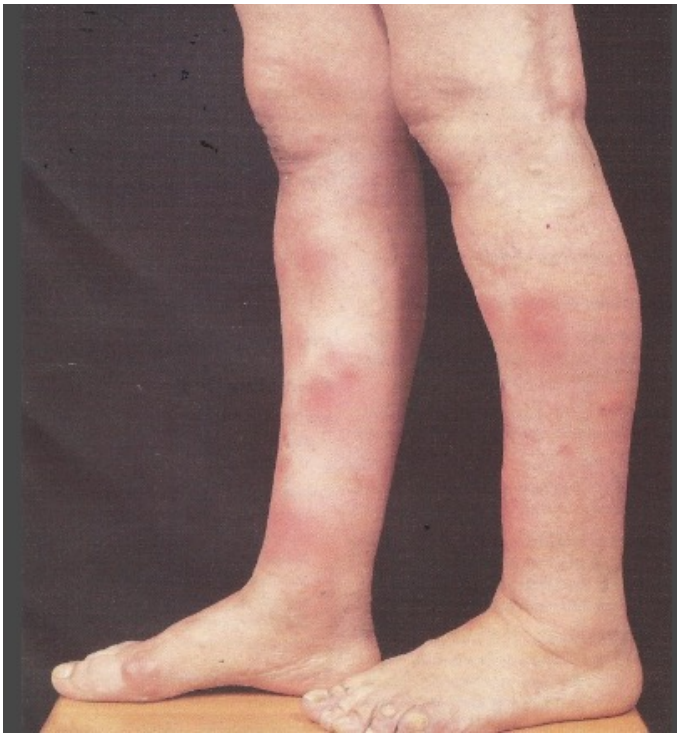

Figure 2: Red-brown indurated plaques on the lower extremity typical of erythema nodosum
Photo courtesy of ©Massimo Defilippo (Symptomeundbehandlung.com)

however the nodules can occur anywhere on the body. Patients may have associated fever, malaise and arthralgias. EN is the most common cutaneous condition affecting patients with IBD, although it is certainly not exclusive to IBD. EN occurs in up to 10% of patients with UC and in up to 15% of patients with CD.[1] It is typically present in the setting of established IBD; however, it precedes IBD in 15% of patients.[11] EN is more common in female patients, patients with arthritis, and in patients positive for human leukocyte

antigen B27 (HLA-B27). In patients with CD, EN is often associated with colonic involvement.[1] EN activity tends to parallel IBD disease activity, often occurring during IBD flares; however, the severity of skin flares does not necessarily mirror IBD flare severity.[1,3,10] Typically, EN is a self-limiting process or resolves with treatment of the underlying condition. Supportive measures such as leg elevation, non-steroidal anti-inflammatory drugs for pain control, and compression are helpful. Some patients may require systemic corticosteroids, steroid sparing anti-inflammatories such as colchicine, dapsone and potassium iodide, and occasionally immunomodulators such as methotrexate, azathioprine, or TNFα inhibitors. Interestingly, infliximab can treat and on occasion trigger EN, in particular in patients with ankylosing spondylitis.[11] EN has been reported to respond to vedolizumab in some reports and not respond in others.[12]

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that can occur both idiopathically and concomitant with a variety of systemic diseases. IBD is the most commonly associated systemic disease, with a reported incidence of up to 3%.[3] PG has greater prevalence in patients with UC, a family history of UC, women, colonic involvement, permanent stoma, ocular involvement, and EN.[3] Patients with IBD and PG are more likely to have arthritis and uveitis.[10] PG has variable presentations with five recognized subtypes. The most common subtypes of PG associated with IBD are ulcerative and pustular, followed by peristomal, bullous and vegetative.[1] PG presents as a papule, pustule or nodule which rapidly ulcerates, becoming a severely tender ulcer with a classic inflammatory gunmetal grey border, ragged undermined edges, epithelial stranding, and a purulent covering **(Figure 3)**.[1] Owing to its appearance and the intense pain it causes, PG is frequently misdiagnosed and treated as an infection. Diagnostic considerations for PG include pathergy (occurring in an area of trauma) and often initiates as a pustule, which occurs in 30% of patients, although this often remains unnoticed before the pustule ulcerates. PG occurs most commonly on the extensor lower extremities and peristomal, though it can occur anywhere on the body.[1] PG classically heals with "cribriform scarring" which has a honeycomb-like appearance.

Similar to EN, patients with PG may have associated fever, malaise, and arthralgias. Unlike EN, which typically occurs in the setting of well-established IBD, PG can precede, coincide with, or occur following the onset of IBD.[3] It does not typically parallel underlying IBD disease activity, with the exception of the pustular variant.

An erosive pustular eruption of the lips and oral mucosa, termed pyostomatitis vegetans, is considered by many as a mucosal variant of pustular PG. This is thought to be more common in men aged 20–59 years, and typically occurs in the course of well-established IBD.[3]

PG treatment initially involves the use of anti-inflammatories and/or immunomodulators to treat the inflammation, followed by treatment of the ulcer with appropriate wound care. Initial treatment may include intralesional and potent topical steroids and/or calcineurin inhibitors if the condition is in the early or mild stages. For more severe disease, prednisone and/or cyclosporine, mycophenolate mofetil, or a TNFα inhibitor are frequently used. To date there are more published reports of patients developing PG while on vedolizumab than there are of PG responding to vedolizumab.[12,13,14] Debridement should not be performed owing to the risk of pathergy. Unfortunately, PG has a recurrence rate of up to 25%.[3]

Sweet syndrome, otherwise known as acute febrile neutrophilic dermatosis, is a rare neutrophilic dermatosis seen in a variety of inflammatory, drug-induced, or malignant settings. It can occur in the context of IBD, both during an IBD flare and in quiescent disease.[15] It is more common in CD, women in the third to fifth decade of life, and CD with colonic involvement.[1] Sweet syndrome presents with tender edematous purple-red papules, plaques, pustules, and sometimes bullae or "pseudobullae," with a predilection for the head and hands. Patients often have systemic symptoms including fever, malaise, and arthralgia and,

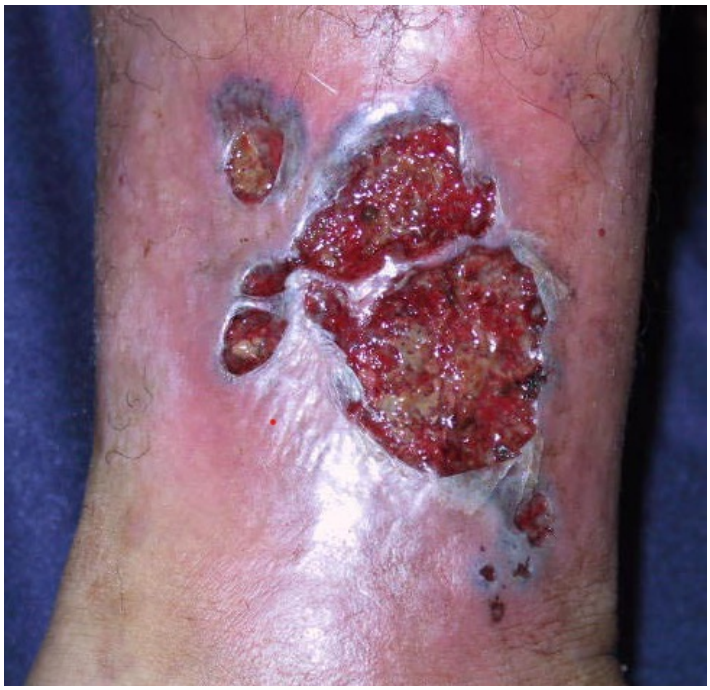

Figure 3. Pyoderma gangrenosum with classic ragged, gunmetal Grey border and epithelial stranding between ulcerations.
Photo credit courtesy of: Healthmd.net

less commonly, can have inner organ involvement. This is often a self-limiting disorder. Treatment is very similar to that of EN and PG, specifically, topical and systemic anti-inflammatories; this disease is highly responsive to systemic steroid treatment.[15] There are reports of Sweet syndrome occurring in a patient with vedolizumab-treated CD,[16] and improvement in a patient with oral corticosteroid UC treatment with the addition of vedolizumab.[17]

Bowel-associated dermatosis-arthritis syndrome (BADAS) is an extremely rare neutrophilic dermatosis which has been reported in patients with IBD or post-gastric bypass surgery. It manifests with fever, arthralgias, myalgias, abdominal pain, and polymorphous skin lesions mimicking PG, EN or hidradenitis suppurativa (HS). It is thought to be secondary to immune complexes which develop due to overgrowth of bacteria in the gut.[1] Treatment includes surgery, antibiotics, and systemic steroids. There are no reports regarding the role of vedolizumab with this condition.

Aphthous ulcers affect approximately 20% of the general population and up to 33% of patients with CD and UC.[3] Aphthous stomatitis manifests with recurring, painful, round, and oval ulcers with an erythematous border and cream-colour base. The presence of aphthous stomatitis should trigger suspicion about IBD, especially in children with IBD because it occurs more frequently in this cohort and may precede the diagnosis of IBD.[7] The oral aphthae correlate with active GI disease and HLA-B27 positivity.[1] A systematic review and meta-analysis identified a trend for lower prevalence of aphthous ulcers in patients treated with infliximab compared to vedolizumab.[18]

Cutaneous polyarteritis nodosa (cPAN) is an uncommon, recurring vasculitis of the small and medium vessels of the skin. Approximately 10% of all cPAN cases are associated with IBD and it can precede the diagnosis of IBD. cPAN presents with erythematous nodules, most commonly on the lower extremities. Clinically, it can mimic EN, PG, or metastatic CD. Biopsy is required for diagnosis. Disease activity does not parallel activity of the underlying IBD.[3] Interestingly, there have been reports of cutaneous vasculitis occurring in patients with both UC and CD on vedolizumab treatment.[19,20]

Epidermolysis bullosa acquisita (EBA) is an extremely rare autoimmune bullous disorder caused by autoantibodies against collagen VII. It presents with non-inflammatory bullae in areas of trauma, most commonly the hands and feet. The bullae heal with scarring and milia formation. Thirty percent of patients with EBA have IBD and CD, more often than UC, and the majority of patients having a long-standing history of IBD. The co-occurrence of EBA and IBD is thought to be due to the phenomenon of epitope spreading.[1] Treatment of the underlying IBD typically results in improvement of the associated skin lesions.[1] There are currently no reports of the effect of vedolizumab on EBA.

Associated conditions

Numerous inflammatory skin conditions are associated with IBD. A recent clinical study demonstrated that rosacea, psoriasis, and atopic dermatitis have a strong association with IBD, while vitiligo and alopecia areata had a lesser or non-existent association.[3]

Psoriasis

The association between psoriasis and IBD is complex. There is a higher incidence of psoriasis, in particular plaque psoriasis, in 11.2% of patients with CD and 5.7% of patients with UC.[1] In addition, patients with psoriasis are predisposed to IBD. The severity of the psoriasis does not correlate with IBD activity. Additionally, certain therapies used to treat IBD can trigger drug-induced psoriasis. The co-occurrence of these inflammatory conditions and their therapeutic overlap suggest shared genetics and inflammatory pathways. In fact, it has been established that these conditions share genetic characteristics.

Psoriasis can be triggered or exacerbated by a variety of medications, including TNFα inhibitors. Drug-induced psoriasis occurs in 2% of patients treated with TNFα inhibitors and appears to occur most commonly in patients with underlying CD and receiving treatment with infliximab.[1,21] Considerations for TNFα-induced psoriasis include a greater proportion of patients with palmoplantar pustular involvement, generalized pustular involvement, severe post-auricular involvement, severe scalp disease resulting in alopecia, and more than one morphology (rather than typical plaque psoriasis).[21] Fortunately, most patients have been reported to resolve (47%) or improve (46%) following cessation of the TNFα inhibitor. However, nearly 50% of patients did not improve after transitioning to a different TNFα inhibitor.[21] Preliminary reports suggest that the phenomenon can occur with other biologics as well, such as ustekinumab.[22] There are also cases of psoriasis induced by vedolizumab.[23,24]

Oral lichen planus can be associated with IBD. It presents with reticulated, white plaques in the mouth (buccal mucosa, tongue, gingiva) which can ulcerate. In addition, oral lichenoid eruptions have been reported with the TNFα inhibitors sulfasalazine and mesalazine.

Cutaneous lichen planus, which presents with itchy, violaceous flat-topped papules and plaques, has

also been reported secondary to TNFα inhibitors.[7,25,26] There are no published reports of vedolizumab induced lichen planus to date.

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease manifesting with open comedones, cysts, nodules, scarring, and fistulous tracts. It occurs predominantly in skin folds. This disease is seen with a 9-fold greater prevalence in patients with IBD, particularly CD. In patients with HS, the CD is often localized to the large bowel. It precedes the HS, which is often located in the perineal or perianal sites.[27] HS activity does not typically mirror luminal activity. Vedolizumab-induced HS has been reported.[28]

Interestingly, the rare syndromes **SAPHO** (synovitis, acne, pustulosis, hyperostosis, osteitis) and **PAPA** (pyogenic arthritis, PG, acne) can be associated with IBD. SAPHO most commonly affects young patients with UC.[1]

Linear IgA bullous dermatosis (LABD) is a rare blistering condition of the skin and mucous membranes which occurs in both children and adults. It is characterized by severe pruritus, with the tense vesicles and bullae appearing in an annular "crown of jewels" arrangement. It has been reported with both CD and UC. In a clinical study, linear IgA in association with UC was reported to remit with colectomy.[29] This disease typically responds well to systemic steroids and the sulfone dapsone. There are no published reports of vedolizumab induced LABD to date.

Additional associated conditions such as vitiligo, finger clubbing, and palmar erythema occur to a lesser degree and have less impact on patients' overall health.

	More common in CD vs. UC	More common in female(F) vs. male(M)	Typically parallels course IBD	Associations	Typically responds to treatment of underlying disase
Erythema	CD > UC	F >M	Yes	Arthritis and uveitis	Yes
Pyoderma Gangrenosum	UC > CD (similar)	M > F	Not necessarily	Increased risk uveitis and arthritis	No
Sweets Syndrome	CD > UC	F > M	Not necessarily	Fever, arthralgias, Other EIMs	Yes
Aphthous stomatitis	CD > UC	M > F Children>adult	Yes	HLA B27+	Sometimes
EBA	CD > UC		-		Yes
PAN	CD > UC		No		No
PsO	CD > UC		No		No

Table 3. Characteristics of common, major reactive and associated mucocutaneous extraintestinal manifestations of inflammatory bowel disease; courtesy of Jennifer Lipson, MD
Abbreviations: CD, Crohn's disease; EIMs, extraintestinal manifestations; HLA B27, human leukocyte antigen B27; IBD, inflammatory bowel disease; UC, ulcerative colitis

The characteristics of various reactive and associated EIMs of IBD are described in **(Table 3)**.

Treatments and treatment-related conditions

Fortunately, treatments for IBD, immune-mediated associated diseases, and dermatologic EIMs frequently overlap, allowing for these diseases to be treated with the same medication. For example, medications include systemic immunosuppressants (prednisone, methotrexate, cyclosporine, azathioprine, sulfasalazine) and immunomodulators (TNFα inhibitors, interleukin 12/23 [IL12/23] inhibitor, IL23 inhibitors, Janus kinase inhibitors). Further research is needed to establish whether the early introduction of advanced therapies, such as biologics and small molecules, to patients with IBD may prevent EIMs, and which treatments are optimal for co-managing IBD and EIMs.

Many of these therapies also have many possible cutaneous side effects. TNFα inhibitors are commonly used to treat IBD and many of the associated immune conditions (psoriasis, psoriatic arthritis, spondyloarthropathies, HS). They have also been reported to cause a variety of skin eruptions including, but not limited to, drug-induced lupus, sarcoidosis, eczema, alopecia areata, pityriasis lichenoides et varioliformis acuta (PLEVA), and vasculitis.[26] Sulfasalazine and azathioprine have both been reported to cause morbilliform eruptions and Sweet syndrome, as well as potentially fatal drug hypersensitivity syndrome,[30] Stevens-Johnson syndrome, and toxic epidermal necrolysis.[31-33] Azathioprine has also been reported to cause azathioprine hypersensitivity syndrome, alopecia, Kaposi sarcoma, and non-melanoma skin cancer. Mesalamine is reported to cause photosensitivity in rare cases, alopecia, and pruritus.[34]

Vedolizumab, a gut-specific monoclonal antibody that targets α4β7-integrin, was approved by Health Canada in 2016 for the treatment of CD and UC. The mechanism of action is through selective inhibition of leukocyte α4β7--integrin binding to its main ligand, mucosal addressin adhesion molecule-1, an adhesion molecule specifically expressed on blood vessels of the GI tract and is upregulated in inflamed venules.[18] This interaction inhibits leukocyte adhesion and migration into the gut, counteracting the lymphocyte trafficking seen in IBD.[35] Vedolizumab has proven efficacy in CD and UC, as well as having a favourable side effect profile. This is currently the only IBD therapy that selectively targets the digestive tract, though more therapeutics are in development. Studying the possibility of gut-specific vedolizumab resulting in an increase in EIMs is challenging. For instance, it is confounded by a significant number of patients transitioning from TNFα inhibitors—which are known to treat numerous EIMS—in order to initiate the gut-specific agent.[36] The effectiveness of vedolizumab in treating the EIMS of IBD is slowly emerging; however, the clinical data have shown inconsistent results. In 2018, a retrospective comparison study reported a lower incidence of EIMs, including EN and aphthous stomatitis, in patients treated with TNFα inhibitors versus vedolizumab.[37] A systemic review that looked at the effect of vedolizumab treatment on EIMs concluded that there is no strong evidence that vedolizumab effectively treats the cutaneous EIMs of IBD, although it may decrease the occurrence of new EIMs.[38] A small prospective study demonstrated the successful resolution of EN and arthritis EIMs in patients with IBD.[12] The efficacy of vedolizumab on EIMs may be due to its enhanced control of gut disease considering that the activity of certain EIMs (including arthritis and EN) parallels gut activity.[11] In a published case report of vedolizumab-induced psoriasis, the condition was shown to resolve with the cessation of the drug.[23] The expectation is that future clinical studies and real world evidence will better clarify the relationship between gut-targeted IBD treatment such as vedolizumab and EIMs.

Conclusion

Mucocutaneous EIMs are common and are important to recognize because they not only cause significant patient morbidity, but may also be the first presentation of IBD, or may indicate ongoing disease activity in the absence of symptoms. With published reports of both improvement and induction of mucocutaneous EIMs with vedolizumab therapy, the final verdict is yet to be delivered regarding the impact of this gut-targeted therapy on these EIMs. With more gut-targeted therapies in development, a deeper understanding of the relationship between this class of drugs and EIMs will be crucial. Moreover, publishing and

Key clinical pearls
Mucocutaneous EIMs are common
Mucocutaneous EIMs may precede the diagnosis of GI disease
Not all EIMs parallel underlying GI disease activity
A growing number of therapies are available which treat IBD and numerous mucocutaneous EIMs
Currently, the impact of vedolizumab on mucocutaneous EIMs is unclear

presenting cases on vedolizumab therapy and EIMs will help bring clarity to this issue. A key take away is that a collaborative relationship between dermatologists and gastroenterologists remains vital in providing comprehensive care to patients with IBD.

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