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CUTANEOUS MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE: CLINICAL PEARLS FOR GASTROENTEROLOGISTS

Introduction
As clinicians' knowledge about the relationship between inflammatory bowel diseases (IBDs) and the integumentary system continues to expand, gastroenterologists and dermatologists need to know about the disease associations involved and understand the impact of treatments on these immune conditions in order to provide care to these medically complex patients.

Extra-intestinal Manifestations (EIMs)
IBD, Crohn's Disease (CD) and ulcerative colitis (UC) carry a broad range of associated extraintestinal manifestations (EIMS) which affect various body systems. The skin is one of the most commonly affected of these. At least 10% of patients with IBD have mucocutaneous EIMs, more commonly with CD where it has been reported in up to 44% of patients.[1,2] In some cases muco-cutaneous manifestations are the presenting feature of IBD.[3] Risk factors for mucocutaneous CD and UC include female gender, younger age of diagnosis and eye or joint involvement. Additional risks in CD include family history of IBD and disease requiring immunomodulatory therapy.[4]

The possible mucocutaneous EIMs of IBD are abundant; therefore, they are best approached by classification according to pathophysiologic origin, including IBD specific; reactive conditions; associated conditions; nutritional deficiencies; and treatment-related conditions **(Table 1)**. Due to their large number, it is not feasible to review every associated condition; only common and significant mucocutaneous EIMs will be addressed in this review. **Table 2** elaborates on the dermatologic conditions associated with nutritional deficiencies.

IBD-specific Mucocutaneous Conditions
IBD-specific mucocutaneous conditions affect the skin by the same mechanisms as in the gastrointestinal (GI) tract. This category is the most common group

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

Table 1. *Common and important mucocutaneous EIMs; courtesy of Jennifer Lipson, MD*

Deficient Nutrients	Name	Cutaneous Manifestations
Vitamin B		Stomatitis, glossitis, angular chelitis
Niacin (B3)	Pellagra	Photosensitivity, sunburn like rash (chest, dorsal hands, dorsal feet) which may blister, then become thick, rough and hyperpigmented. Casals' necklace (pigmentation around neck). Perigential inflammation and glossitis.
Zinc	Acrodermatitis enteropathica	Acral (elbows, knees, fingers, toes) and periorificial (mouth, anus) dermatitis, alopecia, glossitis and nail dystrophy
Vitamin C	Scurvy	Ecchymosis, perifollicular hemorrhage, corkscrew hairs, follicular hyperkeratotic papules, splinter hemorrhages, red bleeding gums
Vitamin A	Phrynoderma	Hyperkeratotic papules on anterolateral thighs and posterolateral arms
Vitamin K		Purpura

Table 2. *Nutritional deficiency associated conditions; courtesy of Jennifer Lipson, MD*

and includes metastatic CD (MCD), oral CD and contiguous lesions (perianal ulcers, fissures/fistulas).[2] 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] This entity typically occurs in well-established GI disease. Skin disease preceding 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. As a result of this, 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 types: ulceration, vulvar swelling, hypertrophic lesions and chronic suppuration.[5] Non-genital MCD most commonly affects the legs, abdomen, trunk and intertriginous sites; it rarely occurs on the face. As MCD is rare, 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; tumor necrosis factor α (TNFα) inhibitors; azathioprine; methotrexate; cyclosporine; thalidomide; and surgical excision.[2]

The granulomatous process of CD extends to the oral cavity (known as oral CD) in 8%-9% of patients. This can present as 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 entity is referred to as granulomatous cheilitis **(Figure 1)**.[6] 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 (ASA) mouth rinses; topical non-steroidal anti-inflammatory paste; and antiseptic washes to prevent infection can also be used.

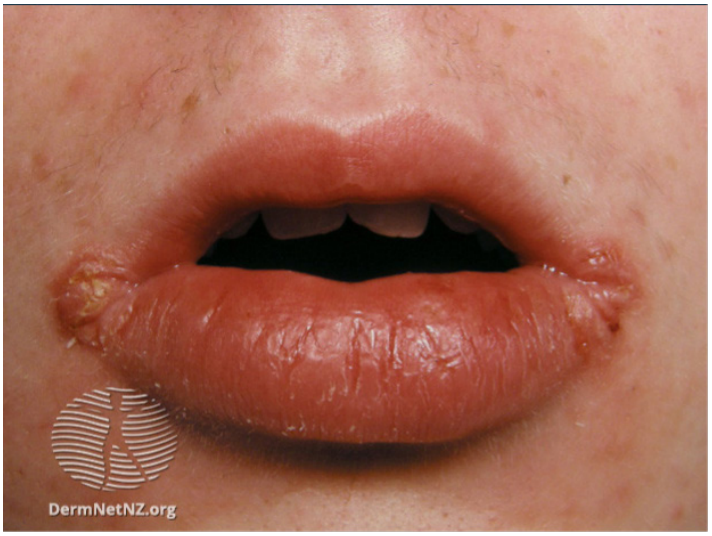

Figure 1. *Typical granulomatous cheilitis with lip swelling and fissuring.*

Controversy exists regarding whether or not perianal fissures and fistulas should be considered EIMs. The European Crohn's and Colitis Organization (ECCO) 2016 guidelines do not consider them EIMs when they occur within the GI tract.[3,7]

Reactive Conditions

The most common mucocutaneous EIMs in the reactive category are erythema nodosum (EN) (7.4%), pyoderma gangrenosum (PG) (2.3%) and aphthous stomatitis.[7]

EN is an acute inflammatory process of the subcutaneous fat (panniculitis) presenting with rapid onset tender, deep, non-ulcerating 1-5 cm red-to-purple-brown bruise-like nodules **(Figure 2)**. The most characteristic location is the shins, but the nodules can occur anywhere in 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 is seen in up to 10% of patients with UC and 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 cases.[8] EN is more common in female patients, patients with arthritis, and HLA-B27 positive patients. In patients with CD, it 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.[1,3,7] In the majority of cases, EN is a self-limiting process or resolves with treatment of the underlying condition. Supportive measures such as leg elevation, non-steroidal anti-inflammatories (NSAIDs) for pain control and compression are helpful. Some cases 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 (AS).[8]

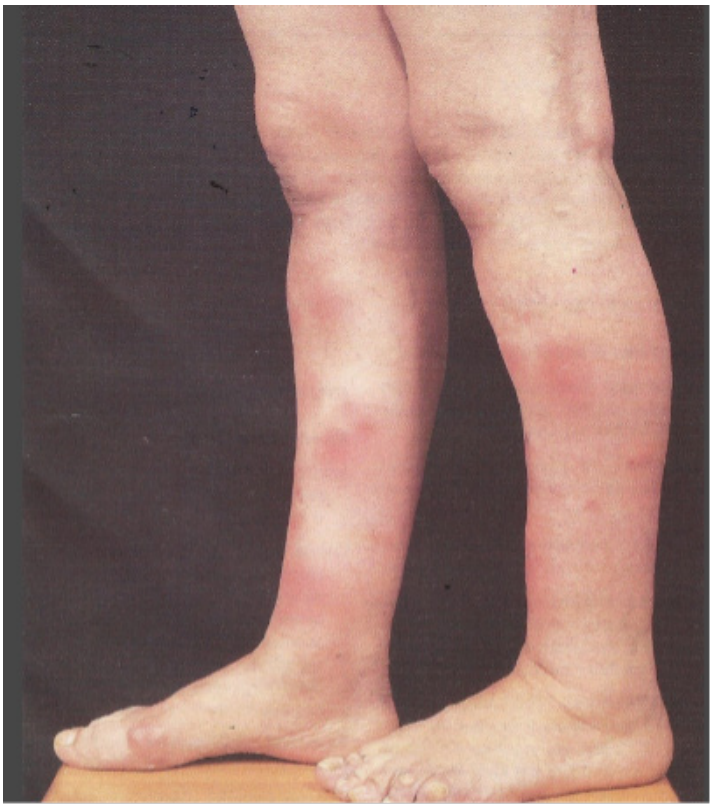

Figure 2. *Red-brown indurated plaques on the lower extremity typical of EN.*
Photo ©Massimo Defilippo (Symptomeundbehandlung.com)

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis seen 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] It 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.[7] PG has variable

presentations with five recognized subtypes. The most common subtypes 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 and a purulent covering **(Figure 3)**.[1] Due 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 initiating as a pustule, which occurs in 30% of cases, although this often remains unnoticed before it ulcerates. PG occurs most commonly on the extensor lower extremities and peristomal, but 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, 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 and typically occurs in the course of well-established IBD.[3]

Treating PG initially involves treatment of the inflammation with anti-inflammatories and/or immunomodulators, 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. Debridement should not be performed due 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 another less common neutrophilic dermatosis seen in a variety of inflammatory, drug-induced or malignant settings. It can occur in the context of IBD, during an IBD flare and in quiescent disease.[9] It is more common in CD, women in the third to fifth decade 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

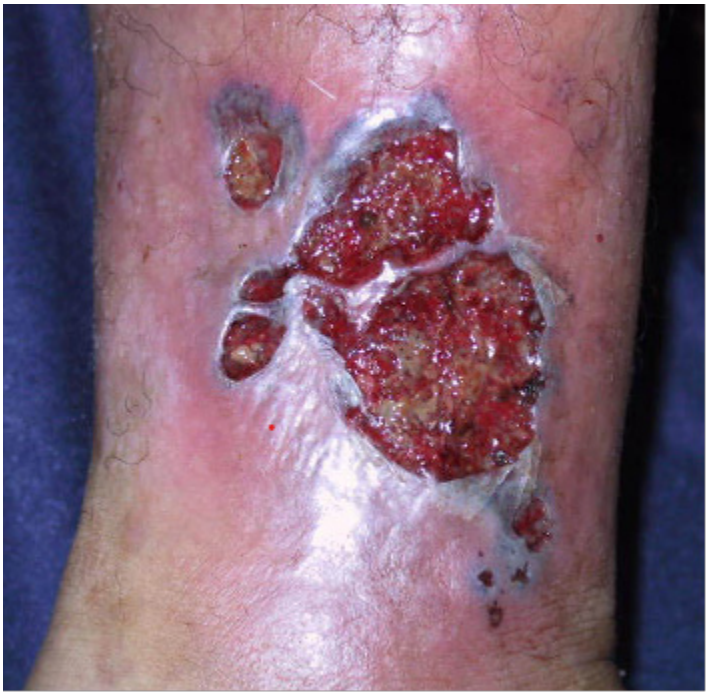

***Figure 3**. Pyoderma gangrenosum with classic ragged, gunmetal grey border and epithelial stranding between ulcerations. Photo credit: Healthmd.net*

have systemic symptoms including fever, malaise and arthralgia and, 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 systemic steroid responsive.[9]

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.

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 as it occurs more frequently in this cohort and may precede diagnosis of IBD.[6] The oral aphthae correlate with active GI disease and HLA-B27 positivity.[1]

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]

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, 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]

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 patients with CD (11.2%) and UC (5.7%).[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; 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 treated with infliximab.[1,10] 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).[10] Fortunately, most patients have been reported to resolve (47%) or improve (46%) following cessation of the TNFα inhibitor. Nearly 50% of patients did not improve after transitioning to a different TNFα inhibitor.[10] Preliminary reports suggest that the phenomenon can occur with other biologics as well, such as ustekinumab and vedolizumab.[11]

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.[6,12,13]

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 9-fold greater prevalence in patients with IBD, particularly CD. In cases of HS, the CD is often localized to the large bowel. It precedes the HS, which is often located in the perineal or perianal sites.[14]

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 of the skin and mucous membranes which occurs in both children and adults. It is characterized by severe pruritis, 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.[15] This disease typically responds well to systemic steroids and the sulfone dapsone.

Additional associated conditions such as vitiligo, finger clubbing and palmar erythema occur to a lesser degree and have less impact on patients' overall health. The characteristics of various reactive and associated EIMs of IBD are described in **Table 3**.

Treatment-related Conditions

TNFα inhibitors commonly used to treat IBD have been reported to cause a variety of skin eruptions including, but not limited to, drug-induced lupus;

	More common in CD vs. UC	More common in Female (F) vs. Male (M)	Typically Parallels course of IBD	Associations	Typically Responds to treatment of underlying disease
Erythema Nodosum	CD > UC	F > M	Yes	Arthritis and uveitis	Yes
Pyoderma Gangrenosum	UC > CD (similar)	M > F	Not necessarily	Increased risk of uveitis and arthritis	No
Sweet 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 EIMs of IBD; courtesy of Jennifer Lipson, MD*

sarcoidosis; eczema; alopecia areata; pityriasis lichenoides et varioliformis acuta (PLEVA); and vasculitis.[13] Sulfasalazine and azathioprine have both been reported to cause mobilliform eruptions and Sweet syndrome, as well as potentially fatal drug hypersensitivity syndrome (DISH),[16] Stevens-Johnson syndrome, and toxic epidermal necrolysis.[17-19] Azathioprine has also been reported to cause azathioprine hypersensitivity syndrome which includes rash, alopecia, Kaposi sarcoma, and non-melanoma skin cancer. Mesalamine is reported to cause rarely-associated photosensitivity, alopecia and pruritis.[20]

Fortunately, treatments for IBD and dermatologic EIMs frequently overlap, allowing for both diseases to be treated with the same medication. This includes systemic immunosuppressants (prednisone, methotrexate, cyclosporine, azathioprine, sulfasalazine) and immunomodulators (TNFα inhibitors, IL 12-23 inhibitors, IL-23 inhibitors, JAK inhibitors). Further research is needed to establish whether or not the early introduction of advanced therapies, such as biologics, to patients with IBD may prevent EIMs, and which treatments are optimal for co-managing IBD and EIMs.

The evolving landscape of IBD treatments, and the increased use of gut-specific therapies introduces the question of whether or not these treatments will have any impact on the incidence and management of EIMs. Vedolizumab, a gut-specific monoclonal antibody targeting a4B7-integrin, was approved by Health Canada in 2016. It has proven efficacy in CD and UC, as well as a favourable side effect profile. The possibility of vedolizumab resulting in increased EIMs is challenging to study: 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.[21] The effectiveness of vedolizumab on 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 vs vedolizumab.[22] A systematic review of the effect of vedolizumab treatment on EIMs concluded that there exists no strong evidence that vedolizumab effectively treats the cutaneous EIMs of IBD, although it may decrease the occurrence of new EIMs.[23] A small prospective study demonstrated the successful resolution of EN and arthritis EIMs in patients with IBD.[24] The efficacy of vedolizumab on EIMs may be due to its enhanced control of gut disease as the activity of certain EIMs (including arthritis and EN) parallels gut activity.[8] In a published case report of vedolizumab-induced psoriasis, the condition was shown to resolve with the cessation of the drug.[25] It is hoped that future clinical studies will better clarify the relationship between gut-targeted IBD treatment such as vedolizumab and EIMs.

Conclusion

Mucocutaneous EIMS occur commonly and are important to recognize as 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. A collaborative relationship between dermatologists and gastroenterologists is proving vital in providing comprehensive care to patients with IBD.

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

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None

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