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Review

Mucocutaneous Manifestations in Inflammatory Bowel Disease

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Abstract

Inflammatory bowel diseases may be associated with extraintestinal manifestations. Among them, mucocutaneous manifestations are relatively common, often difficult to diagnose and treat, and may complicate the course of the underlying disease. Local and systemic immunosuppressive drugs are used in inflammatory bowel disease-related mucocutaneous manifestation treatment, and sometimes dermatological involvement can be improved with effective treatment of inflammatory bowel disease. It should be considered that biological drugs used for the treatment of inflammatory bowel disease may also cause dermatological disorders. A detailed dermatological evaluation is essential in all inflammatory bowel disease patients, particularly biologic therapy candidates. Interdisciplinary cooperation between dermatologists and gastroenterologists is required in diagnosis, follow-up, and treatment. This article aims to review the current literature on the diagnosis and treatment of mucocutaneous disorders that may develop in the course of inflammatory bowel disease.

Keywords: Extraintestinal manifestations, inflammatory bowel disease, mucocutaneous involvement

INTRODUCTION

Many extraintestinal manifestations (EIM) are seen in the course of IBD. They are seen in 47% of all IBD patients, with an overall prevalence of 6%.[1,2] About half of patients develop at least 1 EIM 30 years after the diagnosis of IBD. Although mucocutaneous manifestations are rare, diagnosis is often difficult and may adversely affect the course of the underlying disease. In addition, drug-induced mucocutaneous reactions may develop, and treatment may need to be discontinued or changed, especially in patients treated with biologic drugs. In the literature, different data on the incidence and prevalence of mucocutaneous EIM in patients with IBD are reported in studies of different centers. In the 10-year follow-up of 480 Crohn's disease (CD) in the Portuguese cohort, EIM (45% single, 55% more than 1) developed in 169 patients, mucocutaneous involvement was more prominent in the first 2 years, and colonic involvement was observed.[3]

In the study based on the ENEIDA registry in which 31 077 IBD patients were examined, the global prevalence of EIMs was 19% (more in CD and women) and the prevalence of mucocutaneous EIM was 5% [2.9% erythema nodosum (EN), 0.9% pyoderma gangrenosum (PG), and 1.3% others].[4] In the Greek cohort, 1860 patients with IBD were studied, with a global prevalence of EIM 33.1% (more CD and women) and a prevalence of mucocutaneous EIM 14% [5.3% EN, 0.8% PG, 21.2% aphthous stomatitis (AS), Sweet's syndrome (SS), hidradenitis suppurativa (HS), and others] has been reported.[5] In a multinational study reported from Asia, the global prevalence of EIM was 11.3% (higher in CD and females, usually presenting in the first 2 years after diagnosis) and a prevalence of mucocutaneous EIM of 1.6% in 1764 patients with IBD.[6] In Kayar et al's[7] study, which included an average of 7.5 years of follow-up of 338 CDs, the detection rate of at least 1 EIM was 47.3% (2.19 times more in women), and the rate of mucocutaneous EIM was 9.2%.

Mucocutaneous signs and symptoms associated with IBDs are discussed under 5 different headings in the relevant literature (Table 1), and information on the clinical findings, course, and treatment of these disorders are also summarized in Table 2.

SPECIFIC MUCOCUTANEOUS MANIFESTATIONS

It is characterized by mucocutaneous involvement with histological findings similar to intestinal disease. The cutaneous involvement, which is mainly seen in CD, arises by this mechanism. The metastatic CD was first described by Mountain in 1970.[8] Its frequency is reported to be between 15% and 44%. Lesions characterized by ulcerated nodules, plaques, abscesses, papules, and pustules on the skin are seen in the anterior abdominal wall, under the breast, lower extremities, and intertriginous areas. In its pathogenesis; cross-reactions with antibodies developed for intestinal antigens and/or granulomatous reactions to immunocomplexes accumulated in the skin are suggested. It is more frequently associated with colonic-rectal involvement and parallel to the IBD activity. There may be no recovery response after surgical resection of the affected bowel segment. The differential diagnosis includes cutaneous sarcoidosis, foreign body reaction, PG, HS, EN, and mycobacterial infections.[9-12]

There is very little describing cutaneous metastatic ulcerative colitis (UC). Literature reports describe specific manifestations found only in CD, suggesting metastatic UC is a very rare and underreported manifestation found in UC populations.[13]

Table 1. Classification of Mucocutaneous Manifestations of IBD

Specific Mucocutaneous Manifestations	Disorders Associated with IBD	Reactive Mucocutaneous Manifestations	Mucocutaneous Conditions Secondary to Treatment of IBD	Mucocutaneous Manifestations Secondary to Nutritional Malabsorption
• Continuous Crohn's disease • Metastatic Crohn's disease	• Aphthous stomatitis • Erythema nodosum • Psoriasis • Epidermolysis bullosa acquisita	• Pyoderma gangrenosum • Sweet's syndrome • Bowel-associated dermatosis-arthritis syndrome • Pyodermatitis-pyostomatitis vegetans • SAPHO syndrome • PAPA syndrome	• Adverse mucocutaneous reactions *(injection site reactions, infusion reactions, paradoxical reactions, eczamatiform and psoriasiform reactions, life-threatening disorders)* • Cutaneous infections • Cutaneous malignancies	• Stomatitis • Glossitis • Angular cheilitis • Pellagra • Scurvy • Purpura • Acrodermatitis enteropathica • Phrynoderma • Seborrheic-type dermatitis • Hair and nail abnormalities

IBD, inflammatory bowel disease, PAPA, pyogenic arthritis, pyoderma gangrenosum, acne; SAPHO, synovitis-seronegative arthropathy, acne, pustulosis, hyperostosis and osteitis.

CUTANEOUS DISORDERS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASES

They are mucocutaneous diseases that are relatively common in patients with IBD, and their histology and pathogenesis are different from IBD. Aphthous stomatitis , EN, psoriasis (PS), and epidermolysis bullosa acquisita (EBA) are included in this group.

The prevalence of *AS* and periodontitis is 20%-50%, the frequency is higher in CD, and its recurrence is higher in UC. Aphthous stomatitis is presented before the diagnosis of IBD in 25% of patients. Its clinical presentation is round-oval painful ulcers on the mucosa, pustules, hemorrhagic erosion, and gingival redness. Immunocomplex deposition and aberrant immune response are predicted in the pathogenesis. In addition to IBD treatment, antiseptic mouthwashes, topical corticosteroids/tacrolimus, and anti-tumor necrosis factor (TNF) treatments can be applied in refractory cases. The clinical course is good, and ulcers <10 mm heal without scarring.[10,14,15]

The prevalence of EN is 15%, and its frequency is higher in CD and women. It is characterized by subcutaneous painful nodules 1-5 cm in diameter, usually located on the anterior tibia. Type IV hypersensitivity reaction is predicted in its pathogenesis. The frequency of concomitant arthritis is high, and it is proportional to IBD activity but not correlated with severity and prevalence. It is associated with colonic involvement in CD. Lesions regress after proctocolectomy in UC. The typical course is 3-6 weeks and heals without scarring. In the treatment, analgesics and elevation are sufficient in addition to IBD treatment.[2,16,17]

The prevalence of EBA is about 30%, and it is more common in CD. Increased fragility of the skin, susceptibility to superficial trauma, vesicles, noninflamed bullae, and hyperpigmentation occur; it is often localized in the back of the hand and knee–elbow regions. In its pathogenesis, it has been suggested that inflammation in IBD stimulates the production of autoantibodies and that these antibodies cross-react with type VII collagen in the skin in susceptible individuals. IgG positive for type VII collagen was found in 68% of IBDs. Local and systemic corticosteroids, azathioprine, and antibiotics are used in the treatment, and the lesions heal by leaving a scar.[10,18,19]

Psoriasis. It occurs in 7-11% of patients with IBD, and its frequency is higher in CDs. Some of the cases occur due to the use of anti-TNF; in these cases, the treatment should be changed to ustekinumab.[9,16]

MAIN POINTS

- Mucocutaneous involvement is one of the important extraintestinal manifestations (EIMs) that can be seen in the course of inflammatory bowel diseases (IBD).
- These EIMs require an interdisciplinary approach with dermatologists for their diagnosis and treatment.
- While local and systemic immunosuppressive drugs provide improvement in their treatment, many of these disorders improve or resolve with the control of IBD activity.

REACTIVE MUCOCUTANEOUS MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASES

Under this title, dermatological manifestations that are different from the histopathological findings of accompanying IBD but with a similar pathogenetic mechanism are defined. Pyoderma gangrenosum, SS, bowel-associated dermatosis-arthritis syndrome (BADAS), pyodermatitis-pyostomatitis vegetans, synovitis-seronegative arthropathy, acne, pustulosis, hyperostosis and osteitis (SAPHO), and pyogenic arthritis, PG, acne (PAPA) syndrome are reactive mucocutaneous manifestations that can be classified in this group.[16]

Pyoderma Gangrenosum. Its incidence in IBD is 0.4%-2%, and it is more common in UC and in women. It can occur before, during, and after IBD. Moreover, 15% of cases are diagnosed before IBD; 50% of all PG cases are accompanied by IBD. Lesions are in the form of single/multiple erythematous papules/pustules/sterile necrosis or ulcers. Neutrophil dysfunction and changes in cellular immunity are responsible for its pathogenesis. Pathergy positivity is common in cases. The recurrence rate is high, 25% of the cases have a serious course. The course of PG is independent of IBD activity, and the response to colectomy is poor. Lesions heal, leaving a cribriform scar. Local/systemic corticosteroids tacrolimus, cyclosporine, calcineurin inhibitors, anti-TNF, and ustekinumab can be used in the treatment.[2,10,16]

The success rate of treatment consisting of topical corticosteroid and tacrolimus used in limited disease in ulcers <5 cm^2 has been reported as 44%. In extensive and/or rapidly progressive disease, oral corticosteroids (1-1.5 mg/kg) or oral cyclosporine or infliximab should be preferred as primary care. In a randomized controlled trial involving 32 patients using infliximab, infliximab was compared with a single dose of 5 mg/kg placebo; improvement was 46% and 6% in both arms, respectively. Oral cyclosporine was found to be effective in cases unresponsive to anti-TNF. In the Study of Treatments fOr Pyoderma GAngrenosum Patients (STOP-GAP study), 112 patients were recruited, and cyclosporine and prednisolone were compared.

Table 2. Diagnostic and Therapeutic Management of Mucocutaneous Manifestations Associated with IBD

Mucocutaneous Disorder	Epidemiology	Clinical Presentation	Pathogenesis	Clinical Course	Treatment
Metastatic CD	Prevalence in CD 18-44% very rare in UC	• Subcutaneous nodules, plaque, abscess or nonhealing ulcers • Location:genital (more common in children) vs. nongenital (more commonly affects lower extre mities, abdomen, and trunk) • Affects: adult/female predilection	• Cross-reaction with antibody that develops for intestinal antigens • Granulomatous reaction to immunocomplexes accumulating in the skin	Recovery with sequelae	• Local tx: HLA, Tacro • Systemic tx: CS, Cyc, CNI, anti-TNF, MTX, AZT, Metronidazole
Aphthous Stomatitis Periodontitis	CD ~ UC (AS frequency CD > UC AS recurrence UC > CD) Frequency 10% in 25% of cases, the diagnosis is made before the diagnosis of IBD	• Round-oval painful ulcers, gingival redness, pustule, hemorrhagic erosion • Location: buccal-labial mucosa, lateral - ventral tongue, soft palate, and oropharynx	Immune complexes, aberrant immune response	Ulcers <10 mm heal without scarring	• IBD treatment • Antiseptic mouthwash, topical CS, anti-TNF
Erythema Nodosum	CD > UC F > M Frequency 15%	• 1-5 cm red subcutaneous painful nodule • Location: anterior tibia	Type IV hypersensitivity reaction	Self-limiting Scar-free healing	• Analgesic, limb elevation, potassium iodine • Serious disease: CS and anti-TNF
Epidermolizis Bullosa Aquisita	CD >> UC Frequency ~30%	• Increased fragility of the skin, blister formation, and scarring • Location: back of hand, knee–elbow	Antibody to type VII collagen *(autoantibody reacts with type VII collagen at the dermo-epidermal junction)*	Scarring healing	• Local-systemic CS • AZT, dapsone, antibiotic
Psoriasis	• In 7-11% of patients with IBD • CD > UC • Unrelated to activity and severity of IBD • Psoriasis after anti-TNF use	• Erythematous squamous papules and plaques, pustules • Location: scalp, elbows, palmar, and plantar regions, skin folds	• Genetic (HLA linkage) or Immunologic related mechanisms	• Mild progress • Reversible • %5-35 ned for discontinuation whwn it develops in the course of treatment	• Local tx: CS, UVB • CS, MTX, Vit D, retinoids, anti-TNF • Persistent psoriasis: switch to Ustekinumab
Pyoderma Gangrenosum	UC > CD F > M Frequency 0.4-2% IBD accompanies in 50% of cases	Single/multiple erythematous papules/pustules/ste rile necrosis or ulcer on the skin	• Neutrophil dysfunction • Cellular immunity • Pathergy +	• High recurrence rate • 25% serious course • Cribriform scar • Poor response after colectomy	• Local tx: CS, Tacro • Systemic CS, Cyc, CNI, anti-TNF, Ustekinumab, Anakinra
Pyostomatitis vegetans	• Rare • M > F • UC > CD • All cases associated with IBD parallel course to IBD activity	• Hyperplastic folds of buccal and labial mucosa (‘cobblestone mucosa’) that progress to shallow ulcers • Mucogingivitis	Unclear, but possibly related to cross-reacting antigens between the bowel and skin	Mucosal lesions after regression of IBD flare or after surgical treatment	• Topical CS and antibiotic mouthwashes • Systemic CS • Dapson, AZT, Cyc, Tacro
Sweet’s syndrome	• Rare • Female predominance; IBD is the third most common disorder associated with Sweet’s Syndrome	• Painful exanthema, papulosquamous, or nodules located in face, neck, upper chest, back, and extremities, often accompanied by fever	Histocompatibility antigen association	Acute onset, associated with arthritis, fever, and ocular symptoms; No scarring	• Topical or systemic CS • Immunomodulators
Hidradenitis supurativa	CD > UC	Affects areas of the skin with a high density of apocrine glands (axillae, groin, perianal and perineal regions), characterized by the development of subcutaneous nodules, sinus tracts, fistulae formation, and dermal scarring	Follicular hyperkeratosis, with occlusion, dilatation, and disruption of the follicle resulting in a local inflammatory response		• Topical and/or systemic antibiotics, retinoids, and anti-TNF agents
BADAS	Rare	• Ulcers, plaques and nodules, abscesses and fistulas • No preferential sites or widespread	Unclear neutrophil-mediated inflammation		• Topical or systemic CS • Cyc • Anti-TNF

AZT, azatiopurine; BADAS, bowel-associated dermatosis-arthritis syndrome; CD, Crohn’s disease; CNI, calcineurin inhibitor; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; MTX, methotrexate; TNF, tumor necrosis factor; Tx, treatment; UC, tumor necrosis factor; UVB, ultraviolet B.

A recovery rate of 50% was reported up to 6 months in both groups. The use of ustekinumab, thalidomide, and intravenous immunoglobulin is recommended in refractory cases. Treatment requires a multidisciplinary approach, wound care is very important, and debridement is contraindicated.[20-23]

Pyostomatitis Vegetans. Almost all cases of PV are associated with IBD, and it is common in male patients aged between 29 and 50. Pyoderma gangrenosum association is common, and a course parallel to IBD activity is observed. Hyperplastic folds of ulceration ("cobblestone mucosa") and mucogingivitis are seen in the buccal and labial mucosa. Its pathogenesis is not known exactly, but it is predicted that it may cross-react with intestinal and skin antigens. Lesions regress completely after IBD treatment or surgery. Topical or systemic corticosteroids, antibiotics, tacrolimus, cyclosporine, azathioprine, and dapsone can be used in the treatment.[24,25]

Sweet's Syndrome. It is an acute neutrophilic dermatosis, more common in women and those with CD. It presents as localized painful erythema, papulosquamous, or nodular lesions on the face, neck, upper extremities, and back. The lesions are of acute onset and are often accompanied by fever. It heals without scarring. Topical or systemic corticosteroids and immunomodulators are used in the treatment.

SAPHO syndrome, PAPA syndrome, and BADAS are less common reactive mucocutaneous manifestations.

MUCOCUTANEOUS CONDITIONS SECONDARY TO TREATMENT

Adverse reactions related to drugs used in the treatment of IBD, cutaneous infections, and skin malignancies (mainly basal cell and squamous cell cancer with thiopurines therapy) are included under this title (Table 1). Biologics can however induce a wide variety of skin eruptions, especially those targeting the TNF-α and Th17 pathway.[26] While some of the drug infusion reactions can be prevented with premedications to be applied before the treatment, some others may require discontinuation of the treatment. These dermatological manifestations require cooperation with a dermatologist in their diagnosis and treatment.

MANIFESTATIONS DUE TO NUTRITIONAL MALABSORPTION

The cutaneous manifestations due to malabsorption include diseases that are secondary to deficits in vitamins and trace elements (Table 1). In all these disorders, the substitution of the deficient factor leads to a complete resolution of the cutaneous lesions. Recommended supplements are zinc, vitamin A, E, K, and iron.[26]

CONCLUSION

Mucocutaneous involvements are important extraintestinal manifestations in IBD patients, who should be examined for mucocutaneous alterations upon presentation and during the course of the disease. The etiology of these disorders associated to IBD is quite diverse, and, therefore, treatment should be individualized and directed to treating the underlying IBD as well as the specific dermatologic condition. The treatment of the majority of mucocutaneous disorders associated with IBD is empiric, including topical and systemic immunosuppressants, immunomodulatory, and biological agents. Many of these disorders improve or resolve with the control of IBD activity. An interdisciplinary approach between dermatologists and gastroenterologists plays an essential role in the management of these patients.

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