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Skin manifestations of inflammatory bowel disease

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Abstract Ulcerative colitis (UC) is an inflammatory disorder of the colon that is associated with several extraintestinal manifestations in multiple organs. Several mucous membrane and skin disorders occur in patients with UC. These disorders are not unique to UC and often occur secondary to other causes or in the absence of an apparent cause. One or more such disorders may occur together in association with UC. Mucous membrane and skin disorders may antedate, occur with, or postdate the onset of UC. The dermatologist plays an important role in suspecting the diagnosis of UC that presents with associated mucous membrane or skin disorders. This review covers the clinical presentation, differential diagnosis, workup, and management of selected mucocutaneous manifestations in UC.

Introduction

Ulcerative colitis (UC) affects 0.37% of the population and often presents in 15- to 35-year-old patients with abdominal pain, bloody diarrhea, abdominal distension, anorexia, weight loss, and fatigue.[1] The disease is characterized by continuous colonic inflammation involving the mucosal and submucosal layers and rare involvement of the small bowel.[2] Evidence suggests that genetic and environmental factors contribute to UC. These genetic associations include the major histocompatibility complex locus human leukocyte antigen class II alleles, the interleukin-1 family of genes, and the multidrug-resistance gene *MDR1*.[3] Infectious agents causing an episode of acute gastroenteritis may also play a role in the initiation or exacerbation of UC.[4] The disease may be associated with extraintestinal manifestations that involve multiple organs. These include (Table 1) the eye, joints, liver, mucous membranes, and skin.[5,6] This review will focus on the mucous membrane and skin disorders associated with UC. It has been estimated that 5.2% of patients with UC have mucous membrane lesions and 11% have skin lesions.[7] Patients may present with more than one mucocutaneous complication.[8]

Mucous membrane and skin disorders associated with UC may be divided into 3 groups based on the nature of the association (Table 2): (*a*) disorders secondary to malnutrition, (*b*) disorders secondary to drugs used in the treatment of UC, and (*c*) disorders where the nature of the association is not clear.[9]

Manifestations secondary to malnutrition and malabsorption

Malnutrition occurs in patients with UC particularly when the disease affects the small intestine. The factors implicated in malnutrition are numerous and include low energy intake, poor digestion and absorption, bacterial overgrowth, surgical resection, colonic losses, and metabolic demands. Pharmacologic agents may also play a role. Treatment with sulfasalazine/sulfapyridine, azathioprine, or cholestyramine may contribute to folic acid,[10] niacin,[11] and fat-soluble vitamin deficiencies, respectively.[12] Deficiencies in albumin, water-soluble

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vitamins, and zinc are occasionally reported. Manifestations of these deficiencies include acrodermatitis enteropathica, pellagra, stomatitis, glossitis, and cheilitis.[13]

Manifestations secondary to drug therapy

Treatment of UC often includes systemic glucocorticoids and other immunosuppressive agents; the use of these drugs may be complicated by skin infections and acneiform eruptions.

Other disorders

This group of mucous membrane and skin disorders is associated with UC without a known etiologic link. The occurrence and flare of these disorders usually coincide with the flare of the underlying UC. The connection between these diseases and UC has not been fully elucidated. They are believed to represent reactions to unknown antigens related to UC. Multiple skin and mucous membrane disorders have been reported in association with UC (Table 3). Erythema nodosum (EN), pyoderma gangrenosum (PG), Sweet syndrome (SS), oral aphthosis, and pyostomatitis vegetans are common examples of such eruptions. Psoriasis,[14] lichen planus,[15] erythema multiforme,[16] leukocytoclastic vasculitis,[17] dermatitis herpetiformis,[18] epidermolysis bullosa acquisita,[19] and cutaneous necrotizing vasculitis[20] are less common examples. We will discuss in detail the first 4 conditions.

Erythema nodosum

Epidemiology

Erythema nodosum is the most common cutaneous manifestation associated with UC. Women with UC are more commonly affected than men.[21] When EN occurs in association with UC, it is typically associated with exacerbation of the colitis.[22] Erythema nodosum rarely precedes the diagnosis of UC.[23] The severity of the EN does not necessarily parallel the severity of the UC.[24]

Clinical and histopathology

The primary lesions are deep-red tender nodules distributed symmetrically over the anterior lower legs. Occasionally, they appear on the trunk, upper extremities, and face (Fig. 1). The lesions do no exhibit suppuration or ulceration, and they change in color to a yellowish hue similar to a bruise. They heal spontaneously within 6 weeks. The eruption may be accompanied by fever, synovitis, and arthritis.[25] The differential diagnosis of EN includes other types of panniculitis, cutaneous infections, and subcutaneous lymphomas.

The histopathology is, however, characteristic. It reveals a septal panniculitis characterized by infiltration of the subcutaneous septae by neutrophils and lymphocytes. Later, fibrosis and macrophages predominate; and sometimes, these cluster to form nodular aggregates known as *Miescher radial granulomas*.[26]

Pathogenesis

Erythema nodosum is believed to be a delayed hypersensitivity reaction. The inciting antigen is identified in approximately 40% of cases. In most patients, however, the disease is idiopathic. Identifiable causes include bacterial infections (eg, streptococcal infections), fungal infections (eg, histoplasmosis), drugs (eg, oral contraceptive pills), malignancy (lymphomas), pregnancy, and inflammatory bowel disease[27] (eg, UC) (Table 4). The prevalent underlying cause varies by the population and the geographic location. In children, streptococcal infections seem to be the most common cause.[28,29]

Table 1 Extraintestinal manifestations of UC

Ocular	Uveitis, iritis, episcleritis, cataracts
Rheumatologic	Ankylosing spondylitis, sacroiliitis, hypertrophic osteoarthropathy
Hepatobiliary	Fatty liver, sclerosing cholangitis, autoimmune hepatitis, cholelithiasis, pancreatitis
Mucocutaneous	Multiple

Table 2 Groups of mucocutaneous disorders associated with UC

Disorders secondary to malnutrition/ malabsorption	Anemia, cheilitis, glossitis (vitamin B, Fe), acrodermatitis enteropathica (zinc), pellagra (niacin)
Disorders secondary to treatment	Acne, cushingoid features, infections, drug eruptions
Disorders of unclear association	EN, PG, SS, aphthous stomatitis, pyostomatitis vegetans, etc

Table 3 Mucocutaneous manifestations of UC

Skin	Mucous membrane
EN	Oral aphthosis
PG	Pyostomatitis vegetans
SS	Hemorrhagic ulcers
Vesiculopustular eruptions	Lichen planus
Leukocytoclastic vasculitis	Perianal fissures
Erythema multiforme	
Psoriasis	
Necrotizing vasculitis	
Dermatitis herpetiformis	
Epidermolysis bullosa acquisita	
Polyarteritis nodosa	
Lichen planus	

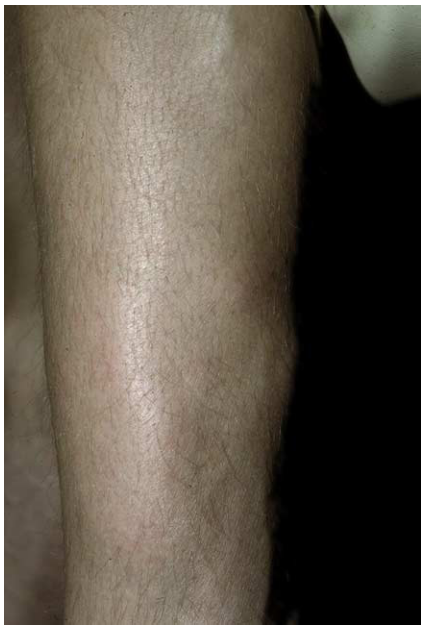

Fig. 1 A child with EN and UC. Tender nodules located on the leg.

Workup

A complete evaluation includes a detailed review of systems and history of abdominal pain and diarrhea, drug intake, pregnancy, and infections. Patients with bowel symptoms may be evaluated by colonoscopy to exclude underlying UC. Laboratory evaluation includes a throat culture, antistreptolysin antibody, blood culture, stool culture, erythrocyte sedimentation rate, chest X ray, and tuberculin skin test.[30]

Treatment

The disease is self-limited with excellent prognosis. In the setting of UC, the time to remission is on the average 5 weeks.[31] Recurrence is rare. Supportive treatment with compression stockings, leg elevation, and rest may be sufficient. For severe cases, nonsteroidal anti-inflammatory drugs (eg, aspirin, naproxen, probenecid, and indomethacin),[32] prednisone, potassium iodide,[33] colchicine,[34] and hydroxychloroquine[35] may be used.

Pyoderma gangrenosum

Epidemiology

Pyoderma gangrenosum affects 0.5% to 20% of patients with UC.[9] A slight female preponderance may exist.[5] Pyoderma gangrenosum tends to appear after the onset of the UC. It usually manifests around the time of exacerbation of the underlying bowel disease.[36] Few cases preceding the onset of the UC or affecting patients with quiescent bowel disease have been documented.[36,37]

Clinical and histopathology

Pyoderma gangrenosum presents in 4 clinical varieties: classic, pustular, bullous, and vegetative.[38] Classic ulcerative PG is characterized by a painful deep ulcer with a violaceous undermined border and a necrotic purulent center (Fig. 2). This variety typically affects the legs, but may occur anywhere including the head and neck, genitalia,[39] and stoma sites.[40] Pyoderma gangrenosum occurs at multiple sites in 70% of the cases.[41] Half of the patients develop ulcers in response to trauma, a phenomenon known as *pathergy*. Pustular PG presents as a painful sterile pustule that does not progress to ulceration. Bullous PG, on the other hand, begins as a tense bulla that rapidly progresses into an ulcer. Vegetative PG starts as a superficial ulcer that slowly develops into a vegetative or exophytic lesion.

The differential diagnosis of PG includes cutaneous infections, SS, cutaneous malignancies, vasculopathies, collagen vascular diseases, and halogenodermas.

A skin biopsy will confirm the clinical suspicion, and it helps exclude other disorders that mimic PG. The histologic findings vary depending on the age of the lesion. Classic PG is characterized by a dense dermal neutrophilic infiltrate, with a central zone of necrotizing suppurative inflammation and a mild perivascular lymphocytic infiltrate. Ulceration appears in the later stages.[42]

Pathogenesis

The pathogenesis of PG is uncertain. A number of systemic disorders have been associated with this disease including myelodysplasia, monoclonal gammopathy, leukemia, rheumatoid arthritis, and inflammatory bowel disease. Ulcerative colitis is the most common of these disorders.[43] It is likely that the trigger inciting PG differs with different underlying diseases. Autoantibodies that cross-react between gut antigens and cytokeratins may play a role in patients with

Table 4 Causes of EN

Bacterial infections	Streptococcal infections, tuberculosis, yersinia enterocolitis, mycoplasma pneumonia, leprosy, salmonella, lymphogranuloma venereum
Fungal infections	Coccidiomycosis, histoplasmosis, blastomycosis
Drugs	Sulfonamides, oral contraceptive pills
Inflammatory bowel disease	UC, Crohn disease
Malignancy	Hodgkin lymphoma, non-Hodgkin lymphoma
Other	Pregnancy

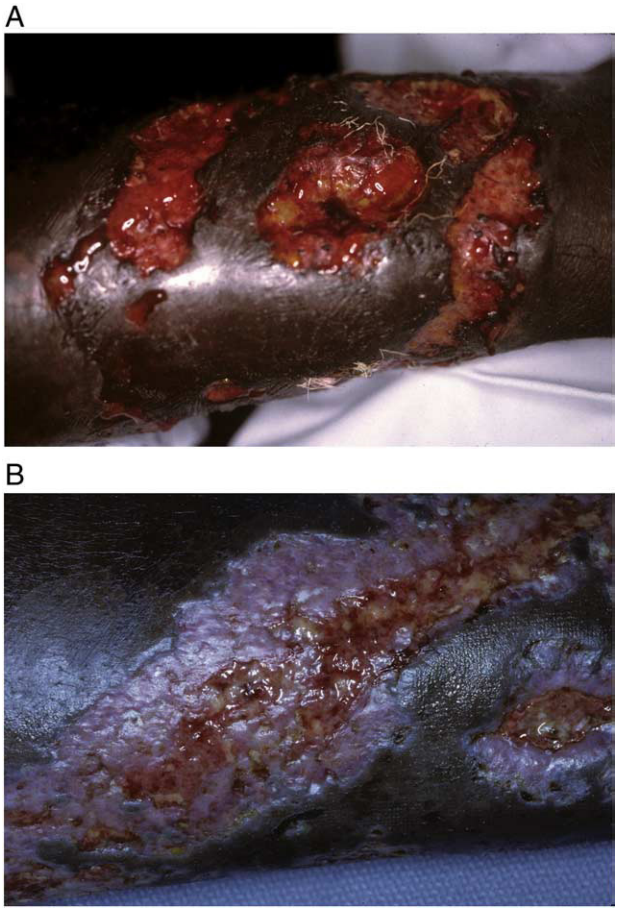

Fig. 2 Classic PG in a patient with UC. A, Multiple deep ulcers with irregular undermined borders. B, Ulcers healing after treatment with cribriform scars.

underlying gut disease.[42] Impaired cellular immunity and altered neutrophil chemotaxis to microbial antigens have been demonstrated in other patients.[44] Classic and pustular PGs are the subtypes commonly associated with inflammatory bowel disease and arthritis. Bullous PG, on the other hand, is frequently associated with myeloproliferative disease.[45,46]

Workup

A detailed history and review of systems should be obtained, with special focus on the organs affected by the systemic diseases associated with PG. Complete blood count with differential, erythrocyte sedimentation rate, liver function test, and renal panel are recommended. Additional studies such as serum and urine electrophoresis, bone marrow aspirate and peripheral smear may be ordered to evaluate for hematologic malignancies.[35,36] In patients with bowel symptoms, colonoscopy is indicated to exclude any underlying UC.[47] Tissue cultures for bacterial, mycobacterial, and fungal infections may be indicated to exclude cutaneous infections.

Treatment

Treatment of PG includes treatment of the underlying systemic disease. No specific therapy for PG is uniquely effective. Management of the ulcers includes topical, intralesional, and systemic therapy. Superpotent corticosteroids or intralesional corticosteroids may be considered in small lesions. Tacrolimus, pimecrolimus, cromolyn sodium, 5-aminosalicylic acid, and platelet-derived growth factor have all been reported as treatment option for PG, with variable success rates.[48] Topical therapy may be used in conjunction with systemic therapy. The mainstay of systemic therapy is oral prednisone or cyclosporine.[49] Other systemic agents for the treatment of PG have been reported with conflicting results. These agents include pulsed methylprednisolone, mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, intravenous immunoglobulins, clofazimine, minocycline, plasmapheresis, and interferon-α.[48] Infliximab, a chimeric anti–tumor necrosis factor α monoclonal antibody, seems to have a favorable outcome.[50] The response to treatment is variable. In the setting of UC, the time to remission is on average 20 weeks.[31]

Surgical treatment of the lesions carries the risk of pathergy. Debridement and grafting for nonhealing ulcers may be considered if the PG is in remission.

Sweet syndrome

Epidemiology

Sweet syndrome is also termed *acute febrile neutrophilic dermatosis*. The classic variant affects women between the ages of 30 and 50 years. Crops of erythematous, edematous papules and plaques appear on the face, neck, trunk, and extremities.[51] Lesions affecting the fingers,[52] external auditory meatus,[53] and oral cavity[54] have been described. Sweet syndrome may mimic palmoplantar pustulosis[55] or cellulites.[56] The eruption is characterized by pain or burning; and it may be associated with fever, arthralgias, headache, and fatigue. Although the skin is the primary target, other organs such as the lungs and, to a lesser degree, the eyes, bones, joints, pancreas, liver, and kidneys may be affected. Pulmonary involvement presents as a chronic cough or pulmonary infiltrates on chest radiographs.[57] Ocular involvement may also occur in the form of conjunctivitis, episcleritis, or keratitis.[58]

Clinical and histopathology

The classic variant usually occurs a few weeks after an upper respiratory or gastrointestinal tract infection. Sweet syndrome may occur in other clinical settings such

Table 5 Causes of SS

Hematologic malignancies	Acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplasia, lymphoma, multiple myeloma
Nonhematologic malignancies	Genitourinary, breast, ovarian, prostate, thyroid, lung cancer
Infections	*Streptococcus*, *Staphylococcus*, salmonella, yersinia, HIV, cytomegalovirus, hepatitis, *Helicobacter pylori*, tuberculosis
Drugs	Granulocyte colony-stimulating factor, trimethoprim-sulfamethoxazole, oral contraceptive pills, minocycline, furosemide, hydralazine, lithium, diazepam, vaccines
Systemic diseases	UC, Crohn disease, Sjögren disease, Behçet disease, lupus erythematosus, rheumatoid arthritis
Pregnancy	

as malignancy (usually myeloproliferative), drugs, systemic disease, and pregnancy (Table 5). An inflammatory systemic disease is identified in nearly 15% of patients with SS.[51] The most common systemic diseases are UC and Crohn disease. Sweet syndrome usually occurs during an acute exacerbation of the underlying UC.[59-61] Less commonly, it precedes the onset and the diagnosis of the inflammatory bowel disease.[62] The differential diagnosis includes PG, erythema multiforme, urticarial vasculitis, granulomatous diseases, cutaneous infections, and malignancy. A skin biopsy helps confirm the diagnosis.

The histopathology occasionally reveals slight spongiosis and vesiculation in the epidermis, which is otherwise unremarkable. The papillary dermis shows moderate to marked edema that may result in subepidermal vesiculation. The main feature is a dense neutrophilic inflammatory cell infiltrate in the reticular dermis. The infiltrate is perivascular and interstitial. It may be admixed with lymphocytes, histiocytes, and eosinophils.[63] Leukocytoclasis is a common feature, whereas frank vasculitis is not.

Pathogenesis

The exact pathogenesis of SS is unknown. The association of SS with systemic conditions suggests that the disease may be a hypersensitivity reaction.[63] The prompt response to treatments that target neutrophils support the role of neutrophils. As expected, granulocyte colony-stimulating factor, a cytokine that suppresses apoptosis and prolongs the survival of neutrophils in vivo, has been reported to induce skin lesions indistinguishable from SS.[64,65] A possible genetic link with human leukocyte antigen B54 has been observed.[66] A report of 2 brothers who developed SS in the neonatal period also supports a role for genetic predisposition.[67]

Workup

Several tests are helpful. A complete blood count with differential is recommended to screen for myelodysplasias and myeloproliferative diseases. Peripheral leukocytosis and neutrophilia are not uncommon. Anemia and thrombocytopenia, on the other hand, are more common in patients with underlying hematologic malignancies.[51] If the history and findings are suggestive of an underlying malignancy, a peripheral smear, bone marrow aspirate, and serum and urine protein electrophoresis may be indicated. If the history and findings are suggestive of underlying UC, a colonoscopy is indicated.[68] Other laboratory abnormalities associated with the cutaneous eruption include elevated hepatic enzymes, erythrocyte sedimentation rate, and C-reactive protein; proteinuria; and hematuria.[57] Imaging studies should be obtained when pulmonary symptoms are present or when a malignancy is suspected.

Treatment

If left untreated, lesions of SS last for variable periods of time; and they mostly heal without scarring. Recurrences have been described in 25% to 50% of the cases.[63] The cutaneous eruption responds promptly to treatment. High-potency topical steroids or intralesional glucocorticoids may be used for localized disease. For severe cases, prednisone 40 to 80 mg/d is highly effective.[63] Other treatments have been reported with variable success. These include azathioprine, indomethacin, colchicine, dapsone, potassium iodide, and thalidomide.[69,70]

Recurrent aphthous stomatitis

Epidemiology

Recurrent aphthous stomatitis affects approximately 4.3% of patients with UC. The onset is abrupt and

Table 6 Causes of recurrent aphthosis

Local	Trauma
Systemic	HIV disease, cyclic neutropenia, UC, Crohn disease, gluten-sensitive enteropathy, Behçet disease FAPA (fever, aphthous stomatitis, pharyngitis, adenitis), MAGIC (mouth and genital ulcers with inflamed cartilage)
Nutritional	Mineral and vitamin deficiencies (iron, zinc, folate, B1, B2, B6, B12)
Microbial	Herpes simplex virus, cytomegalovirus
Genetic	

Fig. 3 Recurrent aphthous stomatitis. Superficial ulcers covered by a yellowish pseudomembrane located on the tongue.

usually coincides with recurrence or exacerbation of the underlying UC.[13,71,72] Many other systemic factors have been associated with recurrent aphthous stomatitis including Behcet disease, HIV disease, cyclic neutropenia, vitamin deficiencies, and gluten-sensitive enteropathy[73,74] (Table 6).

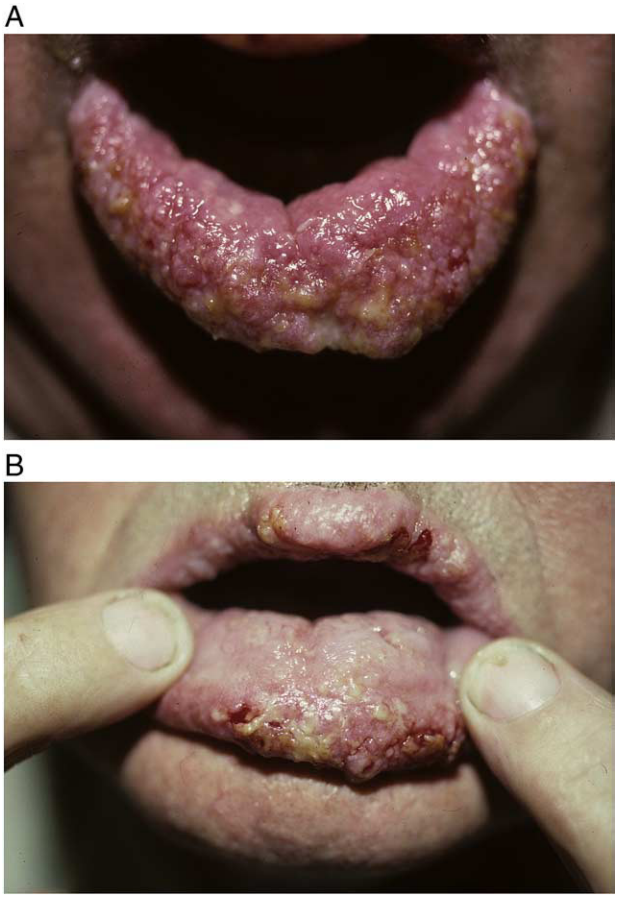

Fig. 4 Pyostomatitis vegetans associated with UC. A, Lower lip is edematous with a verrucous surface. B, Multiple pustules and crusted erosions.

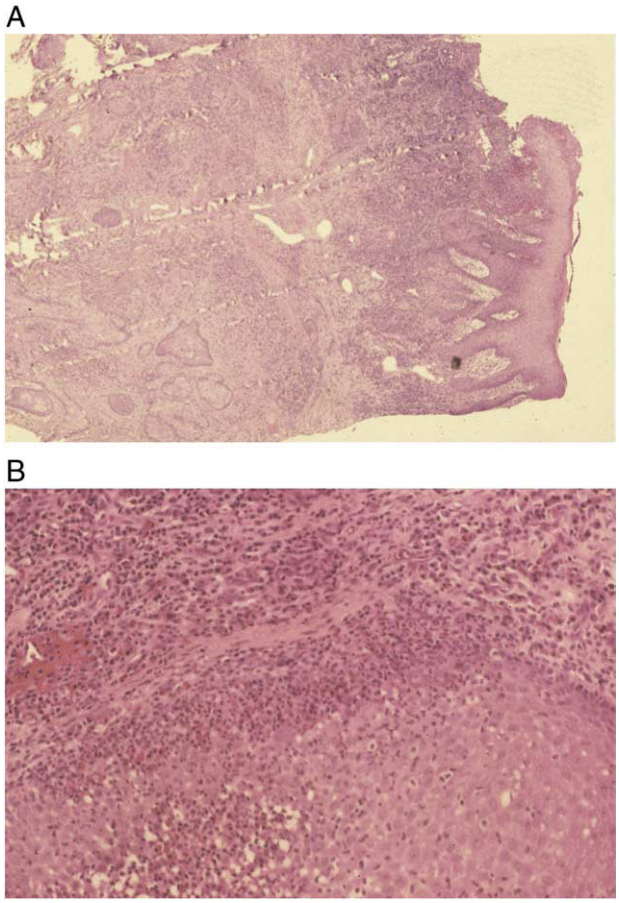

Fig. 5 Histology of pyostomatitis vegetans. A, Intraepithelial abscesses associated with a diffuse subepithelial infiltrate. B, Dense polymorphous infiltrate composed of neutrophils, eosinophils, and mononuclear cells.

Clinical and histopathology

The lesions appear as round or oval painful ulcers, with a yellowish pseudomembranous base and an erythematous border (Fig. 3). They are located on the buccal and labial mucosa, lateral and ventral tongue, soft palate, and oropharynx. Minor aphthae are typically less than 10 mm in diameter, and they heal without sequelae. Major aphthae are larger, deeper, and heal with scarring. The third and least common form of recurrent aphthous stomatitis is characterized by numerous pinpoint ulcers that can fuse to produce herpetiforme lesions.[74] Clinically, the oral ulcers associated with UC resemble either the minor or major variety.[72] The ulcers may interfere with chewing, speaking, and swallowing. The differential diagnosis is broad and includes ulcers of herpes simplex infection, cytomegalovirus, and Coxsackie virus.

The histopathology of aphthae reveals infiltration of the lamina propria and submucosa by lymphocytes, histiocytes, and, less frequently, plasma cells, neutrophils, and eosinophils.[72]

Pathogenesis

The pathogenesis of aphthae associated with UC is unknown; it has been proposed that vitamin B deficiencies in patients with UC may be a contributing factor. Studies have failed, however, to show any correlation between the vitamin levels and the course of the aphthae. In fact, the course of the aphthae is unchanged when these patients are treated with vitamins.[72] There is indirect evidence for the role circulating immune complexes, which is consistent with the occasional finding of vasculitis by microscopy and C3 deposition by immunofluorescence.[75-78]

Workup

A detailed history and review of systems will help identify the underlying inflammatory bowel disease. If bowel symptoms are reported, then a patient needs to be evaluated for UC.[74] A Tzanck smear, culture, or polymerase chain reaction can be used if herpes simplex virus infection is suspected.

Treatment

Treatment of the underlying cause may result in remission of the oral ulcers. Symptomatic relief with corticosteroid pastes and elixirs such as dexamethasone elixir (swish and spit) may be beneficial. Systemic treatment with prednisone, dapsone, colchicine, and thalidomide may be used for refractory cases.[79-81]

Pyostomatitis vegetans

Epidemiology

Pyostomatitis vegetans is a rare disease of the oral mucosa. It is a specific marker for inflammatory bowel disease, particularly UC.[82,83] This disease is more common in females and has been reported in various age groups.[84-88] In general, pyostomatitis vegetans antedates the diagnosis of UC; and it mirrors the activity of the underlying bowel disease.[89] It may occur in patients with asymptomatic UC.[90,91]

Clinical

Pyostomatitis vegetans is characterized by numerous friable pustules producing ulcerations and hemorrhagic erosions (Fig. 4). Any part of the oral cavity may be involved especially the labial, gingival, and buccal mucosa.[85,86] Long-standing disease leads to fissuring with a "snail track appearance," in addition to cobblestoning. The differential diagnosis includes pemphigus vulgaris, mucosal pemphigoid, and infections.[89]

The histopathology is characteristic and reveals intraepithelial abscesses composed of eosinophils and a dense infiltrate throughout the lamina propria composed of eosinophils and neutrophils (Fig. 5).[92] Immunofluorescence studies are negative in contrast to autoimmune bullous disorders.

Pathogenesis

The exact pathogenesis is unknown.

Workup

There is occasional peripheral blood eosinophilia.[93] Viral, fungal, and bacterial cultures may be indicated to exclude infections. Once the diagnosis is confirmed by the histopathology, a patient should undergo a complete gastrointestinal workup.

Treatment

A variety of treatments has been reported with variable success. Typically, the disease is resistant to local treatment with topical steroids, tetracycline mouthwashes, tincture of iodine, or hydrogen peroxide. Treatment with high-dose systemic steroids may be quite effective.[94] Recurrence usually occurs after tapering of the systemic steroid. Other therapies include topical tacrolimus sulfasalazine, dapsone, azathioprine, and cyclosporine.[84,95-97] Few cases of pyostomatitis vegetans resolve permanently after a complete colectomy.[6]

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