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Cutaneous manifestations of gastrointestinal diseases

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There are a myriad of dermatologic disorders associated with gastrointestinal (GI) diseases. This article covers the common dermatologic conditions that may be associated with underlying GI diseases and several uncommon conditions that the dermatologist should recognize as being associated with GI disorders. Table 1 presents an outline of the diseases that are covered.

Inflammatory bowel diseases

Inflammatory disorders of the bowel discussed here include ulcerative colitis (UC), Crohn's disease, and bowel bypass syndrome. Both UC and Crohn's disease (the traditional inflammatory bowel diseases [IBD]) can present with abdominal pain, GI bleeding, or diarrhea. Bowel bypass syndrome consists of a bacterial overgrowth in the blind loop associated with a dermatosis-arthritis syndrome.

Crohn's disease and UC

Crohn's disease is usually subdivided on the basis of involvement of the GI tract (GIT) with regional ileitis-enteritis involving the small bowel, granulomatous colitis involving the colon, and ileocolitis involving both the small and large intestines. The entire mucosal wall is affected in Crohn's disease. Associated extraintestinal findings include arthritis or arthralgias in 10% to 23%; conjunctivitis, uveitis, and episcleritis in 1% to 13%; and many skin findings. Nonspecific skin findings, such as fistulas and fissures, are found commonly in Crohn's disease. Painless anal fissures occur in 50% to 60% of patients. Crohn's disease may have oral findings of cobblestoning, ulcerations, and nodules. Metastatic Crohn's lesions showing sarcoidal-type granulomatous histology can be seen in the skin or mucosa and correlates to disease activity (Fig. 1). Erythema nodosum, pyoderma gangrenosum (PG), pustular reactions including pustular vasculitis, and aphthous stomatitis are associated with both Crohn's and UC and are discussed separately.

In UC, the mucosa and submucosa of the colon are affected. Uncommonly, arthritis or arthralgias are seen in UC. Occasionally, a toxic arthritis with swelling and pain of the large joints is seen. Pustular reactions can be seen and include PG, pustular vasculitis, pustular reactions, and pyoderma vegetans of the Hallopeau type. Fistulas and fissures may be seen but are more common in Crohn's disease. Oral lichen planus (LP) may be seen in UC. Thrombophlebitis develops in up to 10% of UC patients.

PG

Brunsting et al [1] in 1930 described a small cohort of patients who developed characteristic extensive necrotic ulcerations with well-defined undermined borders and that healed with scarring. Four of these patients had underlying UC. Although UC is the most common disease associated with PG in adults, a number of other diseases have been associated with

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Table 1
Cutaneous manifestations of common gastrointestinal disorders

Gastrointestinal disorders	Cutaneous disorders
Inflammatory bowel disease	
Ulcerative colitis	Neutrophilic tissue reactions
Crohns' disease	Pyoderma gangrenosum
Bowel-bypass syndrome	Sweet's syndrome
	Pustular vasculitis or reactions
	Erythema nodosum
	Aphthous stomatitis
Nutritional and metabolic disorders	
Malabsorption	Acrodermatitis enteropathica
Gluten-sensitive enteropathy	Dermatogenic enteropathy
Alcoholic liver disease	Pancreatic panniculitis
	Porphyria cutanea tarda
	Dermatitis herpetiformis
Infections	
Hepatitis B and C	Porphyria cutanea tarda
	Erosive or oral lichen planus
Helicobacter pylori	Sweet's syndrome
Malignancies	
Specific cutaneous signs of gastrointestinal malignancy	
Glucagonoma	Necrolytic migratory erythema
Carcinoid	Flushing
Upper respiratory carcinoma	Bazex's syndrome
Esophageal carcinoma	Palmar-plantar hyperkeratosis
	Koilyonychia
	Glossitis
Nonspecific cutaneous signs of gastrointestinal malignancy	Acanthosis nigricans
	Erythema nodosum
	Metastatic skin lesions
	Sister Mary Joseph's nodules
	Hypertrichosis lanugosa
Gastrointestinal polyposis syndromes and cancer	Gardner's syndrome
	Cronkhite-Canada syndrome
	Peutz-Jeghers syndrome
	Cowden disease
	Muir-Torre syndrome
Gastrointestinal hemorrhage	
Vascular disorders	Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
	Kaposi's sarcoma
	Necrotizing angiitis
	Pseudoxanthoma elasticum
	Ehlers-Danlos syndrome
	Degos' disease
	Henoch-Schönlein purpura

underlying conditions (Table 2). PG occurs in 0.5% to 20% of patients with Crohn's disease.

Pyoderma gangrenosum is an uncommon ulcerative disorder of uncertain etiology. Several hypotheses have been proposed, including a role for impaired cellular immunity and abnormal neutrophil function [2,3]. The clinical presentation may vary but classically begins as a papulopustule that becomes necrotic and expands easily with minimal trauma. Pathergy is invariably present. The clinical presenta-

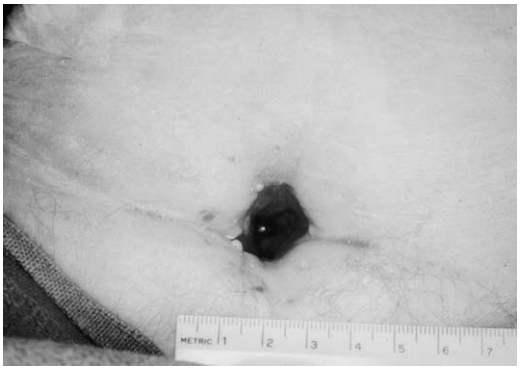

Fig. 1. Metastatic Crohn's disease

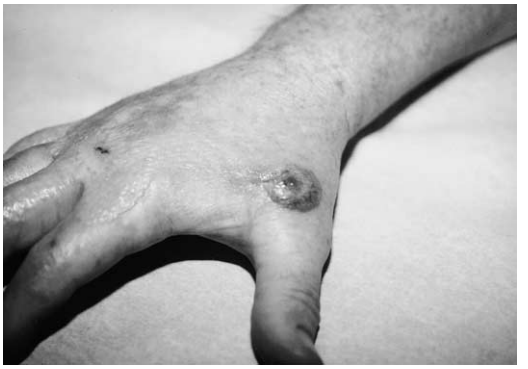

Fig. 2. Ulcerative pyoderma gangrenosum occurring in a patient with ulcerative colitis.

tion is subdivided into four types: (1) ulcerative, (2) pustular, (3) bullous, and (4) vegetative [4]. Classic ulcerative PG presents with a painful necrotic ulcer with undermined border (Fig. 2). This type typically is an enlarging necrotic ulcer with a violaceous undermined border. Although it has the appearance of an infectious ulcer, ulcerative PG typically is sterile. Patients with ulcerative PG often have underlying systemic disease, in particular arthritis and IBD. Pustular PG begins as painful sterile pustules but does not seem to progress to ulceration (Fig. 3). The pustular eruption may persist for months. Pustular PG has been reported in IBD, polycythemia rubra vera, and hepatobiliary cirrhosis [4]. This variant has also been referred to as *vesiculopustular eruption*, *pustular eruption of UC*, *pustular vasculitis*, or *pustular PG*. Since its first description in patients with leukemia, bullous PG has also been reported in IBD, myelofibrosis, and in otherwise healthy individuals [5]. In bullous PG, lesions present first as tense bullae, then painful erosions that rapidly become necrotic ulcers (Fig. 4). Vegetative PG begins as a superficial ulcer without undermined borders and slowly develops into a vegetative or exophytic lesion (Fig. 5). The eruption typically is localized and occurs commonly on the trunk. This variant often occurs in apparently healthy individuals.

Histologic findings may vary somewhat with the age of the lesion and the clinical subtype of PG. Early lesions of ulcerative PG demonstrate mild to moderate perivascular lymphocytic infiltrate and endothelial swelling, and a dense neutrophilic infiltrate in the dermis. Neutrophils may even invade the epidermis. There is neither true vasculitis nor any evidence of circulating immune complexes in lesional skin [6]. Vegetative PG and late stages of PG are characterized by granulomatous infiltrates of histiocytes, neutrophils, and giant cells. The bullous variant shows

Table 2
Diseases associated with pyoderma gangrenosum and Sweet's syndrome

Pyoderma gangrenosum	Sweet's syndrome
Ulcerative colitis	Ulcerative colitis
Crohns' disease	Crohns' disease
Diverticulitis	Diverticulitis
	Helicobacter pylori infection
	Yersinia enterolitica
Rheumatoid arthritis	Rheumatoid arthritis
Behçet's disease	Behçet's disease
Systemic lupus erythematosus	
Lymphoma or leukemia	Lymphoma or leukemia
Myeloproliferative disorders	Myeloproliferative disorders
Carcinoma of breast, lung, colon, and prostate	Carcinoma of breast, lung, colon, and prostate
AIDS	AIDS
	Autoimmune disorders
	Pregnancy

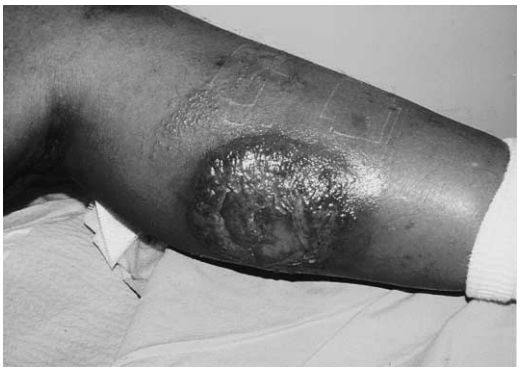

Fig. 3. Pustular pyoderma gangrenosum in a 16-year-old with ulcerative colitis.

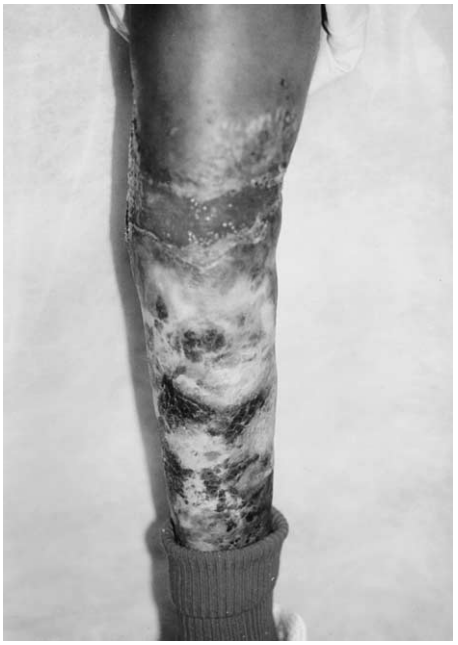

Fig. 4. Extensive scarring caused by erosive pyoderma gangrenosum in a patient with ulcerative colitis.

neutrophil-rich infiltrates and multilocular intraepidermal bullae [3].

Management of PG

Evaluation of a patient with PG is given in Table 3. Once the diagnosis of PG is made, evaluation and treatment of the underlying associated disease are imperative for management of skin involvement. Local wound care is important with careful attention given to minimizing trauma or manipulation of the ulcer. Debridement should be avoided or kept at a minimum. Local intralesional corticosteroid injections

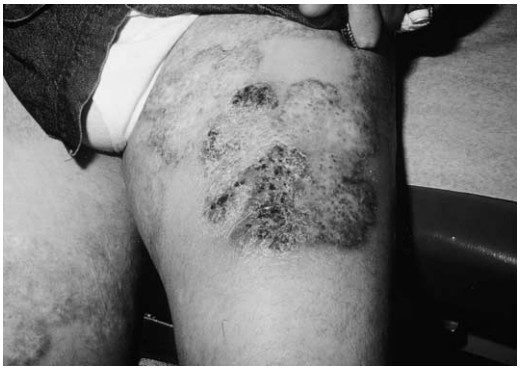

Fig. 5. Vegetative pyoderma gangrenosum.

Table 3
Evaluation of patient with Pyoderma gangrenosum

Complete history, including emphasis on drug intake, GI symptoms, constitutional symptoms
Physical examination, including gynecologic examination in women and prostate examination in men
Laboratory evaluation:
Hematologic
Complete blood count with differential
Estimated sedimentation rate
Peripheral smear
Chemistries
Renal, liver, and bone evaluation
Serum electrophoresis, if indicated
Hormone
TSH and thyroxine
Autoimmune
ANA/ profile; antiphospholipid antibody
RF
Antineutrophilic antibody (p-ANCA; c-ANCA)
Cryoglobulins
Skin
Biopsy
Wound cultures
Chest radiograph if indicated
Gastrointestinal evaluation if suggestive

Abbreviations: ANA, antinuclear bodies; ANCA, antineutrophilic cytoplasmic antibody; RF, rheumatoid factors; TSH, thyroid-stimulating hormone.

may be performed as monotherapy or in conjunction with systemic therapy. Systemic corticosteroids remain the mainstay of therapy with high doses often being necessary (1 to 2 mg/kg/d). Steroid-sparing agents, such as mycophenolate mofetil, azathioprine, cyclosporine, and methotrexate, have been reported to be of benefit [3,4]. In cases of PG associated with UC or Crohn's disease, sulfasalazine and dapsone have been shown to be quite effective for both GI disease and PG. Recent reports of topical tacrolimus ointment have shown promise in local treatment of the ulcer [7].

Sweet's syndrome

Sweet's Syndrome (SS) was first described in eight women as a distinct acute febrile syndrome associated with a neutrophilic dermatosis [8]. The clinical features include (1) fever; (2) peripheral neutrophilic leukocytosis; (3) painful erythematous juicy plaques and nodules on the extremities, head, and neck; and (4) a dense neutrophilic infiltrate within the dermis. These lesions can remain for weeks to months without intervening therapy. Since the initial description, SS

has been associated with many diseases (see Table 2). The most common clinical settings in which SS occurs are (1) classic SS, (2) paraneoplastic or malignancy-associated SS, and (3) drug-induced SS. The disease is more common in women, except for the malignancy-related form where the incidence is about equal in both sexes. Classic SS is usually associated with infection of the upper respiratory tract or GI tract 1 to 3 weeks before the skin manifestations. Recently, SS was reported in association with *Helicobacter pylori* infection [9]. Classic SS is often associated with IBD. Malignancy-associated SS occurs in 20% of SS patients, with lymphoproliferative disorders being most commonly noted. Solid tumors of the GI tract, genitourinary tract, and breasts have been reported in 15% of patient [7]. In drug-induced SS, the medications most frequently incriminated include granulocyte colony-stimulating factor, minocycline, trimethoprim-sulfamethoxazole, all-*trans* retinoic acid, and oral contraceptive pills [10].

Clinically in all forms, abrupt onset of fever and painful erythematous plaques and nodules follows a prodrome of low-grade fever or pharyngitis 1 to 3 weeks before onset. The skin lesions have pronounced edema, making the lesions appear vesicular (Fig. 6). The lesions coalesce into large irregularly shaped plaques. The eruption tends to occur on the head and neck and upper extremity area. The episodes can be recurrent in up to 50% and are associated with arthralgia, myalgia, headache, and generalized malaise and lasts for variable periods of time if untreated. The lesions heal without scarring. Oral lesions are uncommon in classic SS but are more prone to occur in malignancy-associated SS. Pathergy may be present. Extracutaneous involvement in SS includes GI tract, bone, central nervous system, liver, kidney, eyes, and lungs. [10,11]

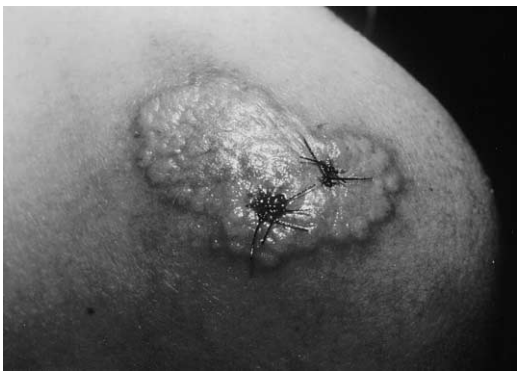

Fig. 6. Erythematous plaque of Sweet's syndrome.

Histologic evaluation of the plaques demonstrates a dense neutrophilic infiltrate in the superficial dermis and edema of the papillary dermis. Leukocytoclasia and karyorrhexis (fragmented neutrophil nuclei) are common findings but no true leukocytoclastic vasculitis is present. Direct immunofluorescence is negative.

When first described by Sweet, there were no associated systemic manifestations. Despite this, Sweet hypothesized that the dermatosis was reactive in nature. The clinical pattern and histology suggest that SS is a hypersensitivity reaction to a bacterial, viral, or even tumor antigen. The pathogenesis, however, remains unclear. Several theories have been proposed, including circulating autoantibodies, immune complexes, and cytokines. Recently, Going [13] and others have demonstrated excessive production of interleukin-1 and other proinflammatory cytokines and have proposed a central role for these cytokines in the pathogenesis of SS [12].

The rapid resolution of skin lesions with systemic corticosteroids supports the reactive nature of this entity. Steroid-sparing agents, such as sulfones, colchicine, and supersaturated potassium iodide, have been used successfully in SS [10].

Bowel-associated dermatosis arthritis syndrome

Bowel bypass syndrome was initially described following bypass surgery for morbid obesity. The condition may begin as soon as several days postsurgery and typically consists of an influenza-like prodrome of fever, chills, and malaise. This is followed by the appearance of small, indurated, painful papules and sterile pustules localized to the upper trunk and upper extremities, commonly in the deltoid area. There is a concomitant nonerosive arthritis and polyarthraligia of the fingers, hands, and wrists. The condition lasts about 2 weeks but has been reported to recur. Subsequent to its initial description, bowel bypass syndrome has been reported in patients with UC and Crohn's disease [14,15].

Histologically, there is a mononuclear perivascular infiltrate, with edema and sometimes neutrophils extending into the epidermis, forming the clinical pustule. There is no true leukocytoclastic vasculitis.

This disorder now is more correctly termed *bowel-associated dermatosis-arthritis syndrome* [15]. The pathogenesis is thought to involve circulating immune complexes, which are deposited into skin and joints. Ely [16] proposed that bacterial peptidoglycans resulting from overgrowth of GI bacteria in the postsurgical blind loop are involved in the formation of immune complexes, in turn activating complement

followed by subsequent deposition into the appropriate site. Immune complex and complement deposition have been reported in the skin but this is not a consistent feature [15,17].

Therapy includes tetracycline, dapsone, prednisone, sulfapyridine, and surgical re-establishment of the bypass segment.

Pustular reactions

Pyoderma gangrenosum, SS, and bowel-associated dermatosis-arthritis syndrome have similar histologic features and as such may represent a spectrum of pustular reactions and vasculitides seen in IBD. In addition to these, pustular reactions have been commonly reported in IBD.

Pustular vasculitis refers to an entity consisting of pustules on a purpuric base, with histologic features of SS or leukocytoclastic vasculitis. It is associated with serum sickness-like manifestations, such as fever, arthralgias, myalgia, and arthritis. Pustular vasculitis has been reported with bowel bypass surgery, UC, Behçet's disease, rheumatoid arthritis, and chronic bacteremia [3]. The pathogenesis of this entity seems to involve immune complex deposition. Treatment includes corticosteroids, colchicine, thalidomide, and dapsone [18].

Nutritional and metabolic disorders

Cutaneous eruptions associated with malabsorption

Many skin findings can be seen in association with malabsorption, some of which are the result of it, some in association with it, some caused by the disease process itself, and some because of a genetic susceptibility to the different diseases. Table 4 lists some of the skin findings seen in patients with malabsorption. Malabsorption can result in loss of many vitamins and essential elements that can result in eczematous eruptions, alterations in nail and hair, and changes in skin texture. There are several cutaneous eruptions specifically associated with malabsorption.

Table 4
Skin findings associated with malabsorption

Nonspecific	Specific
Acquired ichthyosis	Essential fatty acid deficiency
Hair and nail changes	Zinc deficiency
Hyperpigmentation	Acrodermatitis enteropathica
Altered skin texture	Vitamin B deficiency
Eczematous eruptions	Dermatogenic enteropathy
	Dermatitis herpetiformis

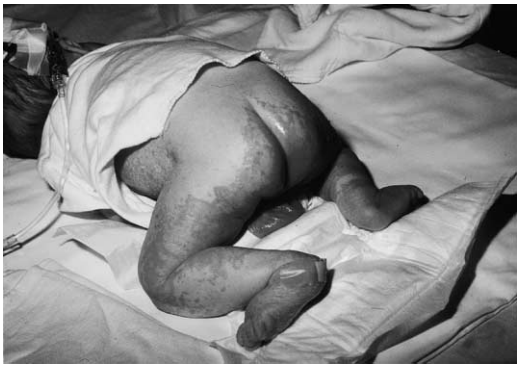

Fig. 7. Acrodermatitis enteropathica–like eruption in an infant with cystic fibrosis.

Acrodermatis enteropathica

Decreases in serum zinc levels secondary to malabsorption result in characteristic cutaneous abnormalities, which include acral dermatitis, alopecia, an eczematous dermatitis, and diarrhea. There is an inherited autosomal recessive disease, acrodermatitis enteropathica, which also results in the same characteristic skin eruption and is caused by a defect in zinc absorption [19]. Patients with acrodermatitis enteropathica develop a periorificial and perianal eczematous erythematous eruption shortly after birth or after weaning off breast milk (Fig. 7). The defect is caused by an inability to absorb zinc from the diet. This distinct cutaneous eruption should be considered when evaluating infants with failure to thrive and diarrhea because infants with cystic fibrosis and other malabsorption syndromes may present with acrodermatitis enteropathica skin findings.

There have been reports of malabsorption occurring in patients with exfoliative dermatitis. Dermatogenic enteropathy, as it is referred, consists of steatorrhea, in proportion to the extent of dermatitis. The steatorrhea reverses with successful treatment of the dermatitis [20]. The mechanism of this entity is unknown.

Dermatitis herpetiformis

Dermatitis herpetiformis is a chronic pruritic subepidermal blistering disease that is associated with mucosal changes in the small bowel indistinguishable from celiac sprue or gluten-sensitive enteropathy

[21]. Although most patients have no intestinal symptoms, 20% to 70% may demonstrate asymptomatic steatorrhea. Clinically, intensely pruritic subepidermal bullae and vesicles develop over the head and neck area and the extensor surfaces of the elbows and knees. Dermatitis herpetiformis usually begins in adulthood but childhood dermatitis herpetiformis has been reported. There is an increased risk for development of intestinal lymphoma in patients with long-standing dermatitis herpetiformis. Histologically, there is a subepidermal bulla with collections of neutrophils in the dermal papillae. Direct immunofluorescence demonstrates granular deposits of IgA in the dermal papillae. The pathogenesis of dermatitis herpetiformis is thought to involve these deposits of IgA with subsequent activation of complement [21]. One hypothesis is that IgA is directed against gluten protein or other antigens, which originate in the GI tract [21]. These immunoreactants are either deposited in the skin or cross-react with skin components, resulting in subepidermal blisters. Factors other than IgA seem to be involved in blister formation. There is no evidence for a role of circulating immune complexes in the pathogenesis of dermatitis herpetiformis.

Miscellaneous cutaneous diseases associated with GI diseases

LP

Lichen planus has been associated with several GI disorders. These include hepatitis B and C, IBD, and primary biliary cirrhosis. Erosive or oral LP seems to be associated most frequently with hepatitis C infection. Skin lesions are very pruritic, flat-topped, polygonal violaceous papules or plaques. The eruption is bilateral and symmetric and involves the wrists and flexor surfaces. There may be lacy white streaking or Wickham's striae on the buccal mucosa. Erosive LP presents as painful erythematous erosions on mucosal surfaces. In addition to erosive LP, there are several clinical patterns seen including follicular, vesicular, annular, hypertrophic, and atrophic LP.

Histologic findings are quite distinctive and include hypergranulosis, necrotic keratinocytes, colloid bodies, and an interface dermatitis of the basement membrane. A band-like infiltrate of lymphocytes is seen in the papillary dermis.

Although LP is a distinct dermatologic disorder, it may also be viewed as a reaction pattern to systemic disease, infection, or a response to an exogenous agent. As such, evaluation for systemic causes is warranted once the diagnosis of LP is made. Although the pathogenesis of LP is unknown, recent data suggest that LP is immunologically mediated [22]. In early lesions, CD4+ helper T cells and Langerhans' cells predominate, suggesting that the pathogenesis somehow involves antigen presentation. Older lesions have a preponderance of CD8+ suppressor cells. These cytotoxic T cells and their cytokines are responsible for the histologic finding of liquefaction degeneration at the dermal-epidermal junction.

Porphyria cutanea tarda

Porphyria cutanea tarda is a photoexacerbated subepidermal blistering disorder seen commonly in patients with liver disease. Porphyria cutanea tarda has been associated with alcoholic liver disease, hepatitis B and C, and hepatic tumors.

In general, the porphyrias are a group of photosensitive blistering disorders resulting from elevated levels of porphyrin intermediates in the heme pathway. Porphyrias result from inherited or acquired enzymatic abnormalities within heme synthesis pathway. Elevated levels of circulating uroporphyrias react with ultraviolet radiation to generated reactive free radical derivatives that induce blister formation in the papillary dermis.

Pancreatic panniculitis

Pancreatic panniculitis occurs predominately in alcoholics but has been reported in patients with pancreatic cancer. It presents as erythematous painful plaques and nodules on the extremities or trunk [23]. In addition to the skin lesions, arthritis, polyserositis, and pancreatitis may be present. This type of lobular panniculitis has characteristic histologic features of basophilic degeneration of lipocytes, leading to the formation of ghost cells, calcification, and saponification of the dermal collagen and necrosis.

Acute pancreatitis may also be associated with periumbilical ecchymosis (Turner's sign) or ecchymosis of the flank (Cullen's sign). This is caused by extravasation of hemorrhagic peritoneal fluid into the skin.

Cutaneous syndromes and the GI tract

There are a number of genodermatoses and cutaneous diseases associated with GI disorders. Table 5 lists some of the more common skin diseases and genodermatoses associated with GI malignancy and their systemic associations.

Table 5
Cutaneous syndromes associated with gastrointestinal diseases and malignancy

Syndrome	Inheritance	Cutaneous findings	Internal associations
With increased risk of malignancy	DEFECT		
Gardner's syndrome (familial polyposis syndrome)	AD Chromosome 5	Osteoma, desmoid tumors epidermoid cysts, dental anomalies	Intestinal polyposis, colon cancer, thyroid cancers, retinal abnormalities
Cronkhite-Canada syndrome	Acquired	Alopecia, nail dystrophy; macular hyperpigmentation	GI polyps, colon carcinoma, diarrhea, abdominal pain
Cowden's disease (multiple hamartoma syndrome)	AD Mutation PTEN Gene/chromosome 10	Hamartomas of mucous membranes, facial tricholemmonas, papillomas Palmar-plantar keratoses, scrotal tongue	Hamartomas and malignancy of colon, breast, thyroid, renal, and bladder; colonic polyps
Muir-Torre syndrome	AD Mutation in MSH2 gene on chromosome 2	Sebaceous gland tumors, BCC with sebaceous differentiation, keratoacantoma, epidermoid cysts	Nonpolyposis colon cancer, laryngeal cancer, duodenal and endometrial cancer
Peutz-Jeghers syndrome	AD	Periorificial and mucosal lentigines, pigmented maculae hands and feet	Hamartomatous polyps throughout GI tract, increased incidence of malignancy throughout GI tract, ovarian tumors, pancreatic carcinoma, gallbladder cancer, GI bleeding, pancreatic carcinoma
Howell-Evans' syndrome		Palmar-plantar hyperkeratosis	Esophageal carcinoma
Bazex's Syndrome	Acquired	Acrodermatitis, nail dystrophy	Esophageal, laryngeal, tongue carcinoma
MEN type I (Wermer's syndrome)	AD Mutation in MEN I gene on chromosome 11	Multiple facial angiofibromas, collagenomas, lipomas, confetti-like hypopigmented macules	Pituitary, parathyroid, pancreatic endocrine abnormalities, peptic ulcer disease, Zollinger-Ellison syndrome, gastronoma, insulinoma, carcinoid
MEN IIA (Sipple's syndrome)	AD Mutation in *RET* gene on chromosome 10	Amyloidosis	Medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism, Zollinger-Ellison syndrome, Cushing's syndrome, malignant melanoma, pituitary adenoma,
MEN IIB	AD Mutation in *RET* gene on chromosome 10	Multiple mucosal neuromas, marfinoid body habitus, nasal neuromas	Hirschprung's disease, cervical medulloblasoma increased risk of malignancy Medullary carcinoma of thyroid, pheochromocytoma, muscle weakness and atrophy, ganglioneuromas of GI tract, colonic diverticula, thickened corneal nerves, diarrhea

Abbreviations: AD, autosomal dominant; BCC, basal cell carcinoma; GI, gastrointestinal; MEN, multiple endocrine neoplasia; MSH, ; PTEN, .

Enodermatoses with malignant potential

Gardner's syndrome

Gardner's syndrome, or familial adenomatous polyposis, is an autosomal dominant inherited disorder with a high degree of penetrance [24]. It is thought to be caused by a gene defect on chromosome 5. The incidence is about 1:3000 to 1:6000. It is important to recognize this syndrome early in life because there is almost a 100% chance of colonic carcinoma in these patients before the age of 40. There are a number of cutaneous findings that should alert the physician to this diagnosis. These include multiple epidermoid cysts, desmoid tumors, osteomas, dental abnormalities, and ocular pigmented lesions (Fig. 8). The epidermoid cysts differ from common cysts in that they are multiple, develop in childhood, and cluster on the head and neck. Desmoid tumors, which are uncommon in the general population, occur in 10% of these patients [24]. The pigmented lesions in the fundus may be congenital and occur in 90% of patients. Other neoplasms may be seen and include duodenal carcinoma, endocrine tumors, thyroid carcinoma, and hepatoblastoma.

Cronkhite-Canada syndrome

Cronkhite-Canada syndrome is a rare acquired disorder presenting in adulthood with diffuse alopecia, macular hyperpigmentation, onychodystrophy, and GI polyposis [25,26]. The cutaneous symptoms often precede the systemic symptoms. Alopecia occurs in all hair bearing areas and is rapidly progressive. The nail dystrophy is generalized and may show onycholysis, onychoschizia, and onychomadesis. The macular hyperpigmentation is lentiginous and diffuse but excludes the mucosa. Laboratory findings usually reflect the degree of diarrhea and protein-losing enteropathy and include hypokalemia, hypocalcemia, and hypoalbuminemia. Anemia may be secondary to chronic GI bleeding from polyps. The polyps are regarded as hamartomatous but as many as 15% of patients develop carcinoma of the stomach, colon, and rectum [24]. Although the pathogenesis in unknown, several hypotheses have been proposed and include nutritional deficiency, enzyme deficiency, altered mucosal vasculature or altered mucosal secretions, infections, and altered immunity. Although many of the cutaneous manifestations can be explained as a consequence of the diarrhea and protein-losing enteropathy, their appearance before the GI symptoms suggests mechanisms other than simple loss.

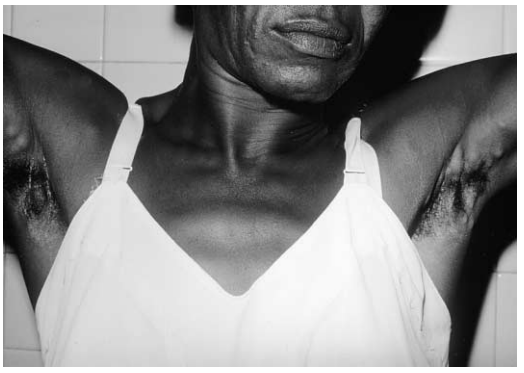

Fig. 8. Multiple epidermoid cysts in axillae of patient with Gardner's syndrome.

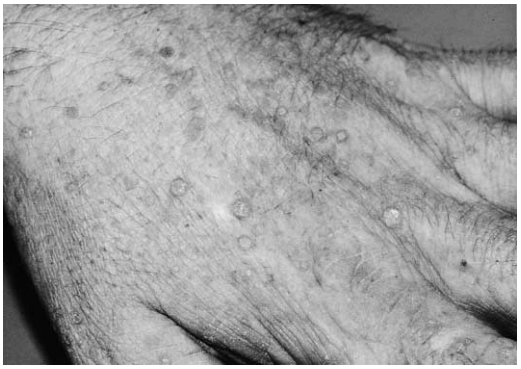

Fig. 9. Acral keratoses in a patient with Cowden's disease.

Cowden disease

Cowden disease, or multiple hamartoma syndrome, is an autosomal dominant disorder of the skin, mucosa, and multiple organs. Recent molecular genetic studies suggest that there is a defect in the gene coding for a tumor suppressor gene on chromosome 10, designated PTEN/ MMAC1 [27]. Distinctive skin findings include multiple facial trichilemmomas and warty acral keratoses (Fig. 9). The mucosal papules often give a cobblestone appearance to the oral cavity and are considered pathognomonic for the syndrome. Other skin findings include lipomas, hemangiomas, scrotal tongue, and neuromas [28]. Approximately one third of patients with Cowden disease have hamartomatous polyps of the GI tract with little potential for malignant conversion. Commonly, bleeding and anemia may be seen. Patients with Cowden disease do have an increased risk of malignancy of breast and thyroid and as such require careful screen-

ing and follow-up. Criteria for diagnosis include family history and the presence of one of the characteristic facial tumors or family history and keratoses of palms and soles and acral areas or the presence of facial trichilemmomas and oral mucosal papillomas or fibroma [29].

Muir-Torre syndrome

In Muir-Torre syndrome, multiple sebaceous tumors with or without keratoacanthomas are seen in combination with low-grade visceral malignancies [24,30]. Most of the malignancies have their origin in the GI tract, usually the colon, and these often arise from adenomatous polyps. Other malignancies reported include non-Hodgkin's lymphoma, and tumors of the larynx, duodenum, stomach, kidney, ovary, and uterus [30]. Sebaceous neoplasms include adenomas, hyperplasia, epithelioma, and carcinoma. As expected, most of these neoplasms are found in the head and neck area. Because sebaceous adenomas are uncommon in general, some authors suggest that the diagnosis of a solitary sebaceous adenoma (especially of the eyelid) warrants further evaluation for internal malignancies.

Multiple endocrine neoplasia syndromes

The multiple endocrine neoplasia (MEN) syndromes are an uncommon group of proliferative disorders that affect endocrine glands. Several of these syndromes also involve the GI tract. The major syndromes include three genetically distinct disorders: (1) MEN I (Wermer's syndrome); (2) MEN IIA (Sipple's syndrome); and (3) MEN IIB (previously referred to as MEN III) [31]. Genetic studies have recently suggested that germline mutations in the *ret* proto-oncogene found on chromosome 10 are involved in malignant transformation in MEN IIA and B [27,31]. The defect in MEN I has been linked to chromosome 11 [27,31].

The MEN I was first described by Erdheim but Wermer [32] subsequently suggested a genetic basis for the disease. In addition to endocrine hyperplasia and neoplasia, many patients have evidence of gastrin-producing tumors of the duodenum (Zollinger-Ellison syndrome); carcinoid tumors of the GIT; and carcinoid of the lung. Skin findings in MEN I include multiple facial angiofibromas, collagenomas, lipomas, hypopigmented maculae, and gingival papules.

The MEN IIA consists of medullary carcinoma of the thyroid and pheochromocytoma. It is inherited in an autosomal dominant fashion, with the genetic defect involving the *ret* proto-oncogene. Hirschsprung's disease or aganglionic megacolon has been associated with MEN IIA and demonstrates the same genetic defect in the *ret* proto-oncogene found on chromosome 10. A variant of MEN IIA demonstrates hereditary cutaneous amyloidosis [31].

The MEN IIB demonstrates more cutaneous manifestations than MEN IIA. The main features of this syndrome include multiple mucosal neuromas, medullary carcinoma of the thyroid, pheochromocytomas, GI ganglioneuromatosis, and ocular neuromas [31]. Other clinical manifestations include a marfinoid habitus, skeletal abnormalities, and joint laxity. The putative defect in MEN IIB maps to chromosome 10 and seems to involve the *ret* proto-oncogene.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome consists of GI polyposis and cutaneous pigmented maculae on the mucosal areas and skin [29]. It is uncommon, with the incidence estimated to be 1 in 29,000 live births. The polyps are most frequently found in the jejunum and ileum but can occur anywhere in the GI tract. Commonly, GI symptoms of bleeding or obstruction are presenting features. Initially, these polyps were viewed as hamartomatous but recent data suggest there is significant increase in the incidence of malignancy of the GI tract, breast, ovary, and testes [29]. The tan-brown pigmented maculae resemble lentigines, appear in early childhood, and cluster on mucosal surfaces but can be also found on soles, palms, and fingers.

Howell-Evans' syndrome

In 1958, Howell-Evans et al [33] reported two kindred with diffuse hyperkeratosis of palms and soles (tylosis) and esophageal carcinoma. In this syndrome, patients develop palmar-plantar hyperkeratosis in adulthood and develop esophageal carcinoma before the age of 65. There may be an associated oral leukoplakia. The association of tylosis and esophageal carcinoma has been reported in other families and seems to be inherited in an autosomal dominant fashion [34]. Adult onset of tylosis or hyperkeratosis palmaris et plantaris has been reported with other malignancies, including colon and lung, but differs from benign tylosis, which has its onset early in life.

Plummer-Vinson syndrome

Plummer-Vinson syndrome is a rare syndrome consisting of palmar-plantar hyperkeratosis and post-

cricoid web [29]. In this syndrome, patients have postcricoid web, koilonychia or spoon nails, angular stomatitis, and painful glossitis. These cutaneous changes may be secondary to long-standing iron deficiency anemia. Esophageal carcinoma occurs in about 15% of patients.

Bazex's syndrome

Acrokeratosis paraneoplastica, or Bazex's syndrome, is an acquired symmetric erythematous psoriasiform dermatosis affecting the hands, feet, ears, and nose [29]. Nail anomalies and dystrophy are common and often are very severe. Bazex's syndrome is usually associated with carcinoma of the larynx, esophagus, and tongue. The cutaneous manifestations may occur years before the malignancy is detected.

Carcinoid syndrome

Carcinoid syndrome represents a constellation of findings secondary to a tumor of amine precursor uptake and decarboxylation cells (APUDoma) of the intestinal or respiratory tract. Symptoms include flushing, diarrhea, wheezing, and abdominal pain, with or without weight loss. Most tumors are found in the GI tract but symptoms develop when the liver is involved. The flushing is episodic at first and consists of a range of skin colors. With time, persistent erythema and poikiloderma may develop. Glossitis and photoaccentuated pellagra-like eruption may be seen. These are thought to be caused by a shift toward increased serotonin production by the tumor, resulting in niacin deficiency [28]. Elevated levels of 5-hydroxyindoleacetic acid are found in the urine of affected patients.

Glucagonoma

Necrolytic migratory erythema is an uncommon cutaneous eruption most often seen in patients with glucagonoma, a tumor of the pancreatic islet cells, but has been reported with other malignancies [29]. This characteristic eruption consists of recurrent episodes of painful erythema, followed by blisters or erosions and desquamation. The perineum, abdomen, perioral, and flexural areas are most often affected. Angular cheilitis and painful glossitis also occur. Pathogenesis may be related to metabolic derangements of amino acid toward excess glucagonoma production [35,36].

Cutaneous syndromes associated with hemorrhage

There are a number of dermatoses associated with GI hemorrhage as a prominent feature. Some of the more common ones are listed in Table 6. Vascular

Table 6
Cutaneous syndromes associated with gastrointestinal hemorrhage

Syndrome	Inheritance	Cutaneous findings	Internal associations
Hereditary hemorrhagic telangiectasia	AD	Telangiectasia of skin, oral mucosa	GI hemorrhage, epistaxis, arterial aneurysms; AV malformations in liver, lung, eye
Blue rubber bleb news syndrome	AD	Compressible SQ hemangiomas	GI vascular malformations, GI hemorrhage
Kaposi's sarcoma		Violaceous papules, nodules	GI lesions, hemorrhage
Necrotizing angiitis		Palpable purpura	GI bleeding, perforation, ischemia
Henoch-Schöenlein purpura		Palpable purpura	Abdominal cramping and pain, hematuria, glomerulonephritis
Degos' disease		atrophic Erythematous papules	Vasculitis of GIT, infarction, bleeding, CNS infarcts
Ehlers-Danlos syndrome type IV	AD, AR	Easy bruising, thin translucent skin	Arterial rupture, GI hemorrhage, uterine rupture
Pseudoxanthoma elasticum	AD, AR	Waxy yellow papules, flexural areas, elastosis perforans serpiginosa	GI hemorrhage, Angioid streaks in eyes, coronary hear disease, vascular calcification

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AV, arteriovenous; CNS, central nervous system; GI, gastrointestinal; GIT, gastrointestinal tract; SQ, subcutaneous.

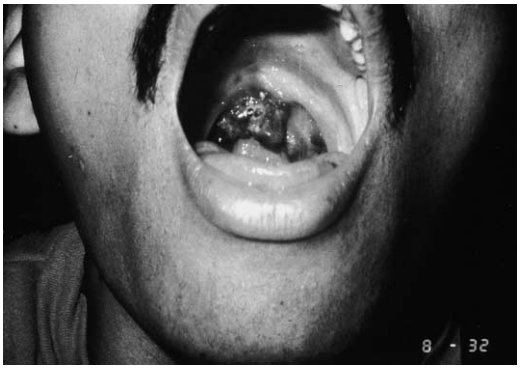

Fig. 10. Oral lesions of Kaposi's sarcoma in a patient with AIDS.

anomalies, connective tissue disorders, vasculitis, and malignancies can have GI bleeding. It is important to recognize those patients at risk for hemorrhage before problems arise.

Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia, or Osler-Weber-Rendu disease, is an autosomal dominant inherited disorder with characteristic small telangiectasia primarily on mucosal surfaces [37]. Telangiectasia are also found on the nose, hands, feet, and chest. The skin findings appear in adolescence or early adulthood. Arteriovenous malformations and aneurysms may develop throughout the GI tract and result in recurrent painless bleeding. GI bleeding usually occurs in the fourth or fifth decade and tends to be chronic. Epistaxis is the presenting sign in over 80% of patients and may present in adolescence. Other organs, such as the liver, lung, and eye, may have vascular malformations.

Kaposi's sarcoma

Kaposi's sarcoma is a vascular neoplasm associated with HIV infection (epidemic) and in elderly men of Mediterranean ancestry. The epidemic variant is often multifocal and occurs in the skin, the mucosa, and the GI tract. GI involvement is seen in 50% to 80% of patients with skin involvement and virtually 100% of patients with oral lesions (Fig. 10). GI bleeding may be significant. The typical lesion is an irregularly shaped violaceous papule, plaque, or tumor. Recently, herpes virus type 8 has been implicated in the pathogenesis of Kaposi's sarcoma [38].

Necrotizing angiitis

Necrotizing angiitis from a number of causes can involve the GI tract, resulting in bleeding, diarrhea, cramps, or obstruction. The ultimate damage depends on the size of the affected vessels. The classic vasculitic process that involves the skin and GIT is Henoch-Schönlein purpura. Henoch-Schönlein purpura is the triad of leukocytoclastic vasculitis of the skin, abdominal pain or cramping, and microscopic hematuria [39]. The disease typically presents in childhood or adolescence but can be seen in all ages. The disease is commonly preceded by an upper respiratory tract infection. It usually lasts about 4 weeks. Leukocytoclastic vasculitis, which is a vasculitis of the capillaries, presents as palpable purpura and recurs in crops and is accompanied by fever and malaise. Direct immunofluorescence of the skin reveals deposits of IgA at the dermoepidermal junction. These IgA deposits are almost pathognomonic for Henoch-Schönlein purpura. In addition to skin deposits, IgA deposits can be found in the kidneys of affected individuals and are thought to contribute to the renal disease seen. The pathogenesis is unclear but most likely involves these IgA deposits.

Degos' disease

Malignant atrophic papulosis of Degos' is a rare disorder manifesting as thrombotic papules in the skin, GI tract, and central nervous system. The very distinctive skin lesions, atrophic porcelain white papules with a rim of erythema, may precede the GI symptoms by months to years (Fig. 11). Histologic examination of a papule reveals epidermal atrophy overlying a wedge-shaped area of dermal necrosis,

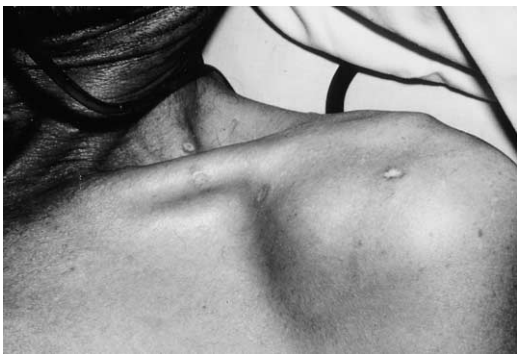

Fig. 11. Atrophic porcelain white papules in a patient with Degos' disease.

mucinous degeneration, and thrombotic vasculitis. It was thought that Degos' disease was uniformly fatal until several years ago when nonfatal familial cases and HIV-associated cases were reported [40,41]. Bleeding may occur as a result of thrombotic vasculitis within GI tract.

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is a genetically inherited disorder of elastic tissue, with an incidence of 0.6 per 100,000 people [42]. It is characterized by abnormal calcification and progressive degeneration of elastic tissue in multiple organs, including the skin, GI tract, the eyes, and the cardiovascular system. The vascular calcification and altered elastin within the GI tract result in hemorrhage early in life, more commonly from the upper GI tract. Skin manifestations are quite distinctive. Small waxy yellow papules typically appear in the skin in early adolescence, giving the appearance of "plucked chicken skin." The lesions have a predilection for flexural areas and the neck and axillae but over time can occur in a generalized distribution. With time, the skin becomes lax and hangs in folds and clinically resembles cutis laxa. Elastosis perforans serpiginosa, one of the perforating collagenoses, may be associated with pseudoxanthoma elasticum.

Angioid streaks, which occur in Bruch's membrance, are seen in the eyes of most patients, as are retinal hemorrhage and detachment. Angioid streaks are associated with pseudoxanthoma elasticum 85% of the time but may be seen in other diseases, such as Paget's disease of bone, lead poisoning, idiopathic thrombocytopenia, and sickle cell disease [42]. Vascular alterations result in peripheral vascular disease, cerebral accidents, premature myocardial infarction, and hypertension subsequent to renal artery involvement.

Pseudoxanthoma elasticum is divided into four subtypes: types I dominant and recessive and types II dominant and recessive. The classic form, type I recessive, has the highest incidence of GI involvement, whereas types II dominant and recessive have minimal or no visceral involvement [37]. Genetic consultation and counseling are important in determining prognosis and potential complications later in life. Although the pathogenesis is not fully understood, there seems to be progressive calcification of elastin fibers with subsequent fragmentation and clumping, abnormal deposition of proteoglycans in the skin and urine of patients, and abnormal elastin degradation [43].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) is an inherited disorder of collagen metabolism, with joint laxity and hyperextensibility, skin hyperextensibility, and skin fragility as common features [37]. Although there are currently 10 distinct subtypes, only type IV EDS is associated with GI findings. EDS type IV may be inherited in an autosomal dominant or recessive pattern. Point mutations, deletions, and splicing defects have been reported but the biochemical defect resulting in abnormal type III collagen is not known. Several studies have suggested that mutations in type III procollagen gene (COL3A1) result in the type IV EDS phenotype [44].

Skin and joint hyperextensibility and abnormal scar formation are not common features of type IV EDS. Type IV EDS is characterized by thin translucent skin, easy bruisibility and ecchymoses, and GI bleeding secondary to rupture of arterial blood vessels or aneurysms. The vascular fragility is manifest at an early age and bleeding can be severe and life threatening. The most common sites of rupture are the large vessels of the abdomen, descending aorta, renal and splenic arteries, and uterine rupture in the postpartum period.

Summary

Prompt recognition of cutaneous diseases or manifestations associated with the gastrointestinal tract may be lifesaving at times, and may lead to early preventive intervention to decrease risk of malignancy.

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