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INTRODUCTION

Gastrointestinal symptoms are common in primary extraintestinal diseases as well as in systemic disorders. Such manifestations may occur in a variety of scenarios including

1. Conditions with pathologic changes common to intestinal and extraintestinal organs, for example, connective tissue disorders
2. Functional abnormalities in the absence of morphologic changes, reflecting altered hormonal or electrolyte changes or neurologic abnormalities, for example, hyperthyroidism or hypothyroidism
3. Mechanical factors, for example, congestive gastropathy or colopathy in portal hypertension or congestive cardiac failure
4. Complications such as infections and neoplasms, in immunocompromised patients
5. Medications frequently administered in certain extraintestinal diseases, for example, nonsteroidal anti-inflammatory drugs (NSAIDs) in rheumatoid arthritis
6. Metastases from extraintestinal neoplasms

The purpose of this chapter is to describe the well-documented morphologic changes that occur in the gastrointestinal tract in extraintestinal disease and systemic disorders and to mention briefly the important functional abnormalities. It should also be noted that there are numerous reports, especially from the older literature, of gastrointestinal abnormalities in extraintestinal disorders whose morphology is poorly documented. We have chosen not to refer to these reports unless they have been confirmed by carefully controlled studies. Finally, some disorders, such as the neuromuscular disorders, are covered in other sections (see Chapter 6), and to avoid duplication, discussion of these conditions is referred to other chapters.

CONNECTIVE TISSUE DISORDERS (COLLAGEN VASCULAR DISEASES)

Gastrointestinal manifestations are common in some of the connective tissue disorders. There are three predominant pathologic changes: (a) deposition of collagen with submucosal fibrosis and muscle atrophy, resulting in motility disorders; (b) arteritis or vasculitis, leading to mucosal erosions, ulceration, or infarction depending on the size of vessel involved; and (c) complications associated with therapy such as NSAIDs and corticosteroids.1,2

The collagen abnormalities are seen mainly in scleroderma and dermatomyositis, while the arteritic lesions occur predominantly in systemic lupus erythematosus (SLE), rheumatoid arthritis, and polyarteritis nodosa. However, not infrequently, there is some overlap between these disorders. Sometimes it is impossible to know if a given lesion is due to the disorder itself or to its therapy or complications. Examples include

1. Patients with rheumatoid arthritis who are on NSAIDs and have gastric ulcers or erosions. Here the drugs rather than the underlying disease are the most likely culprit.
2. Patients with SLE who have renal failure and are on high-dose corticosteroids. In this setting, ulcerative lesions may be due to stress lesions that occur in any seriously ill patient or to opportunistic infections, especially Candida or cytomegalovirus (CMV).

Also see Chapter 2 for a more detailed description of the vascular changes in the connective tissue disorders.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Pathogenesis and Clinical Features

Scleroderma is a systemic disease of unknown etiology, characterized by chronic inflammation, collagen deposition, smooth muscle atrophy and telangiectasia and less commonly, by a vasculitis or immunemediated enteric autonomic neuron dysfunction. Over 80% of patients have alterations in gastrointestinal function,3 about 50% have serious gastrointestinal involvement, and 5% to 10% die from a gastrointestinal-related cause.4 Gastrointestinal involvement is characterized primarily by motility disorders, including gastroesophageal reflux disease, pseudo-obstruction, and bacterial overgrowth, and gastrointestinal hemorrhage.5-7 Gastrointestinal hemorrhage is particularly prominent in patients with CREST (calcinosis, Raynaud’s disease, esophageal dysmotility, sclerodactyly, and gastrointestinal telangiectasia) and is secondary to telangiectasia.8,9 The “watermelon stomach” or gastric antral vascular ectasia (GAVE) is being increasingly recognized as being associated with scleroderma and responsible for upper gastrointestinal hemorrhage in some of these patients.3,10,11

The esophagus is the most commonly involved gastrointestinal site in scleroderma.3,12 As the muscularis externa of the proximal esophagus is composed of striated muscle, involvement is typically confined to the distal two thirds.13 Lower esophageal sphincter
pressure is reduced, and compounding this is ineffective peristalsis with delayed esophageal clearance. Delayed gastric emptying (see below) contributes to reflux by increasing the volume of reflux, which is poorly cleared as a result of the esophageal motor disorder. Thus erosive esophagitis may be severe and associated with stricture formation. In the end stages, the esophagus may appear dilated, with a stricture at the lower esophageal sphincter region and little or no peristalsis in the body of the esophagus. Patients are additionally predisposed to candidal esophagitis due to a combination of poor esophageal emptying, frequent use of immunosuppressive agents, and acid suppression. Dysmotility also predisposes to “pill esophagitis” due to increased mucosal contact with the pill. Bisphosphonates, NSAIDs, quinidine, and potassium chloride have been implicated in these patients. Appropriate counseling is important to prevent this unpleasant complication. Any putative increased incidence of squamous carcinoma or adenocarcinoma of the esophagus in scleroderma is probably due to the associated gastroesophageal reflux disease rather than to any intrinsic risk conferred by the connective tissue disease itself.

In the stomach, significantly delayed gastric emptying occurs in approximately 50% of patients. This results in early satiety, worsening of reflux, and accompanying vomiting. Small intestinal involvement has been reported in 15% to 57% of patients depending on the method of detection and primarily relates to dysmotility. The initial manifestation is that of a dilated bowel, sometimes associated with scattered wide-mouthed diverticula (Fig. 8-1). This may be followed by intestinal pseudo-obstruction (see Chapter 7) of which scleroderma is the most common cause. Stasis predisposes to small intestinal overgrowth, which occurs in 33% to 40% of patients with scleroderma and may result in malabsorption and diarrhea. The frequent use of strong acid-suppressing medications may contribute to bacterial overgrowth by removing the acid barrier to colonization by oropharyngeal bacteria. Bacterial overgrowth may be associated with malabsorption and diarrhea. Other causes of diarrhea and malabsorption in these patients include pancreatic and vascular insufficiency.

In the colon a similar process may also result in pseudo-obstruction or symptoms of severe constipation, with the risk of stool impaction and stercoral ulceration, or sometimes diarrhea. Impaired function of the internal anal sphincter may lead to fecal incontinence. Vascular ectasia may involve the small and large bowel. Rarely, pneumatosis intestinalis, intussusception, and volvulus of the small intestine may complicate scleroderma. A few patients with scleroderma present with vasculitis, leading to ischemic lesions resulting in gastrointestinal hemorrhage, ulcers, or intestinal infarction, depending on the size of vessels involved (see Chapter 2).

Gross Pathology and Histology

The major abnormality consists of smooth muscle atrophy and fibrosis (Figs. 8-2 and 8-3). Most patients have a combination of both, and the histology may vary from patient to patient.

Figure 8-1. Scleroderma of the gastrointestinal tract. Barium enema examination to show wide-mouthed diverticula (arrows). (Courtesy of Dr M Weiner UCLA.)

Figure 8-2. Scleroderma of the gastrointestinal tract. Scanning-power view of the colon showing atrophy and fibrous replacement of the muscularis propria. Note that one segment of the muscularis propria (arrows) is completely replaced by fibrous tissue (trichrome stain).
commonly, the former affects the circular muscle coat. Fibrosis accompanies the muscle atrophy but appears to be the replacement of the atrophied muscle rather than active fibroblastic proliferation. Collagen deposition in the submucosa and subserosa is very variable. Muscle atrophy results in atony and dilatation and may produce flaccid, wide-mouthed diverticula (Fig. 8-1), and, less commonly, megaduodenum or megacolon. Diverticula are better appreciated radiologically when distended with barium than when collapsed at autopsy or in resection specimens. They are not generally complicated by diverticulitis because their wide necks are less prone to obstruction. The muscle changes of scleroderma most closely resemble those of idiopathic familial and sporadic visceral myopathy. The major difference between the two entities consists of muscle atrophy with fibrous replacement in scleroderma compared to vacuolar degeneration resulting in clear spaces surrounded by collagen (stained blue). In contrast, in idiopathic visceral myopathy, there is vacuolar degeneration of muscle fibers encircled by collagen, often resulting in clear spaces surrounded by acellular collagen. (Courtesy of Schuffler, M. M.D., Seattle.) Vascular lesions vary in their endoscopic appearances depending on their type and size. Appearances may range from those of telangiectasia to the broad red antral stripes of the watermelon stomach.
Sometimes the associated vascular abnormality may be masked at endoscopy by an area of subepithelial hemorrhage. If vasculitic lesions have progressed, then the changes may be those of erosions or ulcerations. Lesions vary from small, ischemic ulcers to transmural infarction and perforation, depending on the size and number of vessels involved. Patients are also prone to pneumatosis intestinalis. Histologically, the small vessels of the bowel frequently show a proliferative endarteritis with endothelial swelling, intimal proliferation, and a peculiar mucinous change of the media (Fig. 8-6). In addition, there may be a vasculitis, which can affect the mesenteric arteries at any level.

Clinical Implications

The pathologist most commonly receives tissue in scleroderma from esophageal erosions or ulcers. Here the differential diagnosis includes Candida-associated esophagitis, “pill” esophagitis, reflux esophagitis, Barrett’s esophagus, and carcinoma. Less commonly, small bowel biopsies may be received from patients with malabsorption. The mucosa may exhibit a mild abnormality in the villous architecture and epithelial lymphocytosis compatible with small intestinal bacterial overgrowth (SIBO). Vasculitis, when encountered, is usually an incidental finding. Biopsies of suspected vascular lesions such as in “watermelon stomach” (see Chapter 2) may be disappointing because the mucosal vessels may collapse with the major abnormality being in the submucosa. This difficulty in verifying vascular lesions by endoscopic mucosal biopsy is not unique in scleroderma or to any particular region of the gastrointestinal tract (see Chapter 1).

Figure 8-6. Intestinal scleroderma. Overview demonstrating proliferative endarteritis in two small submucosal vessels characterized by a subintimal mucinous deposition.

Dermatomyositis and Polymyositis

Dermatomyositis and polymyositis are rare connective tissue disorders characterized by symmetric proximal muscle weakness, elevated serum levels of muscle enzymes, and an inflammatory myopathy on muscle biopsy. Skin involvement occurs in dermatomyositis, but not in polymyositis. Gastrointestinal symptoms are not that uncommon, but major complications are rare. The striated muscle of the hypopharynx and cervical esophagus is most frequently affected, and as with the changes in muscle and skin, is manifested by chronic inflammation, edema, muscle atrophy, and on rare occasions spontaneous esophageal rupture. Impaired swallowing, tracheal aspiration, and aspiration pneumonia are common complications. In addition, occasionally, as in scleroderma, smooth muscle atrophy and fibrosis may occur, resulting in dysfunction of the lower esophageal sphincter. Dysmotility in other parts of the gastrointestinal tract may result in delayed gastric emptying, colonic dilatation, constipation, and pseudodiverticula. A small minority of adult patients have been reported to experience more acute and severe gastrointestinal symptoms including abdominal pain, diarrhea, and gastrointestinal bleeding. In such cases gastrointestinal involvement may be diffuse. Histologic findings included ulcers and erosions, severe acute and chronic inflammation, and prominent mucosal and submucosal telangiectasia, but not vasculitis. By contrast, severe gastrointestinal involvement due to vasculitis of the bowel wall is a well-recognized complication of juvenile dermatomyositis.

A variety of malignancies have been reported in dermatomyositis including colorectal and gastric adenocarcinomas. Many or most of the malignancies in this disease are found at presentation or shortly thereafter. In these cases, it is likely that dermatomyositis is of paraneoplastic etiology. The prevalence of associated cancers is that which is unique to a locale or population group. For example, in Singapore and Tunisia nasopharyngeal cancer predominates, whereas in elderly Danish patients it is colon cancer. Once these initial or early cases are detected, there does not appear to be any increased risk with time beyond 1 year. Gastroenterologists are frequently asked to perform endoscopic examinations of the upper and lower gastrointestinal tract to look for cancer. There is however no generally accepted standard for cancer screening in these patients. The starting point is to carefully evaluate for clinical and laboratory clues that might point to a cancer at the time of presentation and in the early follow-up period after diagnosis. The risk of neoplasia in polymyositis is much lower.
Systemic Lupus Erythematosus

SLE is a multisystem disease characterized by immunologic abnormalities, with numerous autoantibodies to a host of nuclear and cytoplasmic antigens (e.g., antinuclear, anti-double-stranded DNA, and anticardiolipin antibodies) and associated with tissue damage. Gastrointestinal manifestations occur in about 25% to 40% of cases and are primarily related to vasculitis or complications of therapy. Vasculitis is the most important intrinsic feature of this disorder, and ischemia is responsible for many of the gastrointestinal manifestations. Small vessels of the submucosa and muscularis propria are typically involved rather than the medium-sized mesenteric vessels. Fibrinoid necrosis is characteristic. Vasculitis may affect the small and large bowel (especially terminal ileum and cecum) and less commonly the esophagus (see Chapter 2). Lupus anticoagulants and anticardiolipin antibodies may contribute to ischemia from vasculitis. The most dramatic gastrointestinal manifestations are abdominal pain with peritoneal signs, penetrating ulcers, and outright transmural infarction. Fortunately these occur uncommonly. Strictures may develop in cases where the ischemia progresses slowly or resolves after a major insult. Whenever diffuse or focal mucosal lesions such as ulcers or erosions are found, the challenge is to try to determine whether these are due to vasculitis or represent infectious complications of the immunosuppressive therapy that these patients receive. Such infections range from common types such as Candida, CMV, and herpes simplex to more exotic types. The challenge is compounded by the fact that endoscopic mucosal biopsies usually do not contain the vasculitic lesions.

Other complications of connective tissue disorders in general have been reported in SLE including amyloidosis and pneumatosis cystoides intestinalis. Reports of functional disorders such as malabsorption or protein-losing enteropathy are presumed to be due to ischemia or perhaps other mechanisms, for example, autoantibodies and bacterial overgrowth, but without proof. When malabsorption is found in a patient with SLE, other known causes of malabsorption, such as celiac disease, should be excluded. Intestinal pseudo-obstruction occurs uncommonly. Esophageal dysmotility can often be demonstrated by manometry but does not correlate well with esophageal symptoms. Peptic ulcer disease is common in patients treated with NSAIDs and corticosteroids. In diseases such as SLE with diverse manifestations, it is not surprising that associated disorders will be reported, such as hyperesinophilia without knowing whether it is coincidence or somehow unmasked by the presence of SLE. Patients treated with steroids may also develop lesions secondary to the steroids such as perforating diseases (stomach, diverticulitis, appendix) that may escape detection until advanced with widespread peritonitis.

Mixed Connective Tissue Diseases and the Overlap Syndrome

Mixed connective tissue disease is characterized by features of scleroderma, SLE, and polymyositis. When some of these features are missing, the disorder is referred to as the overlap syndrome. Gastrointestinal manifestations are common and most frequently resemble those seen in scleroderma.

Rheumatoid Arthritis

Many patients with rheumatoid arthritis have gastrointestinal symptoms, mostly due to drug therapy, especially NSAIDs (see Chapters 14 and 18). The poor correlation between symptoms and the presence of gastroduodenal erosions or ulcers is well recognized. Fifty percent or more of patients on these drugs have gastroduodenal lesions. Gold therapy for rheumatoid arthritis may also cause a colitis or enteritis. Vasculitis was documented even with blind suction biopsy in rheumatoid arthritis, illustrating that at times the gut may be a mirror or a source of diagnosis for vasculitis in connective tissue disorders. The complications listed previously for SLE may occur in rheumatoid arthritis, albeit with a lesser frequency. Involvement of smaller vessels results in multiple ischemic ulcers (Fig. 8-7), which may perforate. Nondescript mucosal lesions such as those described in seronegative spondyloarthropathy have been reported also in rheumatoid arthritis but with a lesser prevalence (see Chapter 18). Lymphnodular hyperplasia and increased intraepithelial lymphocytes have been reported in patients with juvenile idiopathic arthritis who experience gastrointestinal symptoms. It is uncertain whether these findings are related to the underlying disease or treatment.

Miscellaneous Disorders

Intestinal complications may occasionally develop in persons with other connective tissue disorders such as Sjögren's syndrome, Reiter's syndrome, Behçet's disease, and the hereditary connective tissue disorders. Patients with Sjögren's syndrome frequently experience dysphagia, which has been variously ascribed...
Figure 8-7. Rheumatoid arthritis with intestinal vasculitis and ischemic necrosis. A: Low-power view of a segment of small intestine showing ischemic ulceration involving the mucosa and submucosa. Note the vasculitic involvement of submucosal and subserosal vessels (arrows). B: High-power view of one of the vessels showing inflammation of the adventitia and media. (Courtesy of Mitros, F M.D., Iowa City.)

to decreased production of saliva, upper esophageal webs, parasympathetic dysfunction, and esophageal dysmotility, although the role of the latter has been questioned. Atrophic gastritis and duodenal ulcers have been described, but whether this is a true association and not ulcers secondary to medications and long-standing Helicobacter is unclear. Patients with Sjogren's may also be at increased risk for the development of lymphomas including MALT lymphomas of the stomach, and this should be borne in mind when evaluating endoscopic biopsies from such patients.

Reiter's syndrome is characterized by arthritis, urethritis, conjunctivitis, and mucocutaneous lesions and usually follows an attack of infectious diarrhea or urethritis. It appears that some patients have a subclinical colitis characterized by normal endoscopy and microscopic colitis.

In Behçet's disease there is gastrointestinal involvement in up to 50% of patients. In addition to the typical aphthous ulceration of the mouth, patients may have ulcerative lesions throughout the gastrointestinal tract, in particular the ileocecal region, which can mimic Crohn's disease. The underlying abnormality is a vasculitis of small veins and venules, but sometimes affecting larger vessels. Behçet's disease is more fully described in Chapter 23.

The hereditary connective tissue disorders, such as Ehlers–Danlos syndrome and pseudoxanthoma elasticum, are due to structural derangements of elastic tissue and fragility of blood vessels. This results in a variety of gastrointestinal disorders, such as gastrointestinal hemorrhage, ulceration, secondary diverticula, bowel rupture, and rectal prolapse. For a more detailed description, see Chapter 2.

GASTROINTESTINAL MANIFESTATIONS IN ENDOCRINE DISORDERS

Altered hormonal homeostasis due to endocrine-related disorders and functioning tumors can produce disordered function often in the absence of recognized structural change in the gastrointestinal tract. Symptoms may be due to altered motility, altered absorption and secretion, or both. Symptoms of altered motility and mucosal function may include vomiting, diarrhea, or constipation. There is also an association between endocrine disorders and certain gastrointestinal diseases, for example, autoimmune gastritis and thyroiditis. These will be discussed in the chapters dealing with these conditions. In this chapter, we shall concentrate our discussion primarily on the morphologic abnormalities accompanying diseases of the endocrine system.

Thyroid Gland

Hyperthyroidism. The main gastrointestinal manifestation of hyperthyroidism is diarrhea, but some patients have constipation. Accelerated intestinal transit has been a long-standing explanation for the diarrhea, but absorptive or secretory abnormalities might be contributing. Steatorrhea is usually mild. Patients frequently have chronic dyspeptic symptoms including epigastric pain, fullness, and nausea and vomiting. Altered gastroenteric myoelectrical activity has been documented by electrogastrography but does not appear to correlate with gastric emptying or dyspepsia. There is no convincing evidence that
intrinsic gut lesions occur in this disorder. Putative associations with gastritis were claimed on the basis of studies with blind suction biopsies, and claims of mild small bowel lesions need confirmation because the illustrations in one published report are not convincing. A small study in autoimmune thyroid disease suggested that there were more lymphoid follicles present in *Helicobacter pylori*-positive patients than in controls with *H. pylori* infection. The significance of this is unclear. An ileus-like picture with vomiting has been reported in a case of "thyroid storm." The pathophysiologic abnormalities producing these motility changes are not clearly understood, although they appear to be reversible after treatment of hypothyroidism. SIBO was reported in up to 54% (27/50) patients in one study compared to only 2% of matched controls. In these patients, abdominal symptoms were significantly improved following decontamination therapy.

The pathologic changes in the gut consist of marked dilatation and thickening of the bowel wall and microscopic accumulation of mucopolysaccharide substances within the submucosa, muscularis propria, and subserosa. An accompanying increase in the number of mast cells has also been described. These histologic changes have been likened to those found in the subcutaneous tissue of myxedematous patients. Most of the reported pathologic studies were done some time ago on autopsy material, without control groups for comparison, and are poorly illustrated. Thus, the precise histologic changes remain to be confirmed.

**Hypothyroidism**

A variety of gastrointestinal hypomotility disorders have been described in hypothyroidism, such as disturbance of esophageal sphincter function and atony and dilatation of the esophagus, stomach, small intestine, and colon, with consequent reflux esophagitis, bezoar formation, abdominal distention, ileus, and megacolon. The pathophysiologic abnormalities producing these motility changes are not clearly understood, although they appear to be reversible after treatment of hypothyroidism. SIBO was reported in up to 54% (27/50) patients in one study compared to only 2% of matched controls. In these patients, abdominal symptoms were significantly improved following decontamination therapy.

**Autoimmune Thyroid Disease**

The association of autoimmune thyroid disease and autoimmune diseases of the gastrointestinal tract, namely, atrophic gastritis, celiac disease, and microscopic colitis, is well recognized. These conditions may all display the HLA-DR3-DQ2 haplotype common to many autoimmune diseases. These associations are discussed further in the chapters dealing with these conditions.

**Thyroid Neoplasms**

Medullary thyroid carcinoma (MTC) is a tumor of the calcitonin-producing endocrine C cells of the thyroid. It is often familial and associated with the multiple endocrine neoplasia (MEN) syndromes, primarily types IIa and IIb. About one-third of the patients have a secretory (i.e., resistant to fasting) diarrhea. The latter has been attributed to the excessive production of certain peptides including calcitonin, serotonin, and vasoactive intestinal polypeptide. The histology of the intestinal mucosa is normal.

A number of other thyroid neoplasms may sometimes occur concurrently with gastrointestinal tumors. Thus, patients with primary lymphoma of the thyroid are reported to have an increased incidence of lymphomatous involvement of the gastrointestinal tract, and papillary carcinoma of the thyroid is sometimes associated with Gardner's syndrome, in particular the cribriform (morular) variant.

**Parathyroid Gland**

**Hyperparathyroidism.** The classical presentation of hyperparathyroidism as “stones, bones and abdominal groans” as described by St. Goar is now a rarity in most Western countries although still seen in some parts of the world. With routine measurement of blood calcium, most patients now present with asymptomatic hypercalcemia. Even those left untreated rarely develop the “classical” picture. Gastrointestinal symptoms, including abdominal pain and distention, vomiting, and constipation, described in up to 50% of patients in the earlier literature were ascribed to the effects of hypercalcemia, possibly via altered neuronal transmission and neuromuscular excitability. Despite the historical association with peptic ulcer disease, the prevalence of peptic ulcers in sporadic hyperparathyroidism is probably similar to that of the general population. However, in the setting of MEN1, hyperparathyroidism and peptic ulcer disease frequently coexist due to the presence of gastrinomas in 40% of these patients.

**Hypoparathyroidism**

Hypoparathyroidism is associated with diarrhea and sometimes steatorrhea and malabsorption. These changes are related to hypocalcemia and are not associated with any apparent morphologic abnormalities. The precise mechanisms for
the diarrhea remain to be elucidated but impaired enteropancreatic peptide secretion following caloric stimulus and increased epithelial permeability due to cytoskeletal alterations have been suggested to play a role.\textsuperscript{129}

**Endocrine Pancreas**

**Diabetes**

Pathogenesis and Clinical Manifestations Several population-based studies suggest an increased prevalence of upper and lower gastrointestinal symptoms among patients with diabetes, although epidemiologic data are inconsistent.\textsuperscript{130–133} Gastrointestinal symptoms in diabetics may be due to gastroparesis, altered intestinal motility/function, loss of sphincteric control, infection, or associated autoimmune disorders such as celiac disease and atrophic gastritis.\textsuperscript{130,131,134}

Gastroparesis occurs in both type 1 and 2 diabetics but seems to be particularly prevalent in patients with long-standing type 1 diabetes.\textsuperscript{131,135} Symptoms of gastroparesis include nausea, vomiting, epigastric fullness, bloating, and abdominal discomfort. Bezoar formation may sometimes ensue, exacerbating the symptoms of gastroparesis or producing a palpable mass, ulceration, perforation, or small bowel obstruction\textsuperscript{131,135} (Fig. 8-8). The cause of gastric dysmotility appears to be multifactorial with postulated mechanisms including autonomic dysfunction, impaired glycemic control (hyperglycemia disrupts antral motor complexes, delaying gastric emptying), hormonal imbalances (elevations in postprandial glucagon delays gastric emptying), loss of interstitial cells of Cajal, microangiopathy, and psychological distress.\textsuperscript{130,131,134,135}

Diarrhea affects 4% to 22% of diabetics with up to 75% also having steatorrhea.\textsuperscript{131,134} Occasionally this is severe and intractable.\textsuperscript{136,137} Segments of bowel may undergo dilatation with secondary bacterial overgrowth, which may cause or exacerbate diarrhea.\textsuperscript{138} Bacterial overgrowth is present in up to 43% of diabetics with chronic diarrhea.\textsuperscript{138} As with gastroparesis the etiology of diabetic diarrhea appears to be multifactorial. A role of visceral autonomic neuropathy is supported by morphologic changes in both the parasympathetic and sympathetic nervous systems in diabetics (see below) and by the occurrence of diarrhea in other conditions affecting the autonomic nervous system including vagotomy.\textsuperscript{131,140–142} Other postulated mechanisms include pancreatic insufficiency, small bowel bacterial overgrowth, infections, drugs (e.g., metformin) or associated celiac disease or hyperthyroidism,\textsuperscript{131,134,139,143} and a decrease in interstitial cells of Cajal.

In the colon, dysmotility may result in severe constipation and even stercoral ulceration.\textsuperscript{144,145} Autonomic neuropathy is likely a major factor, but a deficiency of ICC\textsuperscript{146} and decreased production of substance P (a stimulant of colonic motility and fluid secretion)\textsuperscript{147} may also contribute. Sometimes, patients develop dysfunction of anal sphincters, resulting in fecal incontinence, often in association with diarrhea.\textsuperscript{131} They may also develop severe, unexplained abdominal pain (diabetic radiculopathy).\textsuperscript{131,140–142}

Although esophageal abnormalities are commonly demonstrated with manometry, esophageal symptoms are uncommon. Diabetics are known to be
susceptible to infections in the gut, especially esophageal candidiasis,146 and in ketoacidosis there may be severe upper gastrointestinal bleeding from gastric erosions, presumably of the stress type. There is an increased incidence of atrophic gastritis with pernicious anemia and celiac sprue among type 1 diabetics. These cases are associated with significant titers of circulating parietal cell antibodies and often thyroid antibodies.140-152 The prevalence of autoimmune gastritis in type 1 diabetics is three- to fivefold higher than that of the general population. Celiac disease is reported in up to 5% to 10% of patients with type 1 diabetes152-154 compared to 0.55% to 1% in the general population in Europe and North America. In most cases the diagnosis of diabetes precedes that of celiac disease. One study found the prevalence of symptomatic celiac disease at diagnosis to be 0.7%, but this increased to 10% after 5 years of annual screening.154 Many centers advocate routine annual screening for celiac disease in type 1 diabetics with a minimum of 2 years suggested.154 (Celiac disease is further discussed in Chapter 20.)

Most studies support an association between diabetes and colorectal carcinoma. A meta-analysis of 15 studies including over 2,500,000 patients confirmed this association, demonstrating a relative risk of 1.3 (95% CI = 1.2–1.4) in diabetic patients compared to nondiabetics. This relative risk was maintained when analysis was restricted to the seven studies, which controlled for body mass index and physical inactivity.155

**Pathology** Surgical pathologists encountering material from the gastrointestinal tract of diabetics are most likely to see esophageal candidiasis, the mucosal lesion of celiac disease, or autoimmune gastritis (see Chapters 14 and 20). Other findings include erosive gastritis in diabetic ketoacidosis, SIBO, and stercoral ulceration. Resection specimens may show features of autonomic neuropathy, which are frequently patchy and may involve both the vagal and the sympathetic nervous systems. Such changes include a marked decrease in the density of unmyelinated axons, axonal degeneration, thickening of the basement membrane of Schwann cells, decreased caliber of vagal nerves, and decreased fiber density of sympathetic nerves.133,156 Myenteric ganglia may also show degenerative changes characterized by distended neurons; enlarged, club-shaped neuronal processes; and accompanying chronic inflammation. Secondary degenerative changes in the muscularis propria may be found.157 A marked decrease in interstitial cells of Cajal has been reported both in the stomach and the colon of diabetics146,158,159 as well as animal models of diabetic gastroparesis145 and may be related to lack of Heme oxygenase 1.158 Patients with diabetes are also at increased risk of atherosclerosis and its complications, such as acute mesenteric arterial ischemia. Microangiopathy is frequently mentioned in the literature, but it has not been conclusively demonstrated in the gut.160,161

**Hyperfunction of Islets of Langerhans**

The hormones produced by the pancreas play an important role in intestinal function. Consequently, alteration of hormonal homeostasis may have profound effects on normal digestion and motility. Islet cell hyperfunction can result from diffuse hyperplasia (nesidioblastosis) or neoplasia,162,163 with the production of a variety of hormones, although in most instances one hormone predominates.164 The hormones produced are those normally found in the cells of the islets of Langerhans such as insulin, glucagon, somatostatin, and pancreatic polypeptide. Sometimes, however, ectopic hormones, such as gastrin, ACTH, calcitonin, parathormone, and serotonin, are the major secretion products. In almost all instances, the gastrointestinal manifestations are a reflection of altered digestive function and motility and are unaccompanied by morphologic changes in the gastrointestinal mucosa. The major islet cell proliferations and their gastrointestinal manifestations are as follows.

**Gastrinoma**

This lesion results in the Zollinger–Ellison syndrome characterized by aggressive peptic ulcer syndrome, severe diarrhea, or both (see “Gastrointestinal Endocrine Disorders,” Chapter 6). In addition to peptic ulceration, gastrin induces prominent trophic changes in the oxyntic mucosa including increased mucosal thickness, increased parietal cell mass, lin-gulate parietal cytoplasmic projections into the gland lumen, hyperplasia of mucin neck cells, mucin hypersecretion, and ECL cell hyperplasia and microcarcinoids. The antral mucosa is diminished in size to accommodate the expanded oxyntic zone, and there is a decrease in the density of antral G cells.165

**VIPoma Syndrome (Verner–Morrisons Syndrome)**

VIPomas constitute about 5% of pancreatic endocrine tumors based on the presence of lymph node, hepatic, or distant metastases.166 The VIPoma syndrome may
also result from diffuse hyperplasia of the islets and occasionally from ganglioneuromas or ganglioneuroblastomas, which secrete vasoactive intestinal peptide (VIP). The syndrome is characterized by profuse watery secretory diarrhea (i.e., resistant to fasting), with hypersecretion of water and electrolytes, resulting in severe dehydration, hypokalemia, and metabolic acidosis. VIPomas may secrete other products such as gastrin, serotonin, gastrin inhibitory polypeptide, and somatostatin, which may contribute to the diarrhea. No morphologic abnormalities have been described in the gastrointestinal tract.

**Somatostatinoma**

Somatostatin-producing tumors including somatostatinoma (and less commonly gangliocytic paraganglioma and poorly differentiated neuroendocrine carcinoma) may occasionally produce the clinical triad of diabetes mellitus, gallstones, and diarrhea (“somatostatinoma syndrome”). The vast majority of somatostatin-producing tumors are non-functional (probably due to the very short half-life of somatostatin), and full-blown somatostatinoma syndrome appears to be uncommon. Diarrhea results from the physiological actions of somatostatin, namely, diminished pancreatic enzyme secretion and delayed intestinal absorption of nutrients. Somatostatinomas are frequently periampullary in location, and psammoma bodies are a typical feature (see Chapter 6).

**Other Islet Cell Tumors**

The other islet cell tumors, such as insulinomas and glucagonomas, may be accompanied by severe angular stomatitis and glossitis. Giant intestinal villi have been described with glucagonomas. Such enterotrophic effects have been reproduced in animals administered glucagon-like peptide 2.

**Adrenal Gland**

Gastrointestinal symptoms are common in Addison's disease with anorexia, nausea, and vomiting occurring in almost all advanced cases. Other symptoms include abdominal pain and diarrhea, sometimes with steatorrhea. The diagnosis is frequently overlooked due to the nonspecific nature of the complaints, particularly when skin pigmentation is absent (5%–8% of cases). Celiac disease is common in patients with autoimmune Addison's disease, with a prevalence of 8% to 12% reported in several European studies. There have been isolated reports of atrophic gastritis with pernicious anemia in Addison's disease, but its overall prevalence is uncertain. Peptic ulceration occurs uncommonly.

Cushing's disease is frequently accompanied by gastrointestinal symptoms including anorexia, nausea, and vomiting. Adrenal tumors may form part of syndromes affecting the gastrointestinal tract for example, adrenal cortical adenoma in Gardner's syndrome and pheochromocytomas in MEN IIa and IIb and von Recklinghausen's disease (sometimes with somatostatin-rich duodenal carcinoids). Adrenal pheochromocytoma may have a number of gastrointestinal manifestations including nausea and vomiting, abdominal pain, and constipation. In addition, intestinal pseudo-obstruction and megacolon may occur due to the inhibition of gastrointestinal smooth muscle activity due to very high circulating catecholamine levels. Rarely, patients may present with ischemic colitis due to catecholamine-mediated vasospasm. Occasionally tumors may produce VIP and present with watery diarrhea, hypokalemia, and achlorhydria syndrome. No recognized histologic changes have been demonstrated in these patients, and symptoms are often reversible with intravenous phentolamine or after surgical excision of the tumor. Rarely gastrointestinal hemorrhage may occur secondary to multiple varices associated with the tumor mass.

**Gonads**

**Pregnancy.** Gastrointestinal symptoms are extremely common in pregnancy and include nausea (80%–90%), vomiting (50%), heartburn (40%–80%), bloating, and constipation (25%–40%). Altered levels of female sex hormones are considered to play a major role in these symptoms by lowering esophageal sphincter pressure, delaying gastric emptying, and decreasing intestinal motility. Other factors, especially mechanical, may contribute but are considered of lesser importance. Severe, intractable vomiting (hyperemesis gravidarum) affects 0.3% to 2% of pregnancies and is strongly associated with elevated levels of human chorionic gonadotrophin (HCG) and estrogen. HCG is thought to act via a stimulatory effect on secretory processes in the upper gastrointestinal tract (and possibly through binding to TSH receptor) while estrogen delays gastric emptying and motility. Patients with hyperemesis gravidarum have an increased prevalence of *H. pylori* infection compared to controls.

**Hypothalamus and Pituitary**

The hypothalamus and pituitary normally function as an integrated unit, and disorders of either may involve gastrointestinal function.
Hypopituitarism

This affects gastrointestinal motility in much the same way as hypothyroidism. For example, a patient may develop nausea and vomiting secondary to gastroparesis on account of T-thyro hormone deficiency. Replacement of the latter will relieve these symptoms.197

Pituitary Adenoma

Acromegaly, a disorder associated with excess growth hormone production, is characterized by overgrowth of the musculoskeletal system and all organs, including the gastrointestinal tract. Acromegolics are at increased risk of developing a variety of neoplasms including those arising in the gastrointestinal tract.96,198-200 They have a three- to eightfold risk of developing colorectal carcinoma in acromegals,199 Risk factors for colorectal cancer in acromegals include male gender, age >50 years, disease duration >5 years, three or more skin tags (to which these patients are prone), a family history of colorectal carcinoma, and a prior history of adenomatous polyps.96,199 One study found elevated levels of insulin-like growth factor 1 (IGF-1) to be associated with an especially high risk of colorectal carcinoma in acromegals,201 but others have not.199 More recently, it has been shown that the risk of colorectal neoplasms is markedly increased in patients with elevated fasting insulin levels.199 Screening colonoscopy is recommended in all patients with acromegaly, with more frequent surveillance in those with additional risk factors for colorectal neoplasia.96,200

Autoimmune Polyendocrinopathy Syndrome Type 1

This rare monogenic autoimmune syndrome, caused by a defect in the AIRE gene on chromosome 21, is characterized by polyendocrinopathy and chronic Candida infection.202,203 The condition usually manifests in childhood or early teenage years with chronic candidiasis (affecting tongue, esophagus, and nails) followed by autoimmune hypoparathyroidism and Addison’s disease. At least two of the three aforementioned conditions are required for diagnosis. Other autoimmune disorders such as type 1 diabetes, autoimmune thyroid disease, autoimmune gastritis with pernicious anemia, celiac disease, and hypogonadism may be present. Patients may also have alopecia, vitiligo, urticaria-like erythema, ectodermal dystrophies affecting nails and enamel, and keratoconjunctivitis. Affected patients may present with chronic unexplained diarrhea and have decreased enteroendocrine cells relative to controls.202 Thus, examination of mucosal biopsies for enteroendocrine cells in patients with unexplained diarrhea may alert the pathologist to the possibility of autoimmune polyendocrine syndrome (or immunological dysregulation, polyendocrinopathy, enteropathy, and X-linkage syndrome) is due to a germline mutation in the forkhead box protein 3 (FOXP3) gene on the X-chromosome, which in young males results in defective development of CD4+ CD25+ T-regulatory cells. This leads to a variety of autoimmune phenomena including autoimmune enteropathy, gastritis, colitis, dermatitis, thyroiditis, and type 1 diabetes and frequently results in death within the first 2 years of life. Some patients have antiparietal cell antibodies, while others may have antiparietal cell and antiislet cell antibodies as well. It is discussed in more detail in Chapter 3.

Multiple Endocrine Neoplasia

The MEN syndromes consist of a group of autosomal-dominant inherited disorders, characterized by hyperplastic or neoplastic involvement of a variety of endocrine glands.205,205a,206 The major manifestations are listed in Table 8-1. The main variants of this syndrome are: MEN I, MEN IIa, MEN IIb, together with FMTC (familial medullary thyroid cancer) that does not have GI involvement. Their gastrointestinal symptoms result mainly from the products of endocrine proliferations, which stimulate or inhibit one or more functions of the gastrointestinal tract.103,207,208 MEN IIb most commonly has major intestinal manifestations.209,210 Patients have a characteristic marfanoid habitus and facies, along with nodular thickening of the lips and anterior tongue. They frequently have chronic constipation, dating from birth, associated with megacolon and narrowing of the lower sigmoid or upper rectum, which mimics Hirschsprung’s disease. This disease is often associated with ganglioneuromatosis, which is thought to be responsible for the constipation, although the pathogenetic mechanism is unclear. A possible association with adenomatous polyposis throughout the gastrointestinal tract and with mucosal ganglioneuromatosis has also been noted.211-213 MTC is the main morbidity in patients with MEN II, and early prophylactic thyroidectomy is indicated in these patients.214 The gastrointestinal manifestations of MEN I and MEN IIa are due to hormone hypersecretion resulting from the endocrine cell proliferations, for example, peptic ulceration in patients with gastrinomas.
Levin, Weinstein, and Riddell's Gastrointestinal Pathology and Its Clinical Implications

Table 8-1  Gastrointestinal Manifestations of Multiple Endocrine Neoplasia (MEN) Syndromes

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>PENETRANCE (%)</th>
<th>GASTROINTESTINAL MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN I (MEN1 gene mutations, rarely CDKN1B gene mutations encoding p27, sometimes referred to as MEN4)</td>
<td>Primary hyperparathyroidism 90–100</td>
<td>Peptic ulceration associated with gastrinoma. Diarrhea associated with carcinoid syndrome or VIPoma.</td>
</tr>
<tr>
<td></td>
<td>Enteropancreatic neuroendocrine tumors 60</td>
<td></td>
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<tr>
<td></td>
<td>Gastrinoma 40</td>
<td></td>
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<tr>
<td></td>
<td>Insulinoma 10</td>
<td></td>
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<tr>
<td></td>
<td>Pituitary adenomas 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenocortical neoplasms 20–30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foregut neuroendocrine tumors (gastric, thymic, bronchial) 10–15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple facial angiofibroma 85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Collagenoma 70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple lipomas 30</td>
<td></td>
</tr>
<tr>
<td>MEN IIa (RET gene mutations—classically codon 634)</td>
<td>Medullary thyroid carcinoma 95–100</td>
<td>Watery (secretory) diarrhea associated with medullary carcinoma (?) due to calcitonin overproduction</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma 50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary hyperparathyroidism 20–30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hirschsprung's disease Uncommon</td>
<td></td>
</tr>
<tr>
<td>MEN IIb (RET gene mutations—classically codon 918)</td>
<td>Mucosal ganglioneuromatosis 100</td>
<td>Nodularities of lips and anterior tongue, gastric and intestinal dilatation, megacolon mimicking Hirschsprung's disease, constipation or diarrhea, hematochezia.</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid carcinoma 95–100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma 50</td>
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</tbody>
</table>


A large number of gastrointestinal complications of renal failure have been reported and are listed in Table 8-2. The major problems, however, are upper gastrointestinal bleeding from erosions, ulcers, or gastric vascular ectasia; infarcts due to nonocclusive intestinal ischemia; and perforated diverticula. Most of these complications seem to be associated with renal dialysis and renal transplantation for reasons that are not always clear.

The pathogenesis of gastrointestinal manifestations of uremia is likely multifactorial and often difficult to dissect. However, gastric hypomotility with delayed gastric emptying, capillary fragility and disordered hemostasis of uremia, effects of unfiltered humoral factors or toxins, comorbidities (including other organ failures or underlying causes, e.g., diabetes or amyloid), and medications (e.g., NSAIDs) may all play a role.

**Acute Renal Failure**

These patients, most of whom are postsurgical or trauma patients, frequently develop multiple gastric and duodenal erosions with gastrointestinal hemorrhage and occasionally perforation. Although high serum gastrin levels are found in some patients, it is probable that the gastrointestinal complications are the result of the physiologic stress with multiple organ failure (see Chapter 14) rather than acute renal failure.

**Chronic Renal Failure**

Seventy-five percent of patients with end-stage renal disease have gastrointestinal symptoms. Nausea, vomiting, and anorexia are most prevalent, with each affecting over 60% of patients. Other common complaints include bloating, heartburn, abdominal pain, and constipation. Major but less common complications include bleeding from GAVE, erosions or ulcers, and infarcts due to nonocclusive intestinal ischemia. Gastrointestinal hemorrhage is particularly important, occurring in up to 15% of patients with chronic renal failure and accounting for up to 15% to 20%
### Table 8-2: Interrelationship of Gastrointestinal and Renal Diseases

<table>
<thead>
<tr>
<th>GASTROINTESTINAL MANIFESTATIONS OF RENAL DISEASE</th>
<th>Renal transplantation</th>
<th>DISEASES AFFECTING BOTH GASTROINTESTINAL AND RENAL SYSTEMS</th>
<th>RENAL MANIFESTATIONS OF GASTROINTESTINAL DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute renal failure</strong></td>
<td>Gastric and duodenal erosions and ulcers</td>
<td>Collagen vascular diseases</td>
<td><strong>Crohn’s disease</strong></td>
</tr>
<tr>
<td>Gastric perforation</td>
<td></td>
<td>Scleroderma</td>
<td>Calcium oxalate stones</td>
</tr>
<tr>
<td><strong>Chronic renal failure</strong></td>
<td>Erosive esophagitis</td>
<td>Vasculitides</td>
<td>Ureteral obstruction</td>
</tr>
<tr>
<td>Erosive and hemorrhagic gastritis</td>
<td></td>
<td>Diabetes mellitus</td>
<td>Entero or colovesical fistula</td>
</tr>
<tr>
<td>(Nodular) duodenitis</td>
<td></td>
<td>Hyperparathyroidism</td>
<td>Perinephric abscess</td>
</tr>
<tr>
<td>? Peptic ulcer disease</td>
<td></td>
<td>Amyloidosis</td>
<td></td>
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<tr>
<td>? Angiodysplasia</td>
<td></td>
<td>Myeloma</td>
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<tr>
<td>Intussusception secondary to mucosal hemorrhage</td>
<td></td>
<td>Henoch–Schönlein purpura</td>
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<tr>
<td>Diverticula in adult polycystic kidney disease (APCKD)</td>
<td></td>
<td>Hemolytic uremic syndrome</td>
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<tr>
<td>Salmonella enteritis</td>
<td></td>
<td>Posttransplant GI lymphoproliferative disorders</td>
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<tr>
<td>Calcific uremic arteriolopathy</td>
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<tr>
<td><strong>Complications of therapy</strong></td>
<td>Kayexalate sorbitol associated GI mucosal injury</td>
<td></td>
<td></td>
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<tr>
<td>Anticoagulant and antiplatelet therapy associated</td>
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<tr>
<td>GI bleeding</td>
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<tr>
<td>Mycophenylate mofetil associated GI mucosal injury</td>
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<td></td>
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<tr>
<td>(transplants)</td>
<td></td>
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<tr>
<td><strong>Complications of dialysis</strong></td>
<td>Acute fluid loss resulting in nonocclusive intestinal ischemia</td>
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<tr>
<td>Peritonitis (bacterial or chemical) in peritoneal dialysis</td>
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<tr>
<td>Hernia (+/− obstruction or incarceration) in peritoneal dialysis</td>
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<tr>
<td>Sclerosing peritonitis in long-term peritoneal dialysis</td>
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<tr>
<td><strong>Renal transplantation</strong></td>
<td>Gastric and duodenal erosions and ulcers</td>
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<tr>
<td>Esophagitis (often candida)</td>
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<tr>
<td>Mycophenylate mofetil associated GI mucosal injury</td>
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<tr>
<td>Perforation of colonic diverticula (especially APCKD)</td>
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<tr>
<td>Cecal ulceration</td>
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<tr>
<td>Pseudomembranous colitis (50% of patients receiving antibiotics)</td>
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<tr>
<td>Nonocclusive vascular insufficiency</td>
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<tr>
<td>Infections due to chronic immunosuppression, especially cytomegalovirus infection and intestinal strongyloidiasis</td>
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<tr>
<td>Posttransplant GI lymphoproliferative disorders</td>
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<tr>
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<td></td>
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<tr>
<td>Hemolytic uremic syndrome</td>
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<tr>
<td><strong>Renal manifestations of gastrointestinal disease</strong></td>
<td></td>
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<tr>
<td>Crohn’s disease</td>
<td>Calcium oxalate stones</td>
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</table>

Gastrointestinal manifestations of extraintestinal disorders and systemic disease can be complex and often interrelated with renal disease. For example, gastrointestinal bleeding (mostly occult) is common in patients with uremia, particularly those on hemodialysis. Gastritis, duodenitis, peptic ulcers, and telangiectasias are more prone to bleed in uremic patients than in the general population. This is due to the disordered hemostasis of uremia resulting from platelet and endothelial dysfunction, associated anemia, and antiplatelet and anticoagulant therapies frequently taken by these patients. Patients with chronic renal failure may lose 3 to 4 mL of blood via the gastrointestinal tract per day (compared to around 1 mL/d in the general population), increasing to 6 mL in patients on hemodialysis. Overt gastrointestinal hemorrhage is a serious complication in uremic patients and is associated with a higher rate of blood transfusion, emergency surgery, and mortality than in the general population. Angiodysplasia (or vascular ectasia) is well described in chronic uremia and may be a cause of severe upper gastrointestinal bleeding. However, it remains unclear whether it has a higher prevalence in uremics than in the general population.

Finally, uremic patients who receive kayexalate sorbitol for the treatment of hyperkalemia may develop mucosal injury and often necrosis, in the
lower and upper gastrointestinal tract. In H&E sections kayexalate crystals appear as basophilic polygonal crystals with a characteristic striped or mosaic pattern.

Patients undergoing dialysis are prone to additional complications including:

1. Acute fluid loss during dialysis, producing hypotension, which may result in nonocclusive vascular ischemia.
2. Peritonitis, the most common complication of peritoneal dialysis, which can be bacterial (most commonly due to staphylococcal or streptococcal species) or chemical.
3. Hernias, a common complication of peritoneal dialysis, posing a risk of acute bowel obstruction or incarceration.
4. Sclerosing peritonitis, which is a rare complication of long-term peritoneal dialysis.

Endoscopic and Histologic Appearances

The gross and histologic features of erosive esophagitis, gastritis, and duodenitis are discussed in their respective chapters.

Other Findings

A number of other abnormalities have been described in association with chronic renal failure, namely, massive small bowel infarction secondary to nonocclusive vascular insufficiency, colonic intussusception secondary to intramural hemorrhage, duodenal pseudomelanosis, and susceptibility to Salmonella enteritis in hemodialysis patients. Diverticulosis is common in patients with autosomal dominant polycystic kidney disease and is particularly prone to complications in the posttransplant period (see below). A peculiar form of “nodular duodenitis” associated with Brunner’s gland hyperplasia has been described in renal failure (see Chapter 14). Calcific uremic arteriolopathy is a rare complication of end-stage renal disease, which may present with intestinal ischemia or infarction.

Renal Transplantation

Gastrointestinal complications are an important cause of morbidity following renal transplantation, with an incidence of around 20% (Table 8-2). Many complications are related to immunosuppressive therapy (especially mycophenolate mofetil [MMF] and corticosteroids), preexisting gastrointestinal pathology, antibiotic therapy, and infections. The most common gastrointestinal complications include nausea, vomiting, and abdominal discomfort (frequent in patients receiving MMF, corticosteroids, or both), candidal and less commonly CMV- or herpes-related esophagitis, peptic ulcer disease, diarrhea, and colonic hemorrhage or perforation. The complications common to organ transplant–related immunosuppression are discussed in detail in Chapter 4 and are mentioned only briefly here.

Until fairly recently, peptic ulcer disease was a frequent cause of morbidity and mortality in renal transplant recipients, accounting for around 4% of deaths in these patients. This picture has changed dramatically with active screening and treatment of patients for Helicobacter and ulcerogenic medications prior to transplantation and with the routine use of prophylactic H2 receptor antagonists, proton pump inhibitors, or sucralfate in the postoperative period by many transplant groups. This practice has reduced the mortality from gastroduodenal perforation or hemorrhage to near zero.

Diarrhea is frequent in renal transplant recipients and is mostly related to infections, drugs, or antibiotics. Self-limited and short-lived viral gastroenteritis is the most frequent cause of diarrhea. Certain immunosuppressives, especially MMF, are associated with diarrhea. Pseudomembranous colitis occurs in about 50% of transplant recipients receiving antibiotics. Other infective agents responsible for diarrhea include bacteria (Shigella, Salmonella, and Campylobacter, etc.), viruses (CMV, herpes simplex virus), and parasites (Cryptosporidium, Giardia, and Strongyloides).

Renal transplant recipients are at increased risk for a variety of colonic complications, which seem to be more common in the elderly and in patients with polycystic kidney disease. These include ruptured colonic diverticula, bleeding from cecal ulceration, and nonocclusive vascular insufficiency. The latter may be patchy and mimic inflammatory bowel disease (IBD). The cause of ruptured diverticula and its relationship to steroids and immunosuppressive therapy are not understood, but its high incidence in renal transplant patients at one stage prompted some to advocate prophylactic sigmoid colectomies in patients with symptomatic disease. Although more common in the elderly, young patients may also be affected.
Chronically immunosuppressed patients are prone to unusual infections. Thus, renal transplant recipients, especially following treatment for rejection, are prone to CMV infection, which in some instances results in colonic perforation\textsuperscript{267,268}, parasitic infections such as cryptosporidiosis, giardia, and blastocystosis\textsuperscript{269}, and hyperinfection with \textit{Strongyloides stercoralis}. The latter may, on rare occasions, result in severe colitis and perforation.\textsuperscript{270,271} Finally, the gastrointestinal tract is a common site for posttransplant-associated lymphoproliferative disorders (see Chapter 5).

**Role of the Pathologist and Clinical Implications**

In examining biopsy and resection specimens from patients with renal failure, renal transplants, or both, the pathologist should always be on the lookout for potentially treatable conditions. This refers mainly to infections such as candidiasis, herpes virus, CMV, and strongyloides. Pathologists should be aware that the commonly used immunosuppressive drug MMF may cause toxic injury throughout the gastrointestinal tract including ulcerative esophagitis, reactive gastropathy, graft versus host disease (GVHD)-like features (i.e., dilated damaged intestinal crypts with increased epithelial apoptosis), crypt architectural distortion, and increased lamina propria inflammation. Caution is thus required when considering a diagnosis of IBD or GVHD in such patients.\textsuperscript{272} Finally, if the cause of a patient’s renal failure is undetermined, gut specimens from the patient should be examined carefully for the presence of amyloid.

**Gastrointestinal Manifestations of Hepatic Disorders**

The major gastrointestinal disorders associated with liver disease are related to portal hypertension and liver transplantation.

**Portal Hypertension**

Portal hypertension is most commonly associated with cirrhosis but can also result from noncirrhotic portal fibrosis, extrahepatic portal vein obstruction, hepatocellular carcinoma, and other hepatic lesions such as polycystic liver disease.\textsuperscript{271} Portal hypertension commonly results in esophageal and gastric varices and portal congestive gastropathy, often causing severe upper gastrointestinal hemorrhage. Endoscopic treatment of varices appears to predispose to the development of congestive gastropathy due to the redistribution of blood flow.\textsuperscript{274} It has now been shown that similar congestive colonic lesions and rectal varices (portal colopathy) are not uncommon and can also result in frequent hemorrhage.\textsuperscript{274–278} A study, using capsule endoscopy, found small intestinal varices in 3 of 19 patients (16%) who had previously undergone eradication of esophageal varices.\textsuperscript{279} Morphologically, the gastrointestinal mucosal changes in portal hypertension involve primarily the mucosal vessels, resulting in an increased number of mucosal capillaries and venules in all portions of the mucosa, with prominent branching and marked dilatation. The best recognized of these is portal hypertensive gastropathy in which dilated mucosal capillaries are present, which by definition have a greater diameter than the gastric pits. Unlike GAVE, they are usually not thrombosed. In addition, some of the venules are tortuous and show thick-walled arterIALIZATION. In addition to the varices, other vascular changes are sometimes found in hepatic cirrhosis such as vascular ectasia, erythematous mucosal patches, red macules, and telangectasia, all of which may also give rise to gastrointestinal hemorrhage. However, some of these lesions, such as vascular ectasia, may be unrelated to portal hypertension and due to other causes such as liver dysfunction.\textsuperscript{280}

Up to 60% of cirrhotic patients have evidence of SIBO, thought to result from small intestinal dysmotility and impaired antimicrobial defenses. SIBO is considered a predictor of spontaneous bacterial peritonitis.\textsuperscript{274} Patients with alcoholic liver disease may display many of the small intestinal mucosal abnormalities seen in SIBO, including partial villous atrophy, increased lamina propria cellularity, increased intraepithelial lymphocytes, and brush border abnormalities.\textsuperscript{281}

**Primary Sclerosing Cholangitis and Autoimmune Hepatitis**

Fifty five to seventy percent of patients with primary sclerosing cholangitis (PSC) and four to thirteen percent of patients with autoimmune hepatitis have IBD, mainly ulcerative colitis.\textsuperscript{282} The finding of PSC therefore demands colonoscopy, and if colitis is present, this counts as the first surveillance colonoscopy, as it is unclear how long the colitis has been present. Patients with PSC are at increased risk for the development of IBD-associated colorectal carcinoma\textsuperscript{283} as well as the development of pouchitis following ileal-anal pouch anastomosis.\textsuperscript{284} One of the problems of PSC is that if the patient is close to a liver transplantation, dysplasia or even carcinoma may be present in the large bowel, raising the question of which needs to be carried out first.
Liver Transplantation

Liver transplantation can give rise to the usual posttransplant complications involving the gastrointestinal tract such as infections, lymphoproliferative disorders, etc. Other complications described include intestinal perforation due to operative injury or infection and eosinophilic gastroenteropathy with intense eosinophilic mucosal infiltration. The latter may be due to immunomodulatory medications such as corticosteroids as suggested by disappearance of the infiltrate after discontinuation of therapy. IBD may develop de novo following liver transplantation, mostly in patients with autoimmune hepatitis or PSC. Continuous immunosuppressive therapy in transplant patients does not prevent flares or de novo occurrence of IBD. In fact the disease may follow a more aggressive course than that prior to liver transplantation; this may be related to immunosuppressive regimens used. Interestingly, in one study of patients transplanted for PSC or autoimmune cirrhosis, de novo IBD was strongly associated with postoperative CMV infection. A causative role of CMV infection in this setting remains to be determined.

Gastrointestinal Manifestations of Skin Disorders

Skin and gastrointestinal tract disorders may occur simultaneously in a number of settings:

1. The skin disorder may be secondary to a primary disease of the gut, for example, ulcerative colitis with erythema nodosum and pyoderma gangrenosum.
2. The gut lesion is in contiguity with the skin disorder, for example, pemphigus and blistering lesions in the esophagus, or is associated with a primary dermatologic disorder, such as dermatitis herpetiformis and celiac sprue.
3. The skin and gut disorders are both manifestations of generalized disease or a genetic disorder, for example, skin and gut disorders in scleroderma, colonic polyps and dermal tumors in Gardner’s syndrome, eczema and eosinophilic esophagitis in atopic patients, and vascular malformations of the skin and mucous membranes in Rendu–Osler–Weber syndrome.

Table 8-3 lists the major disorders in which skin and gastrointestinal manifestations are found. This section will focus on gastrointestinal lesions with documented pathology occurring in the setting of primary skin disorders or generalized disorders in which skin manifestations are the major abnormalities.

The esophagus is the most frequently affected extracutaneous site. Although esophageal involvement is rare in common diseases such as dermatitis and psoriasis, it may be a major manifestation of a number of uncommon skin disorders. Such disorders can be broadly divided into bullous, hyperkeratotic, malignant, and group of miscellaneous disorders.

Bullous Disorders

Epidermolysis bullosa. This heterogeneous group of inherited blistering diseases can involve all organs lined by squamous epithelium, with the esophagus one of the most common extracutaneous sites involved. Gastrointestinal symptoms are reported in up to 58% of patients. The hallmark of epidermolysis bullosa is the development of bullae due to the separation of the dermis and epidermis following minimal trauma. This is seen histologically as subepidermal bullae. The bullae become tense and rupture, producing erosions or ulcers, which often heal poorly with scarring. In the esophagus the scars vary from minor webs in the postcricoid region to long strictures of the esophagus. Because the blisters are so fragile and rupture easily, endoscopy is often avoided (see Chapter 11). The anorectal region may also be involved giving rise to pain on defecation and constipation. Pyloric stenosis or atresia and duodenal obstruction have been described in some patients.

There are 20 different phenotypes associated with mutations in 10 different genes, but they can be broadly classified into four groups based on the plane of cleavage of the basement membrane zone and pattern of inheritance. These include (a) epidermolysis bullosa simplex, (b) junctional epidermolysis bullosa, (c) dominant dystrophic epidermolysis bullosa, and (d) recessive dystrophic epidermolysis bullosa.

Esophageal manifestations are very common in dystrophic epidermolysis bullosa, particularly the recessive form. Dysphagia (70%–94%) and esophageal strictures (65%–80%) are frequent findings in patients with recessive dystrophic epidermolysis bullosa. Some patients may have diarrhea associated with endoscopic and histologic features of colitis, including increased lamina propria cellularity and neutrophil infiltrates. Gastroesophageal reflux and constipation are frequent in both simplex and dystrophic forms (with painful perianal disease likely contributing to the latter), whereas failure to thrive is frequent in patients with junctional and recessive dystrophic forms of the disease. A subgroup of junctional epidermolysis bullosa is associated with pyloric and rarely duodenal atresia (pyloric atresia–junctional epidermolysis bullosa syndrome). Patients with esophageal disease require nutritional support in the...
### Table 8-3 Primary Skin Disorders Associated with Gastrointestinal Disease

<table>
<thead>
<tr>
<th>SKIN DISORDER WITH GASTROINTESTINAL PATHOLOGY</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN DISORDERS WITH GASTROINTESTINAL MANIFESTATIONS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Dermatogenic Enteropathy</strong></td>
<td></td>
</tr>
<tr>
<td>Severe eczema</td>
<td>Malabsorption; pathogenesis unclear.</td>
</tr>
<tr>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td><strong>Bullous Eruptions</strong></td>
<td></td>
</tr>
<tr>
<td>Epidermolysis bullosa dystrophica</td>
<td>Dysphagia, constipation, pain on defecation, esophageal bullae, rupture of bullae, esophageal webs, fibrosis and stricture, pyloric stenosis. See esophageal disease, Chapter 11.</td>
</tr>
<tr>
<td>Epidermolysis bullosa acquisita</td>
<td>Bullae, proximal esophageal webs and strictures, association with Crohn's disease.</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Dysphagia, esophageal bullae, erosions, stricture.</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Dysphagia, esophageal bullae, erosions and stricture on rare occasions. See small bowel mucosal disease, Chapter 2.</td>
</tr>
<tr>
<td>Stevens–Johnson syndrome</td>
<td>Dysphagia, occasionally severe hemorrhage.</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Celiac sprue, rarely esophageal bullae, erosions and stricture.</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Yellow-white plaque with surrounding erythematous base throughout gastrointestinal tract, especially esophagus; vesicles and small, punched-out erosions. Later, diffuse, intensely erythematous mucosa. Intranuclear inclusions in epithelial cells around vesicles or at ulcer margin. See inflammatory disorders of the esophagus, Chapter 11.</td>
</tr>
<tr>
<td><strong>Hyperkeratotic Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Lichen planus</td>
<td>Dysphagia, strictures (usually proximal).</td>
</tr>
<tr>
<td>Tylosis</td>
<td>Esophageal keratotic papules.</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Acrokeratodermatitis enteropathica</td>
<td></td>
</tr>
<tr>
<td><strong>SKIN DISORDERS ASSOCIATED WITH GASTROINTESTINAL MALIGNANCY</strong></td>
<td></td>
</tr>
<tr>
<td>Tylosis</td>
<td>Squamous carcinoma of esophagus.</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Adenocarcinoma of stomach and colon.</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Adenocarcinoma of stomach and colon. See connective tissue disorders, Chapter 9.</td>
</tr>
<tr>
<td>Multiple seborrheic keratosis</td>
<td>Gastrointestinal carcinoma.</td>
</tr>
<tr>
<td>(Leser–Trelat sign)</td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Adenocarcinoma of colon. See immune deficiency disorders, Chapter 4.</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Adenocarcinoma of stomach, nodular lymphoid hyperplasia.</td>
</tr>
<tr>
<td><strong>SYSTEMIC DISORDERS INVOLVING THE SKIN AND GUT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Connective Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Motility disorder resulting in esophagitis and pseudo-obstruction. Atrophy of circular muscle and replacement fibrosis, esophagitis and esophageal stricture. Intestinal atony and pseudodiverticula. See connective tissue disorders, Chapter 9.</td>
</tr>
<tr>
<td>SKIN DISORDER</td>
<td>GASTROINTESTINAL PATHOLOGY</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Arteritis, ischemia, infarctions and perforations. Cervical esophagus—inflammation, edema and muscle atrophy. Lower esophagus—inflammation, muscle atrophy and stricture. Arteritis, ischemic ulcers, segmental bowel infarction, gastrointestinal hemorrhage and perforation, depending on the size of the vessel involved.</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders and Malformations</td>
<td></td>
</tr>
<tr>
<td>Malignant atrophic papulosis (Degos’ disease)</td>
<td>Progressive occlusive vascular disease of small and medium-sized vessels resulting in patchy necrosis, infarction and peritonitis. Structural derangement of elastic tissue with fragility of blood vessels, rupture and ischemic necrosis, diverticula.</td>
</tr>
<tr>
<td>Ehlers–Danlos syndrome</td>
<td></td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>Gastrointestinal hemorrhage, yellow mucosal nodules, proliferation of elastic fibers, which may be calcified.</td>
</tr>
<tr>
<td>Blue rubber bleb nevus syndrome</td>
<td>Mucosal cavernous hemangioma.</td>
</tr>
<tr>
<td>Cutaneous visceral hemangiomatosis</td>
<td>Mucosal cavernous hemangioma.</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Mucosal and submucosal hemorrhagic nodules.</td>
</tr>
<tr>
<td>Miscellaneous Diseases</td>
<td></td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Crohn’s-like colitis.</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>Angiokeratomas on scrotum, extremities, lips and mouth, crampy abdominal pain, nausea, diarrhea, impaired intestinal motility.</td>
</tr>
<tr>
<td>SKIN LESION ASSOCIATED WITH MAJOR GASTROINTESTINAL DISEASES</td>
<td></td>
</tr>
<tr>
<td>Erythema nodosa, pyoderma gangrenosum</td>
<td>Inflammatory bowel disease.</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Celiac sprue.</td>
</tr>
<tr>
<td>Pigmented macules on lips, mouth and feet</td>
<td>Peutz–Jegher syndrome.</td>
</tr>
<tr>
<td>Alopecia, nail dystrophy, skin pigmentation</td>
<td>Cronkhite–Canada syndrome.</td>
</tr>
<tr>
<td>Carcinoid syndrome—flushing, telangiectasia on face and neck</td>
<td>Carcinoid tumor.</td>
</tr>
<tr>
<td>Flushing, telangiectasia, pigmented macules and papules</td>
<td>Systemic mastocytosis.</td>
</tr>
</tbody>
</table>
form of liquid/pureed diets, gastrostomy feeding, or sometimes total parenteral nutrition. Esophageal dilatation may be beneficial in some patients who fail to respond to conservative measures, but requires caution since new bullae may be induced, leading to further structuring.291

**Epidermolysis Bullosa Acquisita**

As with genetic epidermolysis bullosa above, epidermolysis bullosa acquista (EBA) is characterized by bullae following minor trauma. It differs from the former in its adult onset, lack of family history, milder skin disease, and rarity of esophageal involvement. Affected patients may present with dysphagia. Endoscopic findings include bullae, proximal esophageal webs, and strictures.290,296 Bullae may be induced by endoscopy. EBA is associated with circulating autoantibodies against collagen VII.299 As in skin biopsies, endoscopic biopsies may show subepidermal bullae with linear deposition of IgG along the basement membrane. EBA may occur in association with Crohn’s disease300,301 (see also Chapter 11).

**Pemphigus Vulgaris**

This rare autoimmune blistering disease is associated with autoantibodies to the cell adhesion molecule desmoglein 3.299 This results in loss of cohesion between epithelial cells of the suprabasal stratum spinosum, with characteristic acantholytic, suprabasal blister formation. Eighty to ninety percent of patients have both skin and mucous membrane involvement, with 70% presenting initially with oral lesions.291 Esophageal involvement is fairly common if looked for, being reported in 42% to 88% of patients in several small series.302–306 Dysphagia and odynophagia are the most common symptoms associated with esophageal lesions. Endoscopy is considered safe in skilled hands,291 provided care is taken not to damage fragile mucosa or induce new lesions.291 Biopsies should be taken from the junction between the floor and the roof of the blister and the adjacent mucosa (not the blister itself) to best evaluate suprabasal clefting and acantholysis.305 Both formalin-fixed and fresh tissue should be submitted for routine histologic assessment and immunofluorescence studies, respectively. Diagnosis is based on demonstration of characteristic acantholytic lesions on routine stains, intercellular “lace-like” deposition of IgG and C3 by direct immunofluorescence, and binding of circulating antibodies to squamous epithelium by indirect immunofluorescence (a marker of active disease). Esophageal lesions are treated as for other mucocutaneous lesions, that is, with combinations of steroids and other immunomodulatory agents and sometimes plasmapheresis.291 Rare examples of esophageal involvement by pemphigus vegetans are reported.307

**Cicatricial Pemphigoid (Benign Mucous Membrane Pemphigoid)**

This rare autoimmune disease occurs in middle age and predominantly affects women.291,308 Patients have circulating antibodies to bullous pemphigoid antigen 2. The ocular and oral mucosa is most frequently involved, but the upper aerodigestive tract, esophagus, and anogenital regions can also be involved. Skin involvement is present in a minority of patients (25%).291 Esophageal involvement is reported in 2% to 13% of cases. Symptoms include dysphagia, odynophagia, heartburn, or chronic cough due to aspiration.308 Endoscopic findings include bullae, ulcers, webs, and strictures in the upper esophagus. As with other blistering conditions, bullae can be a direct consequence of endoscopy.291,308,309 Characteristic histologic findings include subepidermal bullae with abundant eosinophils, mononuclear cells, and some neutrophils. Direct immunofluorescence shows linear deposition of IgG and C3 at the dermal–epidermal junction.309 Biopsies taken from the edge of the blister and containing underlying stroma have the best diagnostic yield. Treatment is with oral corticosteroids and other immunomodulatory agents or endoscopic esophageal dilation. The latter may provide rapid symptomatic improvement and avoid the need for prolonged therapy, but reports of mucosal injury, bulla formation, and even perforation are on record. Colonic interposition may sometimes be required for refractory dysphagia.300

**Stevens–Johnson Syndrome**

This rare, life-threatening mucocutaneous disorder is characterized by widespread epidermal necrosis secondary to keratinocyte apoptosis. It is most frequently associated with adverse drug-induced reactions and infections such as *Mycoplasma pneumoniae*. It presents with fever and acute bullous skin eruptions, which involve the mucous membranes in over 90% of cases.299,310 The lips, oral cavity, conjunctiva, urethral meatus, vagina, and anus are most frequently involved.291 Gastrointestinal involvement is rare and primarily affects the esophagus.310,311 Patients present with dysphagia or occasionally severe hemorrhage. The endoscopic appearance ranges from solitary or multiple erosions to large erythematous areas of denuded mucosa with overlying white plaques. The histology ranges from an erythema multiforme-like picture to overt necrosis.291 Late sequelae may include esophageal webs or strictures.291,310,311 Gastric and intestinal involvement in Stevens–Johnson syndrome is extremely rare.300,302
Herpes Simplex Virus Infection

Herpes simplex may involve the mouth and pharynx and, not uncommonly, extend to the esophagus, especially in the immunosuppressed patient. In disseminated herpes simplex virus infection, the esophagus is the most common organ involved. The typical endoscopic appearance is that of multiple oval ulcers in the distal esophagus without overlying pseudomembranes.\(^{291}\) Patients respond to corticosteroids but tend to relapse when the dose is reduced or treatment discontinued. Multiple esophageal dilatations are often required for relief of recurring strictures but may exacerbate the condition as patients are prone to developing new lesions in traumatized areas of uninvolved mucosa.\(^{291}\) Strictures complicate symptomatic esophageal involvement in about 80% of cases.\(^{314,315}\) Most patients usually present with dysphagia and sometimes odynophagia. Endoscopic findings are usually nonspecific. Histology shows a band-like lichenoid infiltrate involving the superficial lamina propria and basal epithelium with basal keratinocyte degeneration, Civatte bodies, and overlying parakeratosis. Sawtooth acanthosis and hypergranulosis, typical of skin lesions, do not feature in esophageal keratosis. Sawtooth acanthosis and hypergranulosis, typical of skin lesions, do not feature in esophageal lesions (the esophageal epithelium lacks a granular layer).\(^{314}\) Strictures complicate symptomatic esophageal involvement in about 80% of cases.\(^{314}\) Most patients respond to corticosteroids but tend to relapse when the dose is reduced or treatment discontinued. Multiple esophageal dilatations are often required for relief of recurring strictures but may exacerbate the condition as patients are prone to developing new lesions in traumatized areas of uninvolved mucosa.\(^{314,315}\) Esophageal squamous carcinoma has been reported in a patient with long-standing lichen planus.\(^{316}\)

Hyperkeratotic Disorders

Lichen planus. This idiopathic inflammatory disorder of skin, nails, and mucous membranes is characterized by eruptions of violaceous, polygonal pruritic plaques, predominantly on flexor skin surfaces. Clinically significant esophageal involvement occurs in about 1% of cases and tends to occur proximally.\(^{291,314,315}\) Patients usually present with dysphagia and sometimes odynophagia. Endoscopic findings are usually nonspecific. Histology shows a band-like lichenoid infiltrate involving the superficial lamina propria and basal epithelium with basal keratinocyte degeneration, Civatte bodies, and overlying parakeratosis. Sawtooth acanthosis and hypergranulosis, typical of skin lesions, do not feature in esophageal keratosis. Sawtooth acanthosis and hypergranulosis, typical of skin lesions, do not feature in esophageal lesions (the esophageal epithelium lacks a granular layer).\(^{314}\) Strictures complicate symptomatic esophageal involvement in about 80% of cases.\(^{314}\) Most patients respond to corticosteroids but tend to relapse when the dose is reduced or treatment discontinued. Multiple esophageal dilatations are often required for relief of recurring strictures but may exacerbate the condition as patients are prone to developing new lesions in traumatized areas of uninvolved mucosa.\(^{314,315}\) Esophageal squamous carcinoma has been reported in a patient with long-standing lichen planus.\(^{316}\)

Tylosis

This rare autosomal dominant condition, also known as hyperkeratosis plantaris et palmaris, is characterized by hyperkeratotic thickening of the palms and soles.\(^{291,317,318}\) Two major subtypes have been described. Type A is later onset (5–15 years) and is associated with a high risk of esophageal squamous cell carcinoma. Type B is earlier onset (first year) and does not carry an increased cancer risk.\(^{291,317}\) Type A tylosis is associated with a genetic abnormality, the tylosis with esophageal cancer (TOC) locus on chromosome 17q25. Importantly, this locus has also been implicated in sporadic esophageal squamous cell carcinomas.\(^{319}\) Patients with tylosis patients are prone to reflux esophagitis and develop minor esophageal webs or strictures. Esophageal papillomatosis is a typical finding.\(^{291}\) There is a 40% to 95% lifetime risk of esophageal squamous carcinoma, complicating tylosis depending on the pedigree,\(^{318}\) although it can take up to 30 years to develop.\(^{320}\) Gastric cancer has also rarely been reported. It has been recommended that patients undergo at least annual screening endoscopy with multiple biopsies, but there is no guarantee that this will impact mortality.\(^{318}\)

Miscellaneous Disorders

Acrodermatitis enteropathica. This rare autosomal recessive disorder is thought to be due to an inability to absorb sufficient intestinal zinc. The gene responsible for acrodermatitis enteropathica has been mapped to chromosome 8q24.3 and shown to be a member of the solute carrier 39A superfamily, historically known as the Zrt–Irt-like protein family, which function as zinc transporters.\(^{321}\) Acrodermatitis enteropathica presents, usually at the time of weaning, with eczematous pink scaly plaques on the hands and feet and around the mouth and anus, in addition to paronychia and nail dystrophy. The plaques can become bullous, pustular, or desquamative.\(^{322}\) It is reversed by giving zinc orally. Gastrointestinal symptoms are often intermittent and consist of diarrhea and malabsorption.\(^{323}\) The small bowel shows a patchy villous lesion of variable severity. Abnormal inclusions are found in the Paneth cells (see Chapter 20). Acrodermatitis enteropathica may also result from zinc deficiency secondary to Crohn’s disease and malnutrition.\(^{324,325}\)

Darier’s Disease

This uncommon inherited disorder, characterized by abnormal keratinization of the skin, nails, and mucous membranes, may rarely involve the esophagus.\(^{291,326,327}\) Endoscopy may show keratotic papules,\(^{291}\) while histology shows acantholysis, suprabasal clefs, and submucosal villi projecting into lacunae as seen in Darier’s skin lesions. Esophageal squamous carcinoma has been reported in a patient with long-standing Darier’s disease.\(^{326}\)

Dermatogenic Enteropathy

Patients with extensive skin disease such as eczema and psoriasis may develop steatorrhea; this condition has been named “dermatogenic enteropathy.”\(^{328–330}\) The malabsorption is proportional to the extent of the rash and improves as the rash subsides. The cause for
the malabsorption is not known, and initial claims that it might be due to a small bowel lesion have never been verified.

**Malignant Disease of the Gastrointestinal Tract and Skin Disease**

Some skin disorders are specific for particular tumors, for example, carcinoma of the esophagus, while others indicate malignant disease in general, for example, generalized skin pigmentation and dermatomyositis. In a third group, skin manifestations are those of wasting disease associated with malignancy.

**Acanthosis Nigricans**

This rare mucocutaneous disorder is characterized by brown or black warty, velvety plaques in the axillae and groins. The oral mucosa is affected in 40% to 50% of patients, and the esophagus is rarely involved. The esophageal lesions appear as multiple squamous papillomatous lesions, which may enlarge and obstruct the lumen. Acanthosis nigricans is commonly associated with insulin resistance, type II diabetes, and obesity (i.e., metabolic syndrome) but may also be seen with polycystic ovary disease, certain congenital disorders, acromegaly, certain drugs, and a number of rarer conditions reviewed elsewhere. In the absence of an underlying condition, there is a high association with malignancy, often carcinoma of the stomach and colon. The skin changes may appear before, after, or simultaneously with the tumor and may regress after extirpation of the tumor. However, by the time acanthosis develops, the associated tumors are usually advanced and often metastatic and inoperable. The pathogenesis of acanthosis nigricans appears multifactorial with a likely role for IGF-1 receptors on keratinocytes and fibroblasts, which are activated by elevated insulin levels. Other growth factor receptors such as EGFR and FGFR may also play a role.

**Cowden’s Disease**

This rare autosomal dominant condition is characterized by multiple hamartomas in tissues from all embryonic germ cell layers; mucocutaneous lesions (e.g., facial trichilemmomas, mucocutaneous papillomatous papules, acral keratoses, esophageal glycogen acanthosis); and an increased risk of breast, thyroid, and endometrial cancers. The hamartomatous polyps in the gastrointestinal tract may be indistinguishable from juvenile polyps, but also include inflammatory, lipomatous, and ganglioneuromatous polyps. Cowden’s syndrome is associated with a germline mutation in the PTEN tumor suppressor gene as are Bannayan–Riley–Ruvalcaba and Proteus syndromes; together these are classified under the broad term “PTEN hamartoma tumor syndromes” (see Chapter 26). A subset of individuals with CS and CS-like symptoms not having germline PTEN mutations have germline variants of dehydrogenase complex subunits B or dehydrogenase complex subunits D.

**Dermatomyositis**

Dermatomyositis has a strong association with malignancy in general, including gastric and colonic carcinomas (see “Connective Tissue Disorders”)

**Miscellaneous**

Other nonspecific skin disorders associated with neoplasms, including gastrointestinal carcinomas, are generalized dermal pigmentation, postulated to be due to tumor production of melanocyte-stimulating hormone; migratory thrombophlebitis; and multiple seborrheic keratoses (the Leser–Trélat sign). Familial gastrointestinal stromal tumors due to germline mutations in KIT may be associated with a variety of cutaneous lesions (including hyperpigmentation of perioral, axillary, perineal regions and hands, lentigines, café au lait macules, benign nevi, urticaria pigmentosa, and melanoma) depending on the mutation involved (see Chapter 7).

**Gastrointestinal Manifestations of Cardiac Disease**

**Congestive Cardiac Failure**

Patients with congestive cardiac failure frequently show alterations in gastrointestinal morphology, permeability, and absorption, due to a combination of ischemia and congestion. Nonocclusive mesenteric ischemia can result from both low cardiac output and splanchnic vasoconstriction. Diversion of blood away from the splanchnic system is a well-recognized adaptive mechanism to counteract low cardiac output in congestive cardiac failure. Elevated venous pressure in right heart failure results in splanchnic congestion and mucosal edema, further impairing the mucosal microcirculation.

An upper gastrointestinal endoscopic study of 57 patients with congestive cardiac failure and upper gastrointestinal symptoms found gastric and duodenal mucosal alterations in 88% and 54% of patients, respectively. These changes, termed “congestive
gastropathy/duodenopathy,” correlated with the severity of symptoms and inferior vena cava and hepatic vein diameters. The most frequent endoscopic findings were a mosaic-like pattern and punctate speckling, whereas less common findings included thickened folds, watermelon stomach, and telangiectasias.341 Patients with congestive cardiac failure have been shown to develop increased intramucosal carbon dioxide pressure (pCO2) at low levels of exercise, likely reflecting splanchnic hypoperfusion. 342 Cardiogenic shock is associated with early elevations in intragastric pCO2, whereas persistent elevations (>24 hours) indicate prolonged gastrointestinal mucosal ischemia.343,344

Morphologic and functional changes in the small and large intestine have been described in patients with congestive cardiac failure. Increased ileal and colonic permeability and wall thickening (likely edema) have been reported in patients with a left ventricular ejection fraction of <40%,345 whereas decreased protein and fat absorption has been demonstrated in advanced stages of the disease.346–348 Morphometric studies have revealed a striking increase in lamina propria collagen in small intestinal biopsies from patients with severe cardiac failure, which is most marked in cachectic patients.349 At the extreme end of the spectrum, low perfusion states may be associated with nonocclusive intestinal ischemia or infarction (see Chapter 2). Drugs used in the treatment of cardiac failure, such as the cardiac glycosides, often produce anorexia, nausea, vomiting, abdominal pain, and distention.

**Infective Endocarditis**

Infective endocarditis due to *Streptococcus bovis* has been associated with a high rate of neoplasms (adenomas and carcinomas) in the colon and less frequently upper gastrointestinal tract. Upper and lower gastrointestinal endoscopy has been recommended in patients with *S. bovis* endocarditis, for which no other cause is found.349–351 There are also isolated reports of colorectal neoplasia in association with *Gemella morbillorum*352 and *Streptococcus galolyticus* endocarditis.353

**Open Heart Surgery, Extracorporeal Circulation, and Cardiac Transplantation**

Gastrointestinal complications following open heart surgery are rare, occurring in 0.3% to 2% of cases, and are usually associated with cardiopulmonary bypass and extracorporeal circulation.354,355 The major clinical features consist of upper gastrointestinal hemorrhage secondary to stress ulcers or duodenal ulcers, massive bowel necrosis due to intestinal ischemia from low cardiac output, and acute diverticulitis. Symptoms commonly occur within 7 days of surgery, and the mortality rate is high (about 30%).354,356,357 In contrast to open-heart surgery, gastrointestinal complications are common following cardiac surgery with extracorporeal circulation, including cardiac transplantation, occurring in 25% to 40% of patients.358–360 The most frequent include diarrhea, heartburn, abdominal pain, nausea, and vomiting. Less common but serious complications include gastrointestinal hemorrhage (associated with esophagitis, erosive gastritis, or gastric ulceration), intestinal ischemia, perforated colonic diverticula, and pancreatitis.354,358,360 Since patients are on maintenance immunosuppressive therapy, they are also prone to all the complications of immunosuppression, such as bacterial, fungal, and viral infections and gastrointestinal neoplasms.359,361–363 Similar gastrointestinal complications may also occur after lung transplantation.364

**HEMATOLOGIC DISORDERS**

Gastrointestinal manifestations of leukemia and lymphoma are described with the lymphoproliferative disorders in Chapter 5 and bone marrow transplantation with the immunodeficiency disorders in Chapter 4.

**Dysproteinemias**

Multiple myeloma may affect the gastrointestinal tract in the form of tumor masses (plasmacytomas) or amyloidosis. Plasmacytomas are described with the lymphoproliferative disorders (Chapter 5) and amyloid, separately in this chapter. The dysproteinemias associated with alpha-heavy chain and gamma-heavy chain disease are described with the lymphoproliferative disorders. In Waldenstrom’s macroglobulinemia there is extracellular deposition of IgM in the lamina propria of the small bowel, resulting in malabsorption. This is described further in Chapter 20.

**Hemolytic Uremic Syndrome**

This syndrome is characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.365,366 It is a frequent cause of acute renal failure in childhood367 but can occur in adults.368 About 90% of childhood cases in developed countries are caused by enterohemorrhagic *Escherichia coli* O157:H7, which produce a Shiga-like toxin (verotoxin). This toxin is similar to the cytotoxin produced by *Shigella dysenteriae* type 1 (another cause of HUS).366 This cytotoxin causes damage to the vascular endothelium, thrombosis, and hemorrhage. Acute
transient gastrointestinal symptoms occur frequently, producing hemorrhagic enterocolitis with bloody diarrhea. Other complications include transmural necrosis, perforation, and colonic stricture.\textsuperscript{367,369}

**Coagulation Disorders**

**Hemophilia.** About 10\% to 25\% of patients with hemophilia suffer from gastrointestinal hemorrhage.\textsuperscript{370,371} The hemorrhage originates most often from the upper gastrointestinal tract and is usually spontaneous but may be secondary to peptic ulceration. Gastrointestinal hemorrhage may also result from esophagitis, Mallory–Weiss tears, and erosive gastritis, but the incidence of these conditions in hemophilia seems to parallel that of the general population.\textsuperscript{370,371} Clinically significant upper gastrointestinal bleeding (esophageal varices excluded) has been reported in about 1\% of patients per year. The risk was significantly increased in patients taking NSAIDs.\textsuperscript{371} Endoscopy is helpful in these patients to determine the cause of hemorrhage.\textsuperscript{372} Patients occasionally present with signs and symptoms of an acute abdomen, sometimes in association with a tender abdominal mass due to intramural hematoma.\textsuperscript{370,373–376} The latter produces a fairly characteristic x-ray appearance consisting of a segment of bowel with uniform thickened, rigid mucosal folds and a sharply delineated margin.\textsuperscript{373,377} Intussusception is a rare complication of submucosal hemorrhage.\textsuperscript{370} Histologically, there is intramural hemorrhage, which can involve all layers but is usually most prominent in the submucosa. Hemorrhage may also involve the mesentery and retroperitoneal tissues. Surgical intervention is rarely necessary for gastrointestinal hemorrhage as replacement of the clotting factors usually leads to rapid recovery.\textsuperscript{373}

**Other Coagulation Disorders**

Von Willebrand's disease, heparin or warfarin overdose, vitamin K deficiencies, and platelet deficiency disorders resulting from bone marrow replacement by tumor or the myeloproliferative disorders can all produce gastrointestinal manifestations similar to hemophilia.\textsuperscript{370} Thrombocytosis, resulting from conditions such as thrombotic thrombocytopenic purpura and polycythemia rubra vera, can also produce gastrointestinal bleeding. Clinically, they may resemble hemolytic uremic syndrome, described previously.\textsuperscript{379,380}

**Mastocytosis**

This uncommon condition is characterized by an abnormal proliferation of mast cells in one or more organs. Most cases are confined to the skin (urticaria pigmentosa), but approximately 10\% involve extracutaneous sites, most commonly bone, liver, spleen, gastrointestinal tract, and lymph nodes. Gastrointestinal symptoms are second only to pruritis as a cause of morbidity in these patients. Seventy to eighty percent of patients report gastrointestinal symptoms when a careful history is taken.\textsuperscript{381} These include abdominal pain (dyspeptic and nondyspeptic), nausea, vomiting, diarrhea, malabsorption, weight loss, and occasionally gastrointestinal hemorrhage secondary to ulcers or erosions.\textsuperscript{382–386} Increased systemic levels of mast cell mediators (e.g., histamine, leukotrienes, heparin, and proteases) are likely to play an important role in gastrointestinal symptoms, since the latter are not always associated with mucosal mast cell infiltrates.\textsuperscript{367} The pathogenesis of the malabsorption is unclear.\textsuperscript{381,388}

Endoscopically, the gastrointestinal mucosa may show a variety of changes including mucosal nodularity, urticaria-like mucosal lesions, mucosal thickening, friability, and gastric erosions. Peptic ulceration is found primarily in the duodenum. Mucosal nodularity is a frequent and distinctive finding in these patients, both endoscopically and radiologically\textsuperscript{381,385,386,388–395} (Fig. 8-9). Sometimes colonoscopic findings may closely resemble IBD.

Histologically, mucosal and submucosal mast cell infiltrates vary from heavy to absent.\textsuperscript{391,394–396} Mast cells are arranged in sheets, aggregates, or concentric pericryptal whorls and may expand the lamina propria (Fig. 8-10A,B). They may resemble normal mast cells or can be spindled, fusiform, or histiocytoid (Fig. 8-10C–E). The latter appearances may lead to confusion with a histiocytic infiltrate, compounded by the fact that mast cells are immunoreactive for

**Figure 8-9.** Mastocytosis of the right colon. Mucosal nodularity is a frequent feature observed grossly or at endoscopy (inset).
Figure 8-10. Spectrum of histologic findings in gastrointestinal mastocytosis. A: Expansion of the lamina propria by the mast cell infiltrate. B: Pericryptal whorled distribution of mast cells, which is a frequent feature. C–E: Range of appearances of mast cells including elongated or spindled, plump fusiform or large, round cells with abundant pale to clear cytoplasm; the latter is a result of retraction artifact. The latter two appearances may be easily confused with histiocyte infiltrates. F: Heavy eosinophil infiltrate, which may dominate the picture and at times obscured the underlying mast cell infiltrate (inset: eosinophils at higher magnification).

CD68. Mucosal edema and a patchy mixed infiltrate (including lymphocytes, plasma cells, and eosinophils) may accompany the mast cell infiltrate. Eosinophils may be prominent to the point that they obscure the underlying mast cell infiltrate, raising the possibility of an eosinophilic gastroenteritis383 (Fig. 8-10F). Mucosal architectural distortion is not uncommon383,386–389 and may lead to confusion with IBD, particularly when the colonoscopic findings are suggestive.386,399 Changes secondary to the release of histamine and other vasoactive substances include erosive gastritis, mucosal congestion, and hemorrhage.

The mast cell infiltrate can be confirmed with histochemical stains that highlight mast cell granules (e.g., Giemsa, Leder) as well as immunohistochemical
markers including CD117, mast cell tryptase, and CD25. More than 90% of patients with systemic involvement exhibit the characteristic D816V exon 17 KIT mutation in lesions tissue, and this holds true for cases with gastrointestinal involvement.

Rosai–Dorfman Disease (Sinus Histiocytosis with Massive Lymphadenopathy)

Rosai–Dorfman disease is a rare disease of unknown etiopathogenesis, generally presenting with nodal enlargement usually in the young, who are usually amazingly well considering their huge adenopathy. It is characterized by polyclonal proliferation of histiocytes that show many engulfed lymphocytes and plasma cells in their cytoplasm. The engulfed cells show intact cytologic and nuclear details, and this phenomenon is thought to represent emperipolesis rather than true phagocytosis by the histiocytes. It is believed to be a reactive process due to an abnormal immune response, leading to hyperactivation of the macrophages. Although an underlying infection is suspected, no consistent association with an infection has been shown so far. Few studies showing association with HHV-6 and HIV have been reported; however, several others have failed to confirm these findings. The disease can involve virtually any extranodal site. Gastrointestinal tract is the least common organ system involved, and to date only about nine patients (jejunum n = 1, appendix n = 2, colorectum n = 6) have been reported, many of whom were incidentally detected at resection or autopsy and in some it was the only site of involvement. The gastro-intestinal manifestations are generally nonspecific; however, rarely it may present with gastrointestinal bleeding or intestinal obstruction. The lesions are poorly circumscribed and largely centered in the submucosa. The overlying mucosa often appears smooth and not involved, and hence mucosal biopsies are likely to be negative. Histology is similar to nodal disease with the presence of abundant large histiocytes admixed with various other inflammatory cells, mostly lymphocytes and plasma cells. The histiocytes show pale foamy or lightly eosinophilic granular cytoplasm. They characteristically show prominent emperipolesis with lymphoplasmacytic cells. Such histiocytes may also be seen in dilated lymphatics, and the regional lymph nodes may also be involved. The differential diagnosis includes langerhans histiocytosis and familial hemophagocytosis syndrome. The langerhans cells are easily distinguished by their grooved nuclei and positivity for CD1a, and the background frequently contains a prominent eosinophilic infiltrate. In hemophagocytosis the histiocytes show prominent phagocytosis of red cells, rather than emperipolesis of lymphoplasmacytic cells. The treatment of Rosai–Dorfman disease includes surgical debulking, steroids, and radiotherapy. With multisystemic involvement the prognosis appears to be protracted, and patients reported to date with more than 1 year of follow-up were either alive with disease or died of disease.

Miscellaneous Disorders

A number of other hematologic disorders are associated with gastrointestinal manifestations and morphologic abnormalities. In the Plummer–Vinson syndrome, there is an association between iron deficiency anemia and postcricoid esophageal webs, atrophic gastritis, and achlorhydria. Granulomatous colitis has been reported in chronic granulomatous disease (see “Granulomatous Disorders” below). Patients with thrombocytosis due to myeloproliferative disorders may develop thrombotic or hemorrhagic complications involving gastrointestinal tract. Aspirin or corticosteroids predispose to the latter complication.

Gastrointestinal Amyloid Deposition

General Properties and Classification

Amyloidosis is the final common pathway of a number of unrelated disorders, which have in common the abnormal production and extracellular deposition of proteins with a common tertiary molecular structure. This structure includes antiparallel twisted β-pleated sheet fibrils that have a number of distinct morphologic properties including

1. A glassy, homogenous red appearance by hematoxylin and eosin and Congo red staining (Figs. 8-11–8-14)
2. A red/green birefringence under polarized light after Congo red staining (Fig. 8-13)
3. A characteristic fibrillary, nonbranched structure by electron microscopy

The most widely accepted classifications of amyloid are based on the biochemical composition of the amyloid fibrils. The current nomenclature assigns the letter A (for amyloid) followed by a description of the precursor protein. The most common form is AL (light chain) or primary amyloidosis, derived from portions of immunoglobulin light chains produced in plasma cell
Amyloid deposition. Most patients have a monoclonal protein that is demonstrable by immunoelectrophoresis of the serum or urine, even in the absence of multiple myeloma. The next most prevalent is AA (or secondary) amyloidosis associated with overproduction of the acute phase reactant serum amyloid A protein (A) in various inflammatory, infective, or neoplastic disorders. Up to 48% of such patients have rheumatoid arthritis. Some of the other more common forms of amyloid include dialysis-related amyloid (Aβ2MG, β2-microglobulin), senile amyloid (AβPP, amyloid beta precursor protein), and familial amyloidotic polyneuropathy (transhyretin—ATTR). A number of rarer forms exist. Amyloid per se is quite inert and does not cause tissue injury. However, with progressive accumulation in tissues, it encroaches on adjacent cells to produce pressure atrophy in the muscularis externa, diffusion problems in the mucosa, and ischemia with vascular obliteration.

Clinical Features

Gastrointestinal involvement is common—as reflected by the 85% diagnostic yield for rectal biopsies—but does not necessarily produce symptoms. All levels of the gut may be affected. Infiltration of the mucosa, muscularis externa, and blood vessels may result in a variety of symptoms, such as dysphagia, ulcer symptoms, diarrhea, steatorrhea, malabsorption, intestinal pseudo-obstruction, and hemorrhage. The latter occurs in up to 57% of patients with amyloidosis and may be massive. Motility disorders are
caused by amyloid infiltration of the enteric muscles or nerves or both.\(^{407,408,411}\) Malabsorption results from a number of different mechanisms such as stasis with bacterial overgrowth due to dysmotility, diffusion problems from amyloid infiltration of the mucosa, and vascular infiltration. Vascular involvement by amyloid can also produce petechial hemorrhages of the mucosa (Fig 8-15), ischemic lesions with hemorrhage, mucosal ulceration, occasionally diverticular disease, and lesions that may mimic IBD.\(^{412–414}\) Amyloidosis can sometimes produce solitary masses in the stomach or intestine. These can be confused clinically and radiologically with carcinoma and other intestinal polyps.\(^{415–417}\)

### Histologic Features

Amyloid is found throughout the length of the gut and is distributed primarily within submucosal arterioles; the muscularis propria and mucosae, around the myenteric nerves; and in advanced cases within the lamina propria (Fig. 8-14). On rare occasions a lamina propria amyloid infiltrate may mimic collagenous colitis.\(^{418}\) With progressive accumulation, amyloid causes narrowing of vessels, with consequent ischemic ulcers; hemorrhage; and pressure atrophy of adjacent tissues such as the muscularis externa. With routine hematoxylin and eosin stains, amyloid appears as extracellular amorphous, glassy pink deposits (Figs. 8-11 and 8-12), often with a prominent cracking artifact. Amyloid stains pink-red with the Congo red stain and under polarized light exhibits apple-green birefringence (Fig. 8-13). With thioflavin T, amyloid fluoresces when viewed under ultraviolet light. By electron microscopy, amyloid appears as an interlocking meshwork of nonbranching fibrils measuring 7.5 to 10 nm in diameter but of variable length. Immunohistochemistry is the routine method for determining amyloid type but has limitations. AA amyloid stains consistently with the appropriate antibody, whereas AL deposits fail to stain in a significant proportion of cases. In such cases, AL becomes a diagnosis of exclusion supported somewhat by the demonstration of monoclonal gammopathy (although subtle plasma cell dyscrasias are not uncommon in elderly patients without amyloidosis).\(^{407}\) Other techniques available for amyloid typing include amino acid analysis and proteomics on microdissected tissue.\(^{419}\) The latter is emerging as a highly sensitive and specific technique for the typing of amyloid deposits but is only available at a few specialized centers.

### Diagnosis and Clinical Implications

Rectal biopsy is a widely used procedure for the diagnosis of amyloidosis, with a diagnostic yield of around 85%.\(^{408}\) However, several reports indicate that amyloid deposition is more marked in the small bowel and stomach,\(^{430,431}\) and the latter are preferred over rectal biopsies in cases of suspected AL amyloid.\(^{430,431}\) Although AL amyloid tends to form polypoid lesions and AA amyloid has a more finely granular appearance,\(^{432}\) a characteristic or even visible endoscopic lesion may be lacking. This is another reason why we believe in biopsying all endoscopically normal patients to exclude such lesions as amyloid. Furthermore, it is important to remember that in biopsy material, amyloid is most likely to be found in submucosal arterioles; therefore, the biopsies must be sufficiently deep to include the superficial submucosa.

### DISORDERS OF LIPID METABOLISM

#### Fabry’s Disease

Fabry’s disease is an X-linked disorder of glycolipid metabolism due to deficiency or absence of the lysosomal enzyme alpha-galactosidase A. This results in the cellular deposition of glycosphingolipids in most tissues.\(^{422,423}\) Clinically, there may be dysfunction of the renal, pulmonary, cardiovasculardigestinal, muscular, and nervous systems. Gastrointestinal symptoms consist of impaired motility with crampy postprandial abdominal pain, nausea, and diarrhea. Secondary bacterial overgrowth may also occur.\(^{422,424,425}\) Gastrointestinal symptoms may improve with replacement therapy.\(^{426,427}\) Histologically, lipid inclusions are found in the dorsal root...
ganglia and peripheral autonomic ganglia, including ganglia in the myenteric and submucosal nerve plexuses. Glycolipid deposition may also occur in the small vessels of the bowel with secondary thrombosis, resulting in ischemic bowel lesions and perforation.425,428

**Tangier Disease**

This is an autosomal recessive disorder characterized by accumulation of cholesterol esters in macrophages of reticuloendothelial tissues including tonsils, thymus, lymph nodes, bone marrow, liver, spleen, and gut, and a demyelinating neuropathy429,430 Mutations in the adenosine triphosphate–binding cassette A1 gene that encodes a cellular phospholipid and cholesterol transporter essential for high-density lipoprotein (HDL) biogenesis underlie this condition. Patients have low levels of low-density lipoprotein cholesterol and HDL and high blood levels of triglycerides.429,430 Clinically, patients have enlarged, yellow-orange streaked tonsils; hepatosplenomegaly; and peripheral neuropathy.429,435 They may also have diarrhea for reasons that are unclear. Histologically, there is diffuse accumulation of cholesterol esters in foamy histiocytes. Ultrastructurally, the lipid deposition occurs within vacuoles not bounded by a membrane.432 Foamy macrophages are also found in the mucosa throughout the gastrointestinal tract and appear as orange-brown spots in the rectum on colonoscopy.431,433 Histologically, they consist of clusters of foamy histiocytes in the subcryptal space. Lipid accumulation may also occur in Schwann cells of the myenteric plexus.

**Wolman’s Disease**

This rare autosomal recessive disorder results from mutations in the gene encoding lysosomal acid lipase, an enzyme essential for intracellular hydrolysis of cholesterol esters and triglycerides. It is characterized by massive accumulation of cholesterol ester and triglycerides in several tissues. Wolman’s disease presents early in infancy with vomiting, diarrhea, hepatosplenomegaly, malabsorption, abdominal distention, failure to thrive, and ultimately cirrhosis. It is almost uniformly fatal in the first year of life. Adrenal gland enlargement with conspicuous calcific deposits is a characteristic finding. Intestinal biopsy may be undertaken to exclude a malabsorption syndrome and can show features of a lipid storage disorder, that is, numerous vacuolated lipid-laden macrophages in the lamina propria and submucosa sometimes with crystalline inclusions. Diagnosis is based on reduced acid lipase activity in cultured skin fibroblasts or peripheral blood lymphocytes.534

**Abetalipoproteinemia**

This is an autosomal recessive disorder characterized by anacanthocytic erythrocytes, serum lipid abnormalities, ataxia, and steatorrhea. It is due to complete absence of all lipoproteins containing apolipoprotein B. Histologically, the small intestine is characterized by accumulation of fine lipid droplets within mucosal epithelial cells. For further details, see Chapter 20.

**GRANULOMATOUS DISORDERS**

**Sarcoidosis**

Sarcoidosis is a multisystem, granulomatous disease of unknown etiology. The most frequently involved organs are the lungs and mediastinal and hilar lymph nodes, but the liver, eyes, skin, spleen, and central nervous system are also commonly involved.435 Reports of gastrointestinal sarcoidosis are rare.435–437 A number of autopsy series reported no gastrointestinal involvement in sarcoidosis,438–441 but others report gastrointestinal involvement in 5% to 10% of cases.442–444 The vast majority of these cases are subclinical. Symptomatic gastrointestinal sarcoidosis occurs in <1% of patients with systemic sarcoidosis.435,436

The stomach, particularly the antrum, is the most frequently involved site, usually with subclinical granulomas.435,446 Endoscopy may be normal or show a range of features including mucosal hyperemia, thickening of gastric folds, ulcers, nodular polyoid lesions, or narrowing. The latter may be due to mura infiltration or secondary to diffuse ulceration with fibrosis.435,446,447 Infiltrative gastric sarcoidosis may be localized to the distal stomach, with cone-shaped narrowing, or diffuse resembling *limitis plastic*. Superficial biopsies may not sample these lesions so that the diagnosis may only be made after resection for suspected gastric carcinoma or gastric outlet obstruction.435 When symptomatic, gastric sarcoidosis most commonly presents with epigastric pain but may also result in nausea, vomiting, early satiety, bloating, or bleeding.

The esophagus, small intestine, and colon are rarely involved. Depending on the site, patients may present with dysphagia, diarrhea, malabsorption, protein-losing enteropathy, abdominal pain, tenesmus, or hematochezia.435,437,446–450

Histologically, sarcoidosis of the gastrointestinal tract is characterized by noncaseating granulomatous inflammation. In the stomach this may be associated with ulceration or fibrosis, which may be diffuse.447,451 In the differential diagnosis, it is necessary to exclude other causes of granulomatous inflammation such as tuberculosis, fungal infections, foreign
body reactions, drug reactions, syphilis, neoplasia, parasitic disease, vasculitis, Whipple’s disease, and Crohn’s disease. The latter can be difficult, since Crohn’s disease may also have extraintestinal manifestations, although not normally pulmonary fibrosis or mediastinal lymphadenopathy. Conversely, gastrointestinal sarcoidosis does not produce active mucosal inflammation or perianal fistulae. Schaumann bodies (intracellular concentric calcifications) favor sarcoid, but are not specific. Serum angiotensin converting enzyme (SACE) is elevated in 60% of patients with sarcoid but not in Crohn’s. SACE may, however, be elevated in other granulomatous conditions. In cases of uncertain etiology, a symptomatic response to steroids would favor sarcoidosis. In some cases an unequivocal diagnosis of sarcoid may not be possible. In such patients, careful follow-up with frequent re-evaluation is prudent.

**Chronic Granulomatous Disease**

Chronic granulomatous disease is an inherited disorder of phagocyte function in which defective reactive oxygen species production results in deficient microbicidal activity. Clinically, these patients suffer from recurrent life-threatening infections, and nearly half of them develop a number of gastrointestinal complications such as granulomatous colitis, gastric outlet obstruction, or perirectal abscess and may recur due to the recurrence of endometriosis in other sites. Rectovaginal fistula is an uncommon complication that occurs in up to 3% of patients undergoing surgery for endometriosis. Occasionally, patients present with perforation, usually in pregnancy or postpartum, and associated with decidual necrosis and contraction. In some cases a temporal relationship between symptoms and menses may provide a diagnostic clue. However, in most cases the diagnosis is very difficult and often delayed due to the lack of pathognomonic symptoms. Endometriosis may masquerade as a variety of conditions, including irritable bowel syndrome, Crohn’s disease, acute self-limited colitis, ischemic colitis or enteritis, diverticular disease, or neoplasia. A preoperative diagnosis is often difficult to establish. Intestinal resection can be performed safely in most women with severe endometriosis and bowel involvement, although symptoms may recur due to the recurrence of endometriosis in other sites. Mucosal biopsies may show a range of nonspecific features, which range from mild to severe and include architectural changes and a lymphoplasmacytic infiltrate mimicking IBD, ischemic type changes, villous blunting, and features of mucosal prolapse. Rarely pyloric metaplasia may be seen. A preoperative diagnosis is often difficult to establish. Intestinal resection can be performed safely in most women with severe endometriosis and bowel involvement, although symptoms may recur due to the recurrence of endometriosis in other sites. Rectovaginal fistula is an uncommon complication that occurs in up to 3% of patients undergoing surgery for endometriosis.

Grossly, lesions may be solitary (commonly the rectal lesions) but are usually multifocal. They are frequently confined to the serosa but may involve the muscularis propria. Occasionally they appear as ulcers with rolled margins or polyps that mimic neoplasms (Fig. 8-16). On cut section they appear as firm fibrotic masses, with mural thickening and stenosis. Hemorrhagic punctate areas may be seen. Serosal adhesions may be prominent. Microscopically, endometriotic foci are seen in the subserosal tissue often extending through the bowel wall to the mucosa. Histologically, the foci are characterized by endometrial glands and stroma, are surrounded by fibrosis and smooth muscle proliferation, and often show fresh hemorrhage and hemosiderin-laden macrophages (Fig. 8-17).

Rarely, neoplasms may arise in endometriotic foci, notably endometrioid and clear cell sarcoma but also endometrioid stromal sarcoma. The underlying endometriotic focus is often overrun by the tumor, presenting a diagnostic challenge when tumors arise in the gastrointestinal tract.
Figure 8-16. Endometriosis of the rectum. A,B: Gross specimen showing an ulcerated lesion with rolled margins that was initially thought to be a carcinoma clinically. C: Cut section shows an irregular fibrotic mass. D: Histology showing endometrial glands and stroma throughout the muscularis propria of the rectum. E: Higher magnification showing endometrial glands surrounded by a cuff of stroma.

Figure 8-17. Endometriosis in a large bowel biopsy. A: Biopsy with a small isolated gland within the muscularis mucosae (arrow). B: Detail of (A).
Pellagra is a vitamin deficiency syndrome caused by dietary deficiency or impaired absorption of niacin. Frequently, there is concomitant protein malnutrition and other deficiencies, such as those involving riboflavin, thiamin, and tryptophan. In many parts of Africa and some parts of Asia where maize or certain cereals are the staple foods, niacin is present in the bound form and is not nutritionally available. Thus, unless alternate foods containing niacin are available or added as supplements, pellagra may ensue. Pellagra may also have a number of secondary causes including chronic alcoholism, anorexia nervosa, IBD, carcinoid tumor, and certain drugs (e.g., isoniazid).

Clinically, pellagra is characterized by the three Ds—diarrhea, dermatitis, and dementia. Patients commonly suffer from glossitis and stomatitis. Gastrointestinal manifestations consist predominantly of diarrhea, abdominal pain, and sometimes steatorrhea. On sigmoidoscopy, inflammation is seen in over one-half of all patients. However, histologically, colitis is present in all patients. In the majority of cases, the inflammation is mild or moderate, often with features of colitis cystica superficialis, characterized by cystic dilatation of the crypts and crypt abscesses. Occasionally, inflammation may be severe and necrotizing. The small intestine is usually normal unless there are concomitant multiple nutritional deficiencies.

Familial Mediterranean Fever (Familial Paroxysmal Polyserositis)

Familial mediterranean fever (FMF) is a hereditary disorder transmitted as an autosomal recessive trait. The gene responsible, MEFV (on the short arm of chromosome 16), encodes the inflammatory mediator pyrin, expressed only in myeloid cells. FMF occurs almost exclusively in Sephardic Jews, Arabs, and Turks. Clinically, it is characterized by brief but disabling, self-limited, febrile attacks of peritonitis, synovitis, pleuritis, or an erysipelas-like erythema affecting the legs or feet. It usually starts in childhood or adolescence and recurs at irregular intervals throughout life. Systemic amyloidosis develops frequently in untreated patients, leading to death from renal failure.

Gastrointestinal involvement is characterized by acute inflammation limited to the serosal surfaces of the bowel. Usually, this resolves spontaneously within a few days, but occasionally it may give rise to peritoneal adhesions. Patients who develop...
systemic amyloidosis usually die of renal complications. They may have gastrointestinal deposition of amyloid within the lamina propria and submucosal vessels, although this is usually unassociated with any symptoms. The disease and its complications can be controlled with colchicine treatment although increased intestinal permeability and mild intestinal mucosal injury often occurs. Also, studies have documented a potential role for interferon-alpha in aborting or preventing attacks, and multiple immunosuppressive agents have been used in colchicine-resistant FMF patients.

NEOPLASTIC DISEASE

Extraintestinal tumors can involve the bowel in two ways: (a) with metastases or (b) indirectly via the paraneoplastic syndromes. The paraneoplastic syndromes present either as intestinal pseudo-obstruction, often in association with oat cell carcinoma of the lung, or as an isolated acute colonic dilatation (Ogilvie’s syndrome). These are further described in Chapter 7.

Up to 20% of extraintestinal tumors metastasize or invade the bowel. Frequently, this occurs by direct invasion from adjacent organs, such as prostate (Fig. 8-18); gynecologic and bladder cancers; or peritoneal seeding, primarily from ovarian tumors. In peritoneal seeding the tumor is usually confined to the subserosal tissues; rarely does it penetrate the muscularis propria and into the submucosa and mucosa. Hematogenous and lymphatic spread occurs less frequently, mainly in tumors from the breast, lung, and malignant melanomas. Some metastatic lesions are fairly characteristic, such as the radiologic “bull’s eye” lesions in malignant melanoma. Others may resemble primary tumors. A lack of epithelial dysplasia adjacent to the tumorous infiltration, sparing of the overlying mucosa, prominent lymphatic infiltration, and multiplicity of tumors often allows for differentiation of primary from metastatic lesions. However, in a few instances, distinction may be difficult based on morphology alone. For example, metastatic breast carcinoma to the stomach produces a pattern that may closely mimic those of signet ring cell carcinoma and linitis plastica (Fig 8-19).

References


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