

Gastrointestinal Manifestations in Systemic Autoimmune Diseases

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ABSTRACT

In an autoimmune disease, the immune system attacks and harms the body's own tissues. The systemic autoimmune diseases include collagen vascular diseases, the systemic vasculitides, Wegener granulomatosis, and Churg-Strauss syndrome. These disorders can involve any part of the gastrointestinal tract, hepatobiliary system and pancreas. They can cause a variety of gastrointestinal manifestations that are influenced by the pathophysiologic characteristics of the underlying disease process. There is a wide variation of gastrointestinal manifestations from these autoimmune disorders including, but not limited to: oral ulcers, dysphagia, gastroesophageal reflux disease, abdominal pain, constipation, diarrhea, fecal incontinence, pseudo-obstruction, perforation and gastrointestinal bleeding. Clinical workup should be initiated by the patient's subjective complaints. In this review, we analyze the effects of autoimmune diseases on the gastrointestinal tract.

Keywords: gastrointestinal manifestations, systemic autoimmune diseases

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In an autoimmune reaction, the immune system attacks by mistake and harms the body's own tissues. The autoimmune diseases comprise a group of immunologic disorders whose common denominator is the presence of an idiopathic systemic autoimmune process. The systemic autoimmune diseases can cause a variety of gastrointestinal manifestations. The characteristic gastrointestinal manifestations of these diseases are influenced by the underlying autoimmune process. There is a wide variation of gastrointestinal manifestations. Gastrointestinal manifestations (GI) may be the initial presentation of these disorders, but they may also be the complication of treatment. In this paper, we illustrate the gastrointestinal manifestations of the systemic autoimmune diseases.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown pathogenesis, characterized at histologic examination by deposition of autoantibodies and immune complexes that damage tissues and cells. The presentation is usually systemic and includes fatigue, malaise, anorexia, fever, and weight loss. The disease predominantly affects women (F:M, 10:1) aged 20-50 years. Gastrointestinal manifestations of SLE are common. GI symptoms are common in patients with SLE and can be due to primary gastrointestinal disorders, complications of therapy or SLE itself. Any part of the gastrointestinal tract may become involved in SLE. Many GI conditions can be mimicked by SLE (1,2).

Lupus enteritis refers to the alimentary tract lesions in SLE. The most common area of involvement is the oral cavity, which can present with mucosal ulcers and decreased salivation. Oral ulcers may occur in up to 50% patients. Erythematosus lesions are painless, but discoid ulcers tend to be painful. They usually occur in the hard palate, buccal mucosa, or the vermilion border. Esophageal symptoms are usually dysphagia or odynophagia (3,4).

Systemic vasculitis involving the esophagus can result in esophageal ulceration and perforation. Gastric ulceration with perforation may occur in SLE. Gastric antral vascular estasia may cause a "watermelon stomach" appearance (5,6).

Small and large intestinal abnormalities in SLE include dysmotility, vasculitis and malab-

sorption. Venous occlusion due to thrombosis can lead to ischemic bowel disease and damage to arteries can result in aneurysmal dilatation of intraabdominal vessels (4).

Protein-losing enteropathy is an unusual manifestation of SLE, although its clinical manifestations and management are not well understood. The association of SLE with inflammatory bowel disease is rare (7,8).

Steatosis chronic active hepatitis, granulomatous hepatitis, cholestasis, centrilobular necrosis, microabscesses, primary biliary cirrhosis and hemochromatosis have been associated with SLE. Necrotizing vasculitis can affect the gall bladder and the bile ducts (9).

Pancreatitis is an uncommon initial presentation of SLE. Lupus pancreatitis may result from SLE and most commonly occurs in patients whose flare up involves multiple organs (10). Ascites occurs in approximately 10% of patients, perhaps as a result of peritoneal inflammation of SLE vasculitis (11,12).

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease of unknown pathogenesis that affects 1% of the population, with a 3:1 predilection for women between the ages of 20 and 50 years. The classic clinical manifestation is chronic symmetric polyarthritis due to a persistent inflammatory synovitis. Gastrointestinal manifestations are common and protean. Involvement of the temporomandibular joint impedes chewing. Esophagus may show diminished distal peristalsis, decreased lower esophageal sphincter tone and hiatal hernia. In patients with Felty's syndrome esophageal ulcer may occur. Peptic ulcer disease in RA is probably the result of pharmacologic therapy. Incidence of chronic atrophic gastritis is higher compared with normal control. Colonic inflammation may be accompanied by a subepithelial collagen band and the histologic picture of collagenous colitis. The thick collagen containing colonic wall cannot allow adequate water resorption, resulting in a typical presentation of profuse diarrhea, possibly associated with pain, flatulence and weight loss. Secondary amyloidosis may occur in patients with long-standing rheumatoid arthritis, may involve any portion of the gastrointestinal tract, may be manifest by chronic diarrhea, and can be diagnosed by endoscopic gastroduodenal biopsies. Vasculitis is less common than in other rheumatic diseases;

however, both small and large vessels may be involved in the setting of severe arthritis, subcutaneous nodules. Necrotizing vasculitis of the mesenteric vessels may result in intestinal ischemia, bleeding, and infarction. Cholecystitis, appendicitis, perisplenitis, splenic infarction, pancreatitis, and hepatic arteritis have been described. Small bowel involvement in rheumatoid arthritis is rare and is caused by vasculitis, which results in ulceration, perforation, and necrosis of the small bowel (1,2, 13).

Sjögren's syndrome

Sjögren syndrome is a common autoimmune disease evidenced by broad organ-specific and systemic manifestations. B-cell activation is a consistent finding in patients with Sjögren syndrome, and B and T cells invade and destroy target organs. Sjögren syndrome usually affects women (F:M, 9:1) in the fourth and fifth decades of life. Although Sjögren syndrome affects approximately 2% of the adult population, it remains undiagnosed in more than half. Consequently, the interval between the onset of Sjögren syndrome and its diagnosis is frequently long-10 years, on average, according to one estimate. Patients with Sjögren syndrome may have involvement of their entire gastrointestinal tract. Patients with Sjögren syndrome typically present with dry mouth and dry eyes. Histopathologic examination shows infiltration of exocrine glands by immunoglobulin-producing lymphocytes. The salivary and lacrimal glands are most frequently involved, but extraglandular involvement occurs in 5-10% of cases. Difficulty in swallowing is a frequent problem and may be due to decrease in saliva production or abnormal esophageal motility. The presence of esophageal atrophy suggests that inflammatory infiltrate of esophageal exocrine glands may at times affects the musculature with resultant impairment of motor coordination. Epigastric pain, dyspepsia and nausea are also common clinical symptoms and may result from chronic atrophic gastritis and lymphocytic infiltrates which are common in Sjögren's syndrome. In addition, Sjögren's syndrome patients may have hypochlorhydria or achlorhydria, hypergastrinemia, hypopepsinogenemia, low levels of vitamin B12 and sometimes antibodies to parietal cells.

Subclinical pancreatic involvement is common, but acute or chronic pancreatitis has been

reported rarely. Sjögren's syndrome can also involve the liver and biliary tree. Patients may have hepatomegaly, pruritus, palmar erythema and jaundice. Liver biopsy shows a picture of mild intrahepatic bile duct inflammation or primary biliary cirrhosis. Other gastrointestinal manifestations include jejunitis, sigmoiditis, and inflammatory bowel disease. Malabsorption due to lymphocytic infiltrates of the intestine rarely occurs in patients with Sjögren syndrome, and esophageal dysmotility has been reported in 36% to 90% of patients. Routine laboratory testing frequently reveals mild pancreatitis and hepatitis; the latter requires differentiation from hepatitis C and organ-specific autoimmune hepatitis. Hepatic involvement is indicated in approximately 7% of patients with Sjögren syndrome (1,2,14).

Behçet's disease

Behçet's disease is a widespread vasculitis of unknown origin occurring in young patients, but people of all ages can develop this disease. Behçet's disease is an autoimmune disease that results from damage to blood vessels throughout the body, particularly veins. The exact cause of Behçet's disease is unknown. Most symptoms of the disease are caused by vasculitis. It was first defined as association of uveitis with oral and genital ulcers. However, now, the clinical spectrum also includes vascular, neurological, articular, renal and gastrointestinal manifestations. Gastrointestinal Behçet's disease shows a wide range of sites of involvement and types of lesions. It is difficult to differentiate Behçet's disease from inflammatory diseases, because of similarity in intestinal and extraintestinal symptoms. Gastrointestinal involvement causes nausea, abdominal pain, anorexia, diarrhea which can be bloody and sometimes leads to perforation. Behçet's disease causes inflammation and ulceration (scores) throughout the digestive tracts that are identical to the aphthous lesions in the mouth and genital area. Oral aphthae are painful, shallow, round to oval ulcers with discrete borders which often occur in crops. Mucosal aphthae are more frequent in the esophagus than in the stomach and duodenum. Esophageal involvement may manifest as ulcers, varices and less often perforation. Ulceration may occur anywhere in the gastrointestinal tract from the mouth to the anus. Segmental mucosal ulceration in the ileocecal and colonic area may appear after several years of

recurrent aphthosis and present in the form of acute complications (perforation, massive hemorrhage) or by prolonged bloody diarrhea. A small number of cases have been reported with involvement of the superior mesenteric artery in Behçet's disease, including aneurysm formation and intimal thickening leading to infarction and perforation of the small bowel. Cases of acute pancreatitis have been reported (1,2,15).

Progressive systemic sclerosis

Progressive systemic sclerosis (scleroderma) is a connective-tissue disease of unknown pathogenesis that affects 30- to 50-year-old women four times as often as it affects men. This type of sclerosis is characterized by overproduction of collagen, which leads to fibrosis of visceral organs. The overproduction of collagen is thought to result from an autoimmune dysfunction, in which the immune system would start to attack the kinetochore of the chromosomes. This would lead to genetic malformation of nearby genes. Any part of the gastrointestinal tract can be involved in scleroderma. Many scleroderma patients are without significant symptoms despite demonstrable abnormalities of gastrointestinal function. Gastrointestinal manifestations are found in most patients. Thinning of the lips and reduced oral apparatus are frequent. Tightening of the perioral skin with restricted ability to open the mouth and impaired taste sensation may contribute to malnutrition. Temporomandibular joint involvement may also limit mouth opening in some patients. Atrophy of the mucous membrane and tongue papilla with impaired taste perception has been reported. Esophagus is the most common involved site. It is involved in 80-90% of scleroderma patients. The most common symptoms are dysphagia and dyspepsia. Incomplete closure of the lower esophageal sphincter leads to gastroesophageal reflux with peptic esophagitis. Chronic reflux predisposes to Barrett's metaplasia. Dysmotility of small intestine may cause chronic pseudo-obstruction. Scleroderma can decrease motility anywhere in the gastrointestinal tract. The most common source of decreased motility involvement is the esophagus and the lower esophageal sphincter, leading to dysphagia and chest pain. As scleroderma progresses, esophageal involvement from abnormalities in decreased motility may worsen due to progressive fibrosis (scarring).

The small intestine can also become involved, leading to bacterial overgrowth and malabsorption of bile salts, fats, carbohydrates, proteins, and vitamins. Malabsorption occurs as a consequence of bacterial overgrowth in stagnant intestinal fluid. The colon can be involved, and can cause pseudo-obstruction or ischemic colitis (1,2,12,16).

Polyarteritis nodosa

The signs and symptoms of systemic vasculitis involving the gastrointestinal tract result from mesenteric ischemia. In contrast to patients with chronic mesenteric ischemia due to a low state, who usually give a history of chronic abdominal pain, patients with vasculitis involving the gastrointestinal tract may present with acute abdominal pain. The most common gastrointestinal symptom is abdominal pain which occurs in 23-70% of patients. The pain is vague, non-specific and is thought to be secondary to bowel ischemia, most commonly in the small bowel. Hematemesis, melena and hematochezia may also occur. Gastrointestinal ulceration may be found in 6% of patients and the most common site is the jejunum. Perforation occurs in 5% and bowel infarction in 1.4% of patients with polyarteritis nodosa.

Severe gut involvement is a worse prognostic sign and survival after bowel infarction is rare. Liver involvement is a common finding in autopsy studies but is not usually clinically significant. Liver involvement may be associated with hepatitis B antigen. The only abnormality may be an elevated alkaline phosphatase, without elevated bilirubin or transaminase level. Other gastrointestinal manifestations of polyarteritis nodosa include acalculous cholecystitis, appendicitis, pancreatitis, biliary strictures and a chronic wasting syndrome (1,2,17-19)

Kawasaki disease

Kawasaki disease is a syndrome that usually occurs in infants and children. It is characterized by an exanthem, enanthem, fever, lymphadenopathy, and polyarteritis of variable severity. Patients with Kawasaki disease presented oral mucosal changes (erythema or dryness or fissuring of the lips), strawberry tongue and erythema of the oropharynx. Gastrointestinal manifestations include abdominal pain, vomiting and diarrhea. Small bowel obstruction may occur as a result of ischemia with stricture with

adhesion formation. Mild jaundice may be seen secondary to hydrops of the gallbladder. Paralytic ileus and a slight increase of serum transaminase levels due to hepatitis are other manifestations (1,2,20).

Inflammatory muscle disorders

Polymyositis and dermatomyositis are systemic autoimmune diseases characterized by inflammation of striated and, to a lesser extent, smooth muscle. Muscle biopsy is needed for diagnosis. Patients with polymyositis typically are first seen with progressive weakness of proximal striated muscles. Women are affected more often than men, with a bimodal peak age of occurrence during childhood and middle adulthood. A characteristic skin rash accompanies dermatomyositis. The gastrointestinal tract may be affected throughout its entire length, but the proximal esophagus usually is involved. The most common gastrointestinal manifestations of idiopathic inflammatory myopathies are related to motor abnormalities, but the most serious and life-threatening problems are secondary to ischemic vasculopathy. Gastric and esophageal emptying is compromised in many patients, who may complain of dysphagia, aspiration, regurgitation, early satiety, and bloating. Patients may have difficulty in swallowing and nasal regurgitation, abnormal esophageal and gastrointestinal peristalsis, reduced gastrointestinal motility, hiatal hernia with reflux esophagitis with resultant stricture formation, dilated atonic esophagus associated with delayed gastric emptying and intestinal mucosal thickening. Inflammatory process leads to changes in the endothelium of small arteries and capillaries which may cause ischemia and necrosis in any part of gastrointestinal tract, resulting in ulceration, perforation or hemorrhage. Inflammatory myopathies have an association with inflammatory bowel diseases. Colonic pseudodiverticula and pneumatosis intestinalis also may develop. Constipation is a common complaint. Suggested contributing causes include neurological dysfunction and diminished smooth muscle contractility as a consequence of muscle atrophy, fibrosis, or inflammation. Acute inflammation of smooth muscle may result in gut wall edema, ulceration, or perforation. An association of dermatomyositis and malignancy has long been postulated. (1,2).

Giant cell arteritis

Histologically, giant cell arteritis has a granulomatous inflammation. The lumen is narrowed because of intimal proliferation. Giant cell arteritis is a large vessel arteritis with strong predilection for the cranial and in particular, the temporal arteries. Giant cell arteritis rarely involves other sites. Headache, fever, high erythrocyte sedimentation rate and sudden blindness are major manifestations. Aortitis occurs in approximately 10% of patients. There are case reports of intestinal gangrene and acute pancreatitis. Liver involvement characterized by elevation of transaminases and alkaline phosphatase occurs in approximately 20% of patients. Liver biopsy is either normal or shows non-specific changes, but granulomas, lymphocytic infiltration, dilated bile canaliculi, and even hepatocellular necrosis with dropout have been reported. Giant cell arteritis involving the bowel has been reported in a small number of cases. (1,2,21,22).

Henoch-Schönlein purpura

Henoch-Schönlein purpura is the most common systemic vasculitis in children with IgA-mediated immune complex deposits affecting small vessels. Gastrointestinal signs and symptoms have been reported in up to 75% of cases. The most common presenting symptom is dull periumbilical pain. Nausea and vomiting are common as well. The main cause of abdominal pain is ulceration of the bowel mucosa which is more marked in the second part of the duodenum, but less frequently seen in the stomach, jejunum, colon and rectum (1,2,23,24).

Takayasu arteritis

Takayasu arteritis is a chronic vasculitis of unknown etiology. Women are affected in 80 to 90 percent of cases, with an age of onset that is usually between 10 and 40 years. The inflammatory processes cause thickening of the walls of the affected arteries. Narrowing, occlusion, or dilatation of involved portions of the arteries in varying degrees results in a wide variety of symptoms. The involvement of the descending abdominal aorta and its branches leads to gastrointestinal symptoms including abdominal pain, nausea, diarrhea and hemorrhage. Stenotic and saccular aneurysmal lesions of intraabdominal arteries are reported (1).

Cogan's syndrome

Cogan's syndrome is a chronic inflammatory disorder that most commonly affects young adults. Cogan's syndrome is a rare systemic disease characterized by interstitial keratitis and audiovestibular system involvement. Associations between Cogan's syndrome and systemic vasculitis, as well as aortitis also exist. Clinical features include weight loss, fever, lymphadenopathy, hepatosplenomegaly. Abdominal aortitis and mesenteric vasculitis may cause abdominal pain, nausea and vomiting after meal. On examination abdominal bruit is heard (1,2, 25,26).

Churg-Strauss syndrome

Churg-Strauss syndrome is an allergic angitis and granulomatous necrotizing vasculitis that occur almost exclusively in patients with asthma. The syndrome is most common in patients aged 30-50 years and has no gender predilection. Patients are typically asthmatic and present with eosinophilia, fever, and allergic rhinitis. Gastrointestinal involvement occurs in about 50% of patients. Eosinophilic gastroenteritis may be the prodrome of Churg-Strauss syndrome. Common gastrointestinal symptoms included abdominal pain, bloody stools, diarrhea and occasional nausea and vomiting multiple ulcers may be seen and may lead to perforation. The small intestine is the most common site of involvement and is most commonly perforated, but case report of multiple colonic ulcer and perforation exists. Necrotizing granulomatous vasculitis of the mesenteric artery may occur and lead to mucosal ischemia. Cholecystitis is also reported in Churg-Strauss syndrome (1,2,17,27)

Wegener granulomatosis

Predominantly affecting male patients, Wegener granulomatosis is a systemic autoimmune disease characterized by granulomatous vasculitis of the upper and lower respiratory tracts, glomerulonephritis, and small-vessel vasculitis. The histopathologic hallmark of Wegener granulomatosis is a necrotizing vasculitis of small arteries and veins with granuloma formation. Gastrointestinal manifestations of Wegener granulomatosis are less common, with only scattered case reports of oropharyngeal mucosal lesions and gingivitis, gastric ulcer, small intestinal perforation, colonic ulceration, nonhealing

perianal ulcers, cholecystitis, recurrent acute pancreatitis, pancreatic mass with extrahepatic biliary obstruction and splenic necrosis (1,2,17).

Antiphospholipid antibody syndrome

The antiphospholipid antibody syndrome is a disorder characterized by recurrent vascular thrombosis, pregnancy loss and thrombocytopenia associated with persistently elevated levels of antiphospholipid antibodies. The gastrointestinal manifestations of antiphospholipid antibody syndrome result from vasculopathy and tissue ischemia. Antiphospholipid antibodies in SLE are associated with Budd-Chiari syndrome, which presents with abdominal pain, ascites and hepatic failure due to thrombosis of the portal vein and hepatic veins (28-30).

Spondyloarthropathies

The spondyloarthropathies are a group of interrelated chronic inflammatory rheumatic diseases that includes ankylosing spondylitis, the arthritis associated with inflammatory bowel disease (IBD), and reactive arthritis. The spondyloarthropathies are characterized by inflammation of the entheses, or the points of attachment of ligaments and tendons to bone. The spondyloarthropathies are also strongly associated with the HLA-B27 gene. HLA-B27 also appears to enhance the invasion of enteric pathogens that are known to trigger reactive arthritis. However, routine serologic testing for HLA-B27 is not clinically useful, as the spondyloarthropathies can occur in its absence. One study found that only 36% of patients presenting with reactive arthritis secondary to a dysenteric infection were positive for HLA-B27. Subclinical gut inflammation has been described in up to two-thirds of patients with spondyloarthropathies. Ulcerative colitis and regional enteritis (Crohn's disease) are the most frequently encountered types of idiopathic IBD that are associated with arthritis or spondylitis (31-35). □

CONCLUSIONS

The systemic autoimmune diseases cause a variety of gastrointestinal manifestations. Gastrointestinal complications are one of the major causes of morbidity and occasionally mortality, especially if they are not diagnosed and treated at proper time. □

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