

Endoscopic and radiographic features of gastrointestinal involvement in vasculitis

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Abstract

Vasculitis is an inflammation of vessel walls, followed by alteration of the blood flow and damage to the dependent organ. Vasculitis can cause local or diffuse pathologic changes in the gastrointestinal (GI) tract. The variety of GI lesions includes ulcer, submucosal edema, hemorrhage, paralytic ileus, mesenteric ischemia, bowel obstruction, and life-threatening perforation. The endoscopic and radiographic features of GI involvement in vasculitis are reviewed with the emphasis on small-vessel vasculitis by presenting our typical

cases, including Churg-Strauss syndrome, Henoch-Schönlein purpura, systemic lupus erythematosus, and Behçet's disease. Important endoscopic features are ischemic enterocolitis and ulcer. Characteristic computed tomographic findings include bowel wall thickening with the target sign and engorgement of mesenteric vessels with comb sign. Knowledge of endoscopic and radiographic GI manifestations can help make an early diagnosis and establish treatment strategy.

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Key words: Behçet's disease; Churg-Strauss syndrome; Computed tomography; Endoscopy; Gastrointestinal tract; Henoch-Schönlein purpura; Histopathology; Lupus mesenteric vasculitis; Systemic lupus erythematosus; Vasculitis

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INTRODUCTION

Vasculitis is an inflammation of vessel walls, followed by alteration of the blood flow and damage to the dependent organ. It can affect vessels of all sizes. The clinical course and pathological features are quite variable and

depend on the size and location of the affected vessels^[1,2]. Vasculitis can cause local or diffuse pathologic changes in the gastrointestinal (GI) tract. The variety of GI lesions includes ulcer, submucosal edema, hemorrhage, paralytic ileus, mesenteric ischemia, bowel obstruction, and perforation^[3]. Of note, bowel ischemia and perforations are significantly associated with increased mortality^[4]. Knowledge of endoscopic and radiographic GI manifestations can suggest the possibility of systemic vasculitis and help establish the specific diagnosis^[5-7]. Although radiographic features of vasculitis involving the GI tract have been well studied especially in computed tomography (CT), the combination of endoscopic and radiographic features has not been fully evaluated. We herein review the endoscopic and radiographic features of GI involvement in vasculitis with the presentation of our typical cases.

CLASSIFICATION OF VASCULITIS

Vasculitis is classified as primary or secondary (Table 1). Primary vasculitis was defined by the Chapel Hill International Consensus on the Nomenclature of Systemic Vasculitis^[1]. The conference classified ten vasculitides into large-vessel vasculitis, medium-sized-vessel vasculitis, and small-vessel vasculitis, depending on the types of predominantly affected vessels. Large-vessel vasculitis affects the aorta and the largest arterial branches, and includes giant-cell (temporal) arteritis and Takayasu's arteritis. Medium-sized-vessel vasculitis affects the main visceral arteries and their branches, and includes polyarteritis nodosa and Kawasaki's disease. Small-vessel vasculitis affects arterioles, venules, and capillaries, and includes Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, essential cryoglobulinemic vasculitis, and cutaneous leukocytoclastic vasculitis^[1]. Secondary vasculitis is caused by connective tissue diseases (e.g., systemic lupus erythematosus, Behçet's disease, and rheumatoid arthritis), bacterial and viral infection, malignancy, and drugs. Most cases of secondary vasculitis present with small-vessel vasculitis^[2,5].

GASTROINTESTINAL INVOLVEMENT IN VASCULITIS

Large-vessel vasculitis

Giant cell (temporal) arteritis: Giant cell (temporal) arteritis is a form of granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery^[1]. It is often associated with polymyalgia rheumatica. The frequency of its GI involvement is rare^[5,8].

Takayasu's arteritis: Takayasu's arteritis (TA) is a form of granulomatous inflammation of the aorta and its major branches^[1]. It is characterized by ocular disturbances and decreased brachial artery pulse (pulseless disease). The descending aortic syndrome may cause mesenteric

Table 1 Classification of vasculitis

Primary vasculitis
Large-vessel vasculitis
Giant-cell (temporal) arteritis
Takayasu's arteritis
Medium-sized-vessel vasculitis
Polyarteritis nodosa
Kawasaki's disease
Small-vessel vasculitis
Wegener's granulomatosis
Churg-Strauss syndrome
Microscopic polyangiitis
Henoch-Schönlein purpura
Essential cryoglobulinemic vasculitis
Cutaneous leukocytoclastic vasculitis
Secondary vasculitis
Connective tissue diseases
Systemic lupus erythematosus
Behçet's disease
Rheumatoid arthritis
Infectious diseases
Bacteria
Virus
Drugs
Non-steroidal anti-inflammatory drugs
Anti-cancer drugs
Antibiotics
Paraneoplastic vasculitis
Carcinoma
Lymphoproliferative neoplasm
Myeloproliferative neoplasm

vasculitis, but the frequency of mesenteric or celiac involvement is rare^[3,5,6,8]. Although the precise etiology is unknown, the coexistence of TA and ulcerative colitis or Crohn's disease has been increasingly reported^[9,10].

Medium-sized-vessel vasculitis

Polyarteritis nodosa: Polyarteritis nodosa (PN) is a form of necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules^[1]. Approximately two-thirds of the patients have abdominal pain, nausea, vomiting, or other manifestations associated with GI ischemia and infarction^[3,5-7]. The clinical course is often dramatic. The typical radiographic feature is an angiographic finding of aneurysms up to 1 cm in diameter within the renal, mesenteric, and hepatic vasculature^[3].

Kawasaki's disease: Kawasaki's disease is a form of arteritis involving large, medium-sized, and small arteries and is associated with mucocutaneous lymph node syndrome^[1]. It usually occurs in children and coronary arteries are often involved. GI involvement is relatively uncommon but acute abdomen with paralytic ileus, ischemic enteritis, and vasculitic appendicitis may occur^[6].

Small-vessel vasculitis

Wegener's granulomatosis: Wegener's granulomatosis (WG) is a form of granulomatous inflammation involv-

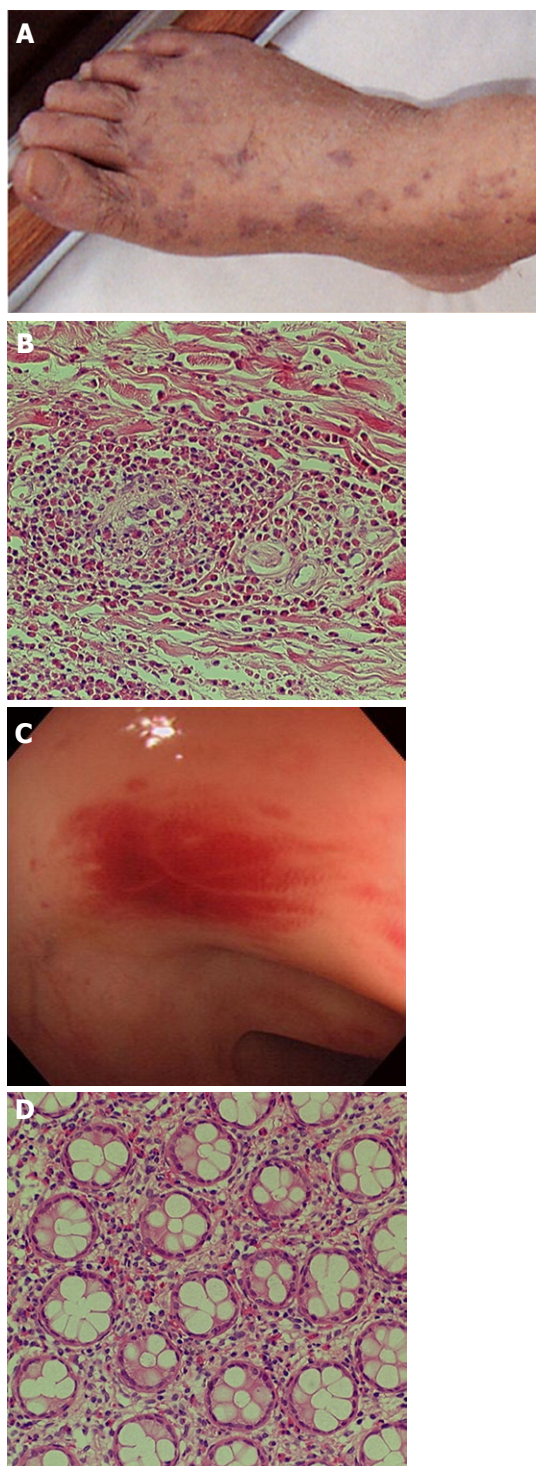


Figure 1 Churg-Strauss syndrome in a 60-year-old man with fever, abdominal pain, diarrhea, facial swelling, and purpura of the lower extremities. A: Purpura of the right foot; B: Biopsy of the purpura revealed small vessel vasculitis with marked inflammatory infiltrate of eosinophils; C: Colonoscopy disclosed numerous areas of patchy mucosal erythema from the sigmoid colon to the splenic flexure; D: Biopsy of erythema showed mild infiltration of eosinophils around crypts. All figures and legends are reproduced from Hokama *et al.*^[11] with permission from Elsevier.

ing the respiratory tract and necrotizing vasculitis affecting small-to-medium-sized vessels^[1]. GI involvement is relatively rare and granulomatous colitis or gastritis may

occur^[5].

Churg-Strauss syndrome: Churg-Strauss syndrome (CSS) is a form of eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-to-medium-sized vessels and is associated with asthma and eosinophilia^[1]. GI symptoms of CSS are abdominal pain and diarrhea caused by eosinophilic gastroenteritis (Figure 1)^[11]. Mesenteric vasculitis may occur, leading to GI ulceration, ischemia, and perforation. Among antineutrophil cytoplasmic antibodies-associated vasculitis which include WG, CSS, and microscopic polyangiitis (MPA), GI involvement increases the risk of relapse in CSS^[12].

Microscopic polyangiitis: MPA is a form of necrotizing vasculitis with few or no immune deposits affecting small vessels^[1]. Although necrotizing glomerulonephritis and pulmonary capillaritis are very common, GI involvement is rare^[6].

Henoch-Schönlein purpura: Henoch-Schönlein purpura (HSP) is a form of vasculitis with IgA-dominant immune deposits affecting small vessels^[1]. Although HSP is typically a disease of children, adult cases present more severe disease compared to children. It involves the skin, joints, GI tract and kidneys. GI symptoms include colicky abdominal pain and bleeding caused by bowel ischemia and edema. Serious complications include intussusception, infarction, and perforation^[6,13]. The descending duodenum and the terminal ileum are frequently involved, with endoscopic characteristics of diffuse mucosal redness, petechiae, hemorrhagic erosions and ulcers^[14]. Longitudinal ulcers may be clear evidence of mesenteric vascular involvement (Figure 2)^[15]. The CT features are bowel wall thickening with the target sign and engorgement of mesenteric vessels with comb sign (Figure 2)^[15].

Systemic lupus erythematosus: Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease with local deposition of antigen-antibody complexes or antibodies inducing necrotizing vasculitis^[3]. It involves the skin, joints, GI tract, kidneys, central nervous system, and blood cells. It frequently involves any part of the GI tract, liver, and pancreas^[16,17]. Acute abdominal pain caused by bowel ischemia secondary to lupus mesenteric vasculitis (LMV) is common^[18]. The ischemic change can differ according to the sensitivity of the vessels in four different bowel layers; mucosal ulceration and hemorrhage, submucosal edema and intestinal pseudo-obstruction due to muscular damage, and ascites and perforation due to serosal damage^[18]. The endoscopic features are ischemic enterocolitis and 'punched out' ulcers (Figure 3). Although histopathological diagnosis of LMV can be obtained^[19], most endoscopic superficial biopsies might not yield a definitive diagnosis because the affected vessels are usually located in an inaccessible area^[18]. The CT features include focal or diffuse bowel

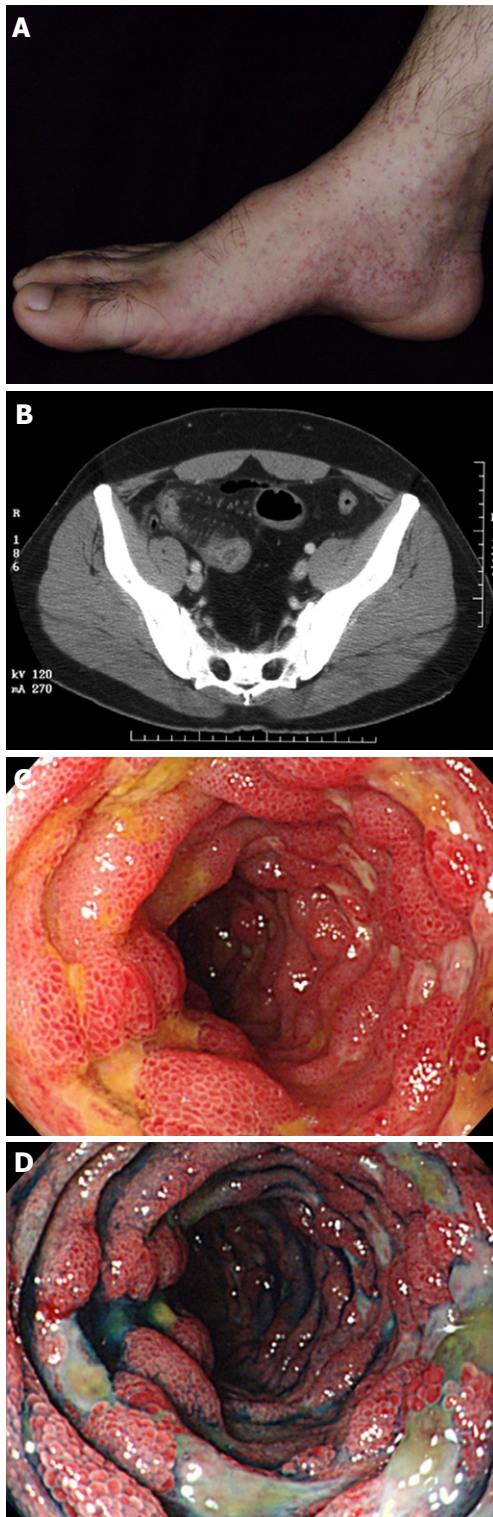


Figure 2 Henoch-Schönlein purpura in a 38-year-old man with hematochezia. A: Palpable purpura of the right foot; B: Contrast-enhanced computed tomography scan of the abdomen showed diffuse thickening of the ileum (target sign) with mesenteric hypervascularity in a palisading pattern (comb sign), suggesting ischemic ileitis; C, D: Single balloon enteroscopy showed edematous petechiae with linear ulcers in the affected ileum. All figures and legends are reproduced from Hokama *et al*^[19] with permission from BMJ Publishing Group Ltd.

wall thickening with the target sign, bowel dilatation, ascites, and engorgement of mesenteric vessels with comb

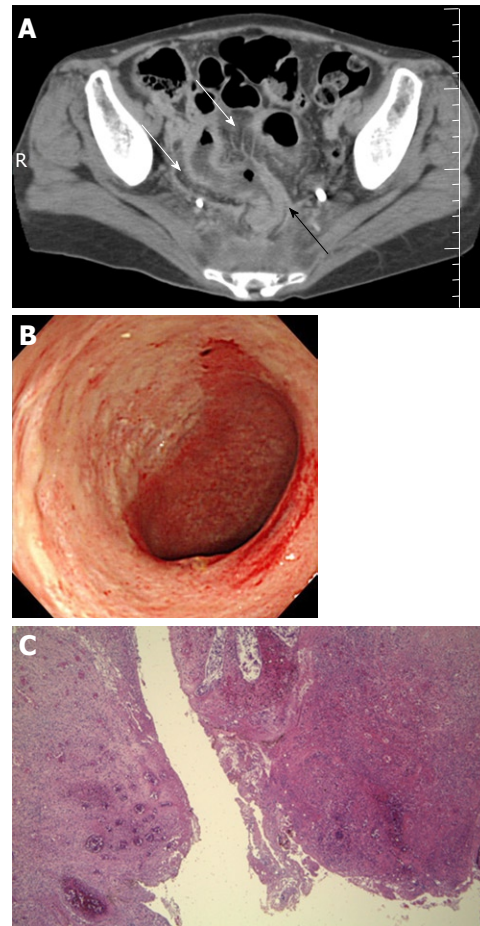


Figure 3 Systemic lupus erythematosus in a 40-year-old woman with lower abdominal pain and fever. A: Contrast-enhanced computed tomography scan of the abdomen showed diffuse thickening of the rectosigmoid colon (black arrow) with engorgement of mesenteric vessels (comb sign, white arrows); B: Colonoscopy disclosed a large punched-out ulcer of the sigmoid colon; C: Perforation of the sigmoid colon occurred despite aggressive immunosuppressive therapy, requiring resection of the affected colon. The resected specimen disclosed bowel perforation with severe transmural inflammation, edema, hemorrhage and vasculitis (hematoxylin-eosin staining, $\times 40$).

sign (Figure 3)^[3,17]. LMV rarely causes pneumatosis intestinalis (PI)^[20], which is gas collection in the bowel wall (Figure 4). PI may result in hepatic portal venous gas with a high mortality rate. Another important GI manifestation in SLE is protein losing gastroenteropathy^[16]. Edematous villi and lymphangiectasia, which may be caused by immunological vascular or mucosal damage, have been the postulated pathology^[20].

Behçet's disease: Behçet's disease (BD) is a nonspecific necrotizing vasculitis characterized by recurrent orogenital ulcers, uveitis, arthritis, and skin lesions^[21,22]. It frequently involves nerves and the GI tract. The frequently involved sites are the ileocecal region and esophagus. The hallmark of BD is the presence of ulceration. Two types of ulceration occur: localized and diffuse^[22]. In the ileocecal region, a localized large deeply penetrating ulcer may present with a high frequency of hemorrhage and perforation. The CT features are mass-like lesions and



Figure 4 Systemic lupus erythematosus in a 23-year-old woman with abdominal pain and fever. Plain computed tomography scan of the abdomen showed intramural gas of the ascending colon, suggesting pneumatosis intestinalis (arrow). Hyperbaric oxygen therapy was effective for improvement of the pneumatosis.

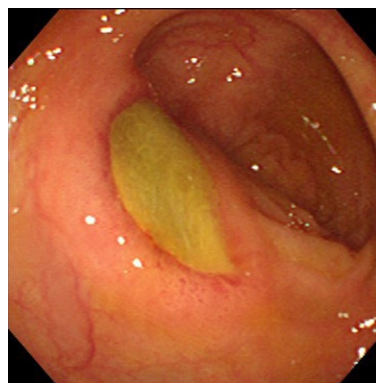


Figure 6 Behçet's disease in a 50-year-old woman with abdominal pain and hematochezia—a large ovoid ulcer in the transverse colon. The figure and legends are reproduced from Hokama *et al*^[23] with permission from Elsevier.

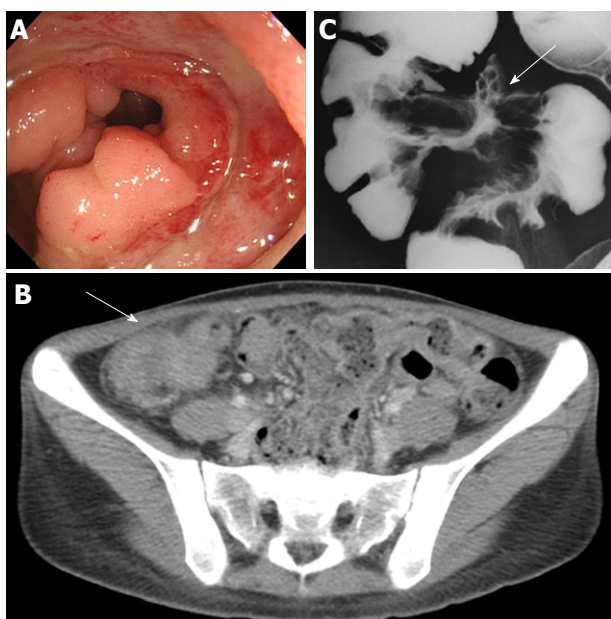


Figure 5 Behçet's disease in a 25-year-old woman with abdominal pain and diarrhea. A: Colonoscopy showed a large punched-out ulcer with elevated margins in the terminal ileum; B: Contrast-enhanced computed tomography scan of the abdomen showed a mass-like lesion with unevenly thickened bowel wall of the ileocecal region (arrow); C: Small bowel barium radiography disclosed the large ulcer (arrow) with convergence of mucosal folds in the terminal ileum.

unevenly thickened bowel wall with marked enhancement^[3,22]. Barium examination shows a large irregular ulcer with marked thickening of the surrounding intestinal wall (Figure 5). Diffuse lesions are small, multiple, discrete, “punched-out” ulcers commonly observed in the colon (Figure 6)^[23]. A recent large scale study confirmed that patients with intestinal BD younger than 25 years, who had a history of prior laparotomy or volcano-shaped intestinal ulcers (the former type) have an increased risk of free bowel perforation^[24].

Other small-vessel vasculitis: Drugs in nearly all pharmacological classes can cause drug-induced vasculitis/drug-induced lupus-like syndrome^[25]. As the clinical presenta-

tion and pathological features are indistinguishable from primary vasculitis, a high index of suspicion is required for the accurate diagnosis of drug-induced vasculitis. Discontinuation of the suspected drugs often enough to induce prompt improvement, obviating immunosuppressive treatment.

Infectious agents often cause vasculitis *via* mechanisms including direct microbial invasion of vascular endothelial cells, immune complex-mediated damage and stimulation of autoreactive lymphocytes through molecular mimicry and superantigens^[26]. Causative pathogens include bacteria (e.g., streptococci, mycobacteria, *Treponema pallidum*), viruses (e.g., cytomegalovirus, herpes virus, hepatitis virus B and C, human immunodeficiency virus), fungi, and parasites.

Vasculitis/connective tissue disease and malignancy are related and this association is bidirectional. Malignancy occurs more frequently in the course of vasculitis and vasculitis occurs in the course of malignancy^[27,28]. Therefore, the presence of vasculitis/connective tissue disease may justify a workup for hidden malignancy. In addition, as blood hypercoagulability frequently occurs in malignancy, leading to thrombophlebitis and thrombosis^[29], we should pay greater attention to vascular diseases in the treatment of cancer patients.

TREATMENT-ASSOCIATED COMPLICATIONS

As immunosuppressive drugs, including prednisolone, cyclophosphamide, azathioprine, cyclosporine A, tacrolimus, and anti-tumor necrosis factor antibodies, have been the key treatment for vasculitis, opportunistic infection can be a life-threatening complication. Cytomegalovirus (CMV) has been increasingly recognized as an important pathogen in such immunocompromised states^[30]. GI symptoms of CMV infection are usually nonspecific and include abdominal pain, diarrhea and GI bleeding, which are similar to those of vasculitis. The colon and stomach are the most common sites of



Figure 7 Systemic lupus erythematosus in a 38-year-old woman with diarrhea. Colonoscopy showed cytomegalovirus-associated round ulcer in the transverse colon.

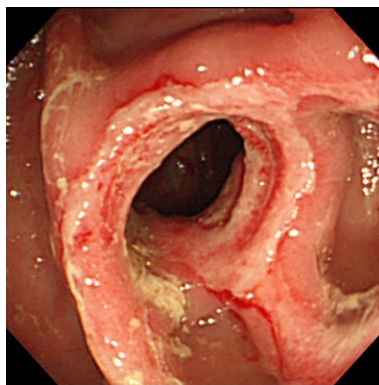


Figure 8 Rheumatoid arthritis in a 75-year-old woman with hematochezia. Colonoscopy showed a diaphragm-like stricture with a circumferential ulcer in the rectum, making the diagnosis of non-steroidal anti-inflammatory drug-induced diaphragm disease. The figure and legends are reproduced from Hokama *et al.*^[33] with permission from BMJ Publishing Group Ltd.

CMV GI infection. Endoscopic features are quite variable and include macroscopically normal mucosa, diffuse erythema^[31], nodules, pseudotumors, erosions and ulcers^[32], which are also similar to those of vasculitis. CMV-associated colonic ulcerin SLE is shown in Figure 7. Pathological proof of classical intranuclear inclusions is not always possible because CMV may infect vascular endothelium or connective tissue stromal cells under the ulcers. Therefore, several diagnostic methods should be used including CMV antigenemia assay and polymerase chain reaction of the specimen. Most GI CMV infections respond well to ganciclovir.

Nonsteroidal anti-inflammatory drugs (NSAID) are widely used in long-standing vasculitis/connective tissue diseases. Although gastroduodenal peptic ulceris well-known as a classic NSAID-induced GI damage, diaphragm disease (Figure 8)^[33] and various types of enteropathy in the small and large intestine have received greater recognition as adverse effects of NSAIDs. Diagnosis is traditionally made by symptom improvement on discontinuation of the NSAID^[34].

CONCLUSION

Any type of vasculitis can involve the GI tract. Bowel ischemia due to mesenteric vasculitis is frequently seen in association with increased mortality. Important endoscopic features are ischemic enterocolitis and ulcer. Characteristic CT features include bowel wall thickening with the target sign and engorgement of mesenteric vessels with comb sign. Knowledge of these GI manifestations can help make an early diagnosis and establish a management strategy with prompt immunosuppressive treatment.

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