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ORIGINAL ARTICLE

Gastrointestinal Tract Vasculopathy

Clinicopathology and Description of a Possible "New Entity" With Protean Features

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动静脉

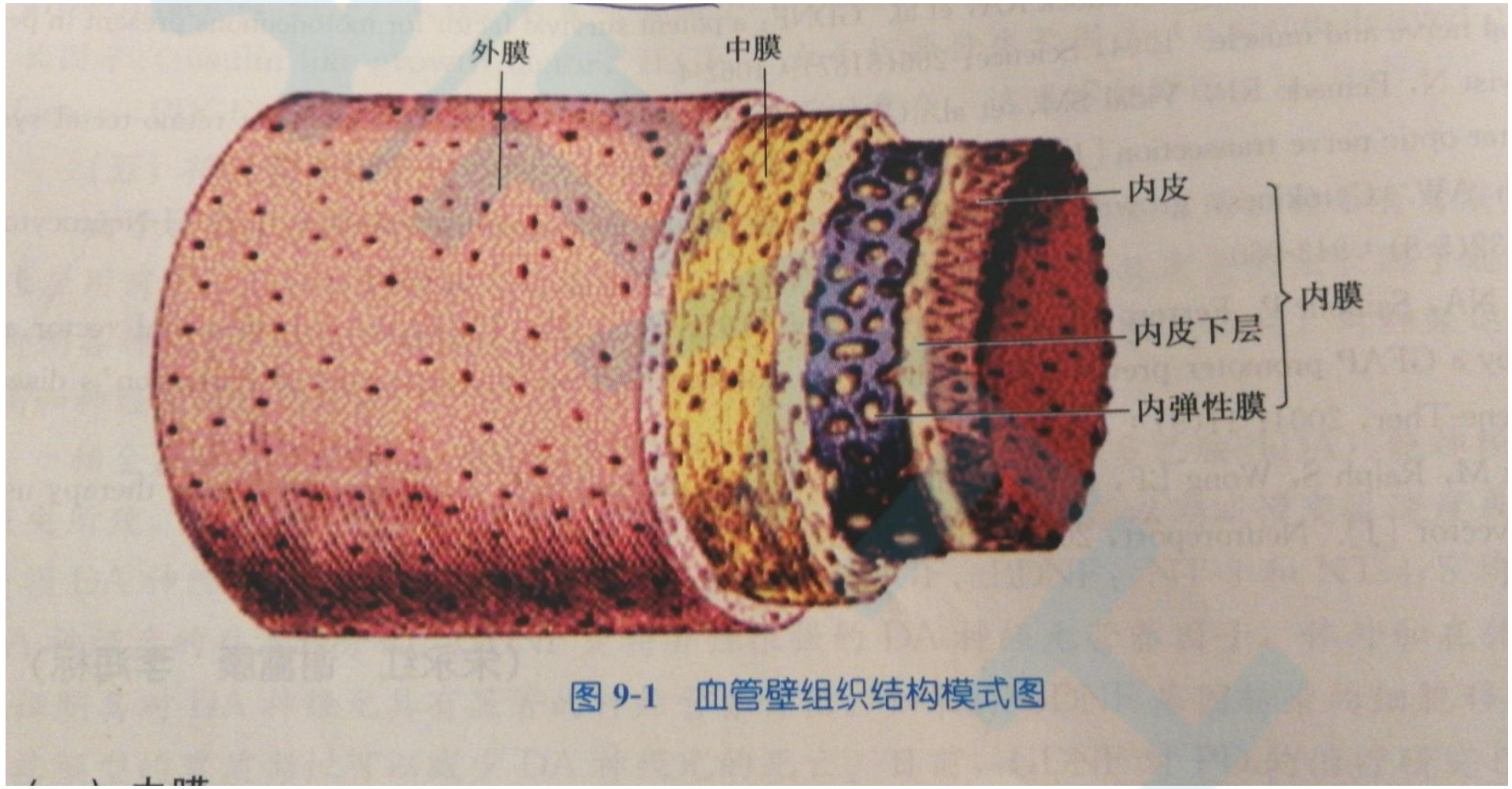
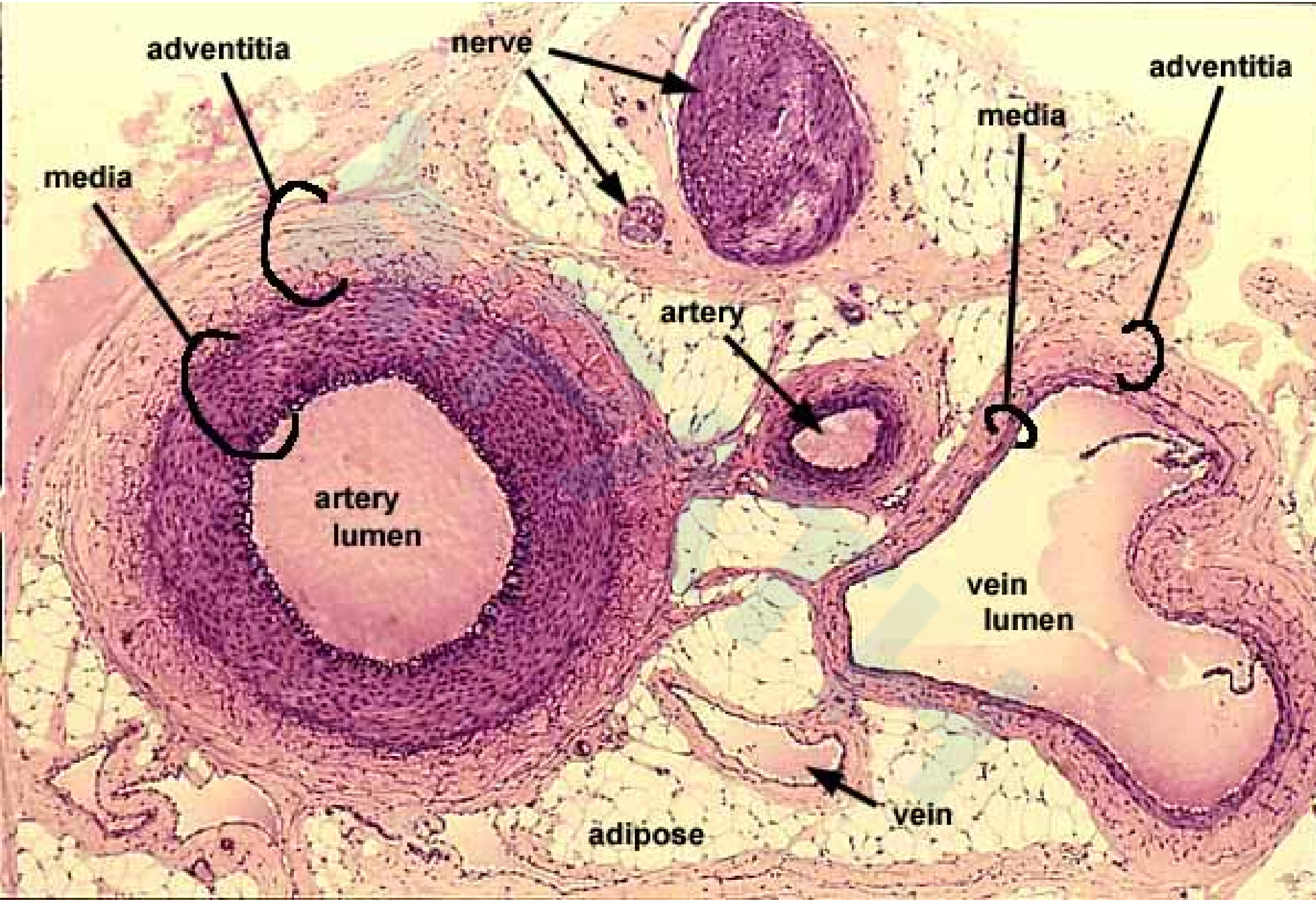
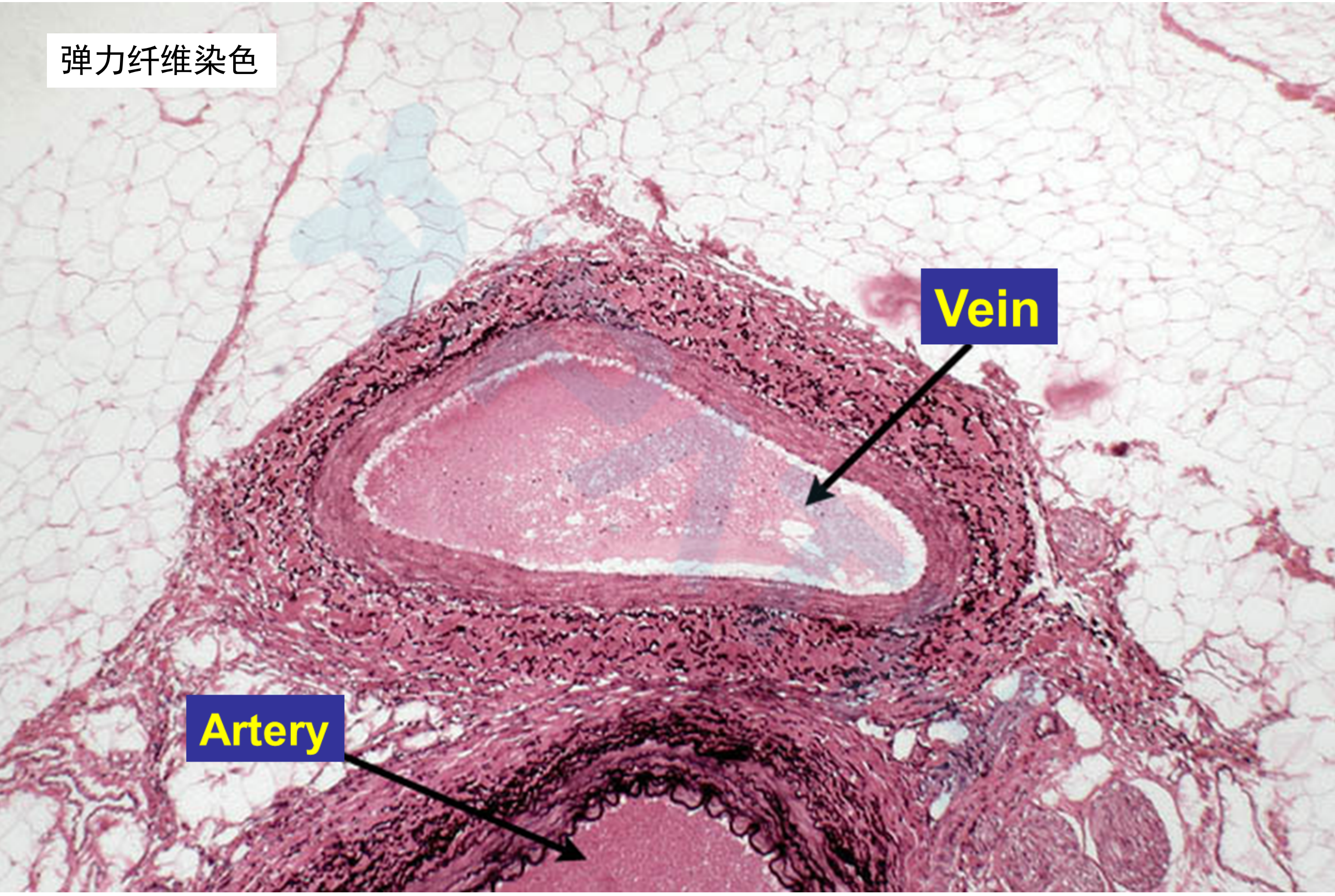


图 9-1　血管壁组织结构模式图

	动脉	静脉
形态	圆、厚、小	扁、薄、大
内膜	内皮+基底膜	
内弹力膜	较大血管有	无
中膜	弹力纤维（大动脉） 平滑肌（中动脉） 厚度>外膜	平滑肌+胶原纤维 厚度<外膜 有血管神经和滋养血管
外弹力膜	较大血管有	无
外膜	胶原+弹力纤维 不同排列方向 血管神经和滋养血管 大动脉无外膜	胶原+弹力纤维+平滑肌纤维 有血管神经和滋养血管


adventitia
nerve
adventitia
media
media
artery
artery
lumen
vein
lumen
vein
adipose

弹力纤维染色



BACKGROUND

- Noninfectious vasculitis :inflammation of blood vessel walls that may affect vessels of all sizes.

- Classification features : size or type of affected vessel, cellular inflammatory components , typical organ distribution, etiology, pathogenesis , and clinical or laboratory parameters.

Immune Complex Small Vessel Vasculitis

Cryoglobulinemic Vasculitis

IgA Vasculitis (Henoch-Schönlein)

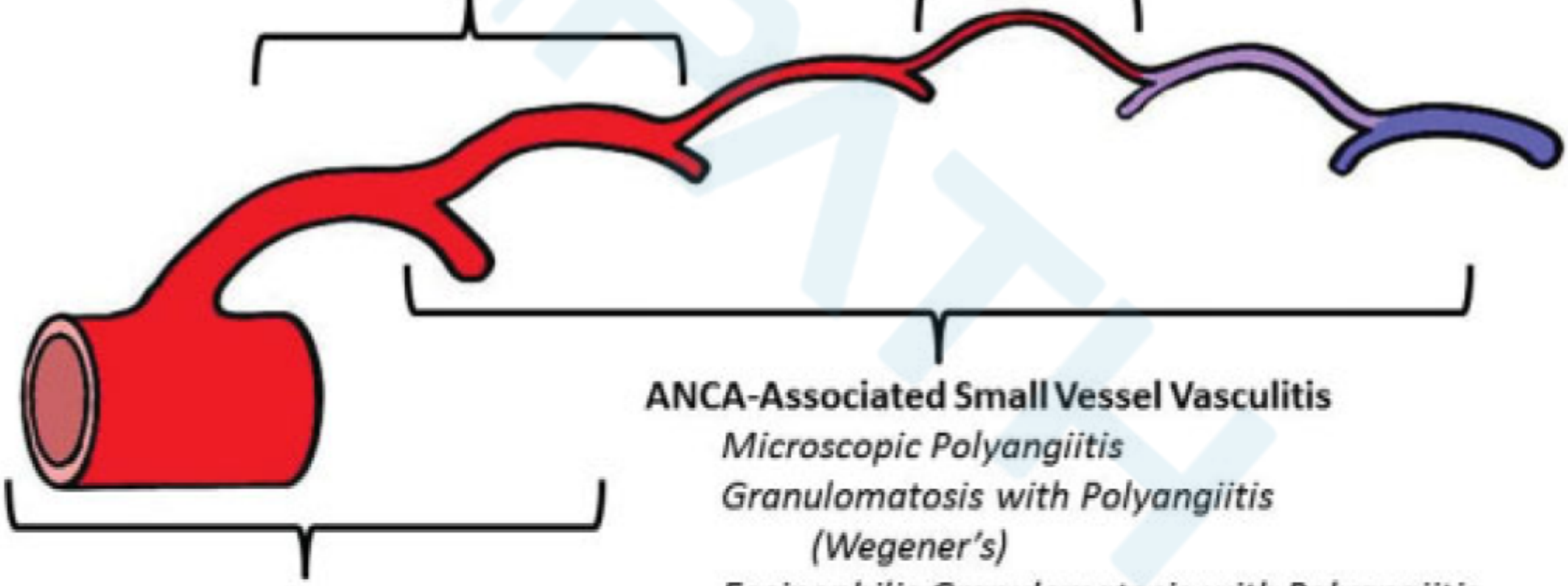
Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Medium Vessel Vasculitis

Polyarteritis Nodosa

Kawasaki Disease

Anti-GBM Disease



ANCA-Associated Small Vessel Vasculitis

Microscopic Polyangiitis

Granulomatosis with Polyangiitis (Wegener's)

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Large Vessel Vasculitis

Takayasu Arteritis

Giant Cell Arteritis

- Involvement of the GI tract by vasculitis is rare and is often overlooked;
- Complications: ischemia and perforation of visceral organs, which may be fatal in the setting of a delayed diagnosis.
- Ability of the pathologist to recognize a GI tract vasculitis may avoid irreversible end-organ damage.
- Reviewed GI tract vasculopathy in order to enhance diagnostic accuracy of these rare lesions.

MATERIALS AND METHODS

- Stanford Department of Pathology

- GI biopsies and/or resections showing involvement by vasculitis or vasculopathy.

- Search terms: “vasculitis,”“vasculopathy,” “capillaritis,” “arteritis,”and “phlebitis.

- 16 GI tract vasculitis or vasculopathy were identified over a 20-year period(excluding 16 IgA vasculitis).

- Clinical information(signs and symptoms, evidence of systemic involvement outside of the GI tract, and endoscopic impressions)

- Relevant laboratory findings(serology)

- The slides for each case were reviewed and pertinent histologic features were confirmed for each case.

RESULTS

- 16 cases of vasculitis or vasculopathy involving the GI tract were identified, included 8 cases with associated systemic disease, and 8 cases appeared to be isolated

TABLE 1. Clinical and Pathologic Features of Systemic GI Tract Vasculopathy

Age (y)	Sex	Vasculitis Type	Classification	Involved Site(s)	Clinical Presentation	Systemic Disease
13	F	Small vessel	Leukocytoclastic vasculitis	Small bowel	Bloody diarrhea	SLE
36	F	Small vessel	Leukocytoclastic vasculitis	Small bowel	Abdominal pain	SLE
47	F	Small vessel	Leukocytoclastic vasculitis	Descending colon	Abdominal pain, anemia	Dermatomyositis
51	F	Small and medium vessel	Dermatomyositis-associated vasculopathy	Small bowel	Abdominal pain	Dermatomyositis
77	F	Small and medium vessel	Necrotizing granulomatous vasculitis	Cecum, stomach	Abdominal pain, anemia	GPA
56	M	Small and medium vessel	Eosinophilic vasculitis	Small bowel, appendix	Abdominal pain	EGPA
74	F	Small and medium vessel	Necrotizing vasculitis	Descending colon	Abdominal pain	Rheumatoid arthritis
15	M	Predominantly veins	Venulitis with thrombosis	Jejunum	Abdominal pain	Crohn disease

EGPA indicates eosinophilic granulomatosis with polyangiitis; F, female; GPA, granulomatosis with polyangiitis; M, male; SLE, systemic lupus erythematosus.

GI Vasculitis associated with SLE case 1

13y ,F, anemia, weight loss, intermittent bloody diarrhea

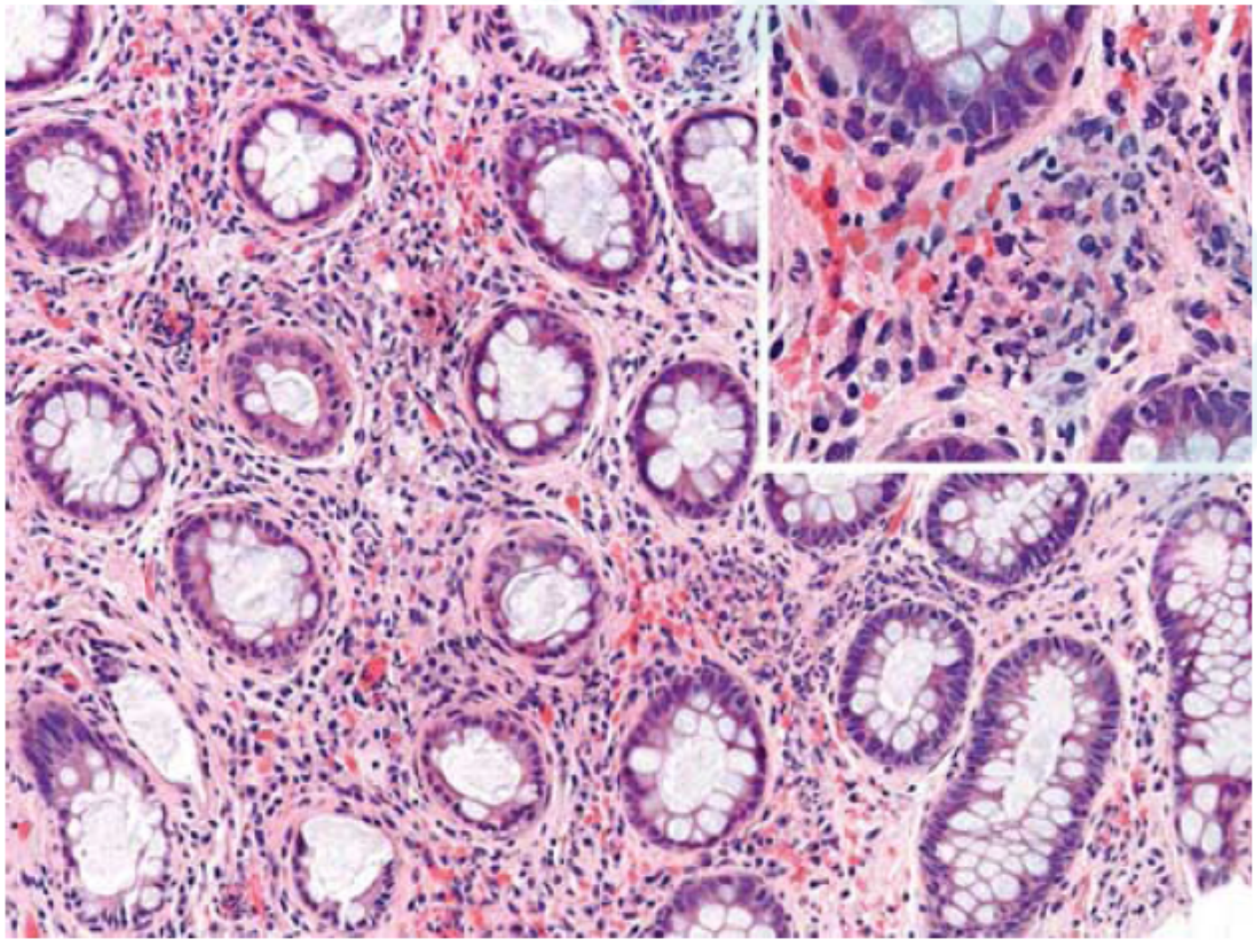


FIGURE 1.
Sigmoid colon biopsy . Scanning magnification shows preservation of mucosal glands with cellular infiltrates in and around intramucosal vessels.
Inset: Leukocytoclastic vasculitis of intramucosal vessel characterized by neutrophilic vasculitis with karyorrhectic debris .

- Biopsies of the sigmoid colon showed leukocytoclastic vasculitis ,while esophagus,stomach,duodenum, terminal ileum, ascending colon, transverse colon, rectum appeared unremarkable
- Laboratory findings : antinuclear antibody (ANA) +, doublestranded DNA antibody +, Smith antibody +, Coombs positive anemia, low complement, lymphopenia
- Renal biopsy demonstrated class IV nephritis
- Pericardial and pleural effusions
- Suspected a vasculitis-associated SLE
- The patient was treated with Cytoxan , solumedrol, and prednisone with improvement of symptoms

Case 2

- 36y , F , with a history of SLE, severe abdominal pain and hematemesis
- Abdominal CT : duodenal wall thickening
- Esophagogastroduodenoscopy : dusky-appearing mucosa in the duodenum with overlying exudate.
- Duodenal biopsies : necrotizing vasculitis within submucosal vessels, neutrophilic and lymphocytic inflammatory infiltrate involving vessel walls, fibrinoid necrosis , Intravascular fibrin thrombi

GI Vasculitis associated with Dermatomyositis case 1

- 47y , F , anemia, a single 1-cm ulcer within the descending colon, with a history of dermatomyositis
- Colonic biopsies: leukocytoclastic vasculitis within the superficial submucosa
- 3 months later, mucosal ischemic changes, but no apparent vasculitis
- 2 years later , abdominal pain , biopsies of ulcers from the hepatic flexure and splenic flexure again demonstrated a leukocytoclastic vasculitis

Case 2

- 51y , F , small bowel perforation, 3 resections, with a history of dermatomyositis
- Small bowel biopsies : vasculopathy involving medium caliber veins and arteries with various degrees of occlusion.
- The arteries showed intimal hyperplasia with scattered foamy macrophages, some of which demonstrated concentric medial hypertrophy
- No active vasculitis ,no fungal organisms
- Interpreted as dermatomyositis-associated GI vasculopathy

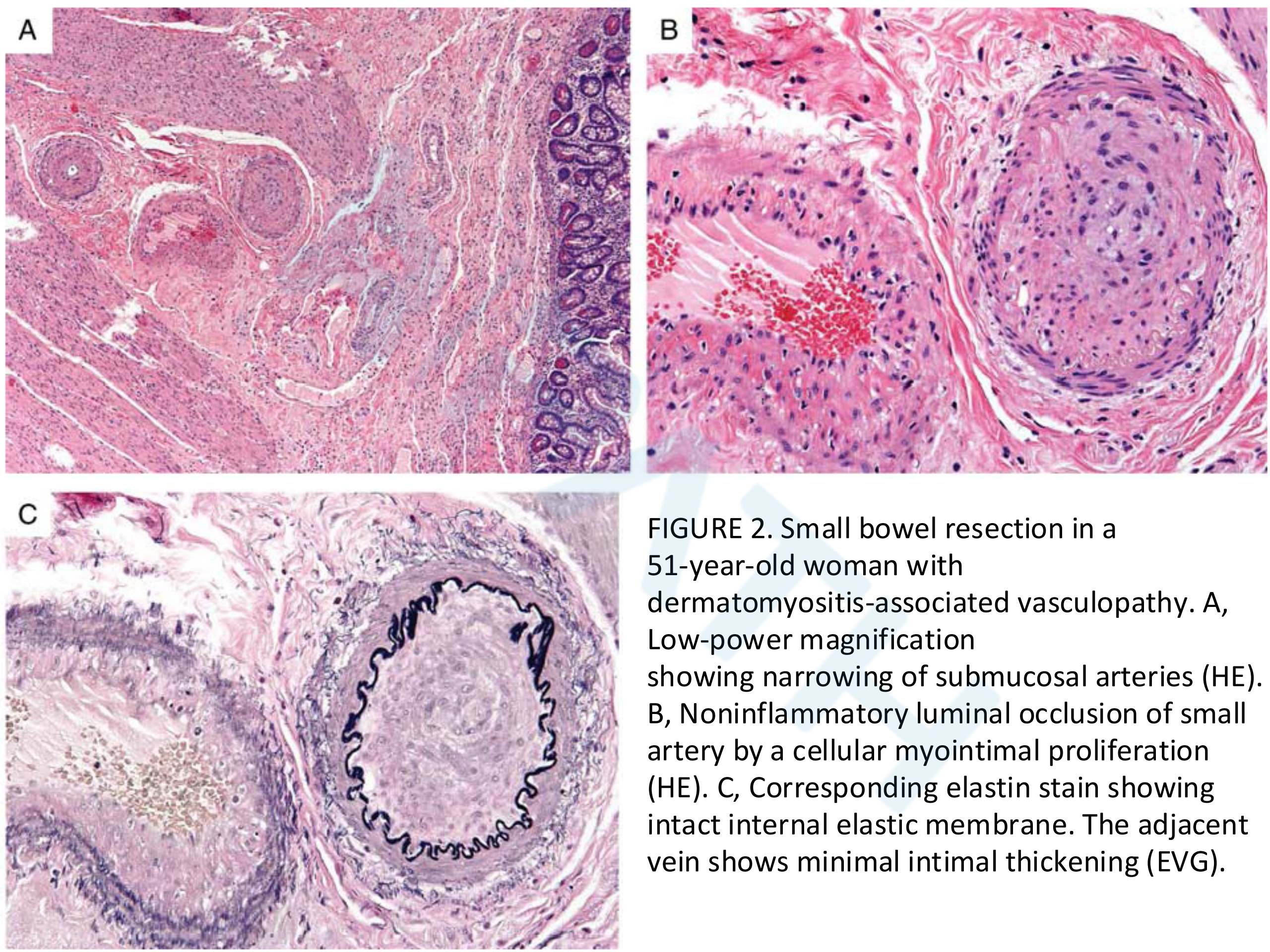


FIGURE 2. Small bowel resection in a 51-year-old woman with dermatomyositis-associated vasculopathy. A, Low-power magnification showing narrowing of submucosal arteries (HE). B, Noninflammatory luminal occlusion of small artery by a cellular myointimal proliferation (HE). C, Corresponding elastin stain showing intact internal elastic membrane. The adjacent vein shows minimal intimal thickening (EVG).

GI Vasculitis associated with GPA (Wegener Granulomatosis)

- 77y , F , abdominal pain, anemia, weight loss
- Panendoscopy :gastric ulcer and a large cecal mass
- Biopsies : necrotizing arteritis
- A large left lower lobe mass , CT-guided needle biopsy :necrotizing granulomatous inflammation with parenchymal necrosis , consistent with a diagnosis of GPA.
- Additional laboratory studies: c-ANCAs +

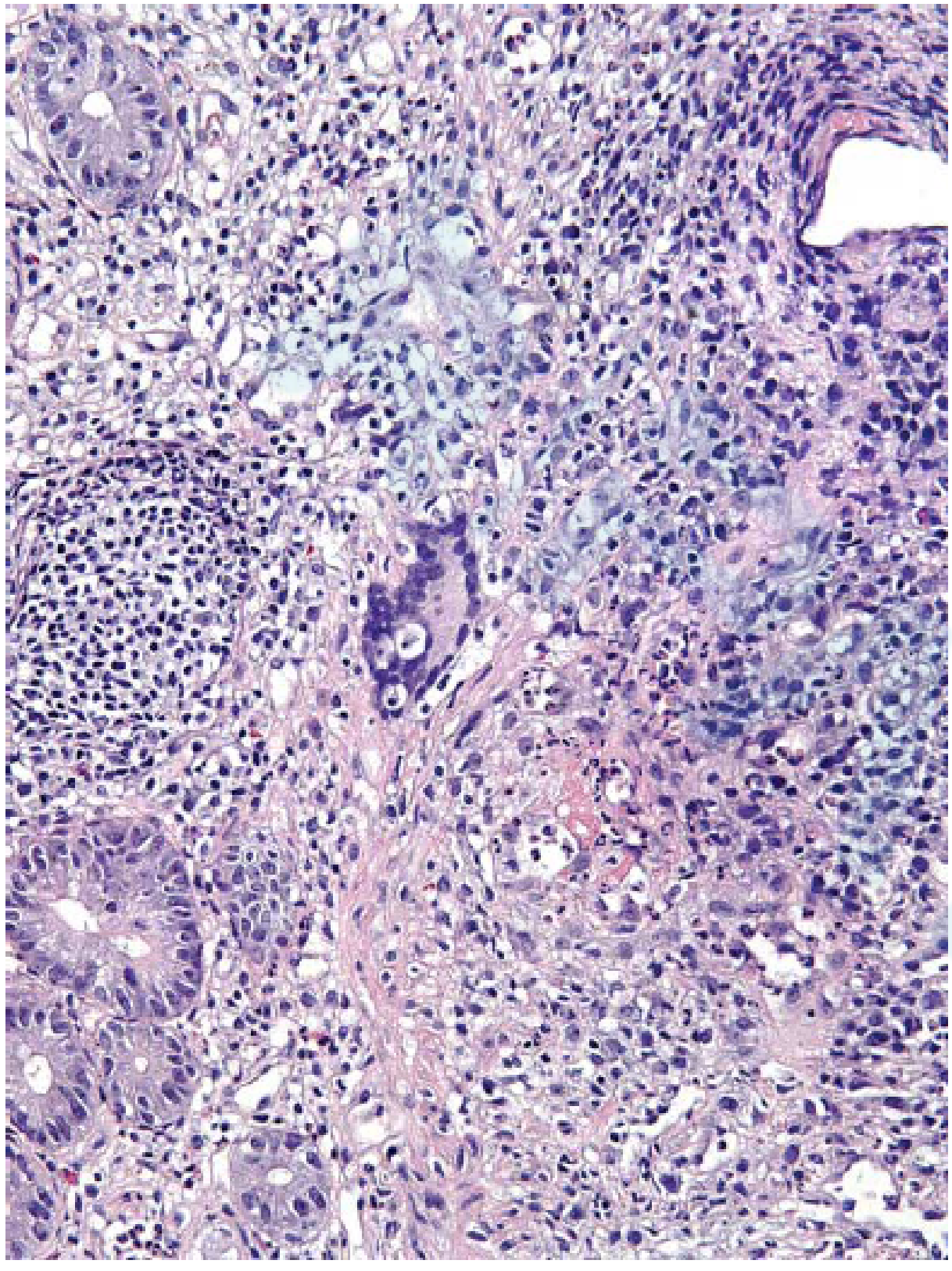


FIGURE 3.
Cecal biopsy :Necrotizing granulomatous arteritis .
The lung needle biopsy showed similar changes and c-ANCA serologies were positive.

GI Vasculitis associated with EGPA (Churg-Strauss Syndrome)

- 56y , M ,EGPA, increasing abdominal pain and distension
- Imaging : peritoneal free air, suspicious for perforation
- A small intestinal resection was performed , multifocal ischemia and perforation
- Histologic :
  - ✓ Necrotizing arteritis of submucosal vessels
  - ✓ The vessel walls were infiltrated by histiocytes and giant cells, with focal vague granuloma formation
  - ✓ Numerous eosinophils were surrounding the affected vessels with only few eosinophils identified within the vessel wall
  - ✓ Lymphocytes, fibrinoid necrosis ,vascular occlusion

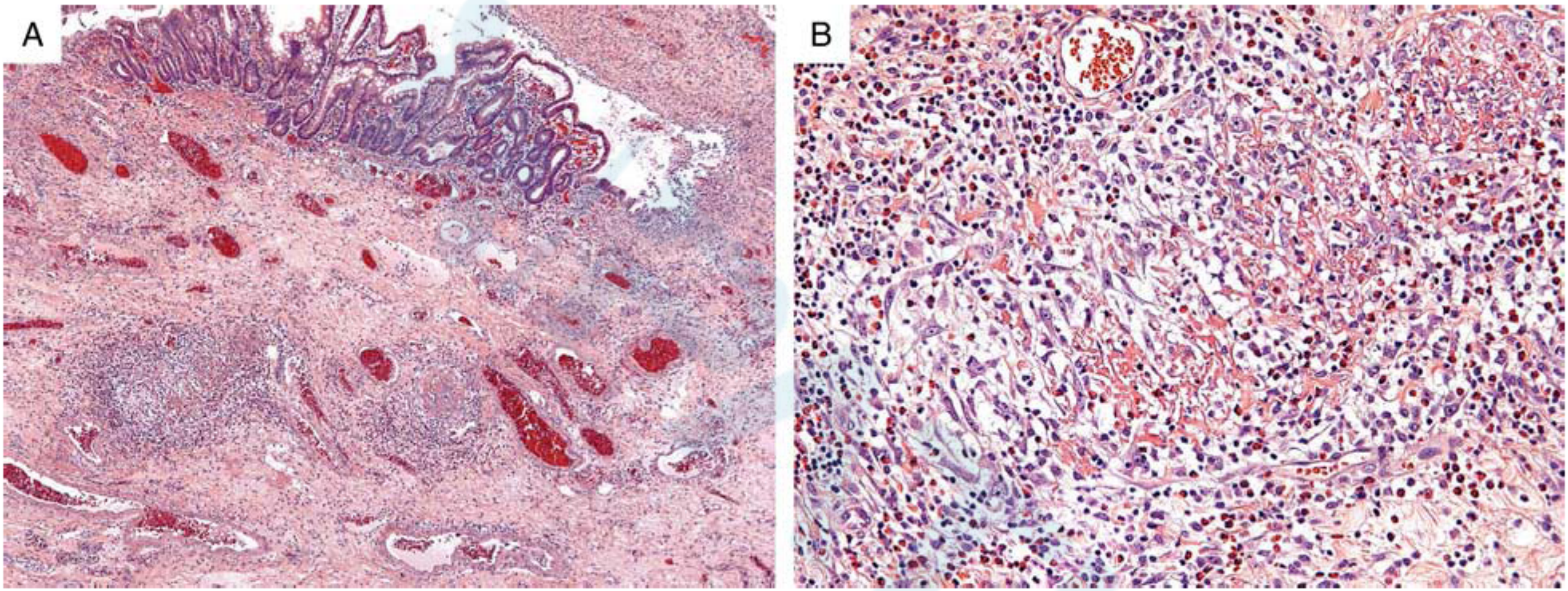
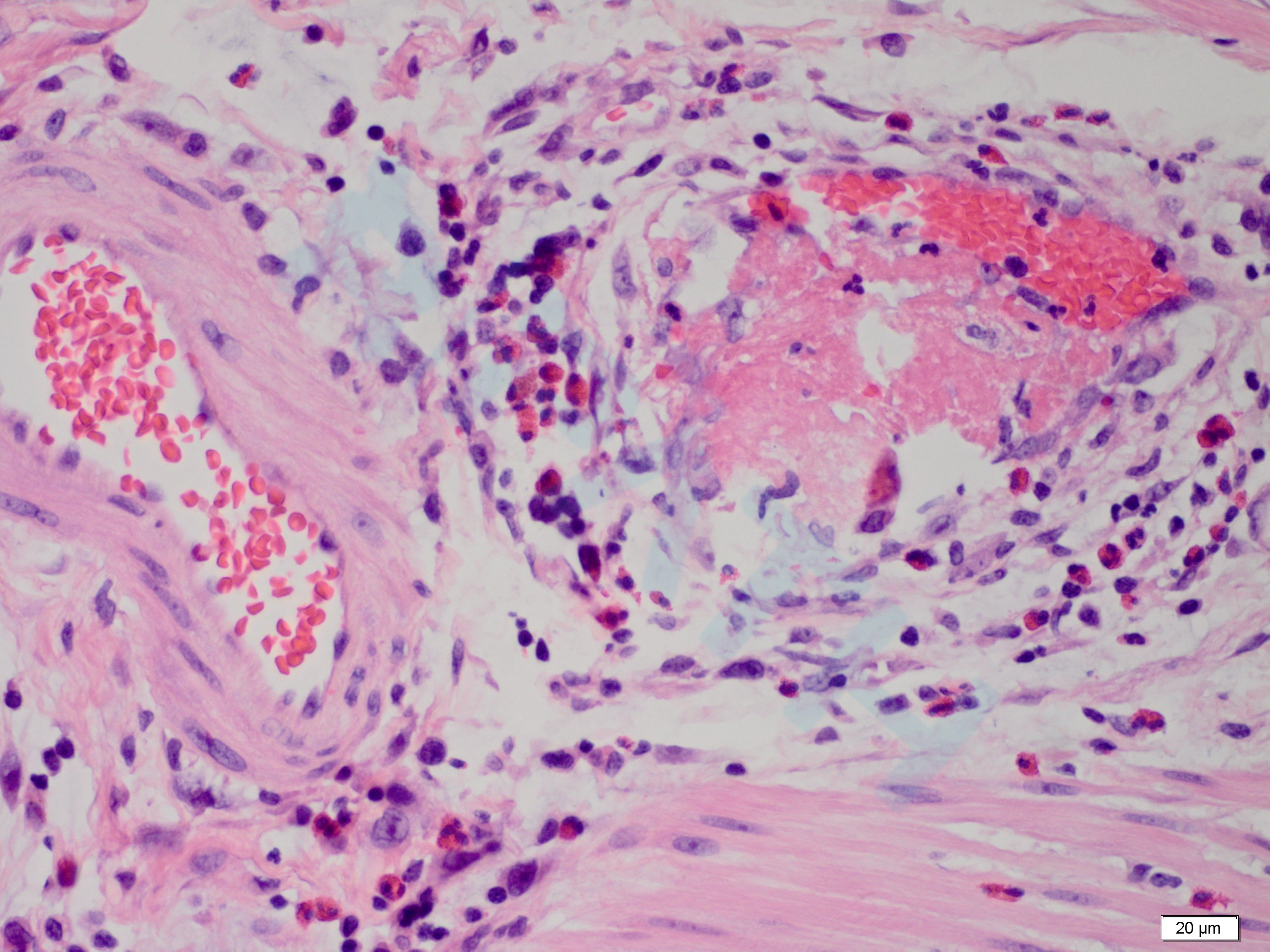


FIGURE 4. Small bowel resection. A, Low-power magnification showing sloughed mucosa. Submucosal vessels exhibit transmural infiltrates .B, High-power magnification showing necrotizing arteritis with numerous .


20 µm

GI Vasculitis associated with Crohn Disease

- 15y , M ,Crohn disease, abdominal pain and shock following a flu-like illness
- Resection of the jejunum : intramural, mesenteric , and nodal thrombosis with organization associated with full thickness gangrenous necrosis
- Minimal venulitis
- The patient was placed on anticoagulant therapy and there were no reported recurrent thrombotic episodes on follow-up.

Isolated GI Tract Vasculitis

- 8 patients had GI resections showing vasculitis or vasculopathy without associated systemic disease

TABLE 2. Clinical and Pathologic Features of Isolated GI Tract Vasculopathy

Age (y)	Sex	Vasculitis Type	Classification	Involved Site(s)	Clinical Presentation	Other History
47	M	Small and medium vessel	Granulomatous vasculitis	Small bowel	Hernia	Alcoholic cirrhosis
45	M	Veins	Idiopathic myointimal hyperplasia	Rectosigmoid	GI bleeding	
55	F	Veins	Enterocolic lymphocytic phlebitis	Left colon	Acute abdominal pain	Prior right colectomy
57	M	Small and medium vessel	Isolated PAN-like vasculitis	Cecum, left colon	Crohn disease vs. ulcerative colitis	
56	F	Veins	Enterocolic lymphocytic phlebitis	Right, transverse, and proximal left colon	Acute abdominal pain	
81	M	Veins	Enterocolic lymphocytic phlebitis	Transverse colon	Incidental finding	Chronic renal failure, gout, hypertension
57	F	Veins	Idiopathic myointimal hyperplasia	Jejunum	Chronic abdominal pain	ITP
17	M	Veins	Enterocolic lymphocytic phlebitis	Cecum, terminal ileum	Acute abdominal pain	Heterozygous Factor V Leiden

F indicates female; ITP, immune thrombocytopenic purpura; M, male; PAN, polyarteritis nodosa.

Histologic findings :

- Granulomatous venulitis(1)
- Necrotizing arteritis and venulitis(1)
- Enterocolic lymphocytic phlebitis (4)
- Idiopathic myointimal hyperplasia (2)

Enterocolic lymphocytic phlebitis

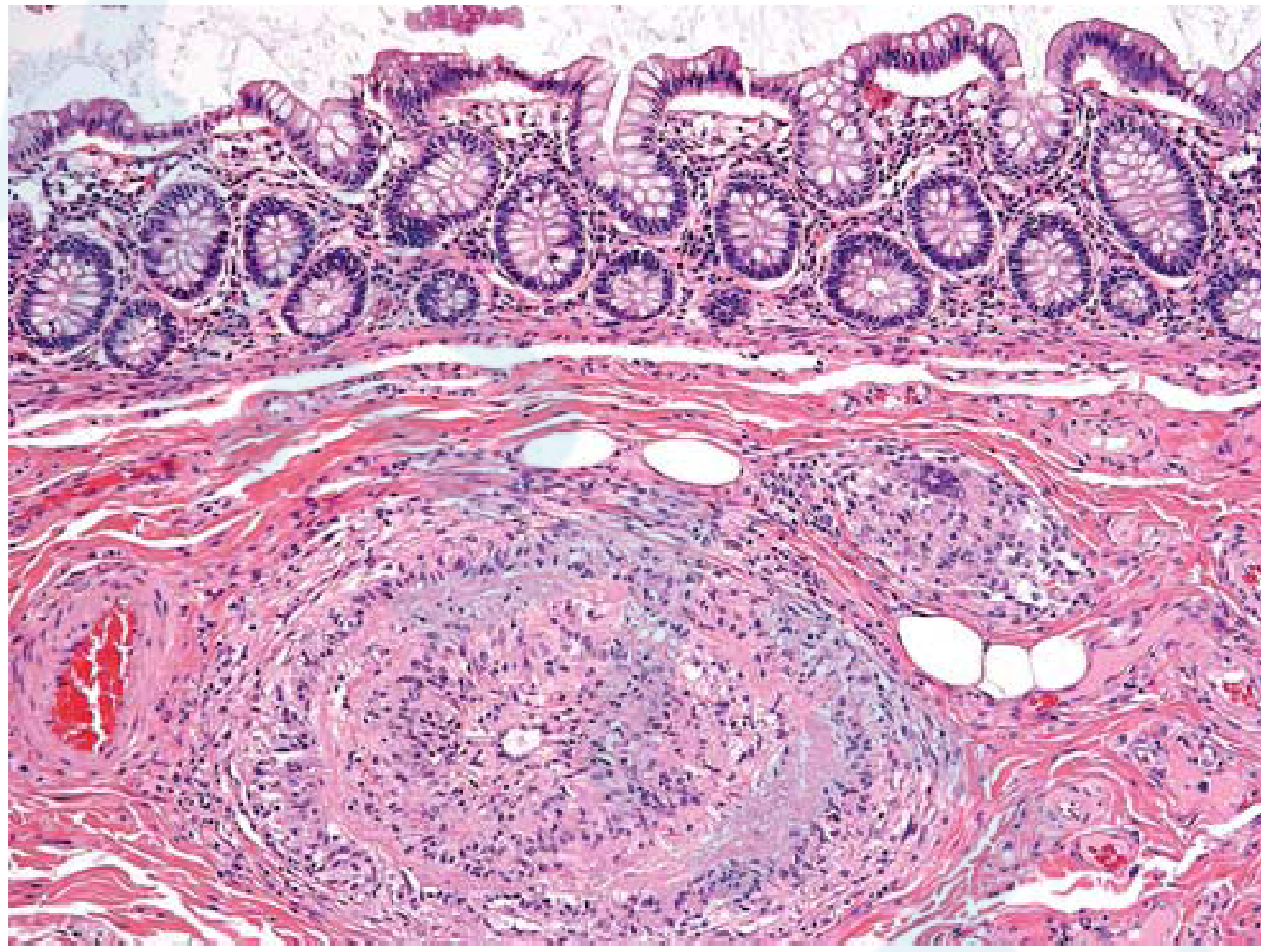
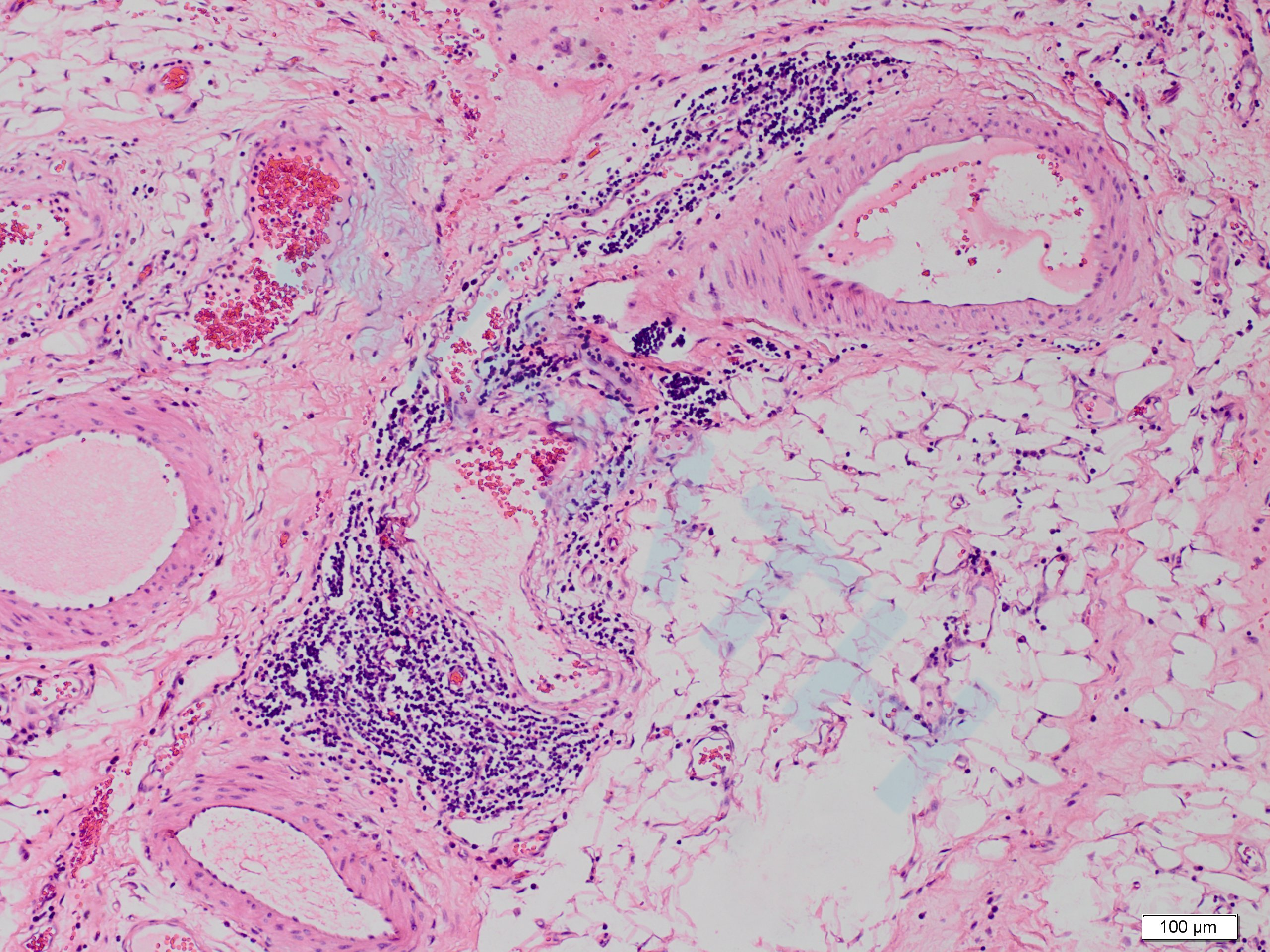


FIGURE 5. Isolated vasculopathy in an 81-year-old man with adenocarcinoma in the transverse colon. High-power magnification from colonic resection showing occlusive narrowing with pinpoint lumen by inflammatory and spindle cells. This vasculopathy was an incidental finding in the resection specimen and the only vasculopathy in this series that appeared to be entirely asymptomatic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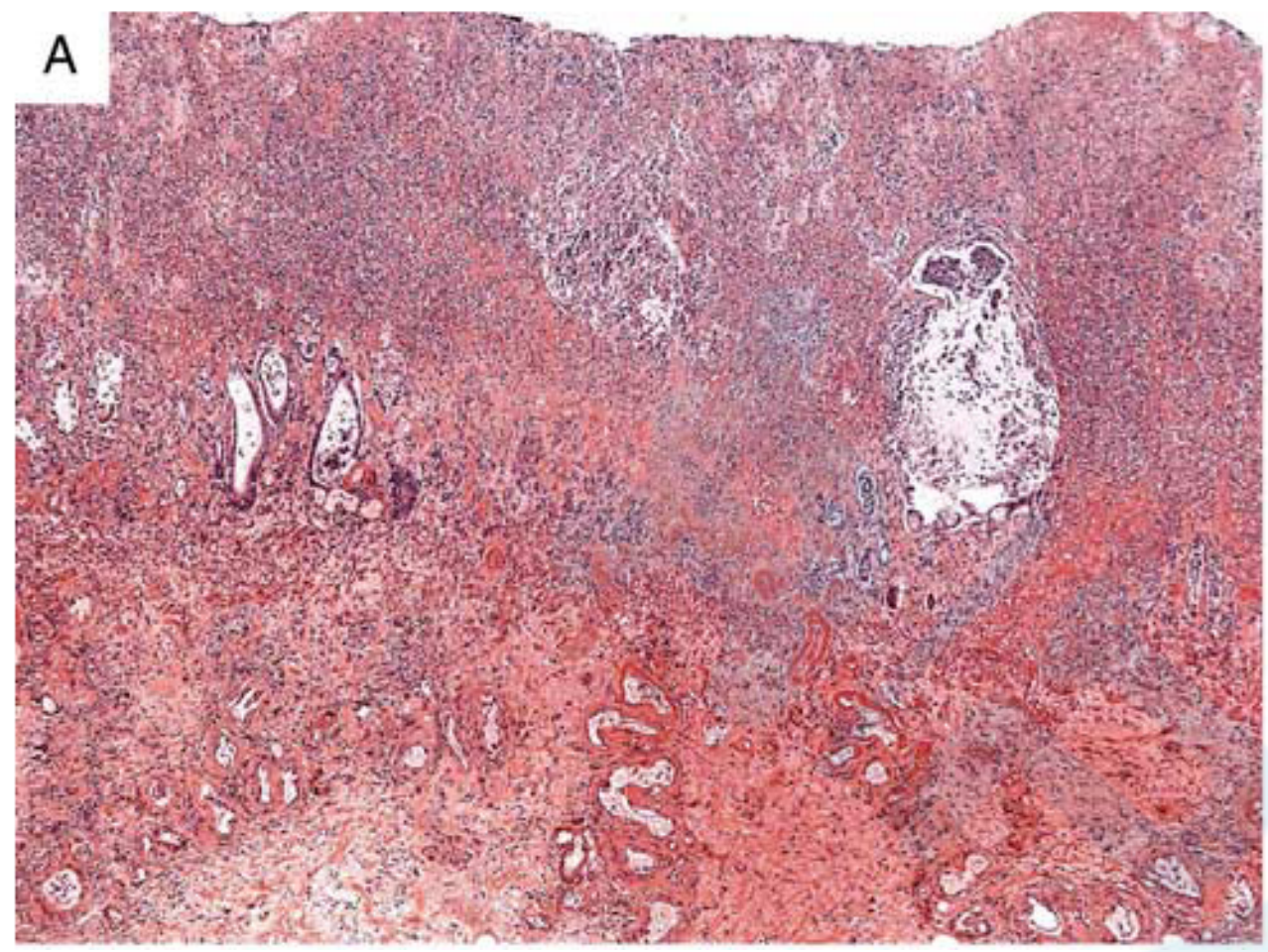

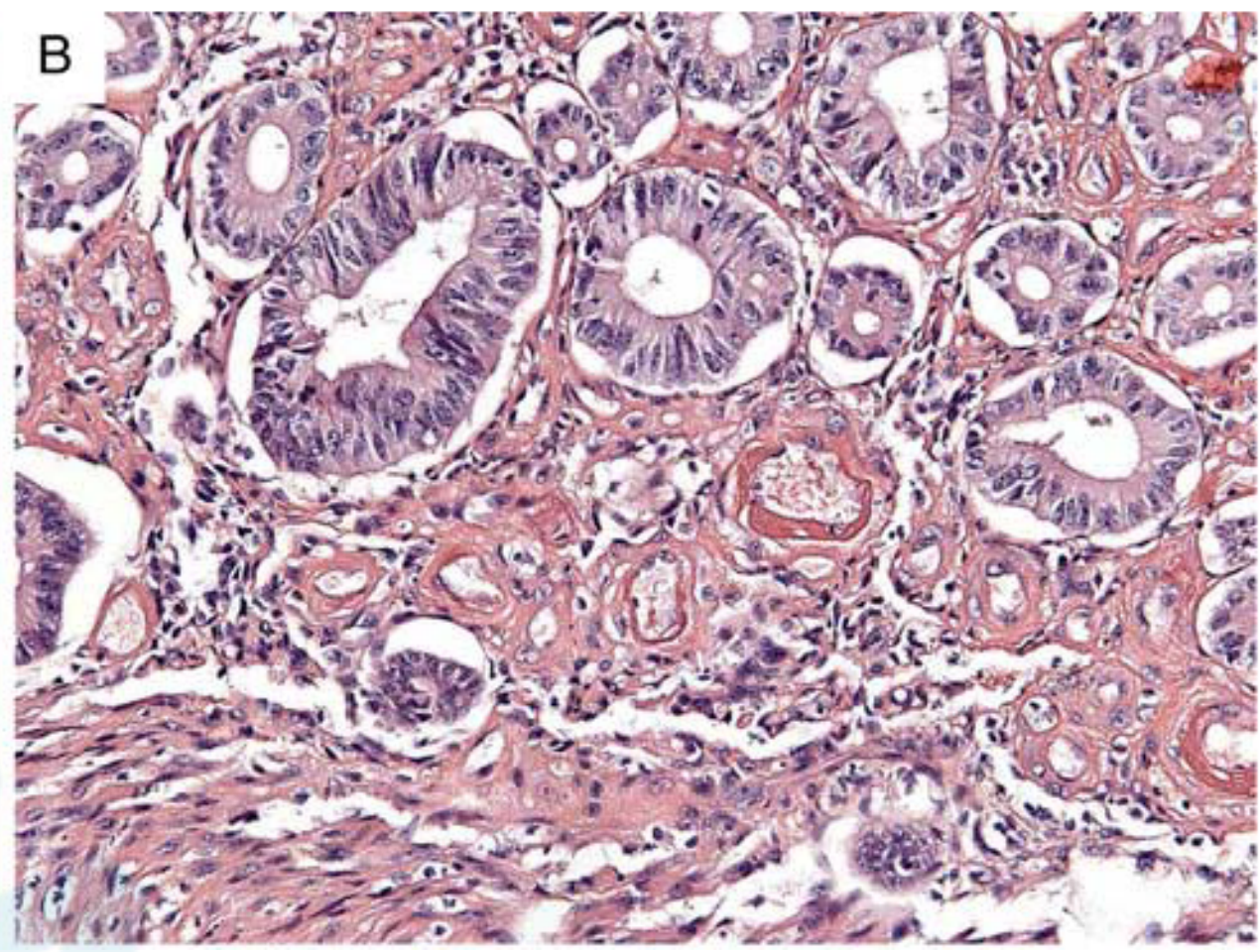

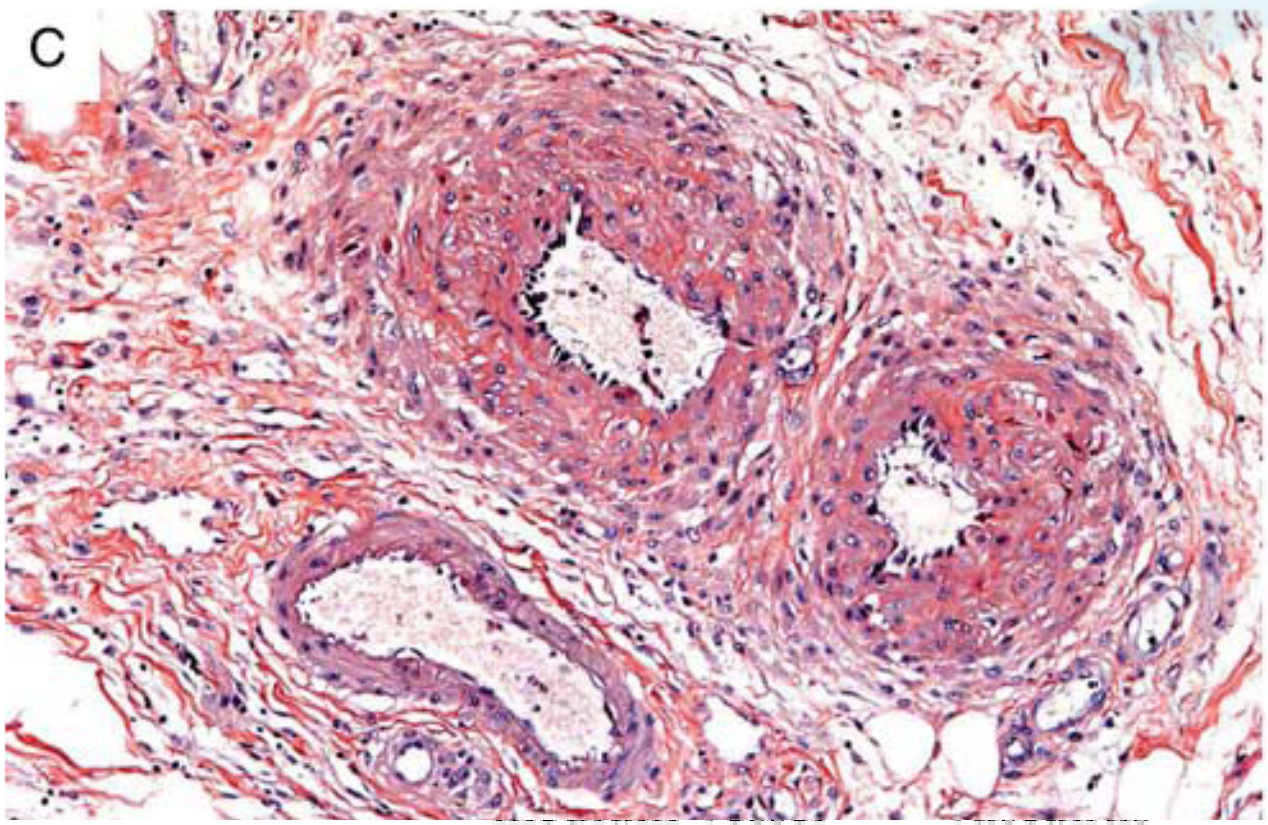

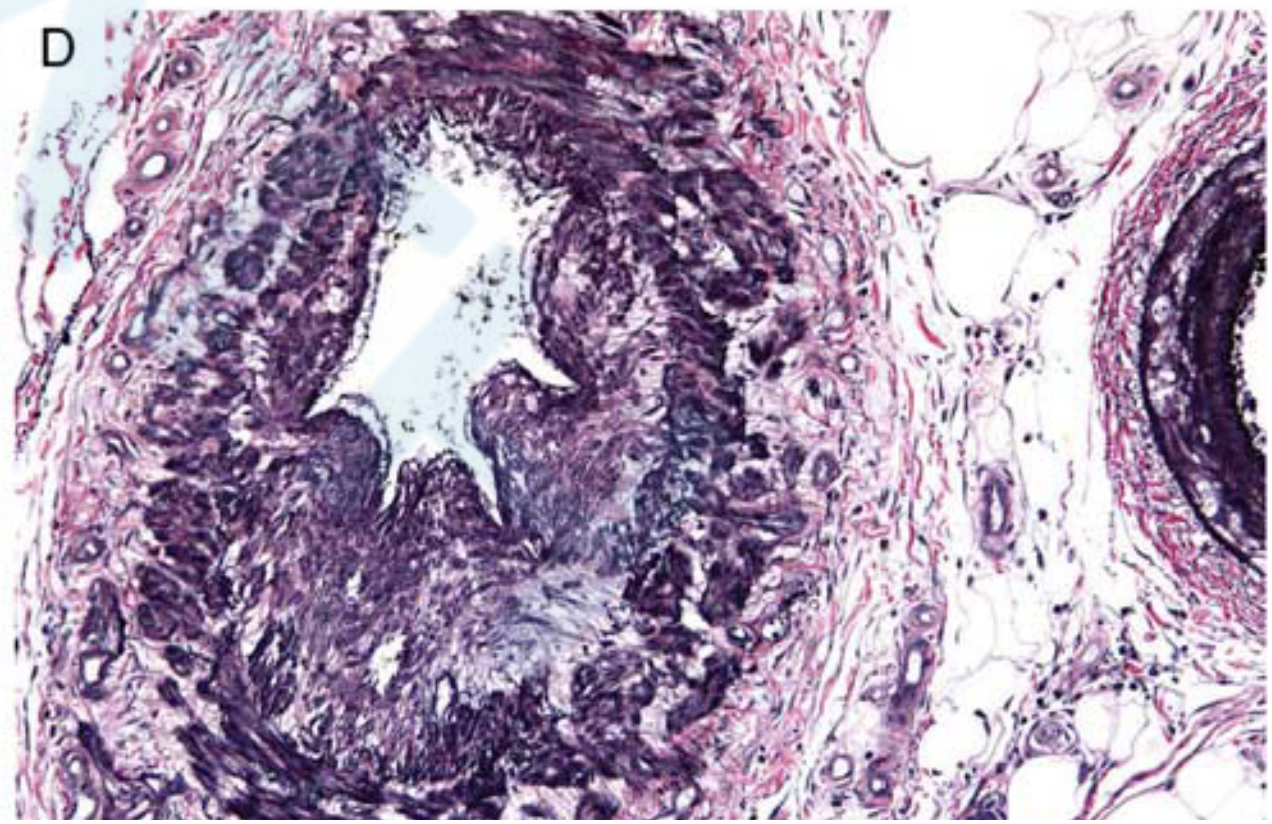

45	M	Veins	Idiopathic myointimal hyperplasia	Rectosigmoid	GI bleeding

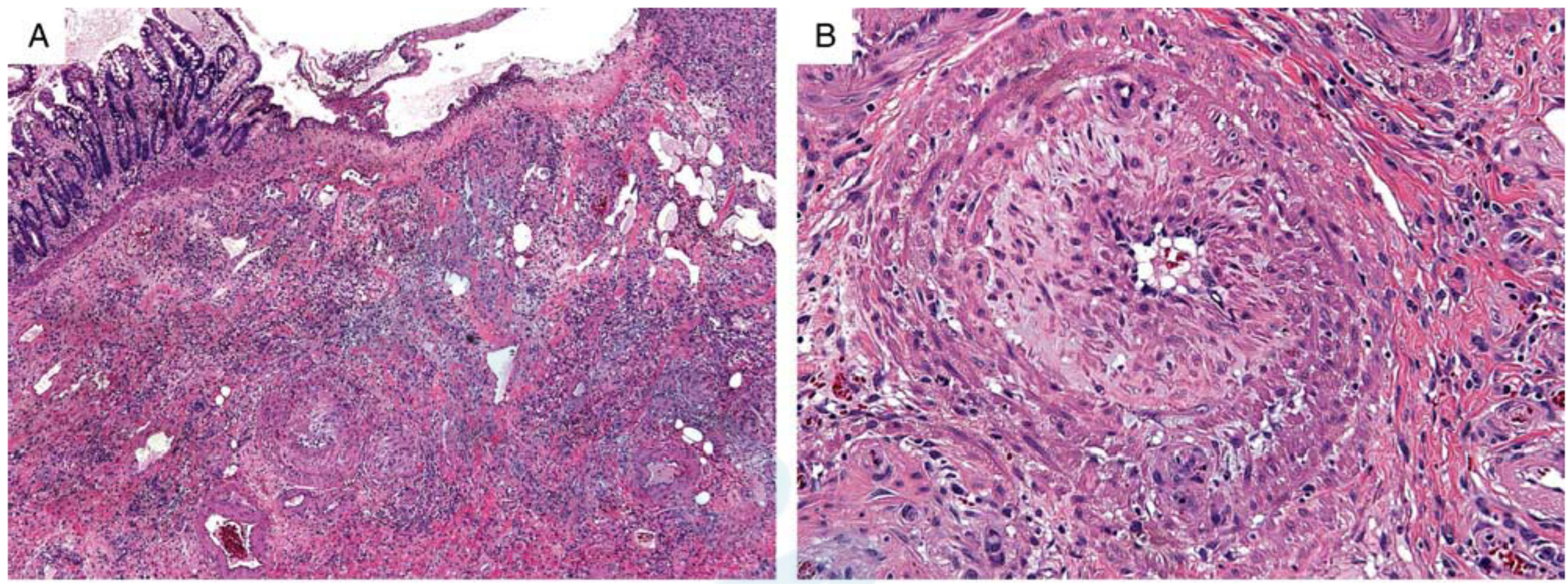

FIGURE 7. Small bowel resection from a 57-year-old woman with recurrent abdominal pain. A, Small bowel segment with mucosal sloughing .B,Submucosal vein showing occlusive myointimal thickening without mural inflammation .C, Elastin stain highlighting the minimal changes and absence of active vasculitic changes (EVG).

DISCUSSION

- Involvement of the GI tract by vasculitis is uncommon, but the ability of the pathologist to recognize a GI tract vasculitis may prove critical to avoid irreversible end-organ damage.

- The most common vasculitic disorders to involve the GI tract are immune complex mediated(systemic lupus, IgA vasculitis ,mixed connective tissue disease, and rheumatoid arthritis,among others) and drug-induced vasculitis.

1. SLE was the most common systemic disorder associated with GI vasculitis, followed by dermatomyositis.

- GI symptoms have been reported in up to 50% of SLE cases, with symptoms including nausea, vomiting, and abdominal pain.

- GI vasculitis has been reported to affect 35% of SLE patients presenting with acute abdomen, with a higher incidence of vasculitis (53%) in patients with active SLE.

- Biopsies of GI sites involved by SLE : variable histologic findings, affecting small to medium caliber arteries and/or veins, inflammation comprised of neutrophils, lymphocytes, plasma cells, and/or histiocytes.

- Fibrinoid necrosis and thrombosis , ischemic changes of the associated mucosa
- Fibrinogen deposition within vessel walls
- Deposition of IgG, IgA, and IgM within the surface epithelial basement membrane of adjacent mucosa

2. Dermatomyositis is a subset of the idiopathic inflammatory myopathies, diagnosis of which requires a combination of signs and symptoms , clinical manifestations , laboratory parameters, and histologic features of muscle biopsy

- Microscopic characteristics of GI involvement in dermatomyositis : nonspecific acute colitis with vascular ectasia , vasculitis or vasculopathic changes with associated ulceration and perforation.

- Vasculitis has been reported more frequently in juvenile dermatomyositis.

3. Wegener granulomatosis rarely shows GI involvement

- Granulomatous vasculitis is characteristic (but may not always be seen in the GI biopsies), sometimes with associated necrosis, usually involving small and medium caliber vessels.
- Severe cases may result in mucosal ulceration , ischemic changes ,perforation and mortality.
- Endoscopic findings may be nonspecific, the clinical picture may mimic inflammatory bowel disease, laboratory studies (specifically, serology for ANCA)will be usefull.

4. EGPA (Churg-Strauss syndrome) is a vasculitis of small and medium caliber vessels, characterized by marked eosinophilia and the presence of asthma

- Histologic examination typically reveals a necrotizing vasculitis with histiocytes and occasional giant cells within the vessel walls, accompanied by an eosinophilic infiltrate surrounding the vessels
- This diagnosis should be considered in a patient presenting with perforation, ischemia, or multiple small intestinal ulcers
- The identification of a granulomatous vasculitis with associated eosinophilic infiltrates is helpful

5. Isolated GI tract vasculitis is classified as“single organ vasculitis,” which is defined as vasculitis of arteries or veins restricted to a single organ without evidence of an accompanying systemic vasculitis(Under the 2012 Chapel Hill consensus nomenclature)

- In our series, the most common form of isolated vasculitis in the GI tract was enterocolic lymphocytic phlebitis followed by idiopathic myointimal hyperplasia.

- Surgical resection is curative.

6. Enterocolic lymphocytic phlebitis is characterized by a lymphocytic phlebitis that involves small and medium caliber veins

- Most cases occur in older adults (median age, 63 y), often with underlying disease (cardiovascular disease, hypertension, renal failure, malignancy, etc.), and the right colon and/or small intestine is typically affected.

- Patients typically present with signs of an acute abdomen (acute abdominal pain,nausea,vomiting, diarrhea, and rectal bleeding)

- Although various degrees of myointimal hyperplasia may also be seen, there is almost always some degree of lymphocytic venulitis, which may be necrotizing or granulomatous

7. Idiopathic myointimal hyperplasia occurs predominantly in middle-aged, previously healthy men and affects the left colon and rectum

- Patients present with complaints of several months (mean,5.3mo) of abdominal pain and bloody diarrhea

- Up to 70% of patients may be misdiagnosed with inflammatory bowel disease before surgical intervention

- There is no venous inflammation; rather, there is a striking narrowing of the lumens of medium and large caliber intramural and mesenteric veins by profound myointimal hyperplasia.

- The presence of arteriolized capillaries, subendothelial fibrin deposits, and perivascular hyalinization may suggest the diagnosis in biopsy specimens.

Conclusion

- A variety of systemic vasculitic disorders are associated with GI manifestations, bona fide GI tract vasculitis is rare,and the diagnosis may be difficult

- Patients present with varied symptoms , and workup for inflammatory bowel disease or malignancy is often initiated

- Endoscopic biopsies have a low sensitivity to diagnose GI vasculitis

- Clinical history, including concurrent disease, renal function, skin rash, lung symptoms,serum Ig profile, tissue immune complex status,and medication history is required

- Extensive sampling of the resection specimen including areas of viable bowel and/or mesentery should be obtained to ensure that there is unequivocal vasculitis present

- Elastic stain is recommended to identify vessel type and confirm vessel damage

- Isolated GI tract vasculitis or vasculopathy is rare,the chief primary vasculopathies are enterocolic lymphocytic colitis and idiopathic myointimal hyperplasia


Thank
You!