Gastrointestinal Vasculitis

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Goal

Classification

Epidemiology

Characteristics

Management of GI Manifestations of Systemic Vasculitis

The Five Factor Score (FFS)?

1. Cardiomyopathy
2. CNS involvement
3. Severe GI Symptoms (?)
4. Renal failure (Cr > 140mmol/L)
5. Proteinuria (> 1g/d)

Polyarteritis Nodosa,
Microscopic Polyangiitis
Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Guillevin, L. et al. Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 75, 17–28 (1996)

- Systemic Vasculitis are caused by;
  - -inflammation of blood vessels, any organ and any part of the GI tract,
  - -most commonly mesenteric, hepatic
  - -classified by the type and size of the involved vessels

- Inflammatory changes, in different layers of arterial vessel walls can lead;
  - -aneurysmatic dilatation,
  - -blood vessel occlusion,
  - -organ ischemia,
  - -lead to mucosal ulcerations,
  - -GI bleeding,
  - -perforations,
  - -or bowel obstruction

Vasculitis Classification

Large vessel vasculitis

- Takayasu arteritis
- Giant cell arteritis

Medium vessel vasculitis

- Polyarteritis nodosa
- Kawasaki disease

Small vessel vasculitis

- ANCA-associated vasculitis
  1. Granulomatosis with polyangiitis (Wegener's disease)
  2. Microscopic
  3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
- IgA vasculitis (Henoch– Schönlein purpura)
- Cryoglobulinemic vasculitis

Variable vessel vasculitis

- Behçet's disease

Vasculitis with systemic diseases

- Systemic lupus erythematosus
- Rheumatoid vasculitis

Single-organ vasculitis

Large Vessel Vasculitis

Takayasu arteritis

- As a “pulseless disease”; is a chronic large vessel vasculitis of unknown etiology

- Takayasu arteritis predominantly affects the;
  - -aorta, subclavian and common carotid arteries
  - -stenotic lesions are found in >90% of patients,
  - -and aneurysms in ~25% of patients

Epidemiology

- Takayasu arteritis predominantly affects young females in their 20s or 30s and is most common in Japan, Southeast Asia, India and Mexico
- In 2012, the prevalence in Japan was >40 cases per million
- The incidence in North America is 1–3 cases per million, much lower than in Asia

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Gastrointestinal features

- GI manifestations of Takayasu arteritis are rare and occur mainly in the;
  - -small bowel or large bowel, spleen,
  - -or more rarely, as liver ischemia due to stenosis,
  - -or occlusion of large or medium GI arteries

For example

- *Chronic ischemic colitis,* in patient with Takayasu arteritis;
  - -MRA of the aorta and abdominal branches showing;
  - -severe narrowing of the infra-renal aorta
  - -complete occlusion just distal to the origin of the IMA



Management

- Cs (0.5–1.0 mg/kg/day followed by a gradual taper)
- MTX (15–25 mg/week) remains the first line Cs-sparing agent
- Cyclophosphamide (2 mg/kg/day orally)
- Cellcept (1–3 g/day) have been used for refractory cases
- Anti-TNF agents for refractory Takayasu arteritis, (IFX and ADA)
- Tocilizumab was also effective in a series of 49 patients with Takayasu
- Open surgery and endovascular *(celiac or mesenteric artery stenosis)* treatments might be needed

Case 1

- 76 years old female presents with painful tongue ulcer, abdominal pain and headaches

  PE: Periumbilical and epigastric bruit

What is your diagnosis?





Giant Cell Arteritis

Mesenteric vessel involvement very rare

12 cases in the literature

More often

Tongue necrosis (dysphagia, pain, edema / gangrene)

Abdominal aortic aneurysm (duration time 6-7y)

Liver enzyme abnormalities (10-50%)

Giant Cell Arteritis

Epidemiology

- GCA is the most common form of systemic vasculitis in elderly patients
- GCA incidence increases with;
  - -age, (peaks at 70–80 years)
  - -10 times more common in patient with 80y compared to patients in 50y

- GCA is most common in Western countries and mainly affects white race

Gastrointestinal features

- A systematic review of the literature found only 12 GCA cases;
  - -75% with a positive temporal artery biopsy result
  - -mesenteric involvement resulting in small bowel infarction
  - -more than 50% of patients had both cranial and abdominal symptoms
  - -abd-pain in GCA patients, due to abd-aortic aneurysm and dissection
  - -all GCA patients should be screened for aortic aneurysm at period of 5ys

- 1/3 to 1/2 of patients with GCA show asymptomatic abnormal liver ENZ;
  - -elevated Alp, and mildly raised Ast, Alt level in 10–40% of patients

Management

- Similar to Takayasu arteritis;
  - -Cs are the cornerstone of treatment for GCA,
  - -immunosuppressant in case of severe GI manifestations,
  - -and surgery and/or endovascular procedures if needed

- Patients with GCA tend to be older than those with Takayasu arteritis, therefore morbidity and mortality are high

- Adjunctive MTX treatment can reduce the relapse rate

- Tocilizumab seems more effective on patients with GCA'
  - -85% of patients achieved sustained remission at 1 year,

Case 2

55 years old man with abdominal pain, and right flank pain, fever, malaise and weight loss

Routine lab non specific

CT Scan: Focal renal infarction

Angiography





Medium-Sized Vessel Vasculitis

Polyarteritis Nodosa

- PAN is a systemic necrotizing vasculitis first described in 1866 by Adolf Kussmaul and Rudolph Maier

- One hallmark of Polyarteritis Nodosa is the;

  -existence of narrow, tapered arteries

  -with saccular, or fusiform microaneurysms on CTA or MRA,

  -in up to 85% of patients with PAN,

  -predominantly in the mesenteric, renal and/or hepatic arteries

- PAN is a necrotizing focal and segmental vasculitis due to;

  -deposition of circulating immune complexes causing edema, inflammation,

  -and vessel wall necrosis

- PAN may present as;

  -an idiopathic primary form (less frequently),

  -or it may be secondary form to;

  *HBV infection,

  *systemic rheumatic diseases,

  *autoimmune inflammatory diseases,

  *malignancies such as hairy cell leukemia

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Epidemiology

- PAN is most common in men in their 50-60 years

- GI involvement in PAN is frequent, *(in 14% to 65% of Vasculitis patients)*

- Annual incidence of PAN was;

    -0-8 cases per million in European countries, Australia in the 2000s

- Decreased prevalence of HBV infection following (vaccination or improved blood transfusion)

Gastrointestinal features

- Severe GI involvement;
  - -bleeding, perforations, infarction,
  - -and necrosis *(transmural ischemia),*
  - -or pancreatitis

- Abdominal pain(35–95%) is often described as;
  - -postprandial pain and the term “intestinal angina” is frequently used

- In these instances, colonoscopies carry a much higher risk of perforations

- Angiography is a primary modality to confirm the diagnosis of PAN

- Abdominal pain is secondary to;
  - -transmural necrotizing inflammation of the mesenteric vessels,
  - -leading to bowel ischemia,
  - -most commonly in the small bowel (jejunal ulcer)

- Other symptoms include;
  - -nausea, vomiting, diarrhea, hematochezia, melaena
  - -and hematemesis

- Ulcers are found in 5–6% of patients with PAN, mainly in the jejunum

Management

- The 5 year survival for patients with polyarteritis nodosa exceeds 80%

- For severe forms including severe GI manifestations;
  -cyclophosphamide are recommended for induction,
  -followed by AZA, or MTX for maintenance

- The treatment of HBV-associated vasculitis relies on antiviral drugs

Case 3

19 years old man, informatics student from Japan

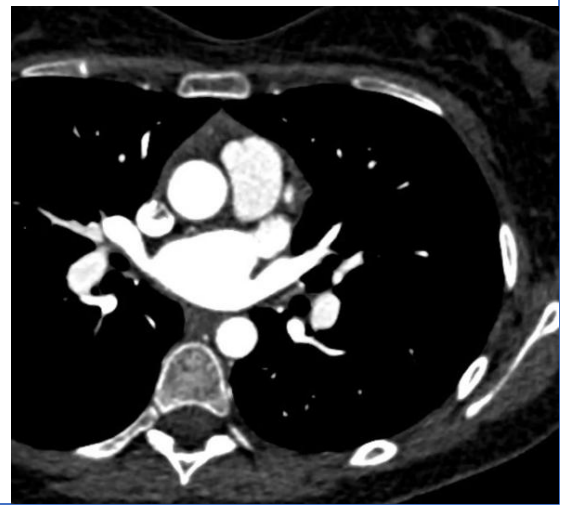
History of some kind of vasculitis…. medical reports

Referred to ER due to acute abdominal pain and vomiting

On day 2 develops acute chest pain

CTA

What is your diagnosis?



Kawasaki disease

Kawasaki disease is;

-a mucocutaneous lymph node syndrome,

-associated with medium artery involvement,

-possibly including the coronary arteries

Epidemiology

- Mostly seen in young children, with>80% in children 6 months to 4 years
- More prevalent in Asian populations, especially in Japan
- Annual incidence rate in 2012 was 265/per 100,000 children<5 years old
- North America, Australia and Europe, 4–25/100,000 children <5 years

Gastrointestinal features

- In a series of 198 children with Kawasaki disease;

  -61% had GI symptoms (abdominal pain, nausea and vomiting) 10 days before the Kawasaki disease diagnosis

- In another cohort of 219 children with Kawasaki disease;

  -10 (4.6%) presented with more severe abdominal symptoms

  -gallbladder hydrops 5-20%,

  -paralytic ileus, appendicular vasculitis

  -and/or hemorrhagic duodenitis

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Management

- Standard treatment consists of aspirin and IVIGs (2 g/kg BW), which reduces the risk of coronary artery aneurysms from 4 to 20%

- The effect of Cs on coronary artery abnormalities been recommended in children with refractory disease

- Other rescue therapies to consider include;

    -infliximab, IL-1 antagonists, plasma exchange

    -and cyclophosphamide

Small Vessel Vasculitis

ANCA Associated Vasculitis (AAV)

-Granulomatosis with Polyangiitis (Wegener)

-Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss)

- AAV are necrotizing vasculitis that predominantly affect small vessels;
  - -capillaries, venules, arterioles and small arteries
  - -with few or no immune deposits

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Granulomatosis with Polyangiitis (GPA)

- GPA commonly involves the upper and lower respiratory tracts and kidneys
- GPA is typically associated with ANCA

Epidemiology

- The global annual incidence of GPA is estimated at 2–15 cases per million, with the lowest incidence reported in Japan
- The global prevalence is 23–160 cases per million
- The disease is rare in non-white individuals and peaks at 55–65 years old

Gastrointestinal features

- GI symptoms are observed in 5–11% of patients with GPA

- Autopsy identified; histopathological evidence of GI vasculitis in up to 24%

- Any part of the GI tract can be involved but the small and large bowel are most common; symptoms range from;
  - -transient abdominal pain, and ulcerations (oral, upper GI)
  - -to bloody diarrhea and intestinal perforations

- GI imaging findings are usually nonspecific, ranging from;
  - -multifocal or diffuse bowel wall thickening,
  - -to mesenteric vascular engorgement
  - -and ascites

- Compared with CD;

  -ulcers seen in GPA are more typically shallow and transversely

- Colon ulcers biopsy might have a slightly increased sensitivity (~30–40%) if;

  -deep ulcers

  -submucosal

  -deep biopsy have a high risk of perforation in vasculitis patients

- Granulomatous cholecystitis, Granulomatous pancreatic mass, and Liver Granulomas may be seen

Case 4

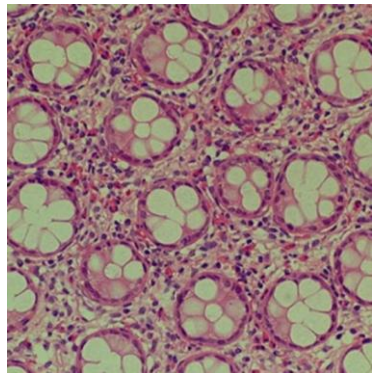
52 years old male presents with worsening abdominal pain

History of new onset worsening episodic Dyspnea (Wheezing), and Peripheral Eosinophilia

CT Scan: Bowel wall thickening

Colonoscopy: Patchy mucosal erythema sigmoid colon to the splenic flexure

What are your differential diagnosis?





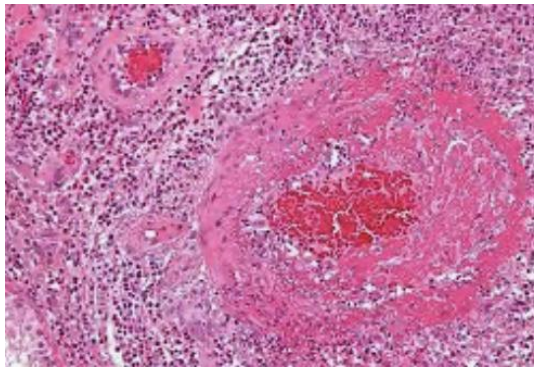
Eosinophilic Granulomatosis with Polyangiitis

- The mean age at diagnosis is 34–54 years
- Late-onset asthma + eosinophilia
- Vasculitis manifestations skin purpura
- Mononeuritis multiplex,
- Only 30–40% of patients have serum ANCAs
- Cardiac involvement, more common in ANCA-negative patients (main mortality risk factor)

Epidemiology

-annual incidence is 0.8–2.8 cases per million

-prevalence is 7–22 cases per million



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GI Involvement in 30–50%

- Abdominal pain (91%), overt bleeding (19–36%), acute abdomen (6–36%)

- Mesenteric artery vasculitis is the most common;
  -can lead to bowel infarction, and perforations, particularly in the small intestine

- GI tract mucosal infiltration by eosinophils can;
  -also cause pain, motility disorders, obstructive symptoms
  -as seen in eosinophilic esophagitis, gastritis or colitis
  -eosinophilic gastroenteritis: nausea and vomiting (18%) - diarrhea (45%)

- Granulomatous and eosinophilic mucosal ulcerations are potential sources of bleeding in;
  -the stomach, duodenum, jejunum, and more rarely, in colon,

- The coexistence of EGPA and IBD has been reported

Management of AAV

- Patients with severe GI manifestations must promptly receive Cs combined with another potent immunosuppressant such as;

  -cyclophosphamide

  -combination of Cs and another immunosuppressant

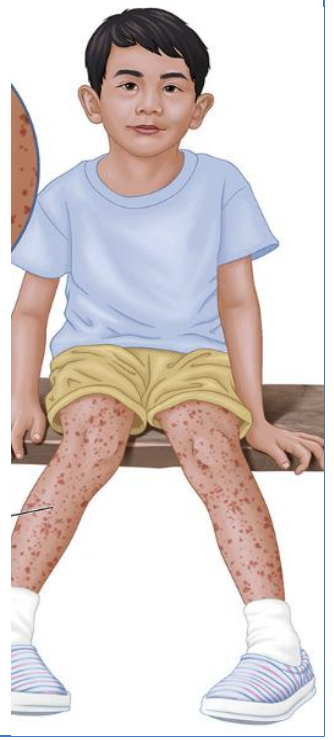
  -rituximab (375 mg/m2 body area, weekly for 4 weeks)

Case 5

- 8 years old boy presented with abdominal pain and skine eruption

What is your diagnosis?





Other Small-Vessel Vasculitis

- Immune-complex small-vessel vasculitis are characterized by;

  -vessel wall inflammation with deposits of immunoglobulins

  -and/or complement

IgA Vasculitis

Epidemiology

- IgA vasculitis (***Henoch Schönlein Purpura***) can develop at any age but is most common in children between 3–10 years old
- Incidence is 2–3 cases/100,000 children and 0.1–1.8 cases/100,000 adults
- The male: female ratio is 1.5:1.0 and the disease is rare in black populations

Gastrointestinal features

- Overall, 50–75% of patients with IgA vasculitis have GI manifestations
- Abdominal pain is the presenting symptom in up to 20% of patients
- GI bleeding due to mucosal and submucosal vasculitis (in 18–52%)
- The duodenum is most commonly involved (and then Descending Colon)
- Esophageal involvement is;

    -rare and can present with ulcers, strictures or severe esophagitis

- Endoscopic findings can reveal;

    -petechial lesions, diffuse mucosal redness

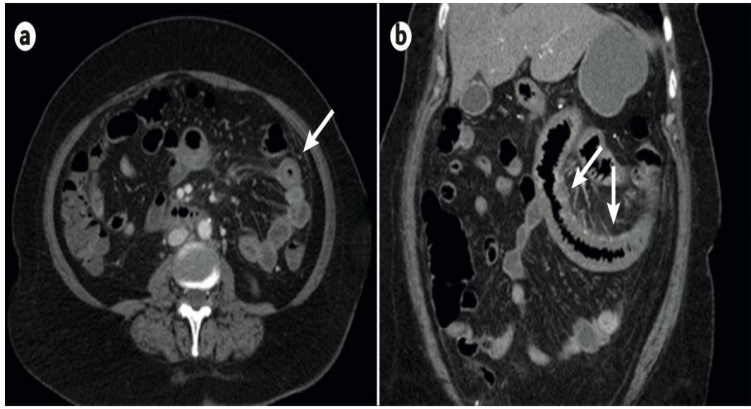
    -and hemorrhagic erosions

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- Most GI manifestations are self-limited
- 3–5% of patients show;
  - -bowel wall edema (on abdominal CT) infarcts, necrosis, perforations
  - -or intussusception

- Other rare manifestations include;
  - -protein losing enteropathy, pancreatitis, cholecystitis and appendicitis

- Hepatobiliary involvement was noted in 1.8% of 225 children with IgA vasculitis, who had;
  - -RUQ pain (80%), elevated transaminase (75%),
  - -hepatomegaly on ultrasonography (75%)
  - -and gallbladder wall thickening (25%)



Management

- IgA vasculitis is usually benign and self-resolving in a few weeks
- Recurrence is more common in patients with renal involvement
- Cs should be used for patients with abdominal manifestations
- Mycophenolate mofetil or Rituximab can help achieve remission in some patients who do not respond well to Cs
- Overall, 5–12% of patients require laparotomy due to intussusception, bowel perforations and/or severe bleeding

Case 6

32 years old with new diagnosis Hepatitis C presents with pain and rash in the upper and lower extremities

What is your diagnosis?

- **Lab tests?**
- **Treatment?**

Cryoglobulins

- Cryoglobulins are circulating immunoglobulins at <37 °C

Lab tests

- Low complement C4 with normal C3
- Positive RF would strongly suggest the presence of cryoglobulins
- Cryoglobulins themselves difficult to detect

Main involvement

- Skin, Kidneys and/or peripheral nerves

Cryoglobulinemic vasculitis

- Three subtypes of cryoglobulins have been described:

  -type I refers to a single monoclonal immunoglobulin, usually related to underlying lymphoproliferative disorder

  -type II is composed of both polyclonal IgG and monoclonal immunoglobulin

  -type III are polyclonal immunoglobulins

- Cryoglobulinemic vasculitis is mainly observed with;

  -type II and III cryoglobulins, can affect the skin, kidneys and peripheral nerves

Epidemiology

- Cryoglobulinemic vasculitis is most common;
  - -in patients in their mid-50s, and
  - -with a male : female ratio of 3:1

- HCV infection is the main cause of mixed Cryoglobulinemia in up to 98% of cases

- Up to 50% of patients with HCV infection have circulating cryoglobulins

- Vasculitis develops in only 5–10% of Cryoglobulinemic patients

- Other causes of cryoglobulinemia and cryoglobulinemic vasculitis include;
  - -HBV and HIV infection,
  - -autoimmune disorders such as Sjögren syndrome
  - -and lymphoma

Gastrointestinal features

- GI involvement in cryoglobulinemic vasculitis is rare

- GI symptoms range from;
  -abdominal pain and bloody stools to intestinal perforations,
  -intestinal ischemia, acute cholecystitis and pancreatitis

- Liver involvement is observed in
  -up to 60% of HCV-infected patients with cryoglobulinemic vasculitis,
  -25% showing progression to cirrhosis
  -HCC is seen less frequently in HCV patients with cryoglobulinemic vasculitis

Management

- Treatment is guided by the underlying disorder such as;
  - -HCV infection
  - -or lymphoma
  - -and cryoglobulinemic vasculitis severity

- New anti viral therapies are the cornerstone of treatment for virus cryoglobulinemic vasculitis

- Rituximab can also be used with antiviral agents to induce remission in severe disease

- Cs might be useful in non-HCV cryoglobulinemic vasculitis

Case 7

45 years old man

Recurrent abdominal pain, diarrhea and oral aphthous lesions, ER visit, suspicion of CD, calprotectin 982 mg/Kg, presents with new ocular inflammation

Colonoscopy showed a large ulcer with elevated margins in the terminal ileum

What is your Differential Diagnosis?





VARIABLE VESSEL VASCULITIS

- Vessels of any size in the venous and arterial circulation can be affected in variable-vessel vasculitis include;

  -Behçet's disease

Behçet's disease

- Typical clinical manifestations include;

  -recurrent oral and genital ulcerations,

  -eye lesions *(anterior or posterior uveitis or retinal vasculitis),*

  -skin lesions *(EN, PG-like lesions, papulopustular lesions, or pseudo-folliculitis),*

  -vascular involvement *(arterial thrombosis, large vein thrombosis, aneurysms),*

  -and positive pathergy test

  -thrombotic and/or CNS inflammatory lesions

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Epidemiology

- Behçet's disease is most common in Asia and Mediterranean regions

- The prevalence in;
  - -Turkey is 80–420 /100,000
  - -Asian countries 13.5–85/100,000
  - -Western counties 0.12–0.64/100,000
  - -Iran prevalence 80-100/100000, (GI manifestation of BD 6.8%)

- The male: female ratio varies by region;
  - -males most commonly affected in Mediterranean and Asian countries,
  - -females most commonly affected in the USA and Northern Europe

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Gastrointestinal features

- Reported frequencies of GI involvement in Behçet’s disease;
  - -2.8% of patients in Turkish,
  - -32% in Taiwan,
  - -37–43% in the USA
  - -50–60% in Japan
  - -6.8-10% in Iran

- Two types of GI involvement have been described:
  - -Intestinal ischemia and infarction secondary to large vessel vasculitis,
  - -and mucosal ulcers from neutrophilic infiltrates that can mimic IBD

- Behcet's can affect any segment of the GI tract;
  - -ileocecal involvement being the most common
  - -deep ulcers were more common than superficial (68% *vs.* 38%)

- Significant rectal involvement in Behcet's to be extremely rare (< 1%)

- Diagnosis of Behcet’s remains challenging, it is difficult to distinguish CD from Behcet’s syndrome;

  -both diseases may present with EIMs that can overlap

  -and both have chronic waxing and waning course

- There is no standardized treatment for GI Behcet’s disease

- Like in patients with IBD, surgical interventions are indicated in those patients who develop;

  -bowel perforation, fistula formation, intestinal obstruction, GIB

  -or abdominal mass, those who are refractory to medical therapy

- As for GI vascular involvement such as;

  -arterial aneurysms, an endovascular approach

  -or surgical repair continues to be the preferred method

- For those with hepatic vein or IVC thrombosis, medical treatment with cyclophosphamide and Cs has been recommended

- Any part of the GI tract can be involved;

  -most commonly the terminal ileum and ileocecal junction

- Esophageal ulcers are most often found in the inferior part of the esophagus

- Esophageal varices have also been reported in patients with occluded vena cava

- Gastric involvement includes ulcers and pyloric stenosis

- In the colon, three types of ulcers have been described:

  -Volcano ulcers have the highest risk of perforation, especially in<25y old patients

  -geographic ulcer

  -and aphthous ulcer

- ***Rectal and/or anal involvement is rare***

- Budd –Chiari syndrome affects 1.3–3.2% of patients with Behçet's disease, especially young males

Management

- Colchicine is the cornerstone treatment for oral and genital ulcers
- Other agents are often required for GI manifestations, such as;
    - -Cs, sulfasalazine, AZA
    - -or, for more severe cases, cyclophosphamide
    - -or eventually anti-TNF agents, such as IFX or ADA

- Surgery can be required for perforations, fistulas or obstruction

- The rate of disease recurrence at the site of anastomosis is high

- The use of anticoagulation therapy for Behçet's disease related;
    - -venous thrombosis remains debated,
    - -but a potent immunosuppressive treatment is mandatory

Vasculitis with systemic diseases

Systemic lupus erythematosus

- GI manifestations are common in patients with SLE

- GI manifestations of SLE;
  - -affect 1.3–27.5% of patients

- The prevalence of vasculitis in SLE;
  - -is 11–36% of patients,
  - -and is mainly cutaneous

- Mesenteric vasculitis prevalence;
  - -is less, at 0.2–9.7%, predominantly affecting the SMA
  - -resulting in ischemia of the ileum
  - -and in jejunum with risk of perforations and hemorrhage

- Treatment of SLE-associated mesenteric vasculitis includes;
  -high-dose Cs and complete bowel rest

- Cyclophosphamide is added;
  -when other major organs are involved (for example, CNS or GN)
  -or in case of intestinal necrosis
  -or persistent abdominal pain despite Cs treatment

- Remission is achieved in 85% of patients

- Relapse rate is 23% at 1 year, but relapse lower in patients on Cs and cyclophosphamide

- Surgical intervention is required in patients with large intestinal necrosis or perforation

- Mortality is up to 50% in patients with perforations

Rheumatoid Vasculitis

- Rheumatoid vasculitis can develop in patients with long standing (usually 10–15 years) erosive RA

- Rheumatoid vasculitis usually involves vessels of small and medium size and is associated with poor prognosis:

  -mortality is ~25% at 5 years

- In 10–38% of patients with rheumatoid vasculitis have GI involvement, can result in;

  -ischemic ulcers, perforations

  -and segmental or extensive bowel infarction

- Similar to SLE, Cs and cyclophosphamide are commonly used to treat severe rheumatoid vasculitis

Gastrointestinal Vasculitis Mimickers

- IBD can mimic;
  - -AAV or Behçet's disease
  - -and is occasionally associated with vasculitis

- Eosinophilic esophagitis, gastritis and colitis fall within pathogenic spectrum of;
  - -hyper-eosinophilic syndrome,
  - -or *Eosinophilic Granulomatosis with Polyangiitis* remains unclear

- IgG4-related disease can cause various GI manifestations, including;
  - -aortitis
  - -periaortitis with involvement of GI arterial branches of the aorta,
  - -or enterocolic lymphocytic phlebitis

Summary

- GI manifestations are rarely the features of Systemic Vasculitis
- GI manifestations rapidly life threatening
- Small Vessel Vasculitis can cause various GI manifestations, including;
  - -mucosal purpura (risk of hemorrhage),
  - -patchy granulomatous
  - -or ischemic ulcerations that can mimic IBD and can perforate

- Liver involvement is rarely clinically significant in systemic vasculitis;
  - -rare infarcts due to large or medium-sized vasculitic occlusions,
  - -and Budd–Chiari syndrome in patients with Behçet's disease