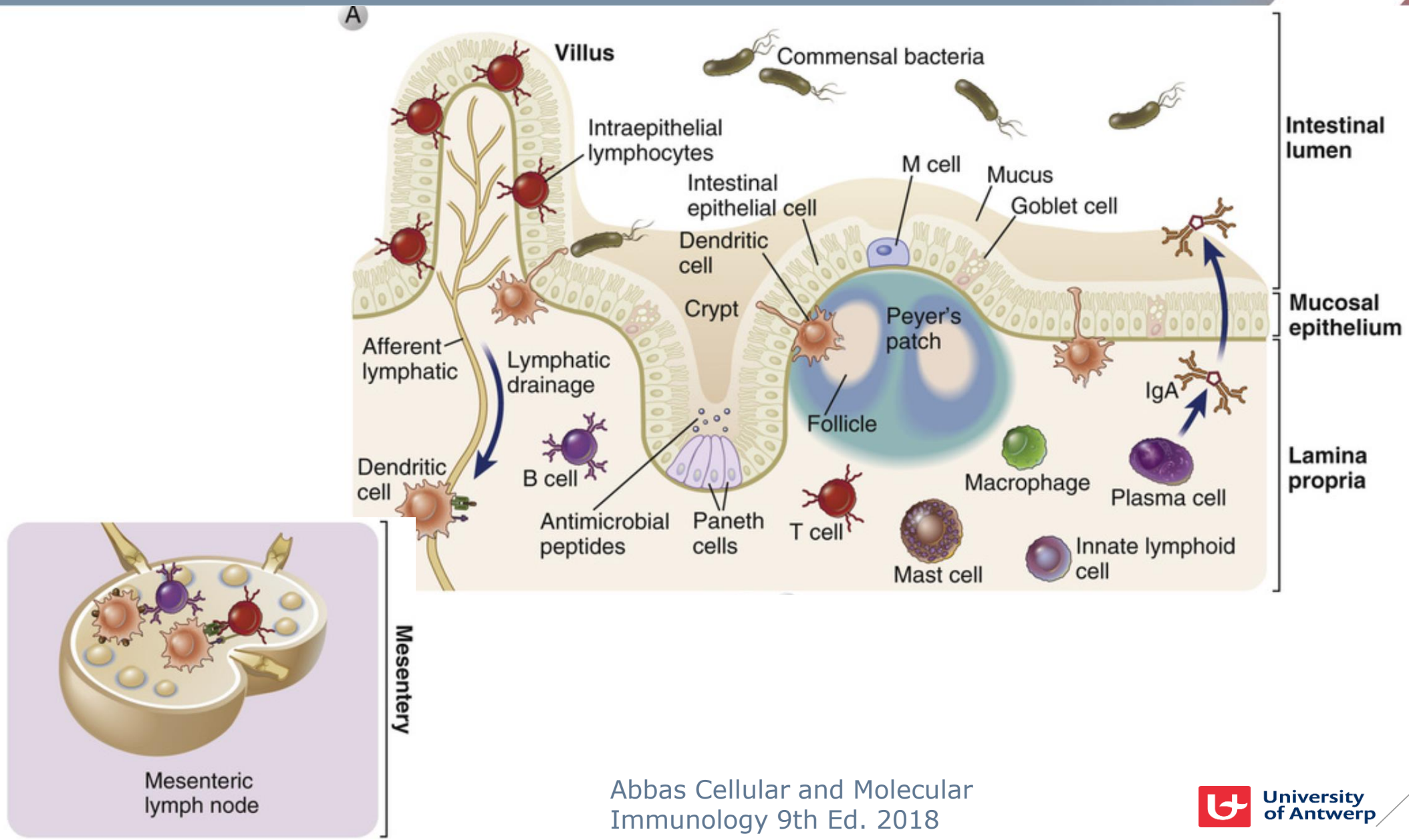
Histiocytic disorders / Granulomas of the gastrointestinal tract

Prof. Dr. A. Driessen
Dept. of Pathology
University Hospital Antwerp
University Antwerp

Gert De Hertogh, Charlotte Schepers
Pathology UZLeuven

HISTIOCYTIC DISORDERS OF THE GI TRACT : OVERVIEW



Abbas Cellular and Molecular Immunology 9th Ed. 2018

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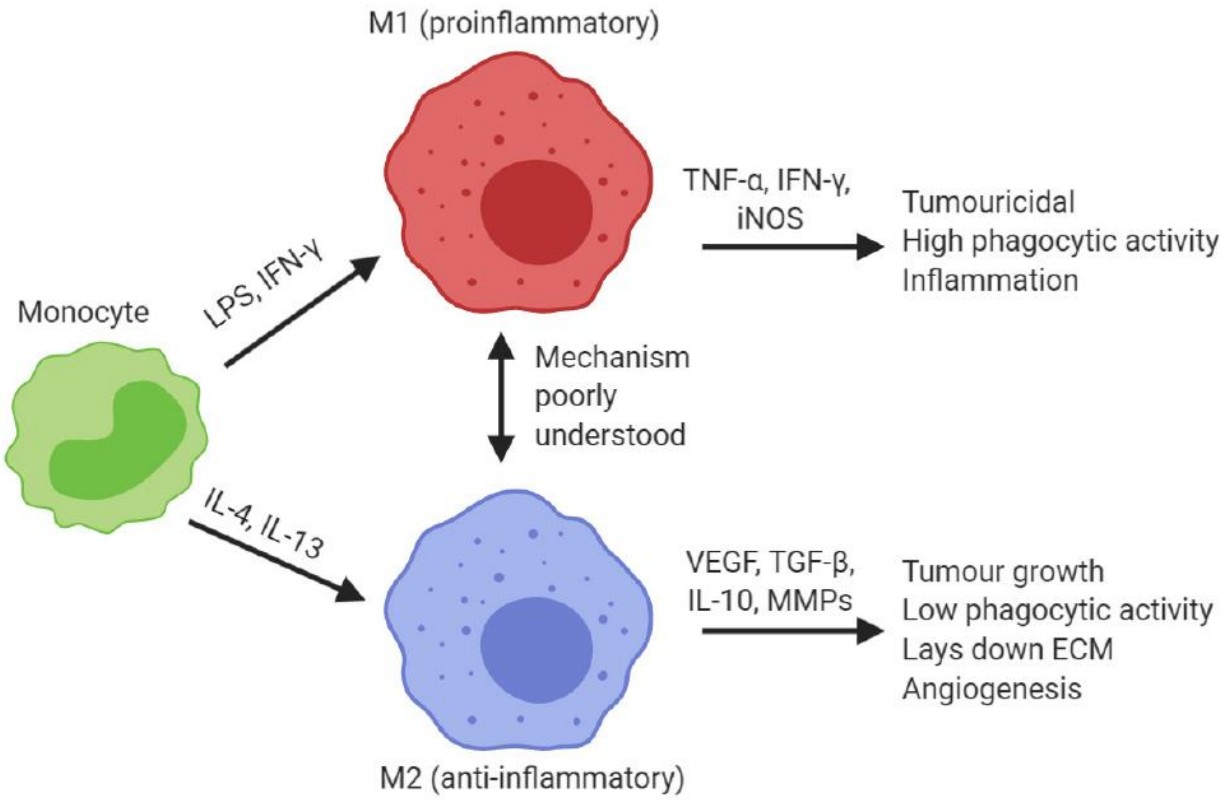
Macrophages/Histiocytes

- Part of innate immune system
- Origin:
  - Embryonal: Liver, yolksac
  - Postnatal: Bone marrow



Histiocytic disorders of the GI tract

Table 18-27 Disorders Associated with an Excess of Abnormal Histiocytes/ Macrophages

- Pigmented macrophages
  - Pseudomelanosis (lipofuscin)
  - Chronic granulomatous disease
  - Hermansky-Pudlak syndrome
  - Aluminum/silicate/titanium
- Iron-containing macrophages
  - Iron ingestion/Iron-containing pills
  - Hemochromatosis
  - "Melanosis" duodeni
  - Following hemorrhage
- Muciphages
- Xanthelasma
- Infections
  - *Mycobacterium avium-intracellulare*
  - Whipple's disease
  - *Yersinia*
  - Fungal infections
- Diseases associated with granulomas
  - Crohn's disease
  - Behcet's disease
  - Mycobacteria
  - *Chlamydia*
  - Others
- Storage disorders
  - Wolmann's disease
  - Neutral lipid disorder
- Malakoplakia and xanthogranulomatous disease
  - Primary
  - Secondary (usually to carcinoma, diverticular disease)

Macrophage-related diseases of the gut: a pathologist's perspective

Xavier Sagaert · Thomas Tousseyn · Gert De Hertogh · Karel Geboes

Virchows Arch (2012) 460:555–567
DOI 10.1007/s00428-012-1244-9

Histiocytic disorders of the gastrointestinal tract

Sönke Detlefsen MD, PhD[a,b,*], Christina R. Fagerberg MD[c], Lilian B. Ousager MD, PhD[c], Jan Lindebjerg MD[a], Niels Marcussen MD, DrMedSc[b], Torben Nathan MD[d], Flemming B. Sørensen MD, DrMedSc[a]

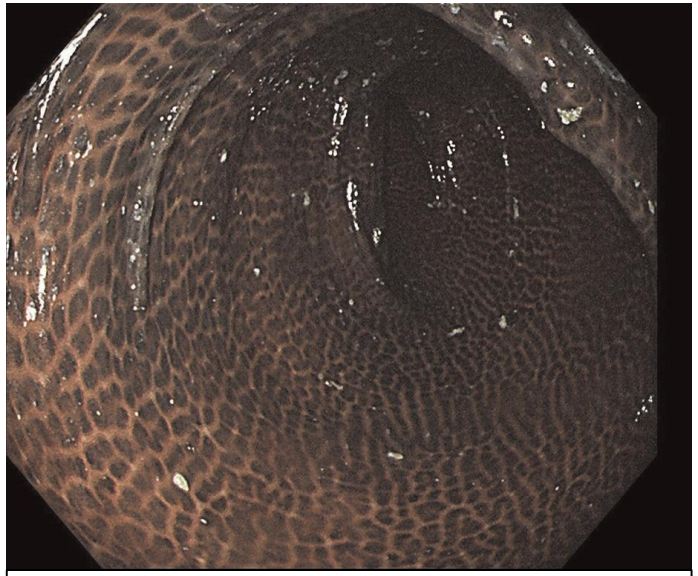
Human Pathology (2013) **44**, 683–696

Lewin, Weinstein and Riddell's GI Pathology

PIGMENTED MACROPHAGES

(PSEUDO)MELANOSIS COLI

- Brown discoloration of the mucosa
- Accumulation of lipofuscin pigment in macrophages
- Main cause : habitual use of laxatives containing anthraquinone glycosides
- Increase in colonic epithelial apoptosis (chronic constipation)



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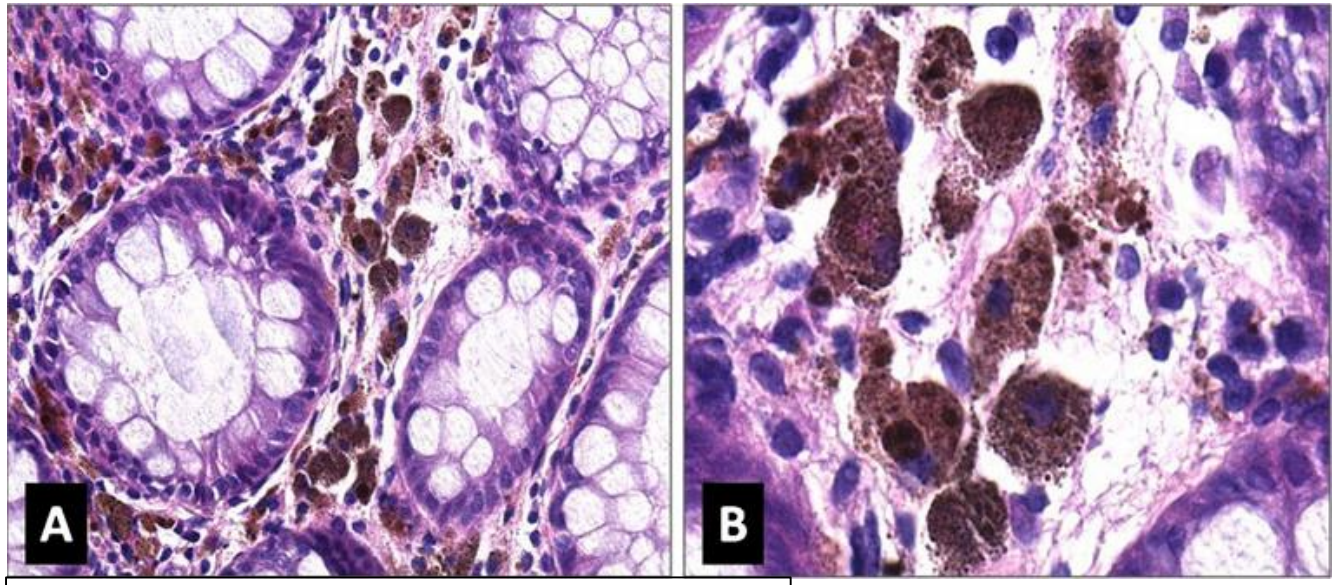

(a) 400x, (b) 1000x PMID: 22576700

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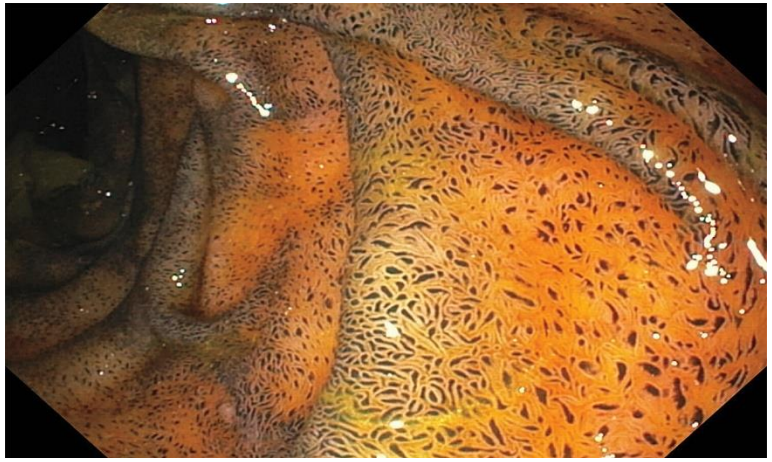
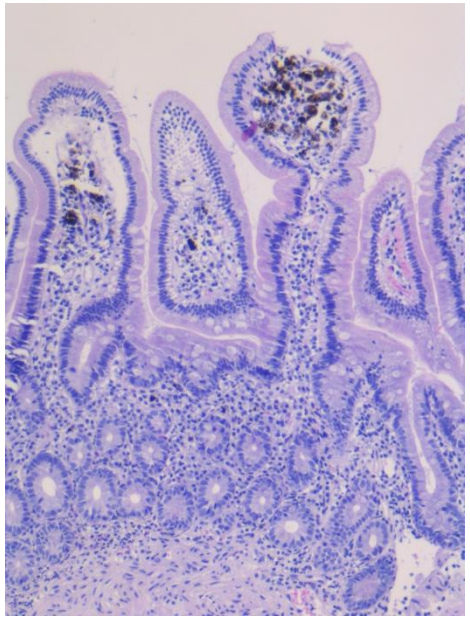
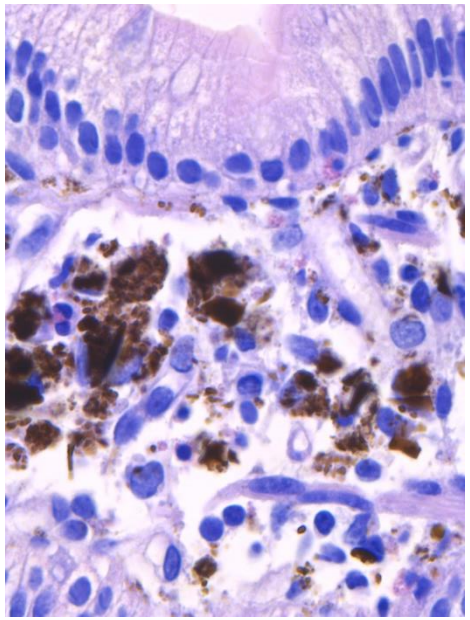
PIGMENTED MACROPHAGES

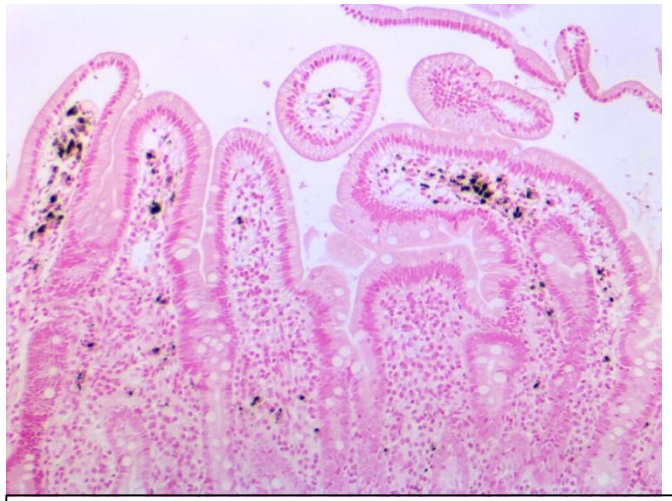
“Melanosis” duodeni



Hydralazine
Propanolol
Thiazides
(Iron supplements)
…







Cook D, Napthali K. N Engl J Med 2020;383(20):e113. PMID: 33176086.

PIGMENTED MACROPHAGES

Iron (hemosiderin pigment)

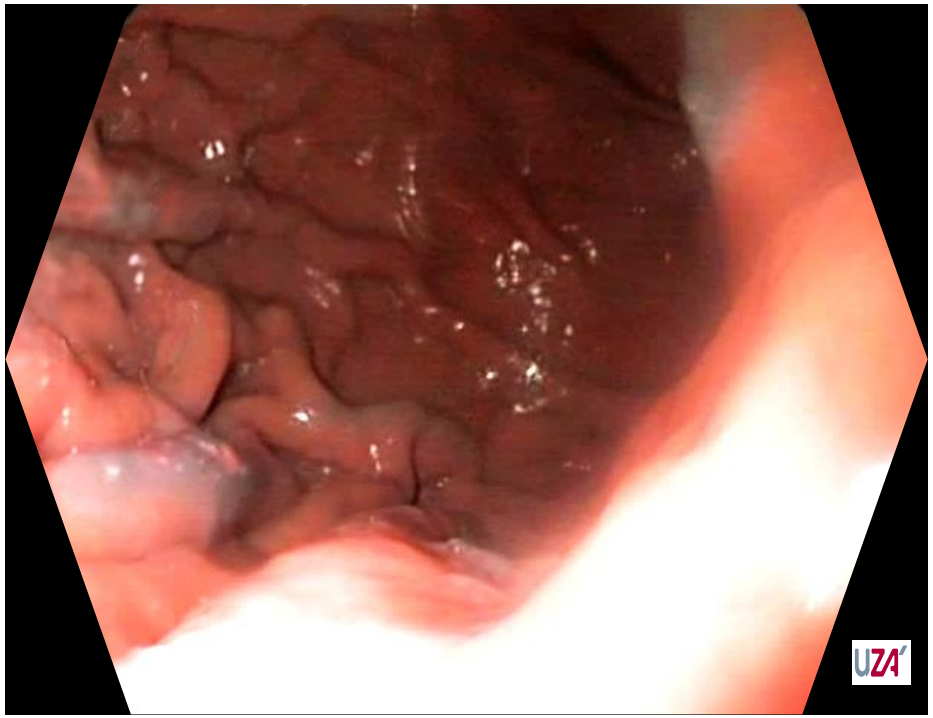
In the gastric mucosa

1. Clearing RBC debris after intramucosal hemorrhage
2. After iron-ingestion (medication)
3. Hereditary hemochromatosis

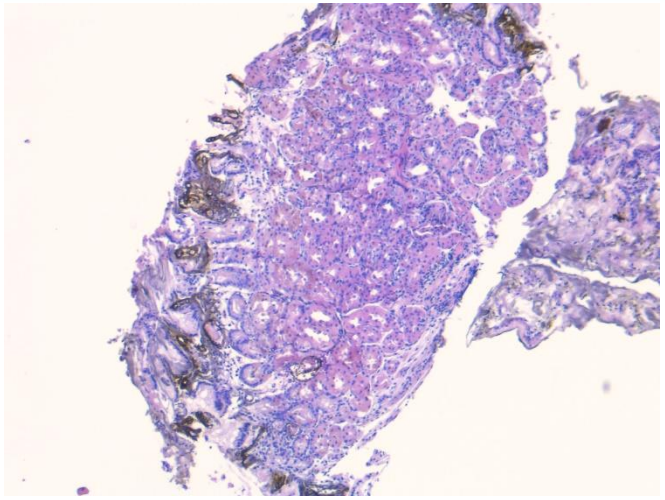
In the small intestine & colon

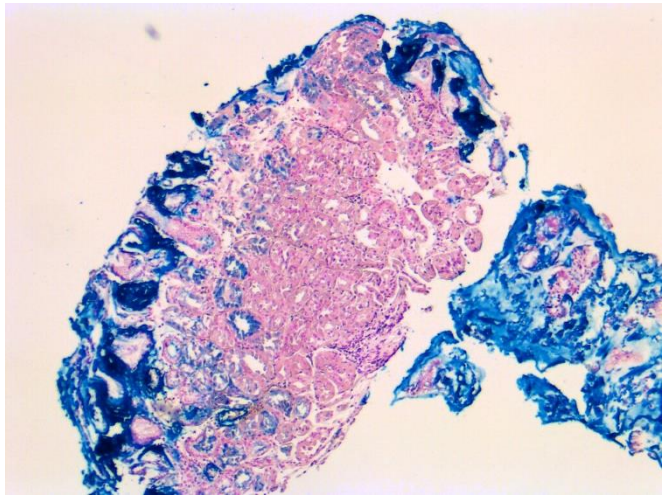
1. Following hemorrhage & ischemia
2. Diverticular disease, endometriosis, internal mucosal prolapse, various polyps

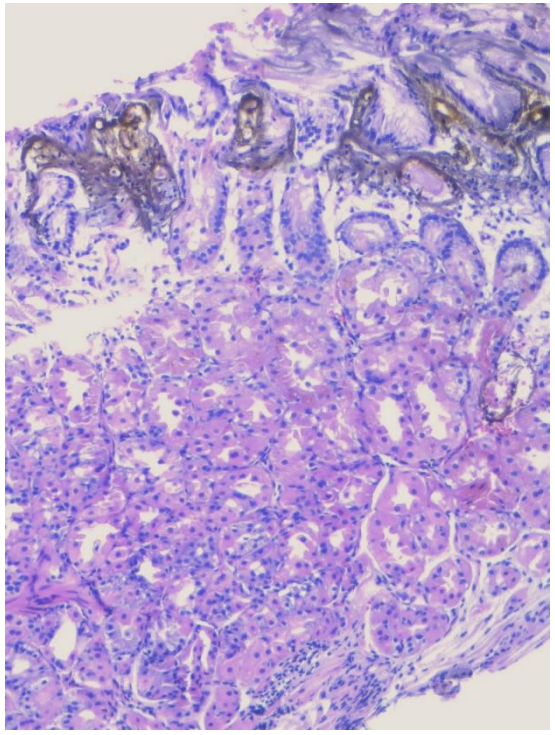
- Iron pill gastritis, endoscopy:
  - erosions, ulcers, erythema, yellow-brown discoloration mucosa

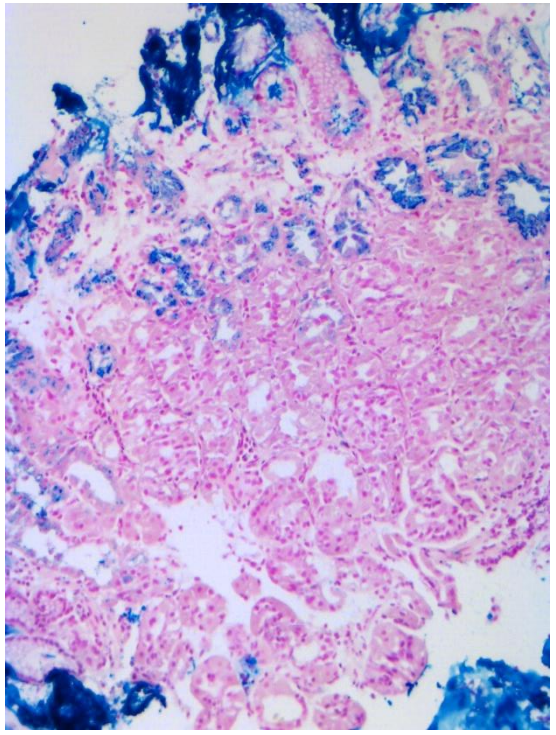


Iron-pill gastritis





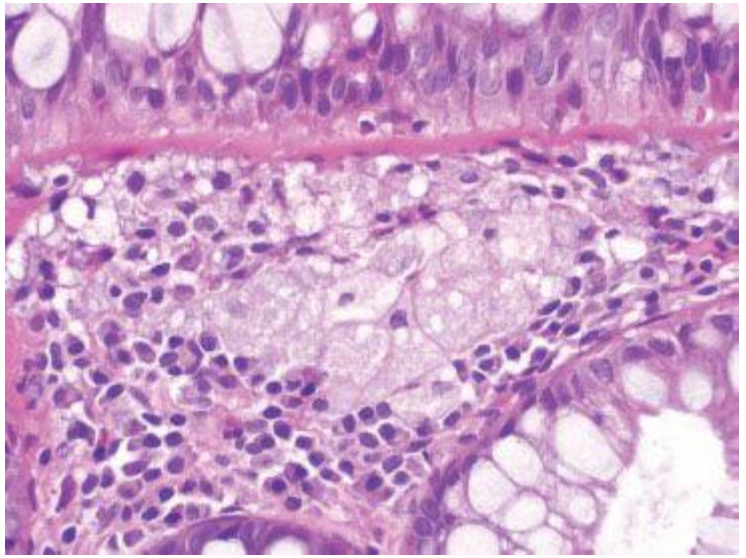




FOAMY MACROPHAGES

MUCIPHAGES (~ MUCIN COMPONENTS)

- Typically in rectal mucosa
- Small collections of histiocytes with bubbly, amphophilic cytoplasm
- (weakly) PASD+
- Epithelial turnover after previous low-grade injury ?

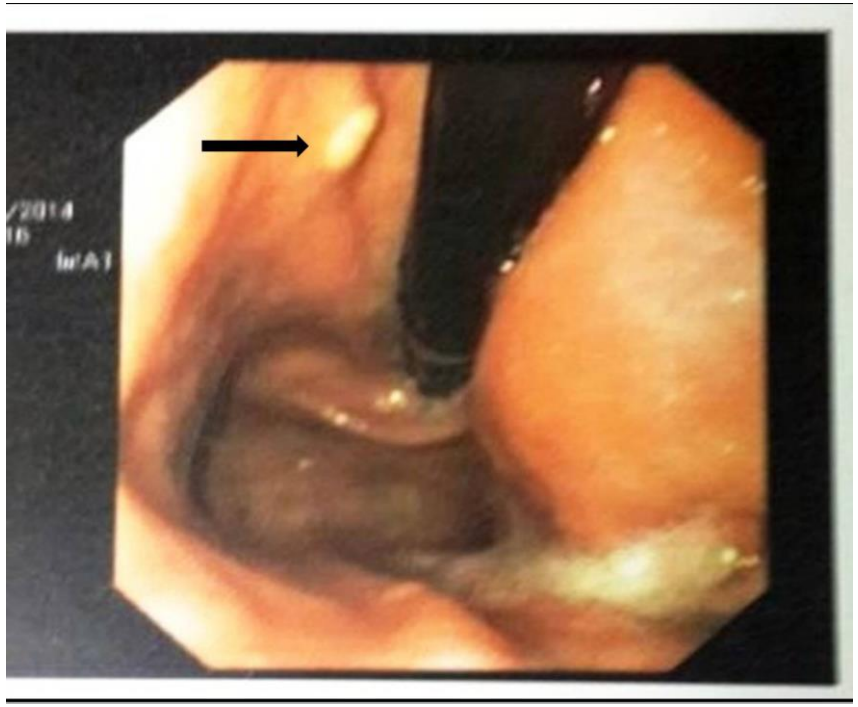


https://abdominalkey.com/colon-6/

FOAMY MACROPHAGES

XANTHELASMA / XANTHOMATOSIS

- Small /larger collections of foamy histiocytes in the lamina propria
- Yellow point lesions / endoscopically visible nodules or plaques (pseudotumoral)
- Rare in the GI tract
- Stomach > duodenum, colon
- Clearing of lipid-laden debris after trauma / chronic inflammation
- DD NETs, (hyperplastic) polyps



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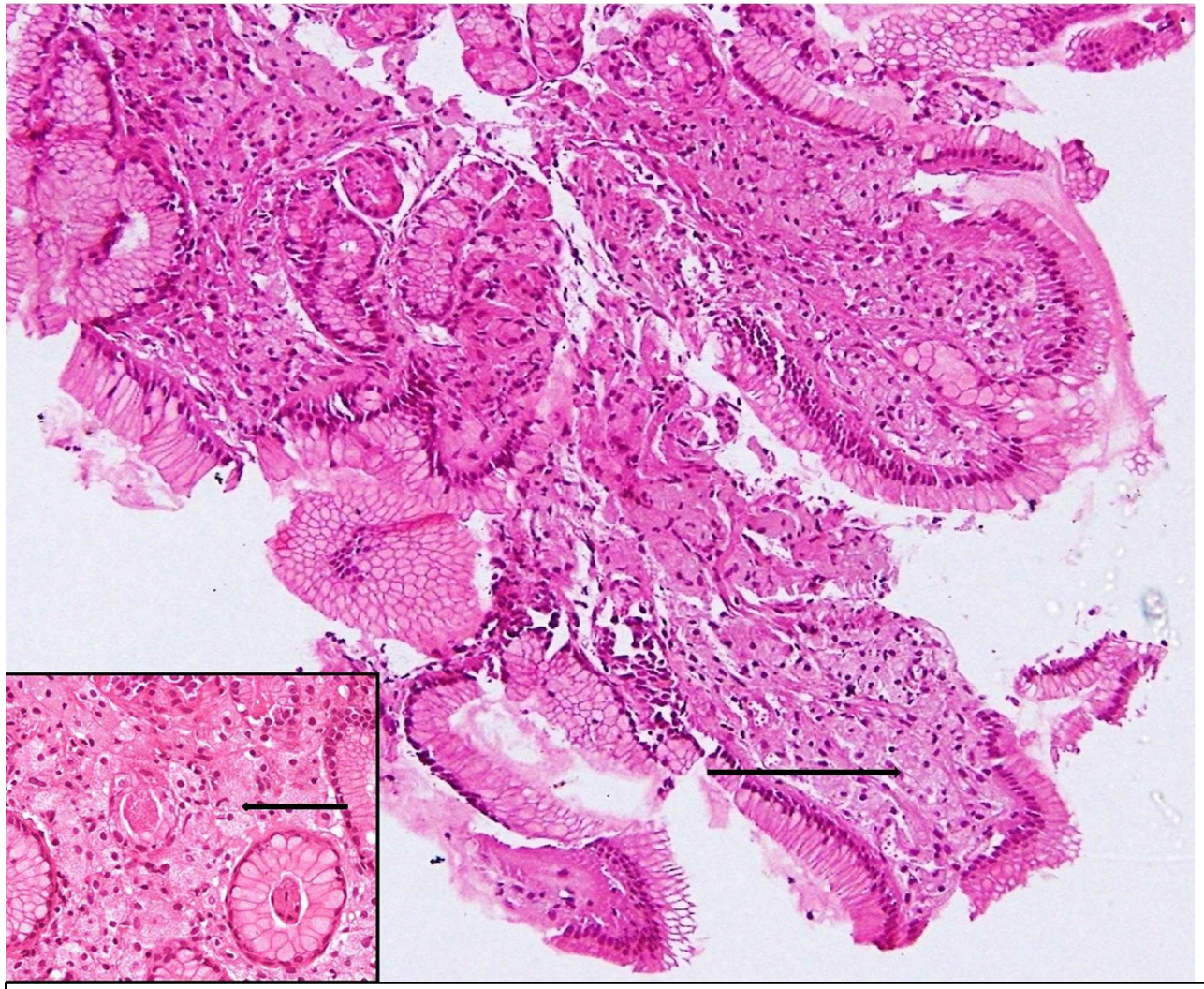
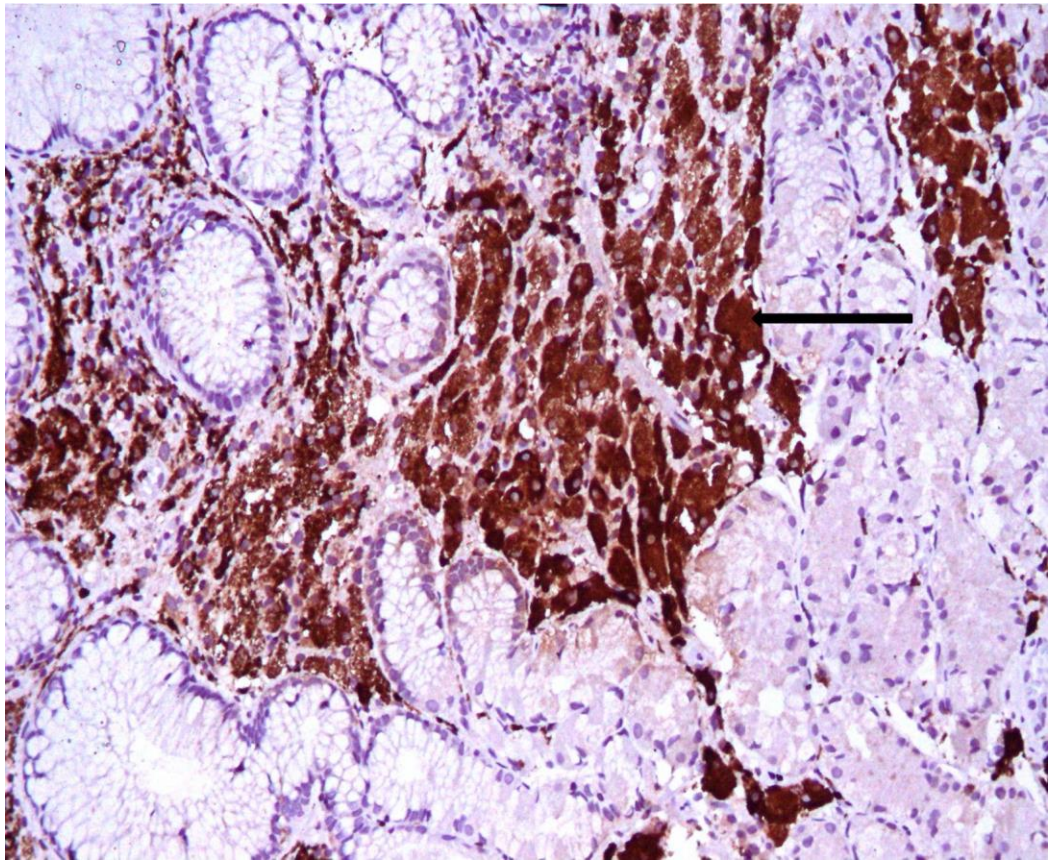
FOAMY MACROPHAGES

XANTHELASMA / XANTHOMATOSIS





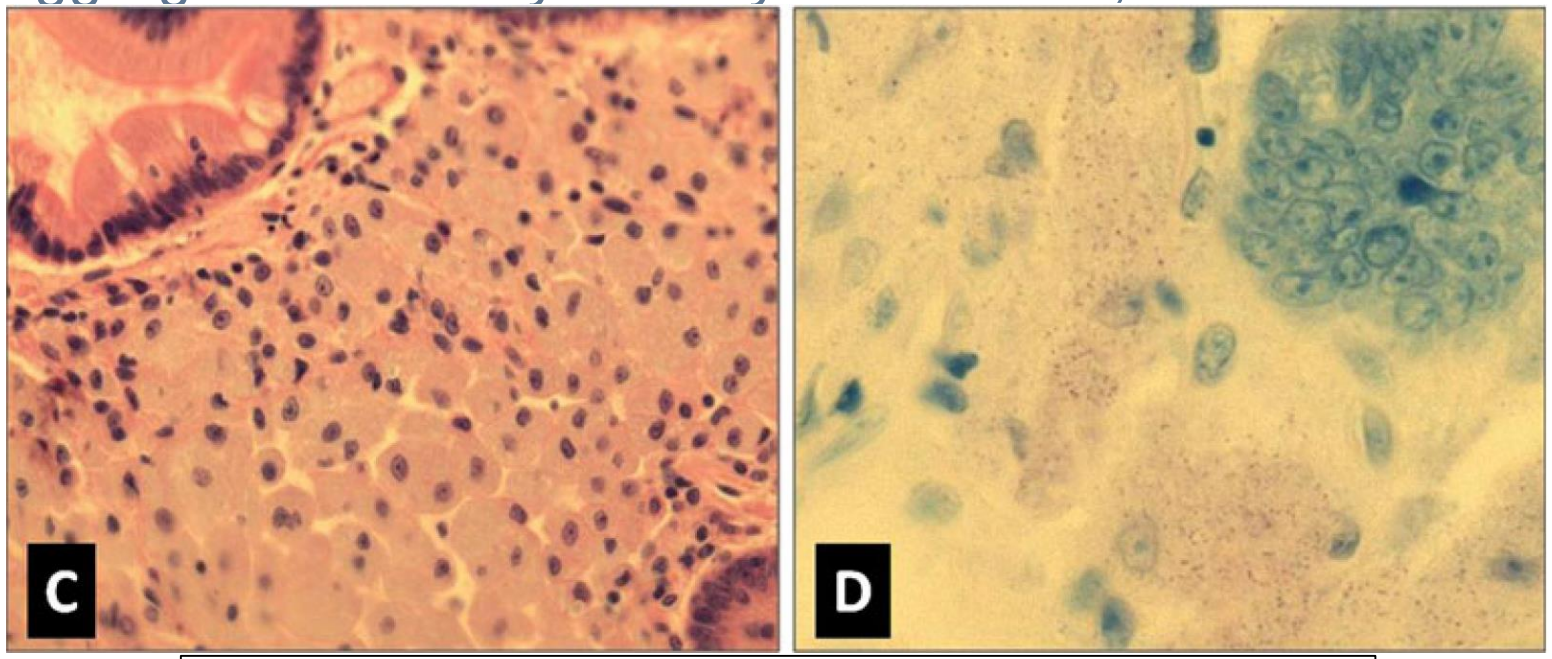
CD68 stain (400x)

Jain S, Mahajan V, Kumar M. Trop Gastroenterol 2015;36(3):198-200. PMID: 27522743

FOAMY MACROPHAGES

INFECTIOUS DISEASES : ATYPICAL MYCOBACTEROSIS

- Mycobacterium avium-intracellulare / paratuberculosis
- Water- / food-borne infection; transepithelial uptake; fagocytosis by macrophages
- Inhibition of formation of phagolysosomes; defective killing; intracellular proliferation
- CLIN Malabsorption, ENDOSC edema / erosions / ulcers; DD Crohn
- Aggregates of foamy histiocytes in the LP, Ziehl-Neelsen + (DD Whipple)



(c) 400x, (d) Ziehl-Neelsen stain1000x PMID:

FOAMY MACROPHAGES

INFECTIOUS DISEASES : CASE 1

- Male, 80 yrs
- History of seronegative polyarthritis, R/ Cxs, JAK inh
- Clinic ⇔ Inflammatory parameters ⬆
- Investigations: US, PET-CT, serology, bronchoscopy, gastroscopy, …
- Broad spectrum antibiotics: Doxycyclin → Inflammatory parameters ⬇
- Bacterial Infection ?

FOAMY MACROPHAGES

INFECTIOUS DISEASES : CASE 1 (ctd)

- Scattered clusters of foamy histiocytes with a pink, granular cytoplasm
- Granular content in the histiocytes:
  - PAS-D +
  - Ziehl-Neelsen –
  - Grocott +/-

FOAMY MACROPHAGES

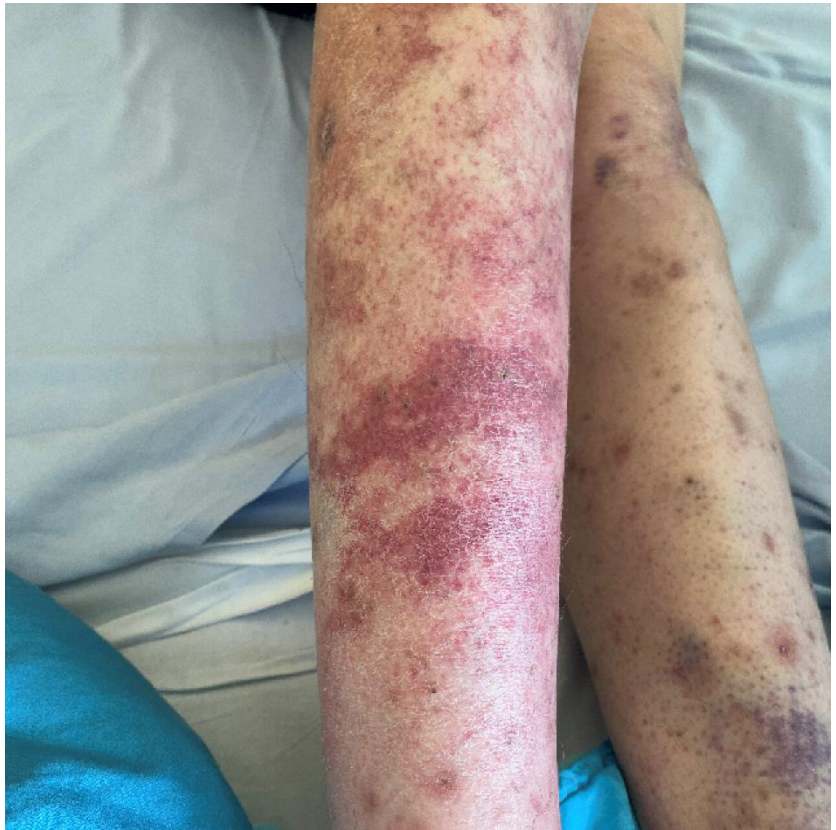
INFECTIOUS DISEASES : CASE 1 DIAGNOSIS: WHIPPLE'S DISEASE

- Tropheryma whipplei
- Men > women
- Mean age at diagnosis: 50y
- 3-10/1.000.000
- Primarily affects the small intestine (but can involve other organs / systems)
- Malabsorption symptoms
- Lamina propria expanded by foamy histiocytes infiltrate (diffuse or patchy)
- Diagnosis ?
  - **Granular PAS(D) positive** macrophages → typical, but not specific
  - 16S PCR = specific (ref lab)
  - (Immunohistochemical staining for antibodies against T. whipplei)

FOAMY MACROPHAGES

INFECTIOUS DISEASES : CASE 2

- Female, 54 yrs
- Medical history:
  - Polycystic kidney disease → transplantation (2020): Prograft, Cellcept and medrol
- Since a few months: “acneiform” lesions on the face, the arms, and the legs



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FOAMY MACROPHAGES

INFECTIOUS DISEASES : CASE 2

- During follow-up:
  - NEW: diarrhea, urgency (20x/day)
  - No blood or mucus
  - No abdominal pain
  - Coloscopy: ulcerative pancolitis (most prominent on the left side) → biopsy

FOAMY MACROPHAGES

INFECTIOUS DISEASES : CASE 2 (ctd)

- Diffuse infiltration of the lamina propria by foamy histiocytes, associated with lymphocytes and eosinophils.
- Numerous oval to spherical micro-organisms in the cytoplasm of the histiocytes
  - PASD +
  - Grocott +
- ~ Narrow-budding yeasts. Which fungus ?

TIP

Pt was originally from the state of Mississipi, USA

Went back there recently …

FOAMY MACROPHAGES

INFECTIOUS DISEASES : CASE 2 DIAGNOSIS : HISTOPLASMOSIS

- USA, Mississipi and Ohio river valleys
- Histoplasma capsulatum
- Dimorphic fungus. Grows in soil. Spores can be inhaled. Usually asymptomatic lung infection.
- May disseminate in immunocompromised patients
- GI tract : Predilection for the ileocaecal region
- Diffuse expansion of mucosa & submucosa by foamy histiocytes
- Clustered ovoid-to-spherical micro-organisms in the cytoplasm of the histiocytes
- **Grocott +**
- Confirm diagnosis by direct antigen detection in blood or urine

FOAMY MACROPHAGES IN METABOLIC DISORDERS

- Important but rare cause of accumulation of foamy histiocytes in GI tract mucosa
- Three groups:
  - Disorders leading to acute / chronic intoxication
    - e.g. inborn errors of amino acid metabolism
  - Disorders involving energy metabolism
    - glycogen metabolism, glycolysis, gluconeogenesis
  - Disorders involving complex molecules / cell organelles
    - e.g. lysosomal & peroxisomal disorders

Table 2 Accumulation of endogeneous material in macrophages and/or endothelial cells in storage diseases

	Mucosal and submucosal macrophages	Endothelial cells
Tay Sach's disease	−	−
Krabbe disease	−	−
Gaucher's disease	−(+)	−
Fabry's disease	−	+
Batten's disease	−	+
Niemann Pick		
Type A	+	+
Type B	+	+
Type C	+	+
Pompe's disease	+	+
Tangier's dsease	+	−
Wolman's disease	+	+
Cholesteryl ester storage disease	+	+
Mucopolysaccharidoses	+	+
Cystinosis	+	−

PMID: 22576700

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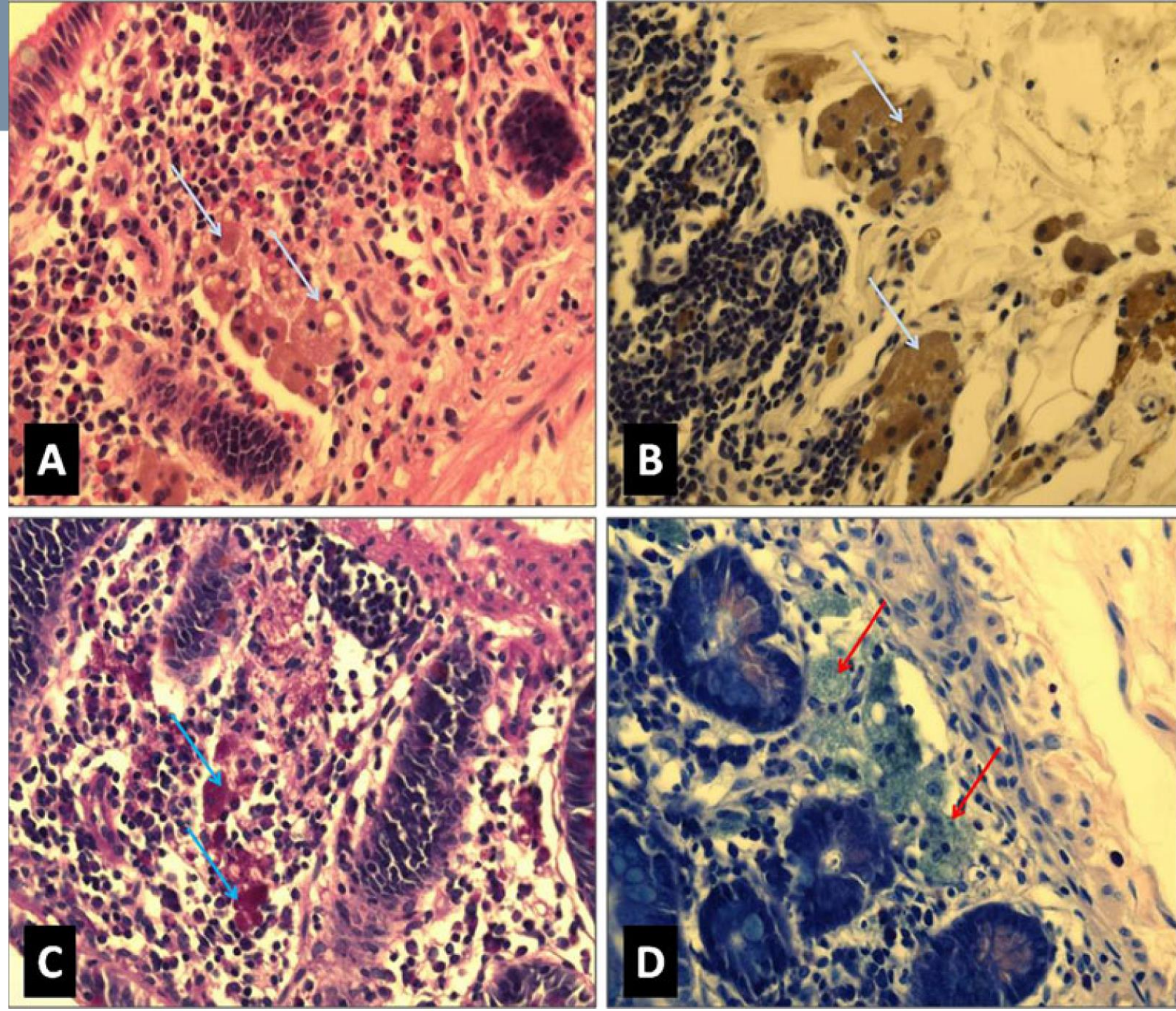
Niemann Pick disease type B

- Lipid storage disorder
- Due to mutations in the **SMPD1 gene**
- Deficiency in the activity of the lysosomal enzyme **acid sphingomyelinase** that breaks down the lipid sphingomyelin.
- Foamy histiocytes accumulate in the liver, the spleen and sometimes the GI tract
- "**Sea-blue histiocytosis**" (Giemsa stain)

PMID: 22576700



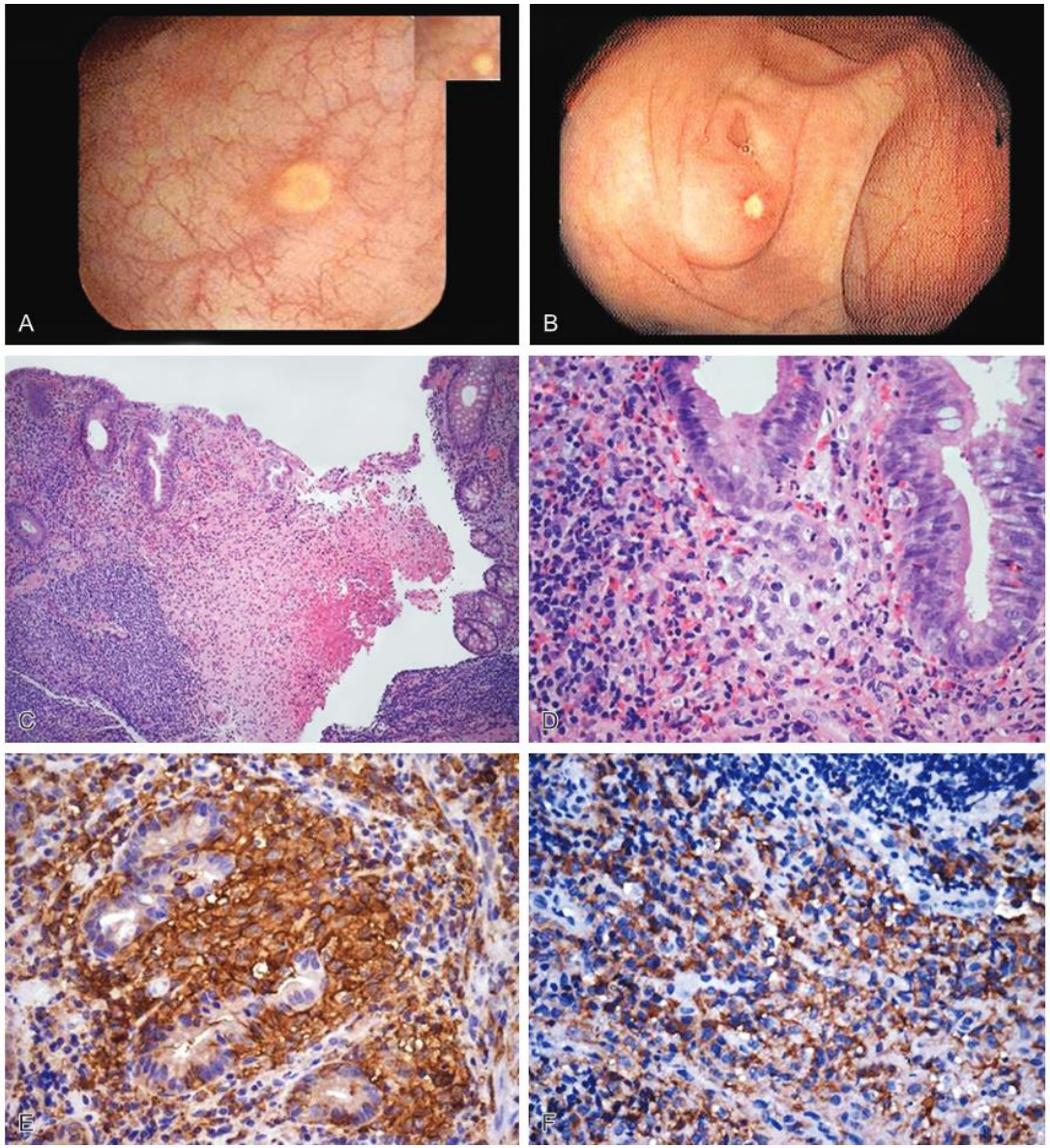
HISTIOCYTIC DISORDERS OF UNCERTAIN / NEOPLASTIC ORIGIN

PMID: 23063502

Histiocytic disorder	Light microscopic features	CD1a	CD68	Factor XIIIa	S100	Additional features
Primary histiocytic disorders of uncertain origin						
Rosai-Dorfman disease (RDD)	Large histiocytes with oval vesicular nuclei and pale cytoplasm Prominent emperipolesis Many plasma cells	−/+ [a]	+	NA	+	Frozen section: neutral lipids can be visualized by Oil Red O stains
Langerhans cell histiocytosis (LCH)	Langerhans cells show nuclear grooves and have pale cytoplasm Sometimes eosinophilic infiltrates	+	+/− [b]	−	+/−	EM: Langerhans cells show foldings of the nuclear membrane and Birbeck granules in the cytoplasm IHC: Langerin positive
Erdheim-Chester disease (ECD)	Large histiocytes with eosinophilic, pale cytoplasm Sometimes Touton-type giant cells Intense fibrosis	−	+	+/−	−/+	EM: histiocytes with indented nuclei and numerous intracytoplasmic lipid vacuoles, only few mitochondria
Primary histiocytic disorders of neoplastic origin						
Histiocytic sarcoma	Highly pleomorphic neoplasms. In H&E stains indistinguishable from diffuse large-B-cell lymphoma	−	+/−	NA	−/+	IHC: ≥1 of the histiocytic markers CD68, CD163, or lysozyme are positive, whereas Langerhans and follicular dendritic cell markers (CD1a, CD21, CD35) as well as myeloid markers (CD13, CD33, myeloperoxidase) have to be negative
Follicular dendritic cell sarcoma	Tumor cells often spindle shaped or ovoid, with elongated nuclei, storiform pattern Also epitheloid variants	−	+/−	NA	+/−	IHC: positive for at least one of the follicular dendritic cell markers (CD21, CD23, CD35), whereas CD1a, lysozyme, myeloperoxidase, CD3, CD30, CD34, and CD79a are negative

Adult Langerhans cell histiocytosis presenting as metachronous colonic polyps

Aloísio Felipe-Silva[a,b], Mauricio Saab Assef[a,c], Rodrigo Azevedo Rodrigues[a,d], Carla Pagliari[e]



CD1a

CD207, “Langerin”

Autopsy and Case Reports 2013; 3(1): 39-44

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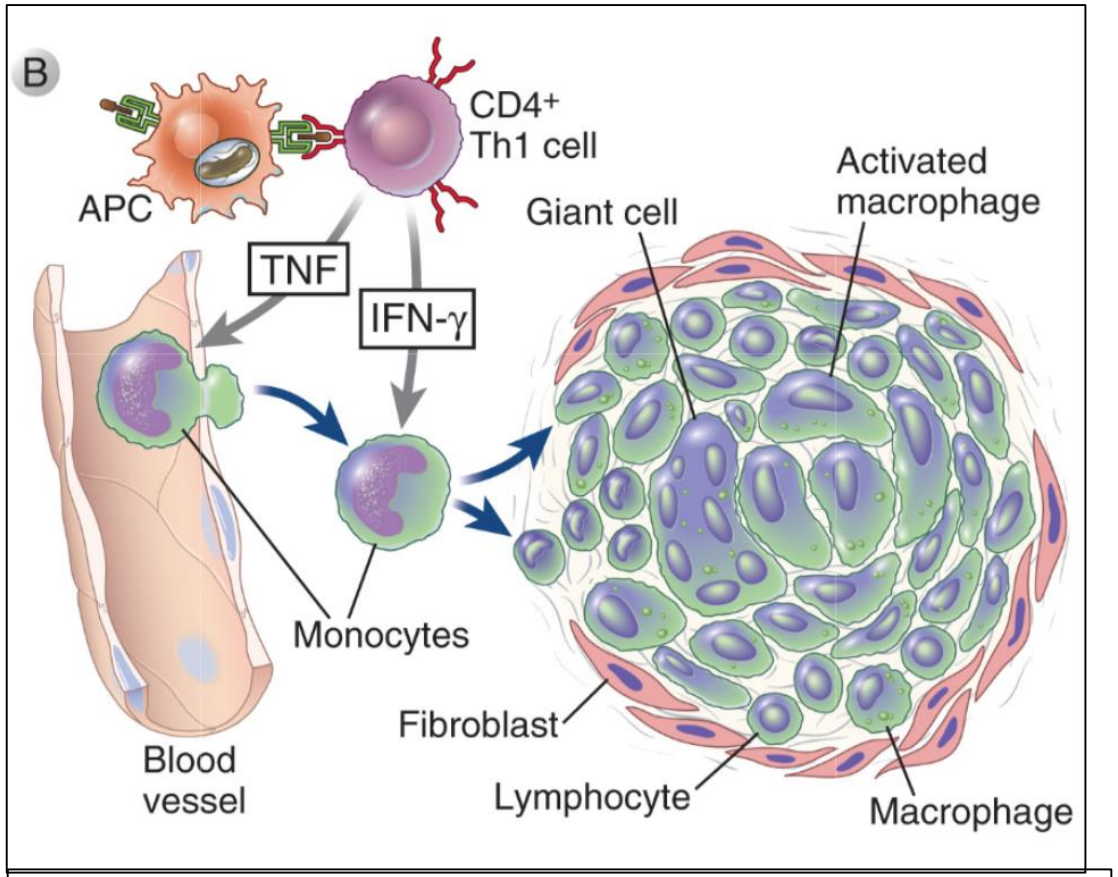
GRANULOMATOUS DISORDERS OF THE GI TRACT : OVERVIEW

GRANULOMA

= organized collection of activated macrophages, including epithelioid histiocytes and giant cells, surrounded by lymphocytes



Abbas Cellular and Molecular Immunology, 9th Ed, 2018

DD Granuloma

Infectious

- Systemic (tuberculosis, histoplasmosis, Whipple disease)
- GI specific infections (*Salmonella*, *Yersinia*, *Campylobacter*, *Helicobacter*)
- Parasites (schistosoma, enterobius)
- Venereal infections (syphilis, lymphogranuloma venereum)

Non-infectious

- Crohn's disease
- Drugs (non-steroidal anti-inflammatory drugs—diclofenac, biologics)
- Foreign material (talc, starch, barium, faecal material including pulse granuloma, pneumatosis)
- Crypt/gland rupture associated granuloma
- Sarcoidosis
- Inherited disorders (chronic granulomatous disease, Hermansky-Pudlak syndrome, Blau syndrome)
- Autoinflammatory granulomatous diseases
- Diverticular colitis
- Malignancy/neoplasm related
- Vasculitis (granulomatosis with polyangitis, Churg-Strauss syndrome, Behcet's disease, giant cell arteritis)
- Common variable immunodeficiency
- Cord colitis syndrome

Idiopathic

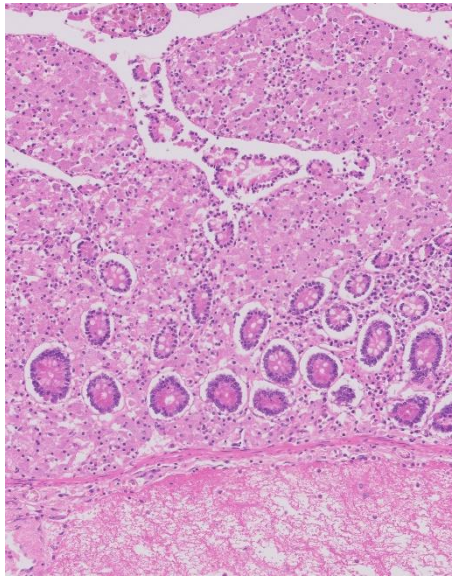
Brown et al.
Virchows Archiv 2018

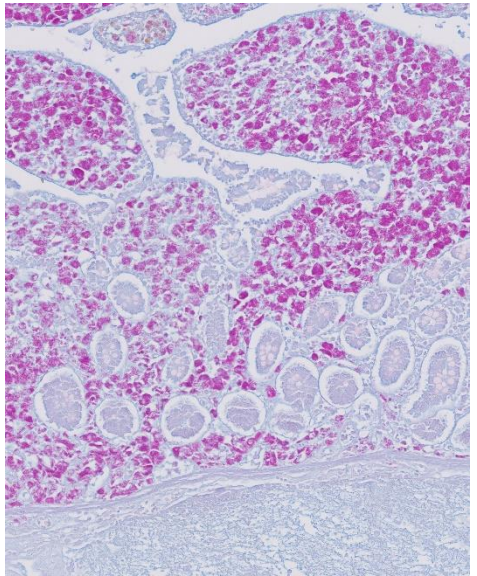
DD Granuloma

TABLE 3. Differential Diagnosis of Colonic Mucosal Granulomatous Inflammation

Disease	Typical Granuloma Type
Crohn disease	Small intercryptic non-necrotizing; giant cells uncommon*
Ulcerative colitis	Cryptolytic with residual epithelial fragments†
Other infections (eg, Yersiniosis, LGV, fungi)	Confluent histiocytes to granuloma with central neutrophils or microabscesses
Tuberculosis	Caseous necrotizing granuloma‡
Mycobacterium avium complex	Xanthogranulomatous reaction§
Sarcoidosis	Well-formed intercryptic non-necrotizing with giant cells‖
Eosinophilic granulomatosis with polyangiitis	Perivascular granuloma with numerous eosinophils
Tissue invasive parasites (eg, Schistosomiasis)	Foreign body type with numerous eosinophils¶
Drug-induced (eg, immune checkpoint inhibitors)	Usually cryptolytic with residual epithelial fragments, sometimes true epithelioid granulomas
Foreign material (eg, Orise gel)	Foreign body type with exogenous material

Mycobacterium avium





Kövári et al.
Adv Anat Pathol 2022

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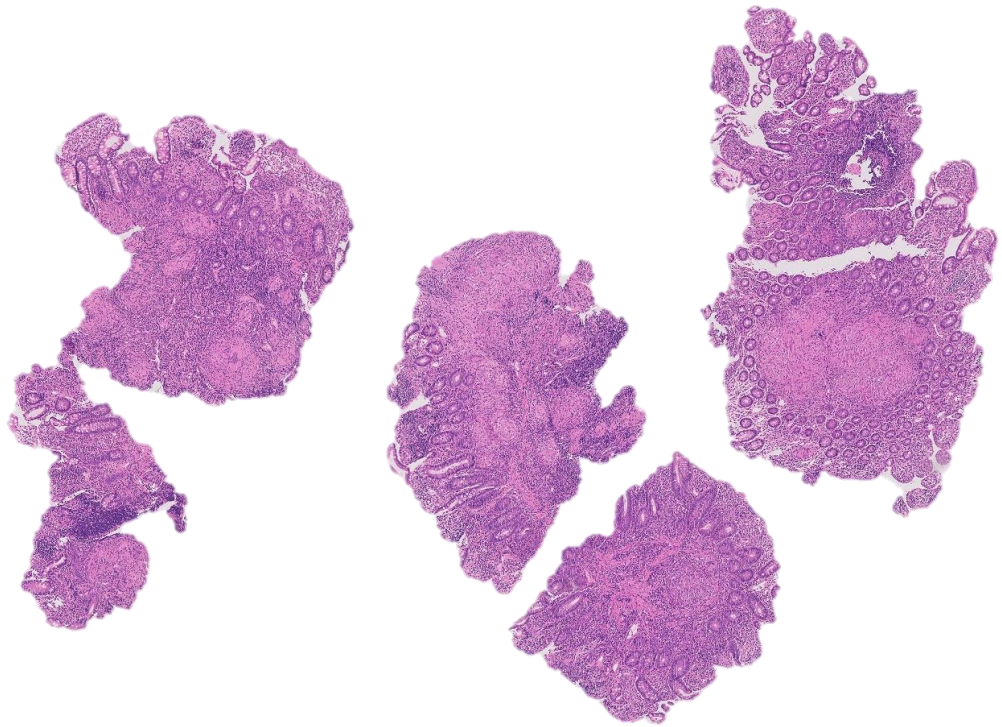
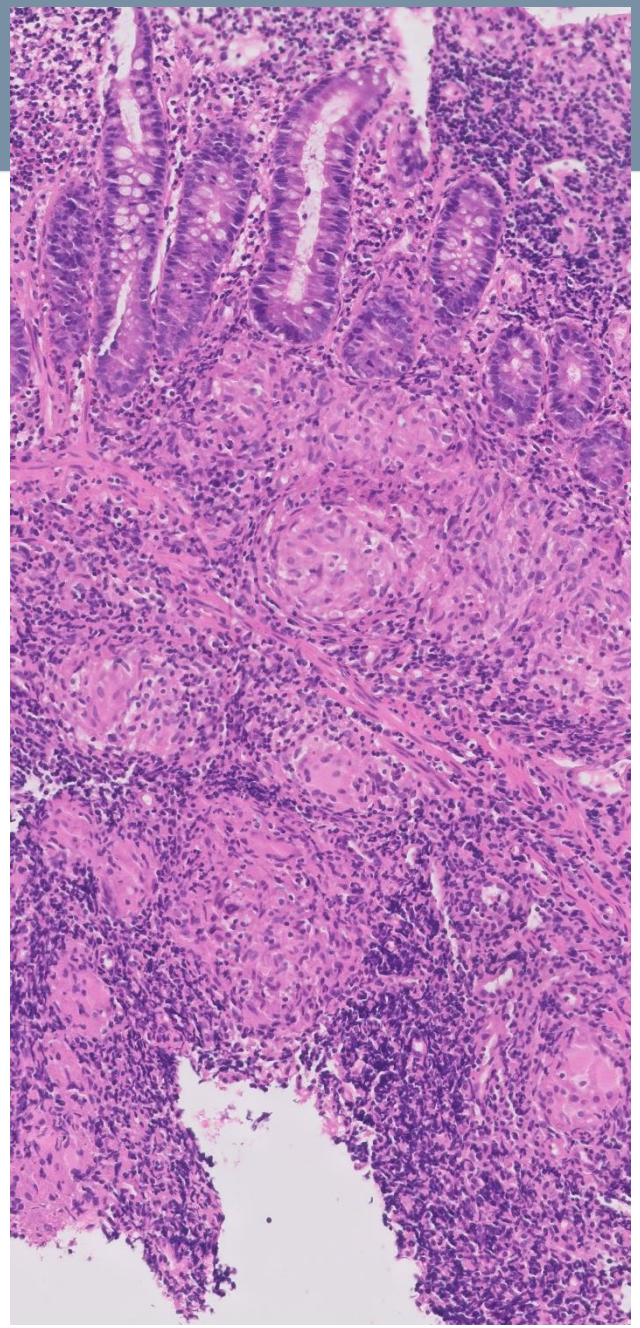
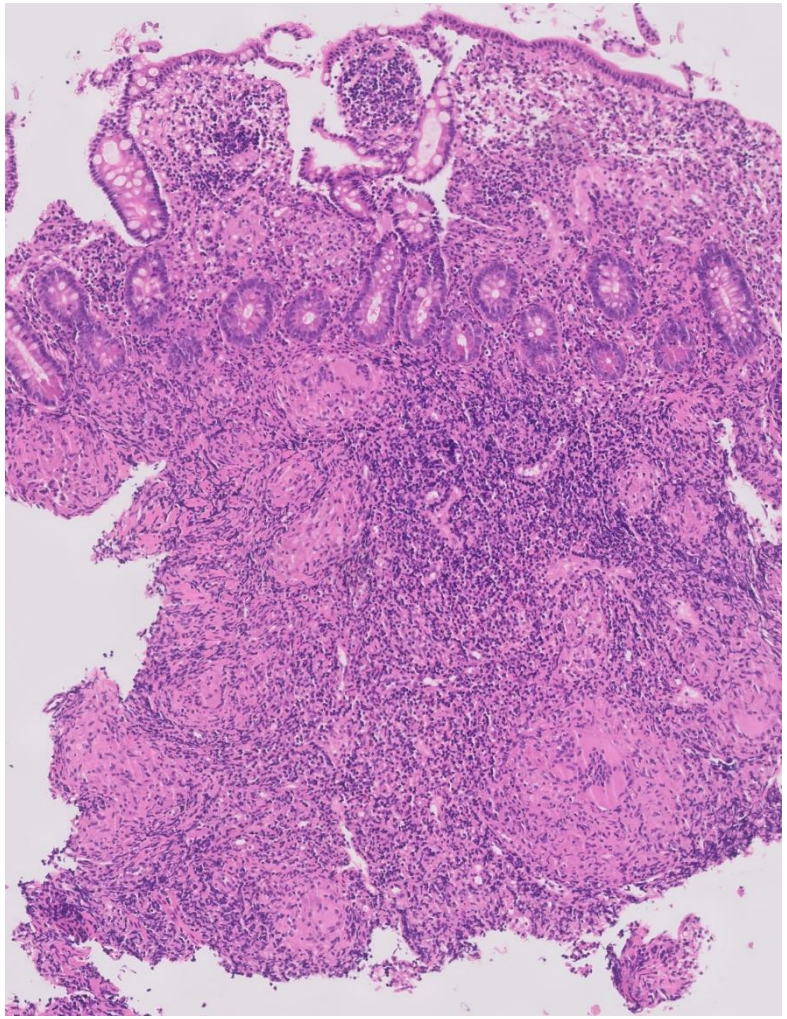
Ileocaecal valve biopsy
Epithelioid granulomas
Quid ?

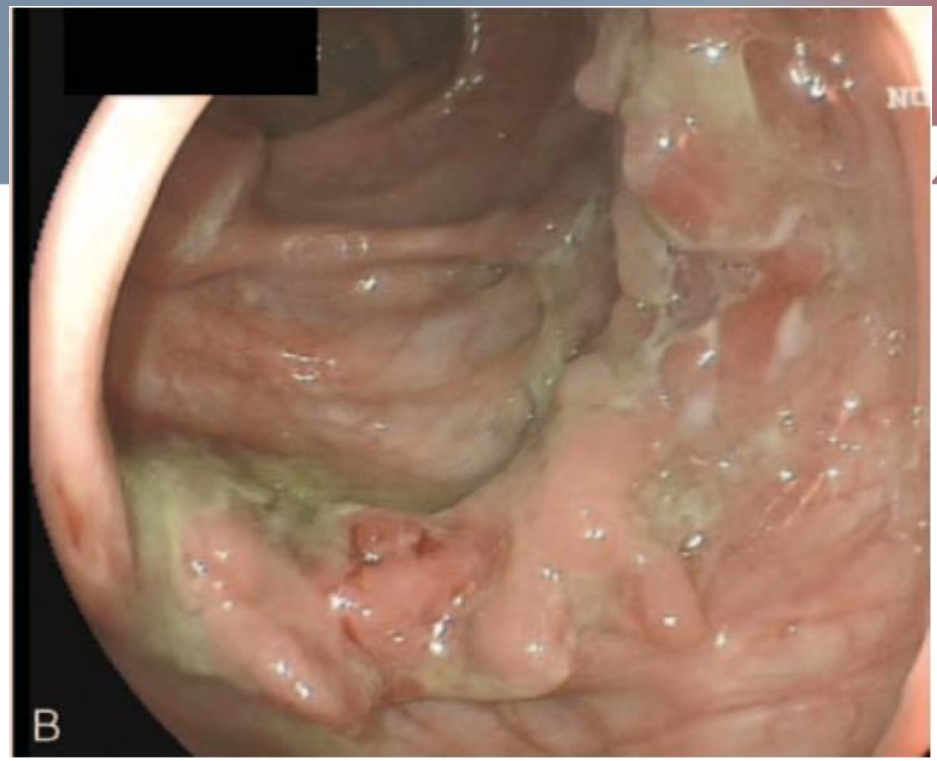


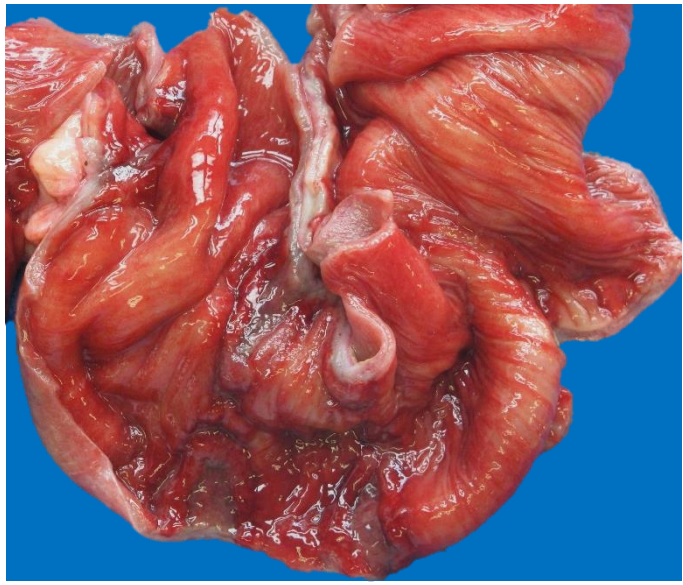




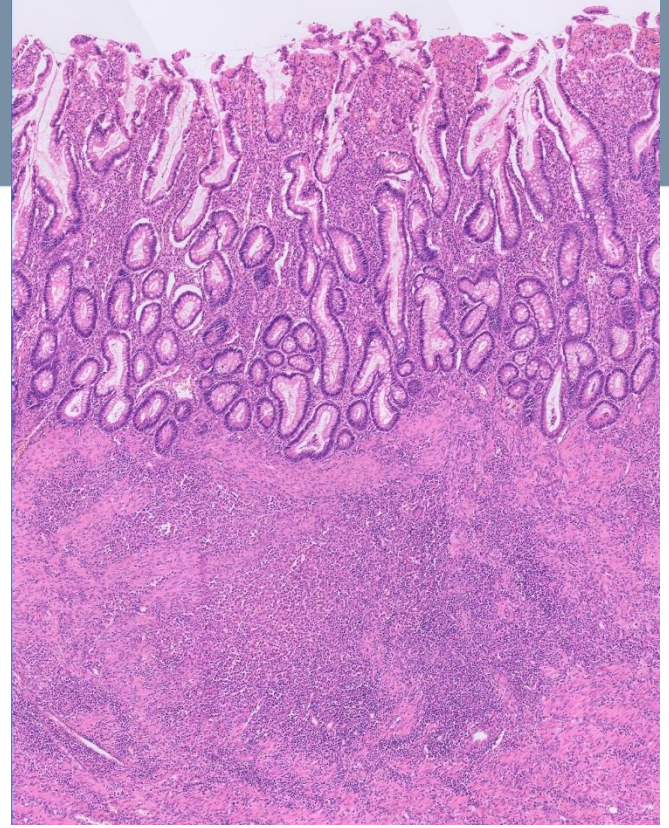
INTESTINAL TUBERCULOSIS

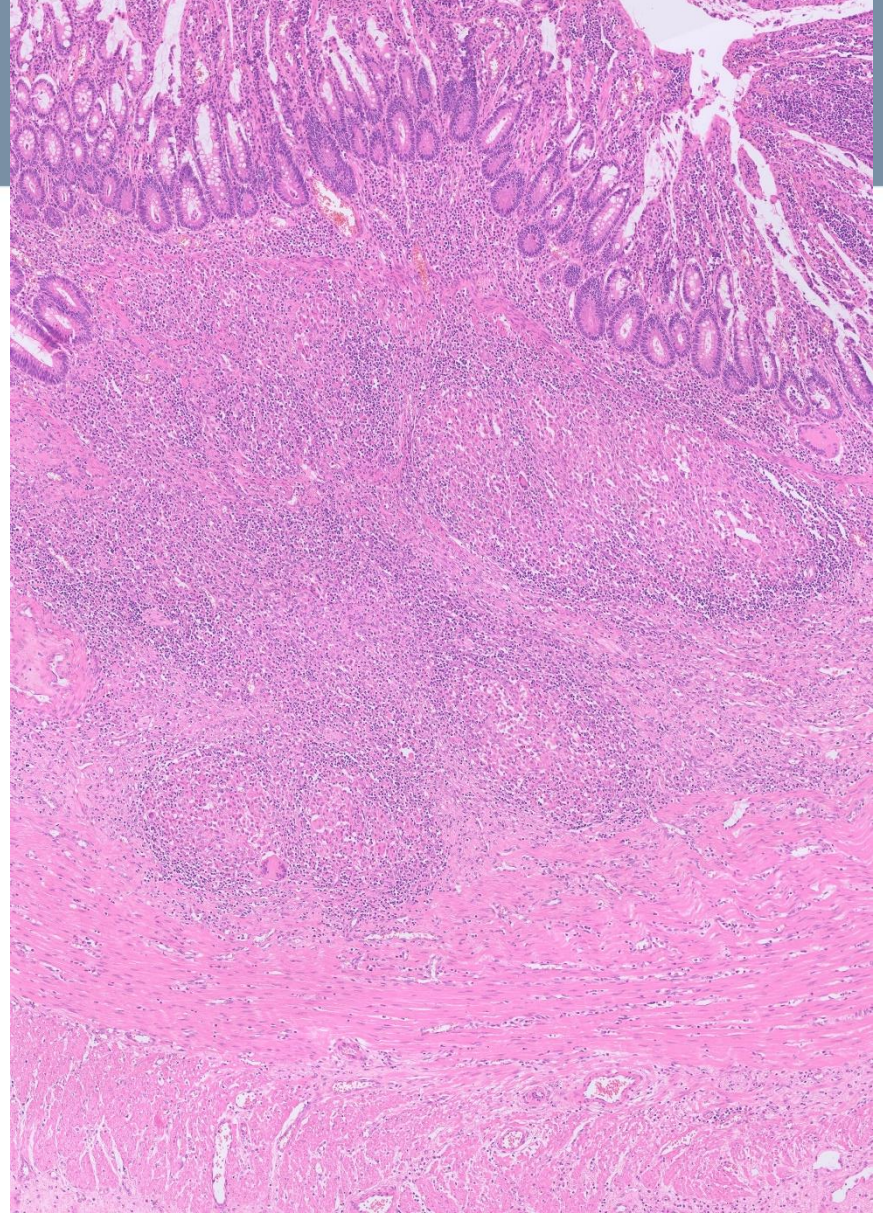
- Typical location: ileum, proximal colon
- Detection of acid-fast bacilli
  - Ziehl-Neelsen stain
  - Auramine stain
  - Molecular techniques (FFPE)

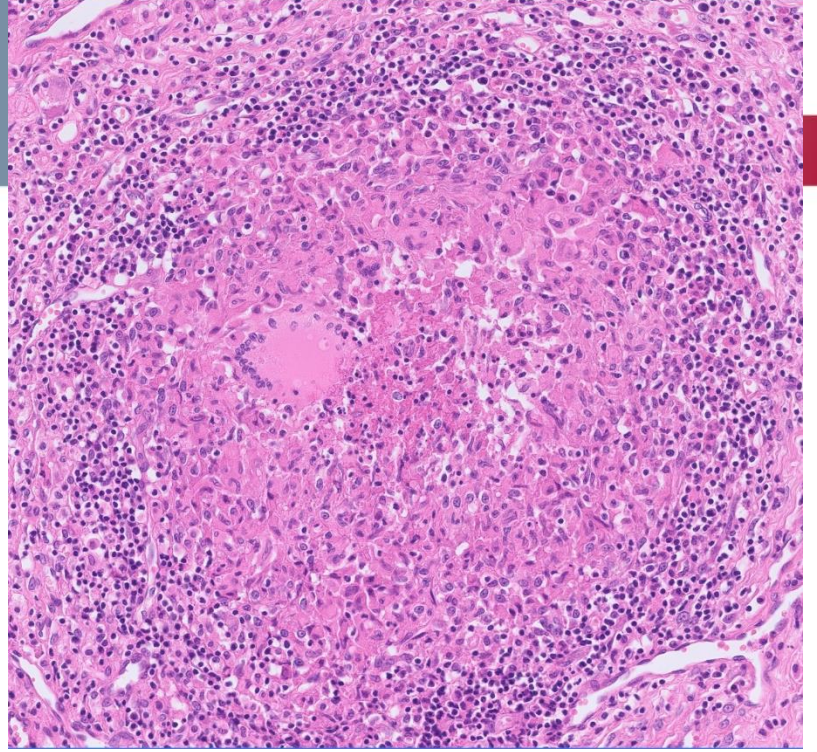


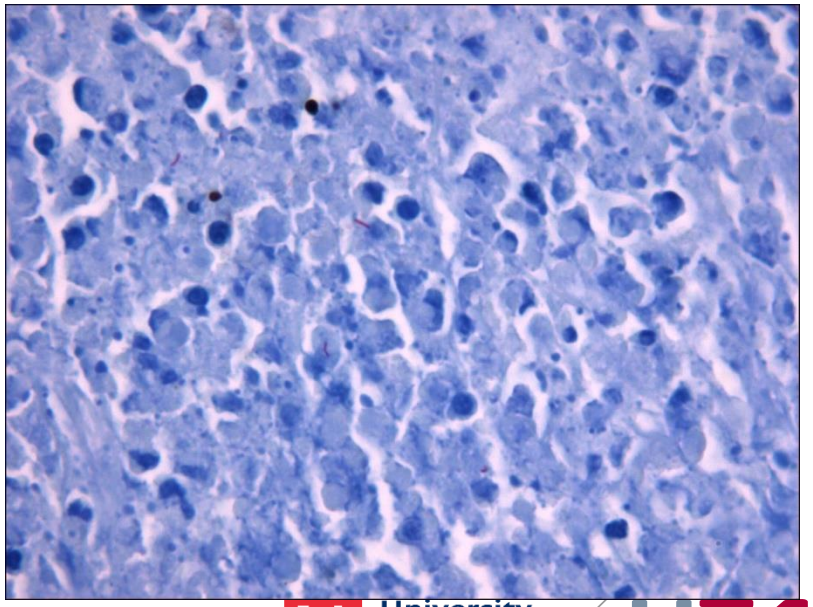


Ye et al. Medicine, 2015





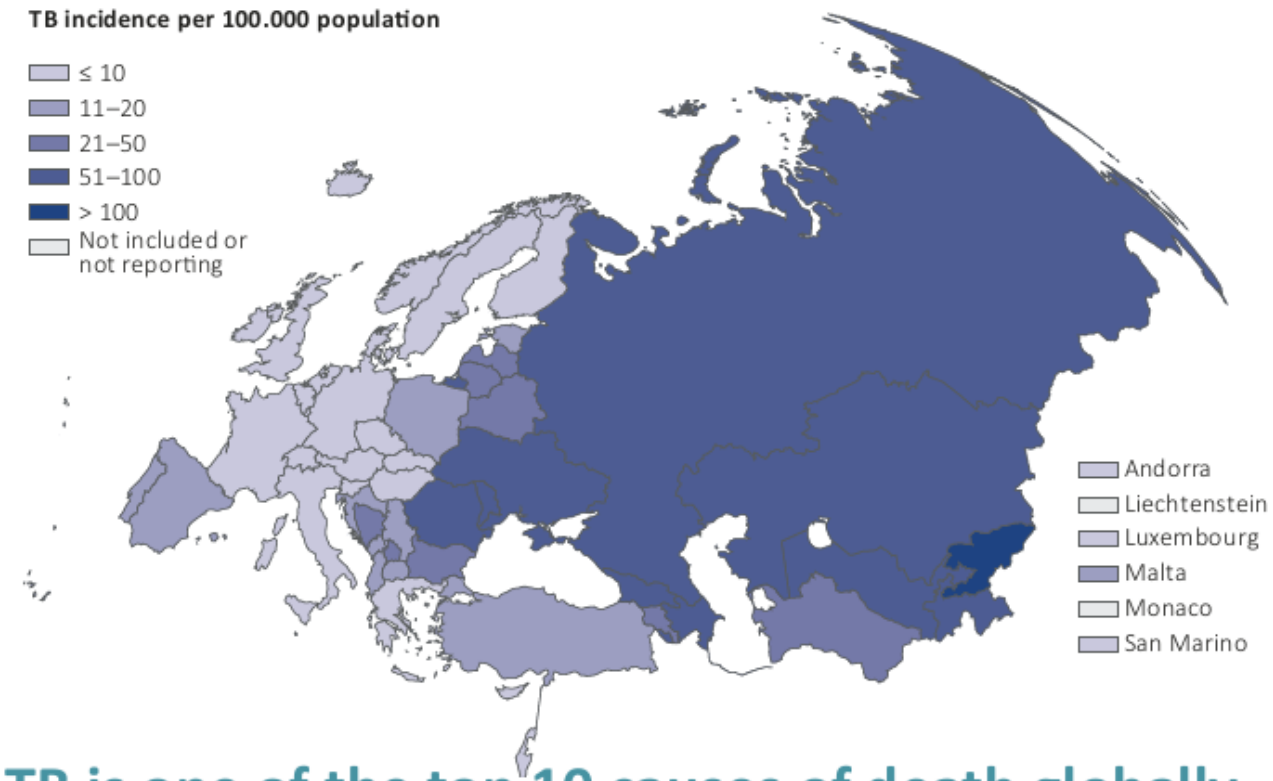




- Histological features:
  - Epithelioid granulomas
  - Numerous
  - Large
  - Confluent
  - Langhans giant cells
  - Caseous necrosis !

Tuberculosis

Each day 1000 people fall sick with TB in the WHO European Region



TB is one of the top 10 causes of death globally

Who is at a higher risk of developing active TB?

- Vulnerable people, including the elderly and children
- People with a compromised immune system

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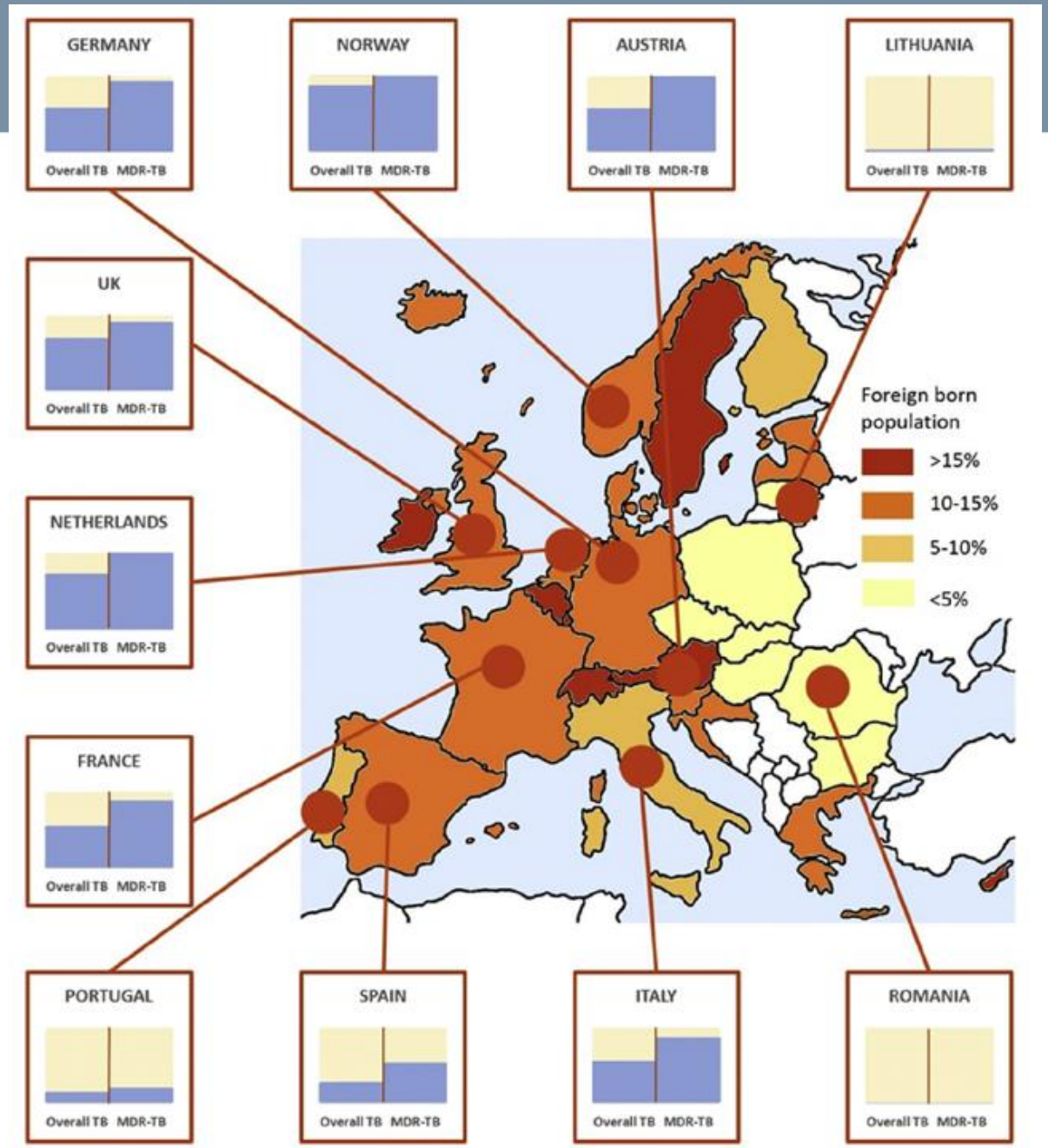

TBC

- Europe : rising incidence
- 2019:
  - New diagnoses 216000
  - Incidence 23,2/100000 cases

Hargreaves et al.
Clin Microbiol Infect 2017

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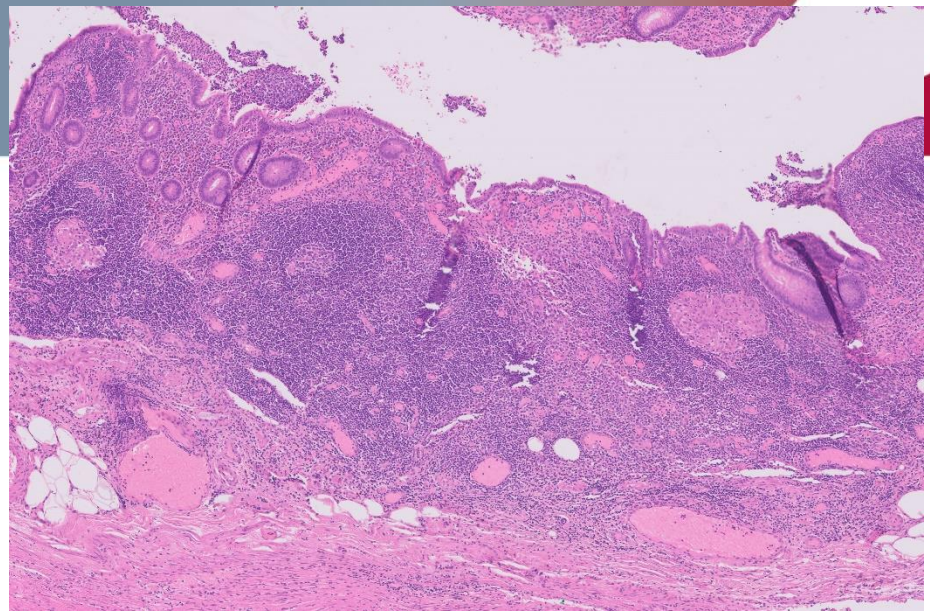
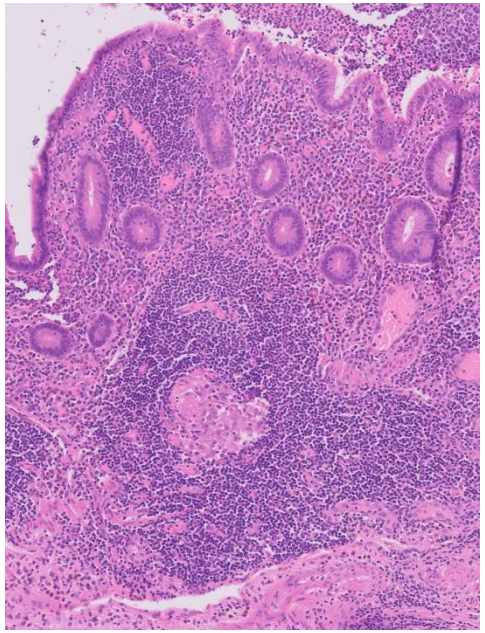
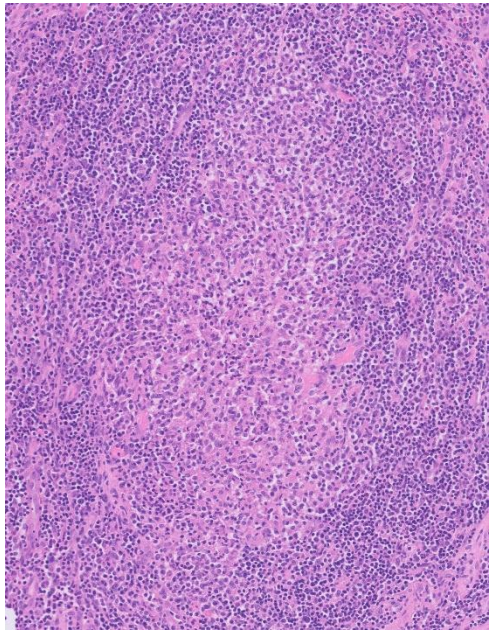
Yersinia

- Y. enterocolica, Y. pseudotuberculosis
- Location: ileocaecal region, appendix > other areas
- Histology
  - Chronic inflammation
  - Lymphoid hyperplasia
  - Epitheloid granulomas, eventually with necrosis
  - Transmural lymphoid aggregates
  - Less crypt distortion
  - Basal plasmacytosis uncommon

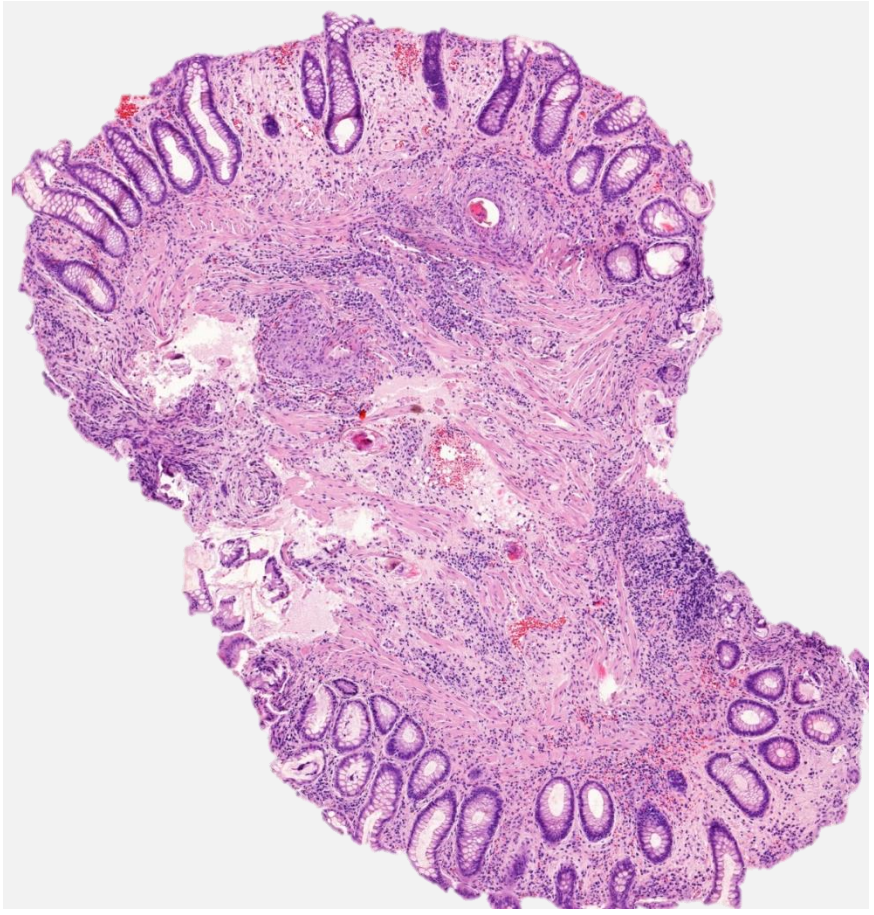


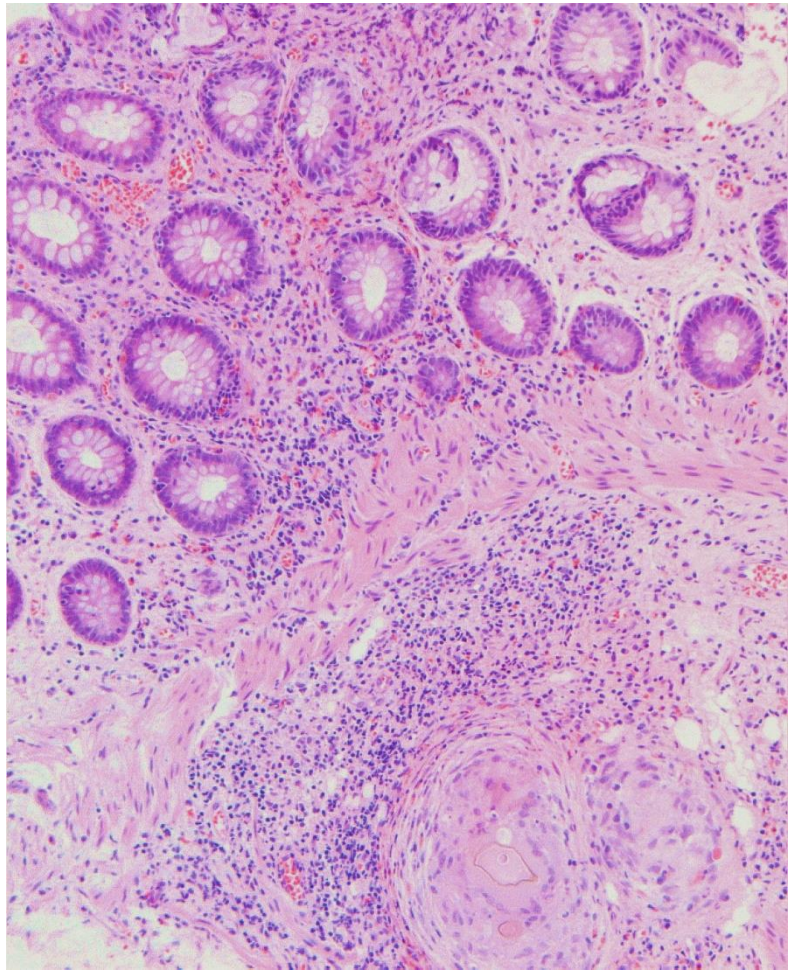


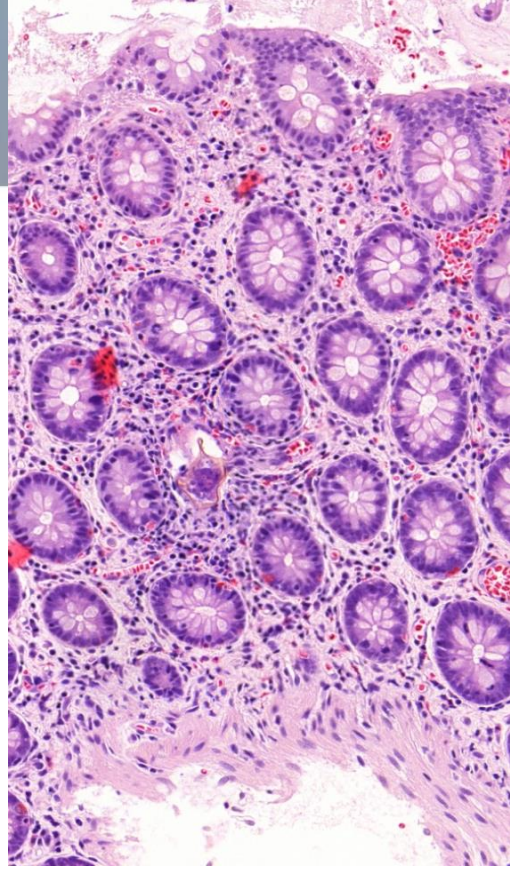


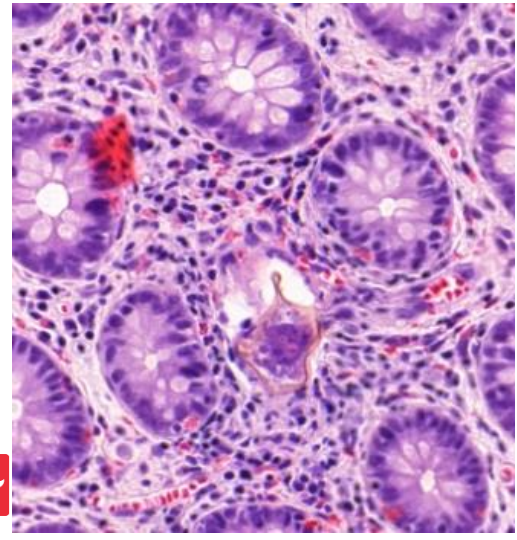
Lamps et al. AJSP 2001;25:508

Schistosomiasis



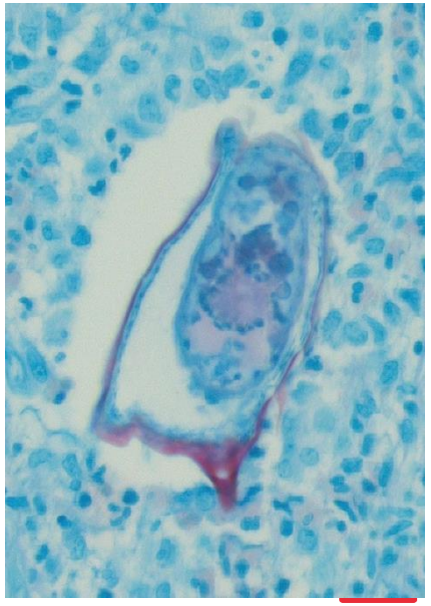






Schistosomiasis

- Theodor Bilharz 1851 → “Bilharziasis”
- Africa, Asia, parts of America
- Travellers to foreign countries, immigration
- Source: contaminated water
- Involves liver and GI tract
- S. mansoni, S. hematobium, S. mekongi, S. intercalatum, S. japonicum

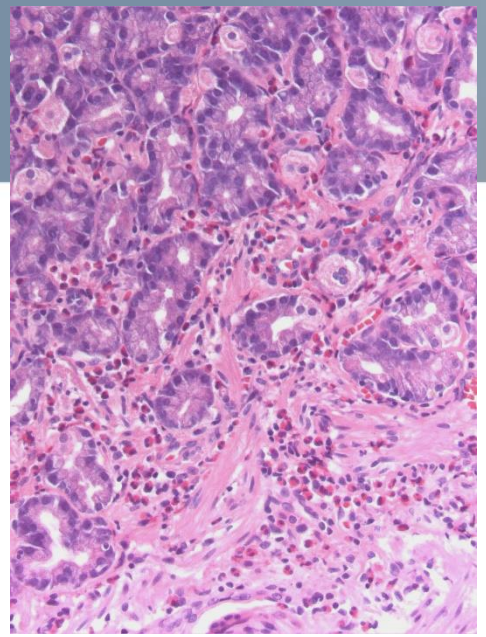
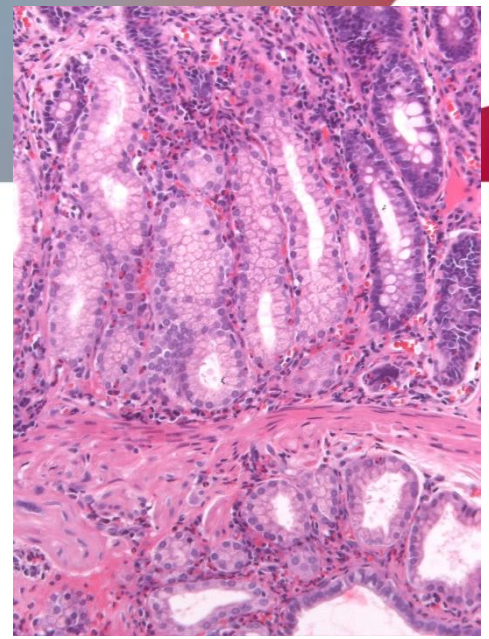
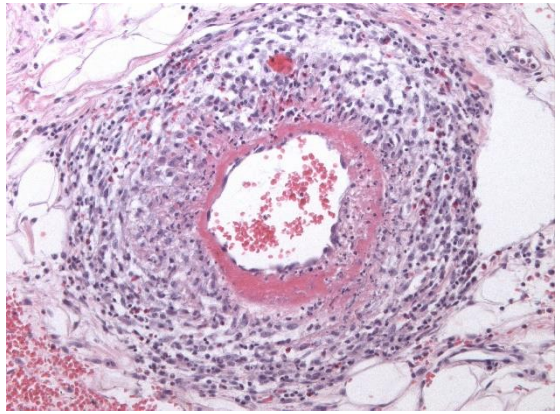
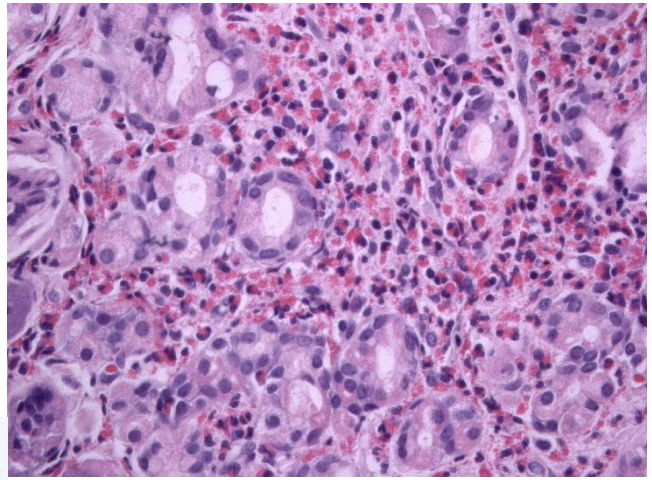
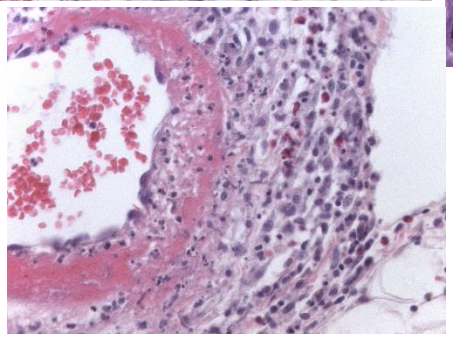


Vasculitides

CHURG-STRAUSS SYNDROME

= eosinophilic granulomatosis with polyangiitis

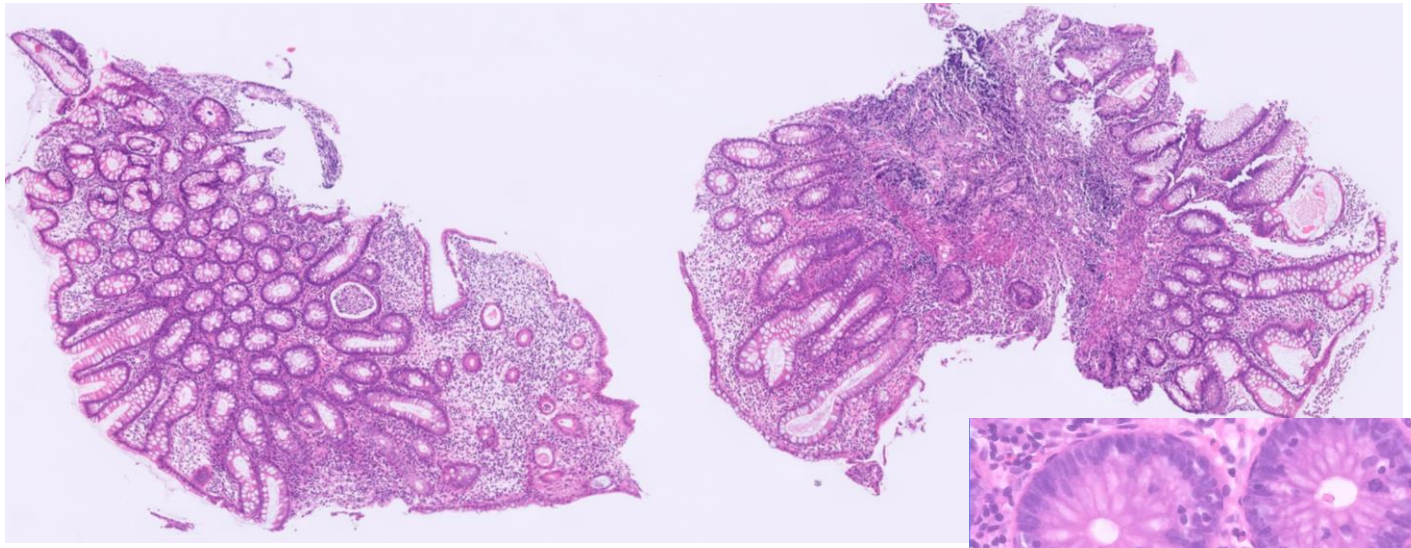
- 3 stages
  - 1st : Airway allergic hypersensitivity : rhinitis, asthma
  - 2st : Blood – tissue eosinophilia
  - 3rd : Systemic vasculitis
    - Small to medium-sized blood vessels
    - +/_ vessel wall necrosis
  - GI ulcers, perforation, peritonitis

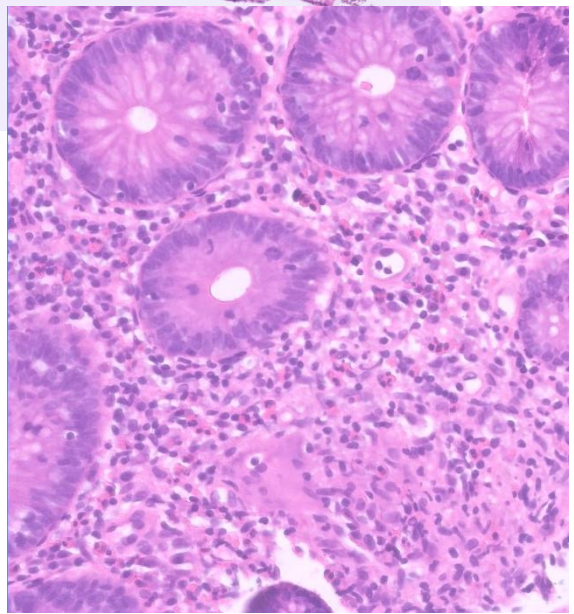






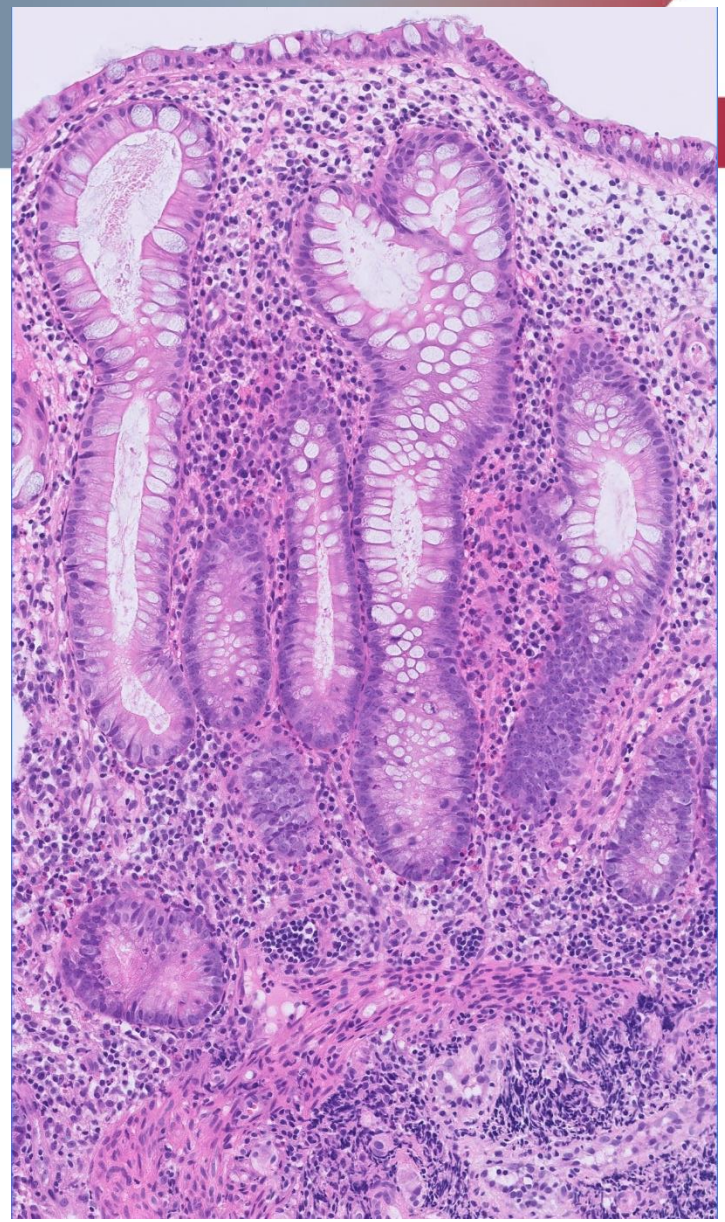
Vasculitides

BEHCET'S DISEASE

- Orogenital ulcers, eye inflammation, arthritis
- Phlebitis and ulceration in the terminal ileum . Ileocaecal valve region





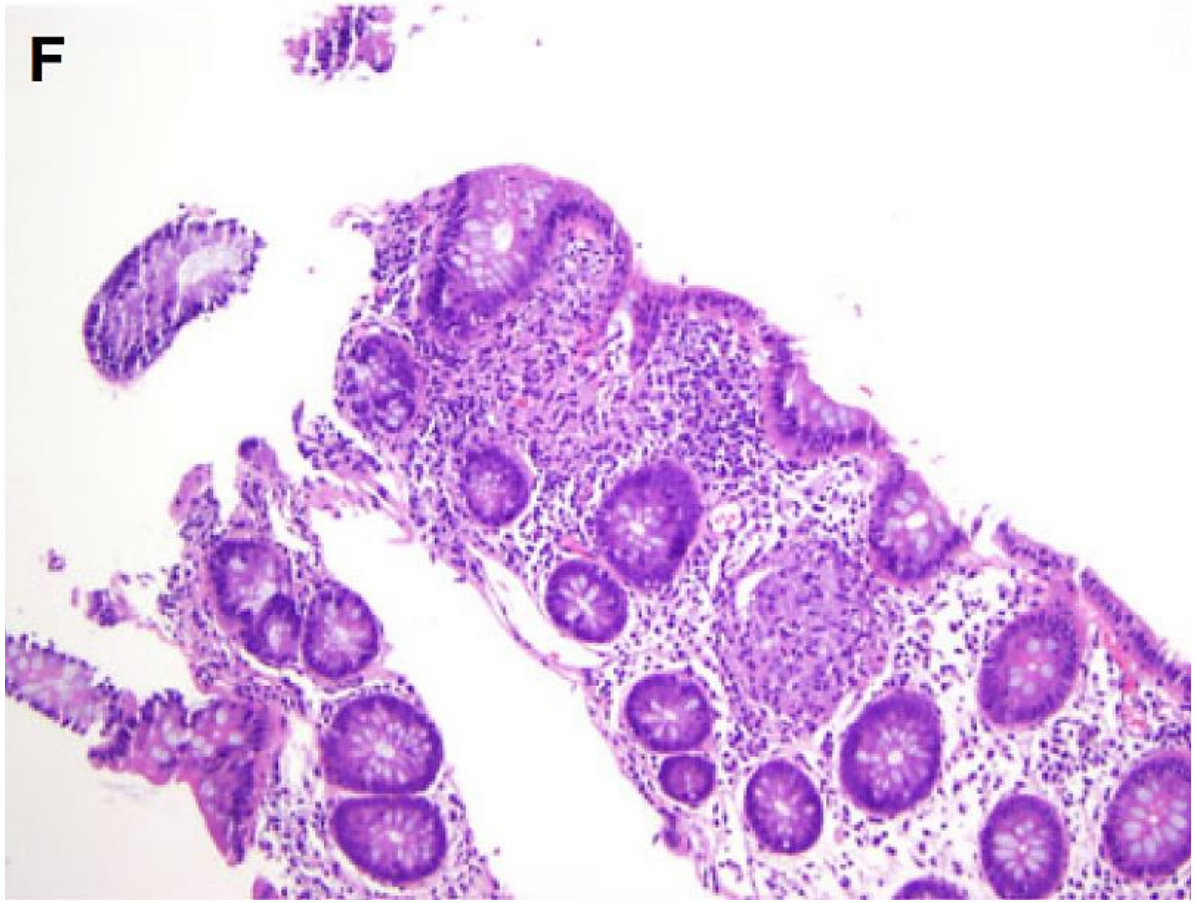


DD with IBD

- Mild architectural disarray, mainly in the area of ulcers
- Basal plasmocytosis uncommon
- Granulomas uncommon

MEDICATION

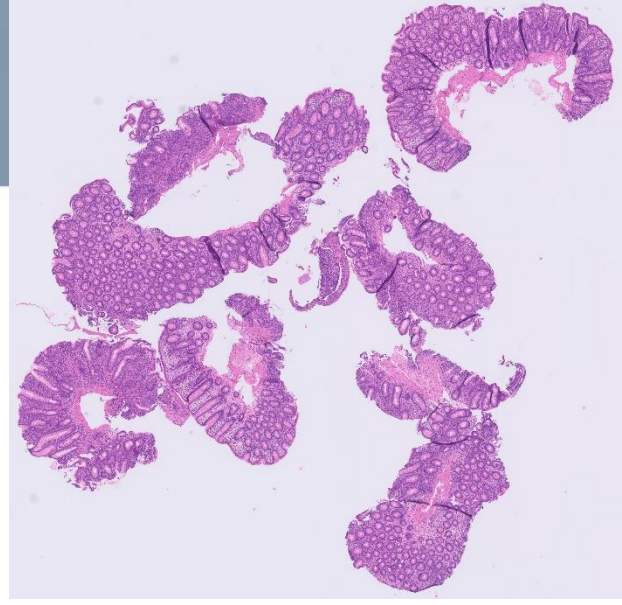
- NSAIDs, Diclofenac, PD1-inhibitors (Pembrolizumab, Nivolumab)

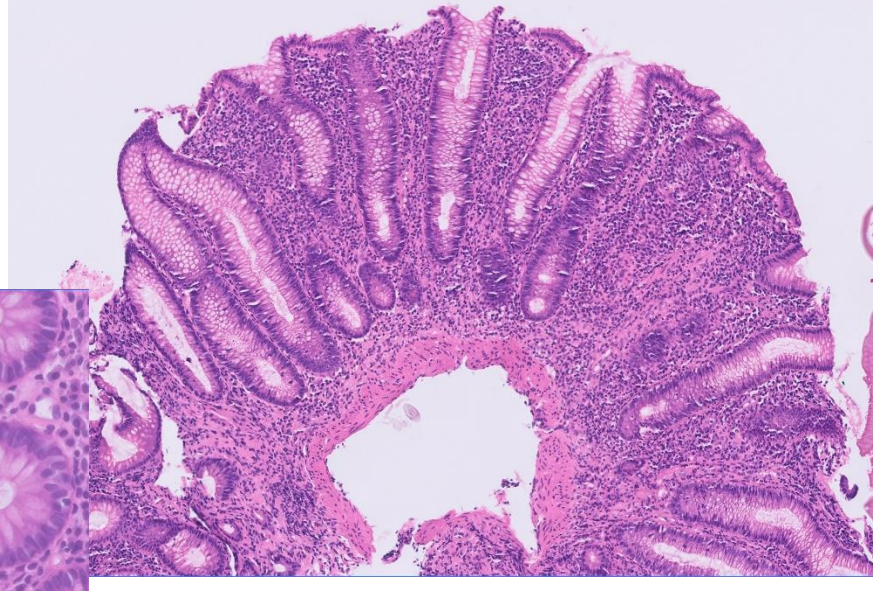


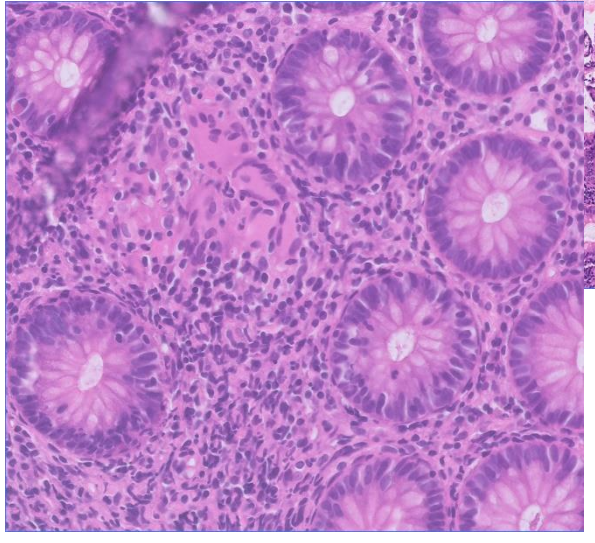
Gonzalez R. et al., Histopathology 2017

Cord-colitis

- Uncommon disease
- Colitis in patients after HSCT from umbilical-cord derived blood
- Persistent diarrhea > 7 days (5-59d)
- Histologic features ≈ Crohn's disease
  - Mild crypt distorsion
  - Mononuclear infiltrate
  - Basal plasmacytosis uncommon
  - Apoptosis limited
  - Granuloma







Gupta et al., AJSP 2013;37:1109
Herrera et al., NEJM 2011;365:815

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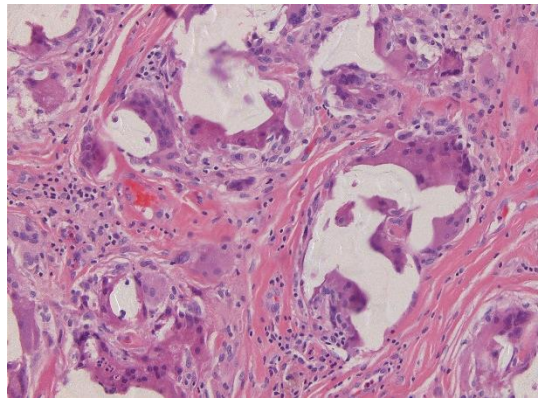
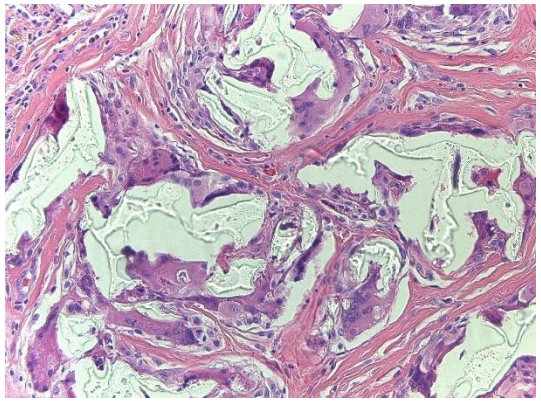
Granuloma Crohn's disease

- Clues for the etiology
  - Morphology e.g. foreign body granuloma, necrosis, sarcoid type
  - Background inflammation
  - Clinical history
    - Significant medical history
    - Extra-intestinal disease
    - Treatment
    - Travelling to foreign countries
    - …
- Be aware of infectious disease, in particular TBC !





QUESTIONS ?

UZ LEUVEN

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