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Extraintestinal Manifestations of IBD

Wednesday seminar 5.2.2025
Niklas Krupka

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Introduction

Literature

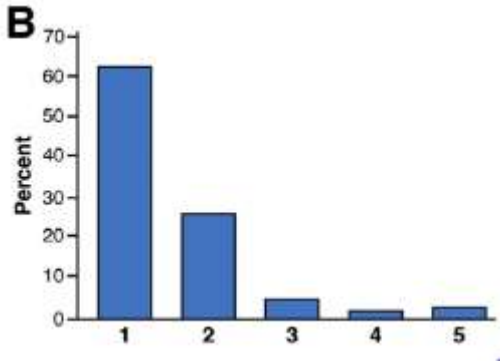
- **Gordon H et al. ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024;18(1):1-37. doi: 10.1093/ecco-jcc/jjad108**

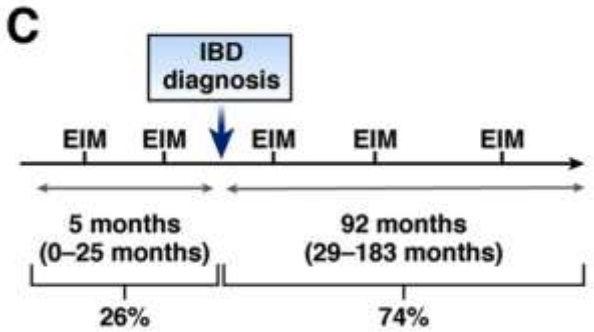
- Rogler G et al. Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. Gastroenterology. 2021;161(4):1118-1132. doi: 10.1053/j.gastro.2021.07.042

- Hedin CRH et al. The Pathogenesis of Extraintestinal Manifestations: Implications for IBD Research, Diagnosis, and Therapy. J Crohns Colitis. 2019;13(5):541-554. doi: 10.1093/ecco-jcc/jjy191

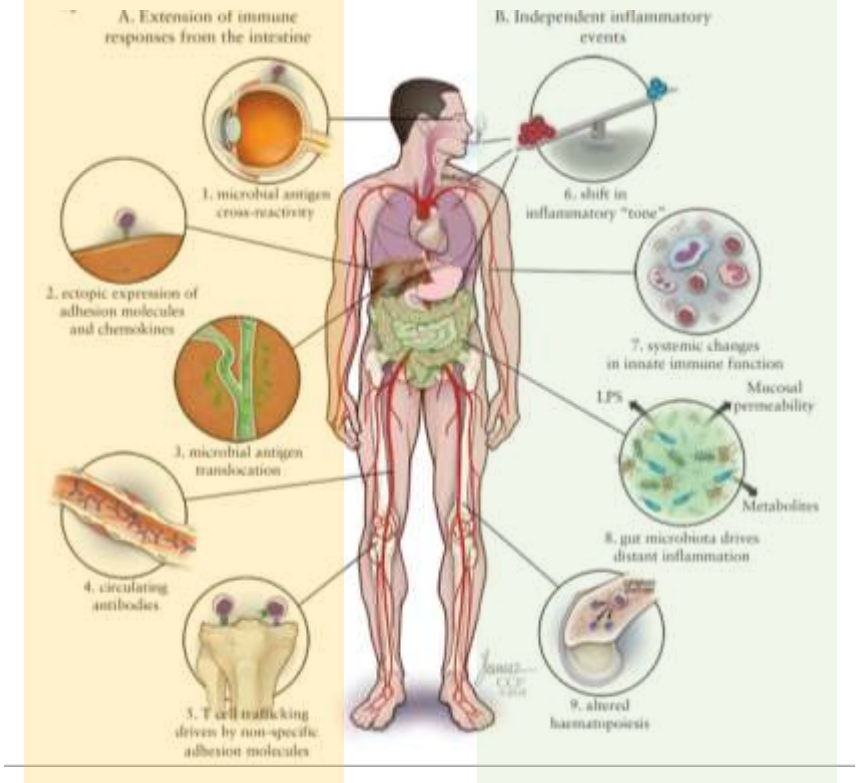
Some interesting facts

- Up to 50% of patients with IBD will develop at least one EIM in their lifetime
- Over 30% of IBD patients with EIM have more than one EIM
- EIM can occur at any time, even before IBD diagnosis (~25%)

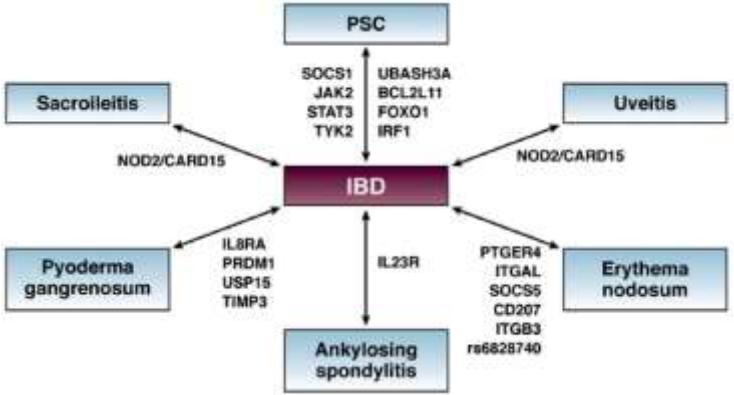




Pathophysiology of EIMs

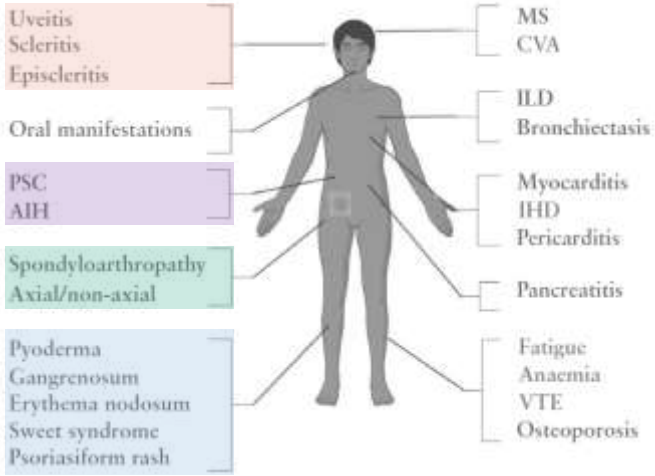


Shared genetic risk factors



EIMs that we will discuss today

1. Joint disease
2. Skin disease
3. Ocular manifestations
4. Hepatobiliary disease (very briefly)
5. Non-classical EIM



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Joint disease

Types of joint disease in IBD and diagnosis

Axial spondylarthritis (axSpa)

back pain
morning stiffness of the spine
spondylarthritis
sacroiliitis

ASAS classification criteria for axSpA
For patients with ≥3 months of back pain and age at onset <45 years

Sacroiliitis on imaging[a] plus ≥1 SpA feature[b]	Or	HLA-B27 positivity plus ≥2 other SpA features[b]
[a]SpA features:		[a]Sacroiliitis on imaging:
- Inflammatory back pain - Arthritis - Enthesitis [heel] - Uveitis - Dactylitis - Psoriasis - IBD - Good response to NSAIDs - Family history of SpA - HLA-B27 - Elevated CRP		- Active [acute] inflammation on MRI highly suggestive of sacroiliitis associated with SpA - Definite radiographic sacroiliitis according to modified New York criteria

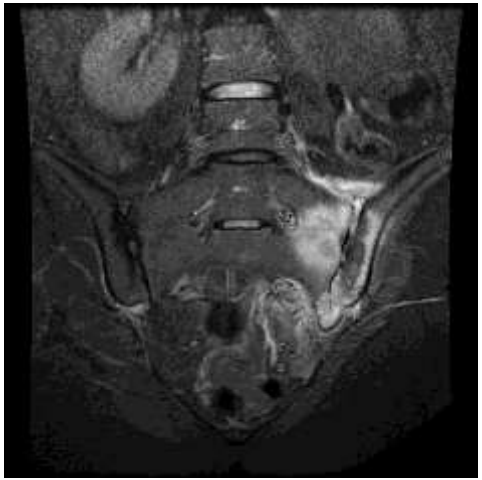
Peripheral spondylarthritis (pSpa)

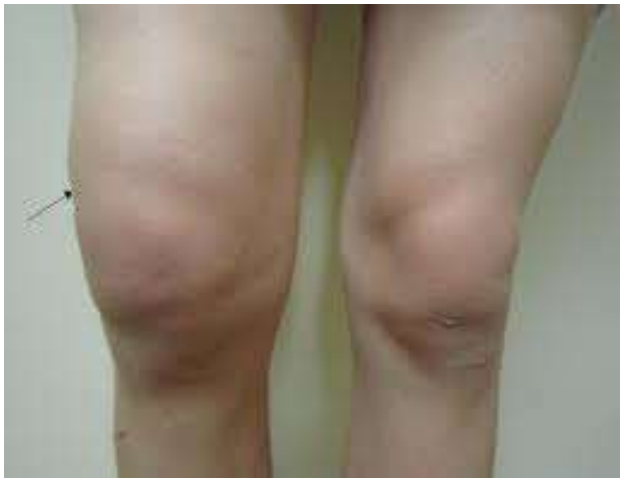
symptoms in the limbs
formerly subdivided into
Type I: often knee, with IBD flares
Type II: often MCP joints, independent of flares

Table 6. Criteria for classification of peripheral spondyloarthropathy [pSpA] [adapted from Rudwaleit *et al.*[2021]

Arthritis, enthesitis, dactylitis, or combinations thereof Plus		
≥1 of:	Or	≥2 of the remaining:
– Psoriasis – IBD – Preceding infection – HLA-B27 – Uveitis – Sacroiliitis on imaging [radiographs or MRI]		– Arthritis – Enthesitis – Dactylitis – Previous IBD – Positive family history for SpA

Clinical presentations





How do we treat joint pain?

Statement 17

There is no evidence of an association between NSAID use and UC flare [EL1], although there is potentially an association with CD flare [EL2]. We recommend that the decision to use NSAIDs for the management of arthropathy is made on a case-by-case basis [EL3]. Selective COX-2 inhibitors may be used for short periods of time [EL2] [consensus: 91%]

How do we treat persistent axial spondylarthropathy?

Statement 18

TNFα antagonists are recommended for treatment of axial spondyloarthropathy associated with IBD. Vedolizumab and ustekinumab are not recommended in axial spondyloarthropathy associated with IBD [EL2] [consensus: 96%]

... or JAK inhibitors

evidence very limited due to lack of RCTs

How do we treat persistent peripheral spondylarthropathy?

Statement 19

TNFα antagonists are recommended for treatment of IBD-associated non-axial spondyloarthropathy [EL2]. There are also data to support use of methotrexate, sulfasalazine, and ustekinumab [EL3] [consensus: 100%].

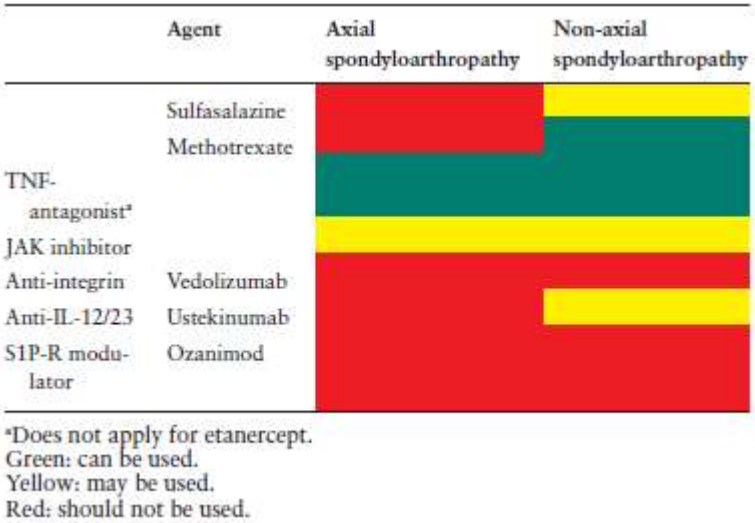
Sometimes we don't want to change main therapy

500 mg 1-0-1
max 1g 1-0-1
High rate of side effects

10 mg s.c. per week
max 25 mg per week
Important:
contraception, folic acid

Summary of treatment for joint disease

- First try NSAIDS (i.e. COX-2 inhibitors)
- If unsuccessful or persistent:



[a]Does not apply for etanercept.
Green: can be used.
Yellow: may be used.
Red: should not be used.

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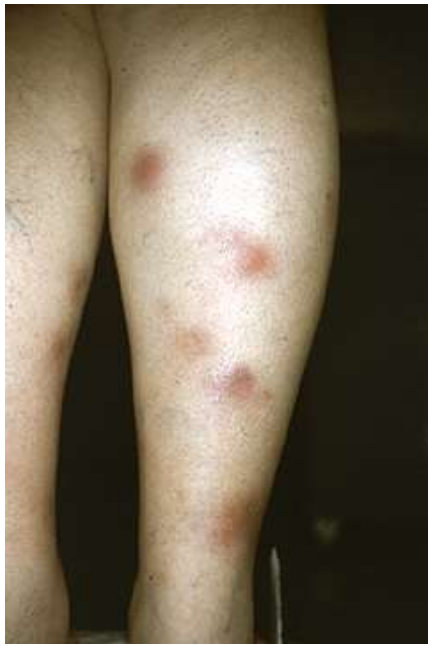
Skin disease

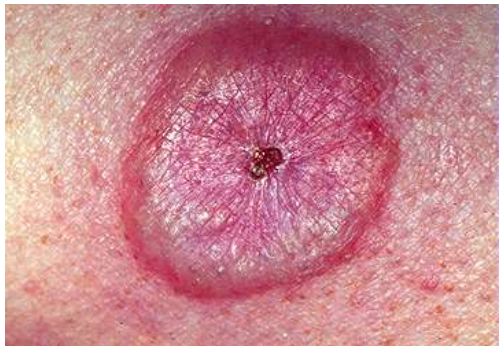
Erythema nodosum



- Painful erythematous nodules
- Often lower extremities
- Clinical diagnosis, rarely skin biopsy
- Usually associated with IBD activity

→ **Resolves when intestinal inflammation is controlled**

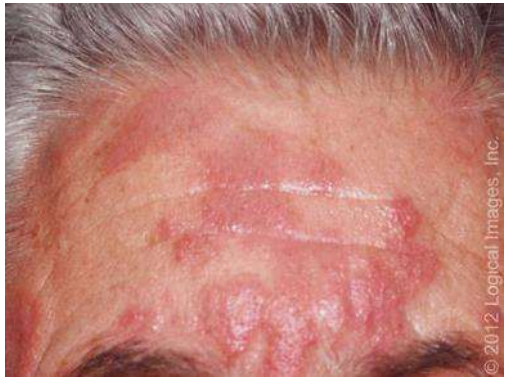
Pyoderma gangrenosum



- Single or multiple erythematous papules
- Rapid expansion to painful ulcerations
- Pathergy
- Location: often legs, peristomal
- Biopsy: sterile abscess
- Does **not** parallel IBD activity

→ anti-TNF therapy, call the dermatologist!

Sweet syndrome

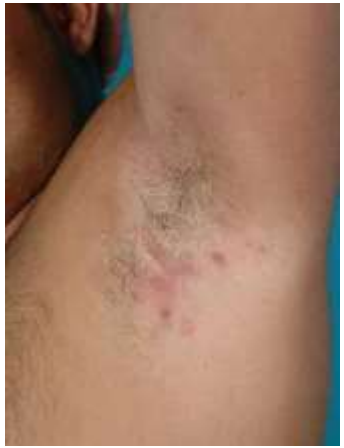


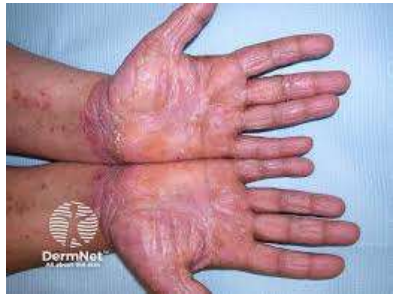
- Very rare
- Acute eruption of erythematous, tender papules
- Biopsy: neutrophilic infiltration of the dermis without vasculitis.
- Fever, peripheral neutrophilia, CRP elevation
- Follows the activity of intestinal inflammation.
- May be triggered by azathioprine

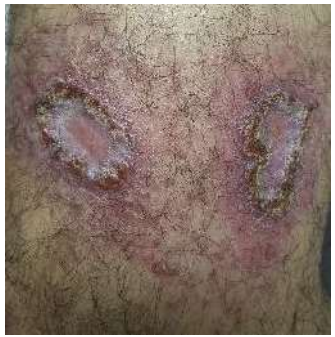
→ Steroids, improve intestinal inflammation, stop AZA

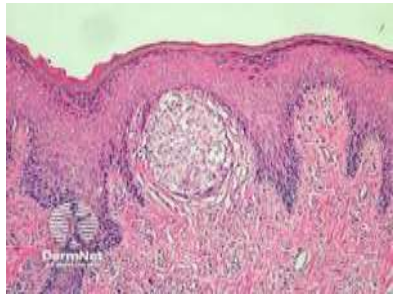
Other IBD-related skin conditions

- Hidradenitis suppurativa
- (Paradoxical) psoriasis
- Rosacea
- Atopic dermatitis
- Non-melanoma skin cancer (AZA, anti-TNF)
- Mestastatic Crohn’s disease









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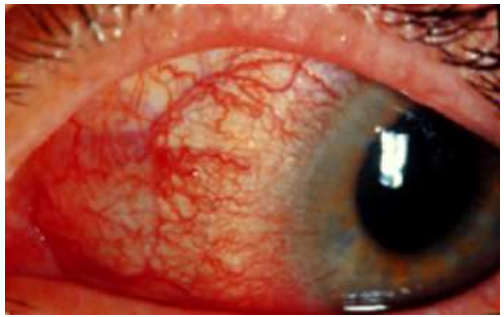
Ocular manifestations

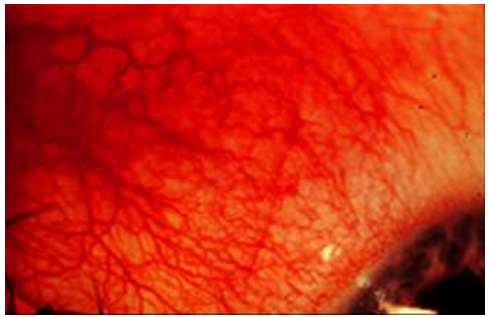
Episcleritis



- Inflammation of layer directly beneath the conjunctiva
- Common (up to 5% of IBD patients)
- Follows intestinal inflammation
- Clinical: acute redness in one or both eyes. Itching, burning. No vision impairment

→ Improve intestinal inflammation, topical therapy

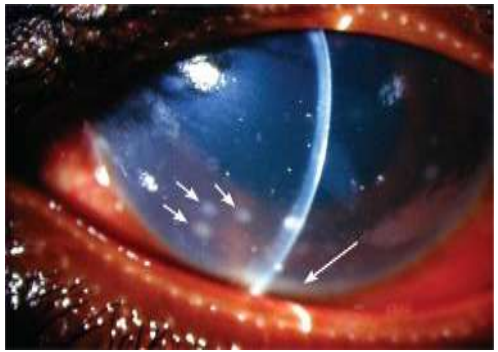
Scleritis



- Inflammation of layer directly beneath the conjunctiva
- Rare (max 1% of IBD patients)
- Does **not** follow intestinal inflammation
- Clinical: acute redness in one or both eyes. Severe **pain**. Often vision impairment
- Can lead to permanent eye damage / vision loss

→ Steroids, emergency ophthalmology consultation

Uveitis



- Inflammation of the middle layer of the eye
- Anterior uveitis: pain and redness;
- Posterior uveitis: vision loss, often no pain
- Diagnosis by slit-lamp examination
- Usually does not parallel the activity of IBD.

→ Emergency ophthalmology consultation (steroids, anti-TNF)

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Hepatobiliary disease (...briefly)

Liver disease in IBD

- Overall risk of autoimmune liver disease 5%
- Risk of NAFLD markedly increased in IBD patients compared to general population

How should we monitor?

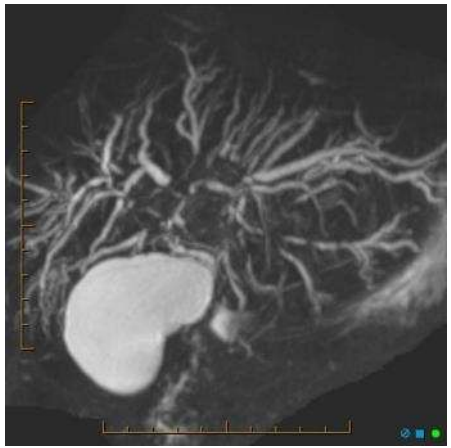
Statement 8

Alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase and total serum bilirubin should be determined in the treatment-naive patient with suspected IBD, and then at 6-month intervals throughout follow-up [EL4] [consensus: 97%]

PSC

What should we do if there is a persistent elevation of cholestatic liver enzymes?

MRI

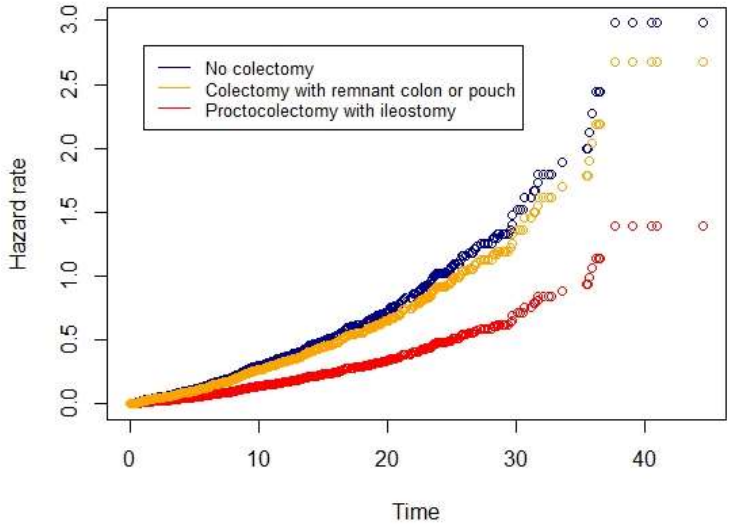


Hepatology referral

Sometimes liver biopsy
(small-duct PSC)

PSC – What should we do as gastroenterologists?

- Yearly surveillance colonoscopies (CRC risk increased)
- Sometimes ERC (dominant stenosis, malignancy?)
- Earlier referral for colectomy?



Mol, B. et al. ECCO 2024

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Non-classical EIMs

Anemia

Statement 5.2

Patients with IBD should be regularly assessed for anaemia, due to its high prevalence and considerable impact on quality of life and comorbidity. Anaemia parameters should be evaluated every 6–12 months in patients in remission or with mild disease activity; patients with active disease should be monitored at least every 3 months [EL5]. In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anaemia of chronic disease (ACD) are serum ferritin >100 µg/L and transferrin saturation <16%. If the serum ferritin level is between 30 and 100 µg/L, a combination of true iron deficiency and ACD is likely [EL2] [Consensus: 100%]

Table 2. Causes of IBD-related anaemia [adapted from Martin *et al.*[831]

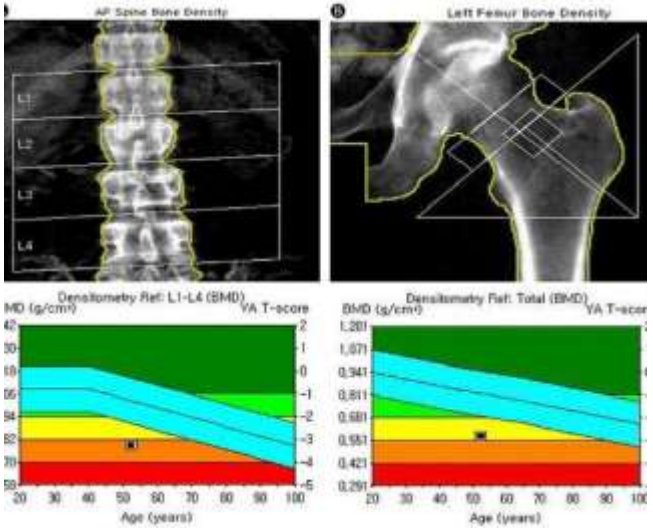
Very common	Iron deficiency anaemia Anaemia of chronic disease
Common	Cobalamin [vitamin B_{12}] deficiency Folate deficiency Drug-induced [sulfasalazine, 5-ASA, thiopurines, calcineurin inhibitors, JAK inhibitors]
Less common	Autoimmune haemolysis Myelodysplastic syndrome Aplastic anaemia Glucose-6-phosphate dehydrogenase deficiency
Rare	Vitamin D deficiency Vitamin A deficiency Vitamin B_6 deficiency Copper deficiency

5-ASA, 5-aminosalicylic acid; JAK, Janus kinase.

In most cases of iron deficiency: intravenous replacement

Low bone mass and osteoporosis

- Increased risk of osteoporosis and osteoporotic fractures in IBD patients
- Reasons: not only corticoids, but: systemic inflammation, low BMI, malabsorption in CD, genetic factors
- Risk estimation: **Dual-energy x-ray absorptiometry (DEXA)**
- Supplementation with calcium and vitamin D in patients treated with corticosteroids
- Smoking cessation, physical activity



Summary

- EIM are relatively common in IBD patients
- Some follow the course of intestinal inflammation, some do not (study this for the exam!)
- Know which IBD medication may be benificial for certain EIMs and which should be avoided
- Know when to refer to other specialties (i.e. ophtalmologic/dermatologic emergiencies
- Know what to monitor: anemia, liver function, BMD, skin cancer

EIM	Parallel Course of IBD	Separate Course of IBD	May or May Not Parallel Disease Activity
Axial arthropathy		✓	
Peripheral arthropathy	✓ (Type I)	✓ (Type II)	
Erythema nodosum	✓		
Pyoderma gangrenosum			✓
Sweet's syndrome	✓		
Oral aphthous ulcers	✓		
Episcleritis	✓		
Uveitis			✓
PSC			✓

Adapted from Trikudanathan et al.[2]