Extra intestinal manifestations of IBD- what they imply

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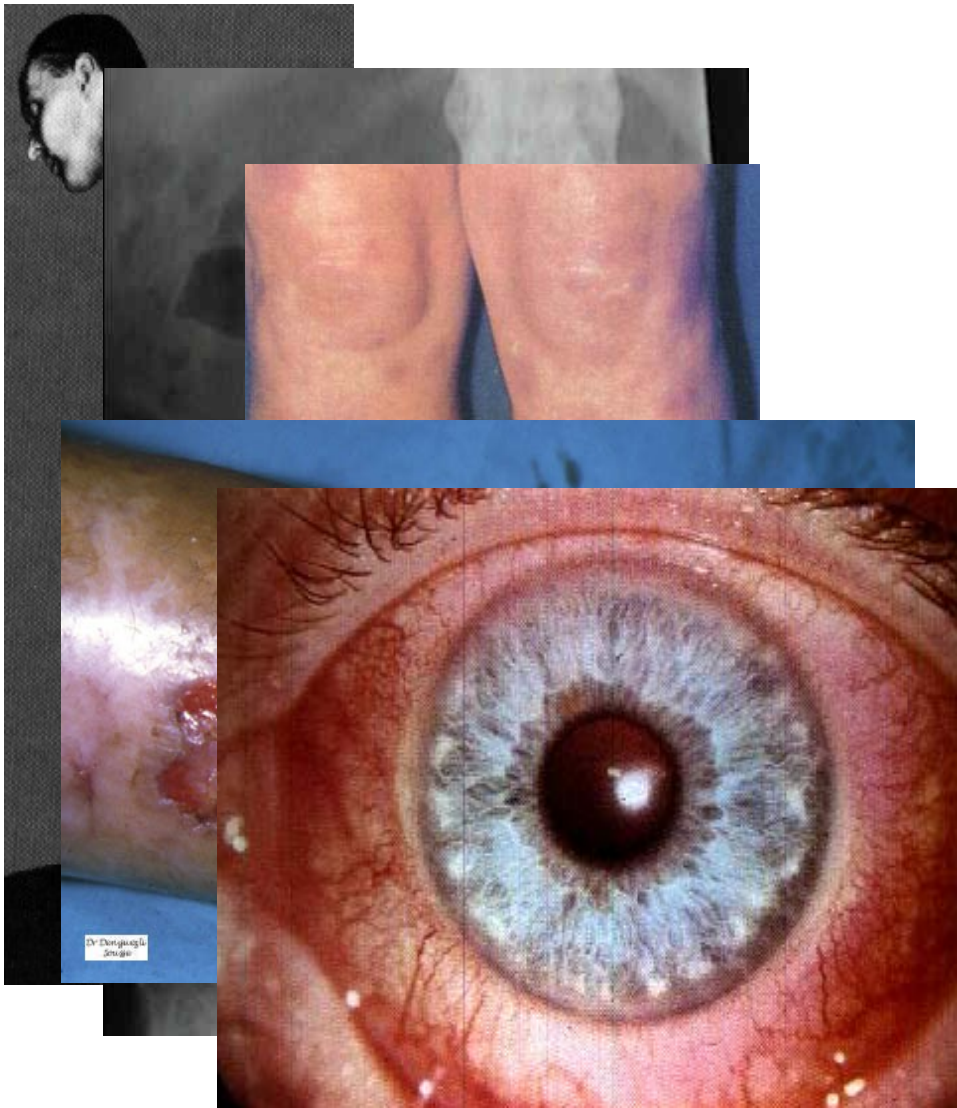
How common are EIM's

<u>36%-46% - at least one extraintestinal manifestation</u>

- Arthritis- 40 %
- Anaemia -30%
- Skin- 6 %
- Eyes- 6%
- Liver- 2.2–7.5 %



Indian Picture

- **ISG-IBD Task Force –**

  50.6 % of patients

  with UC had extraintestinal symptoms

Indian J Gastroenterol (November–December 2012) 31(6):307–323

- Extraintestinal manifestations in 34.7 % of UC
- Sacroiliitis in 14 %
- Peripheral arthritis in 10.7 %
- Ocular manifestations in 8 %,
- Mucocutaneous lesions in 2.7 %,
- Vascular complications in 2 %
- Hepatobiliary complications in 1.3 %.

Kochhar R, Mehta SK et

Indian J Gastroenterol. 1991

- Extraintestinal manifestations -39 % I
- Arthralgia in 21 %
- Sacroiliitis in 5 %.
- Ocular involvement in 7 %

Habeeb et al
Am J Gastroenterol 1997

Data on CD with EIM

- Musuloskeletal- 12%
  - Arthritis- 8%
  - Sacroilleitis – 4%
- Cutaneous – 8%
- Ocular – 4%

C Ganesh Pai, Ganesh Kumar khandige,
IJG 2000(19)17-19

Musculoskeletal- Arthralgia (34%) Backache (21%) Peripheral arthropathy (6%) Sacroilitis (3%)	
Skin lesions- Recurrent oral ulcers (16%) Other skin lesions(3%)	Hepato biliary – 4 patients PSC

Dig Dis Sci (2009) 54:1099–1107
Kshaunish Das , Uday C. Ghoshal et al

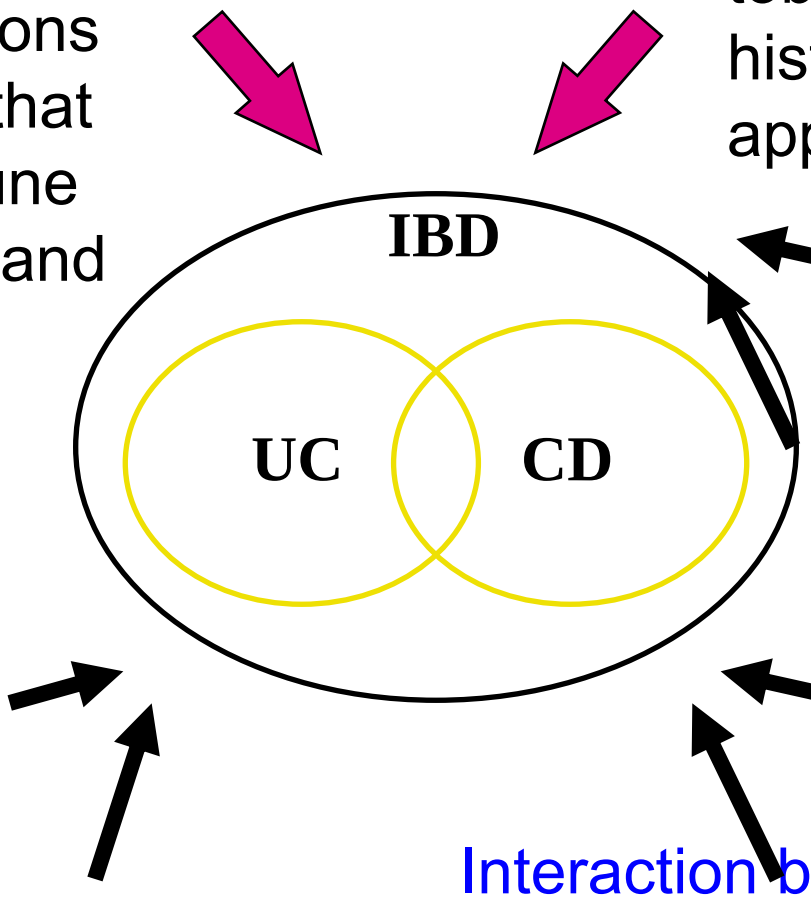
EIMs: Why do they occur?

World J Gastroenterol. Nov 28, 2009

Tatiana Sofía Rodríguez-Reyna et al

Susceptibility Genes
Sharing of alterations in key molecules that regulate the immune response by SpA and CD
-E-cadherin
-Th17 : Tregs

Environmental Factors
tobacco use and history of appendectomy



Toll-like receptors (TLRs) /innate immune response

Molecular mimicry

Increased intestinal permeability

Interaction between APCs and intestinal bacterial flora - uncontrolled CD4+ cell activation

HLA-B27 , - SpA

EIM's Disease activity

Parallel

- Peripheral arthritis
- Erythema nodosum
- Episcleritis
- Oral aphthous ulcers

Independent

- Axial arthropathy
- Pyoderma gangrenosum
- Uveitis
- Primary sclerosing cholangitis (PSC)

Musculoskeletal manifestations

- 33%- 40% of patients with IBD

Classification

A) Rheumatic

- Peripheral arthritis
- Axial involvement
- Periarticular manifestations

.

B) Metabolic

- Osteoporosis
- Osteomalacia

Peripheral arthritis

- 17% to 20%
- More common in CD

Oxford Group classification	
Type I	Pauci-articular
Type II-	Polyarticular
Type III-	Peripheral and axial

FEATURE	TYPE 1	TYPE 2
Frequency	35%	24%
Duration of attacks	<10 wk (median, 5 wk)	Months to years (median, 3 yr)
Association with bowel disease activity	Parallel	Independent
Joints Affected		
Number	<5	≥5
Type	Mainly large joints	Mainly small joints

AS and other forms of axial involvement

- More common in CD (5%-22%) than in UC (2%-6%)
- General, the prevalence is

  - 10%-20% for sacroiliitis
  - 7%-12% for AS

Clinical picture

- Virtually the same as Idiopathic AS
- Ankylosing spondylitis associated with IBD can develop at any age
- In AS associated with IBD, the male to female ratio is 1:1

Modified Rome criteria

- Chronic inflammatory back pain (at night and at rest, improving by exercise)
- Morning stiffness
- Limited spinal flexion
- Reduced chest expansion (later stages)

- Axial symptoms usually precede gut symptoms
- Clinical course is totally independent of the intestinal manifestations
- Even intestinal surgery does not alter the course of SpA

Diagnosis

- Radiographs : demonstrate sacroiliitis, syndesmophytes and bone proliferation evolving to ankylosis (“bamboo spine”).
- Gold standard : MRI

  - Ability to demonstrate inflammation before bone lesions occur

Treatment

- Type I peripheral arthritis
  - Emphasis on treatment of the underlying colitis
- Type II peripheral arthritis
- Axial arthritis
  - treating underlying colitis may not treat EIM

Journal of Crohn's and Colitis (2013) 7, 1–33
Journal of Crohn's and Colitis (2010) 4, 63–101

TREATMENT

- **Depends on the severity of the clinical picture**
- Patients with mild arthritis

  - Rest
  - Physiotherapy
  - Intra-articular steroid injections
  - NSAIDS --Use must be limited to the minimal effective dose and time
  -- COX-2 inhibitors safer with a lower risk of disease flare than conventional NSAIDs

World J Gastroenterol. Nov 28, 2009; 15(44): 5517–5524.
Tatiana Sofía Rodríguez-Reyna, Cynthia Martínez-Reyes, and Jesús Kazúo Yamamoto-Furusho

- For moderate disease:
  - Sulfasalazine and 5-aminosalicylic acid
  - Efficacious in peripheral arthritis > SpA
  - Particularly in UC > CD

- Severe disease :

  - Methotrexate, azathioprine, 6-mercaptopurine, cyclosporine and leflunomide

  - TNF-α blocking agents –infliximab, adalimumab and certolizumab

  - Infliximab - first-line treatment - active AS associated with IBD

Experimental

- IL-10, IL-11, IL-6
- Intercellular adhesion molecule 1
- Mitogen-activated protein kinase
- Integrin (α4 and α4β7) blockade
- TLR modulation
- Probiotics

Metabolic bone disease

- Low bone mass and osteoporosis are common (20%–50%)

- Contributing factors
  - Chronic inflammation
  - Corticosteroid treatment
  - Age
  - Smoking
  - Low physical activity
  - Nutritional deficiencies

Diagnosis

- T score < −2.5 on bone densitometry (DEXA scanning) in patients over 50 years

- Patients under 50 “low bone mass” is defined by a Z-score < 2.0

Treatment – all patients

- **Decrease steroid use**

- Weight-bearing exercise
- Stopping smoking
- Avoiding alcohol excess
- Maintaining adequate dietary calcium

Treatment

- Treat osteoporosis
- However if the T score is less than −1.5, treatment with calcium and vitamin D should be recommended
- Pre-existing history of fracture– Treat even if the T score is normal

Bisphosphonates

- Clearly established in-
  - postmenopausal women
  - steroid-induced osteoporosis
- Besides , calcitonin and its derivatives, raloxifene can be used in such females
- In young, premenopausal patients with IBD- not recommended

- Newer drugs like teriparatide, strontium ranelate :

  should be prospectively studied in IBD before their use can be recommended

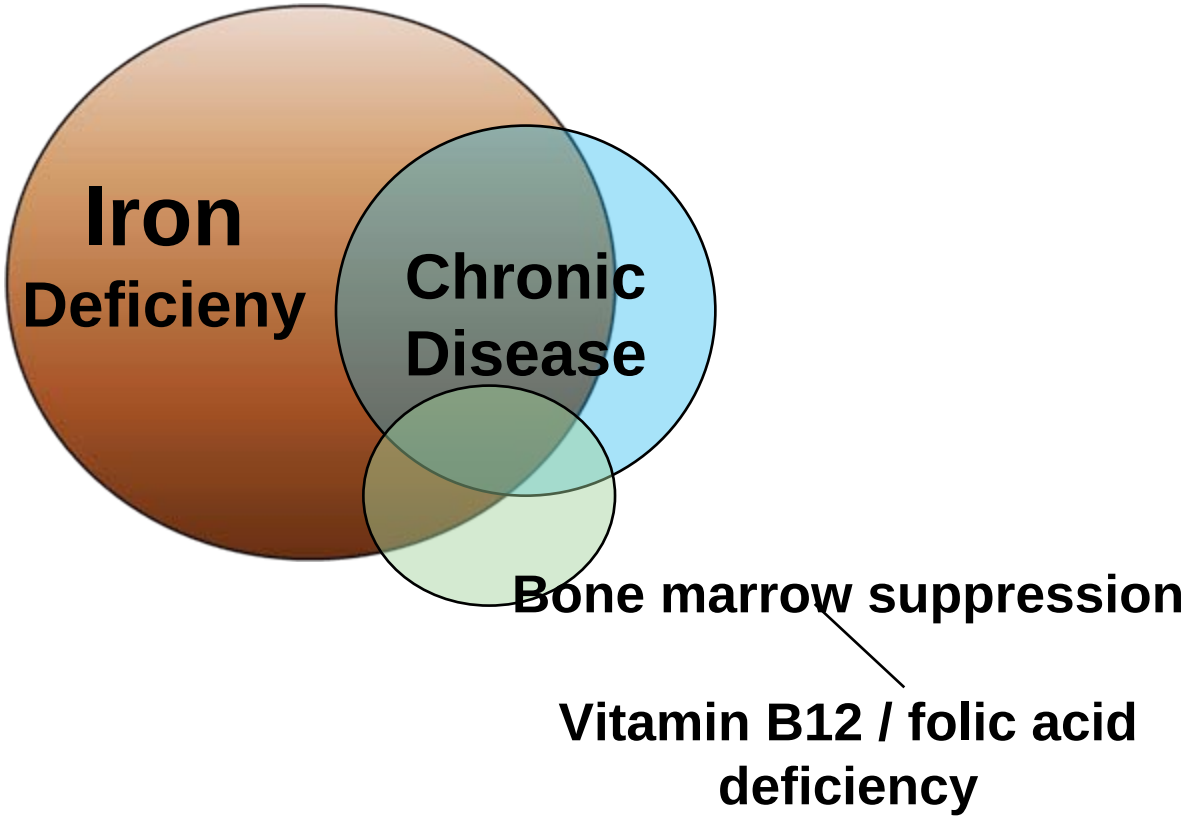
Anaemia

- In severe disease - 66% of all inpatients have anaemia
- Iron deficiency is more prevalent than anaemia, being present in up to 45% of all IBD patients

Journal of Crohn's and Colitis (2013) 7, 1–33
Journal of Crohn's and Colitis (2010) 4, 63–101

Has previously received little attention

Causes of Anemia in IBD



WHO definition

- Haemoglobin < 12 g/dL in women
- < 13 g/dL in men

- Severe anaemia (Hb level < 10 g/dL)

Diagnosis

Serum ferritin < 30 mcg/L and Transferrin saturation < 16%	IDA
Serum ferritin > 100 mcg/L and Transferrin saturation < 16%.	ACD
Serum ferritin - between 30 -100 mcg/L and Transferrin saturation < 16%.	Combination of IDA and ACD

Treatment

- Treating the underlying IBD
- IDA- iron supplementation

Goal of therapy for IDA

- **To increase haemoglobin levels** :

  by > 2 g/dL or increase them to normal values within 4 weeks

- **To replenish iron stores:**

  - Transferrin saturation > 30%
  - Serum ferritin > 200–500 mcg/L

Ganzoni Formula

- Iron deficit [mg] =

Body weight [kg]

×

target Hb−actual Hb [g/dL])× 2.4

+

stored iron (500 mg)

What is treatment of choice in IDA in IBD

- Oral iron
- IV iron
- Erythropoieses stimulating agents
- Blood transfusion

Oral or IV

- > 90% oral iron remains unabsorbed
- Oral iron GI side effects
- Generation of ROS (Fenton reaction) by non-absorbed iron

  - can potentially lead to the exacerbation of IBD

Intravenous iron therapy is advisable

- Intolerant or unresponsive to oral iron supplementation
- Severe anaemia (Hb level < 10 g/dL)
- Patients with pronounced disease activity
- Patients being treated with erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents

- Anaemia does not improve in spite of intravenous iron therapy and control of inflammation
- Treatment should be combined with intravenous iron supplementation

Blood transfusion

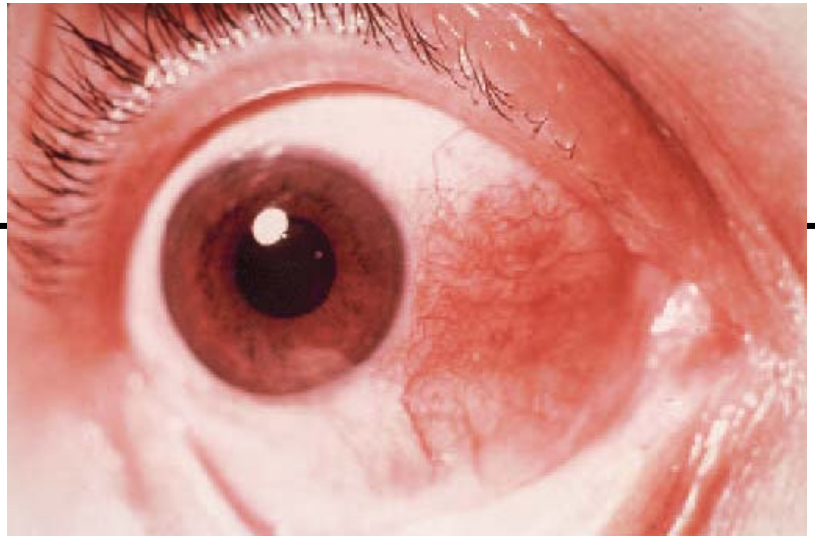
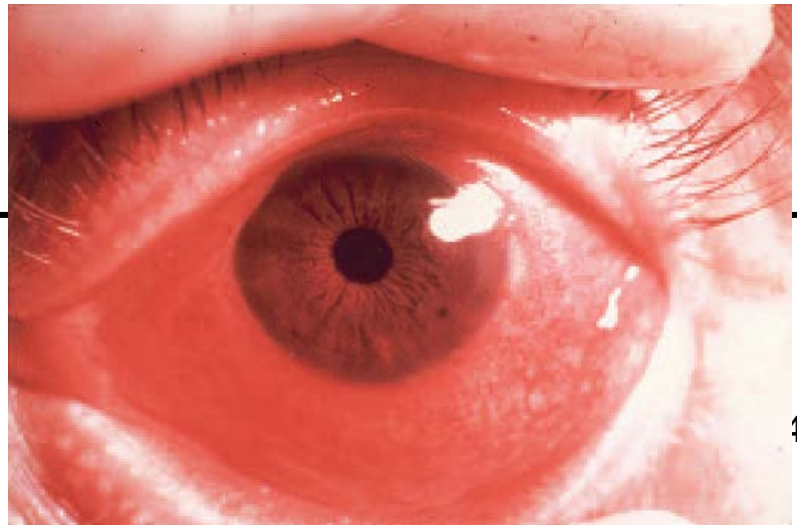
- Acute severe anaemia with hemodynamic instability
- Severe anaemia-related weakness and fatigue
- Failure of all other treatments

Ocular manifestations

- **Patients with ocular manifestations should be referred to an ophthalmologist**

- Uveitis and episcleritis are the most common ocular manifestations of IBD

Seema A. Patil & Raymond K. Cross
Curr Gastroenterol Rep (2013) 15:314

Episcleritis	Uveitis
Painless	Eye pain
•Hyperaemic sclera and conjunctiva •Itching and a burning sensation	•Blurred vision •Photophobia •Headaches
•Diffuse dilation of all vessels is seen, but normal vasculature is not disturbed. •Absence of circum-limbal injection •A normal appearing pupil	•The superficial conjunctival injection extends to the limbus with involvement of the circum- limbal vessels (ciliary flush) •Abnormally reacting pupil
	

Episcleritis may be self-limiting	•Less common but has potentially more severe consequences •Frequently bilateral, insidious in onset and long-lasting •**The possibility of progression to loss of vision**
•Treatment of the underlying IBD •Usually respond to topical steroids or NSAID	•Slit-lamp examination •The treatment will usually consist of both topical and systemic steroids •Resistant cases – - Azathioprine, methotrexate, - Infliximab and adalimumab

Cutaneous manifestations of IBD

Specific lesions
(Same biopsy)

- Fissures and fistulas
- Aphthous stomatitis
- Mucosal nodularity (cobblestoning)
- Pyostomatitis vegetans
- Metastatic Crohn's disease

Reactive lesions

- Erythema nodosum,
- Pyoderma gangrenosum
- Vesiculopustular eruptions
- Necrotising vasculitis
- Cutaneous PAN

Cutaneous disorders associated with IBD

Autoimmune skin disorders
- Acquired epidermolysis bullosa
- Bullous pemphigoid
- Linear IgA bullous dermatosis
- Vitiligo
- Psoriasis

Hidradenitis suppurativa
Lichen planus
Erythema multiforme
Urticaria ,Phlebitis
Secondary amyloidosis

Secondary to nutritional malabsorption

- Acrodermatitis enteropathica (zinc)
- Scurvy (vitamin C)
- Purpura (vitamin C ,K)
- Pellagra (niacin)
- Stomatitis-glossitis angular cheilitis (vit- B)
- Non-specific eczema and dry skin (EFA)
- Abnormal hair and nails (protein)

Cutaneous manifestations secondary to treatment:

- Drug eruption
- Peristomal dermatitis

Miscellaneous

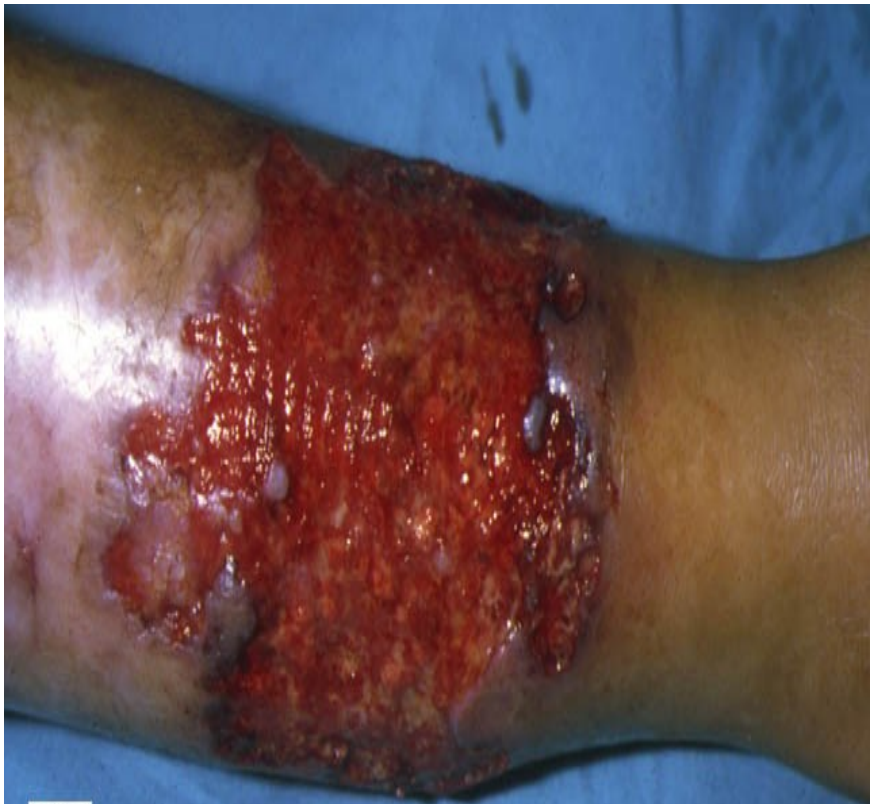
- Bowel associated dermatosis-arthritis syndrome

PYODERMA GANGRENOSUM

- More common in UC(5–12%) :CD (1–2%)
- Equal in men and women
- Peak age incidence - 25 to 54 years

Angelo V. Marzano, MD,* Alessandro Borghi, MD et al
Inflamm Bowel Dis Volume 20, Number 1, January 2014

- PG can occur before, during, or after the onset of IBD
- Can occur independently of IBD
- Most commonly - lower extremities
- Large ulcers in response to minor trauma



- Pain- pustule - ulceration
- Surrounded by a bluish border

Diagnosis

Differential diagnosis:

- Infection
- Sweet's syndrome
- Malignancy
- Vascular disease
- Systemic disease

Diagnosis

- Tissue should be examined histologically to rule out other diseases.
- In classic ulcerative PG, there is neutrophilic infiltrate centrally in the ulcer and lymphocytic infiltrate in the periphery

Management

- Management should be directed at both the lesions of PG and at the underlying IBD
- Most lesions take one year to heal

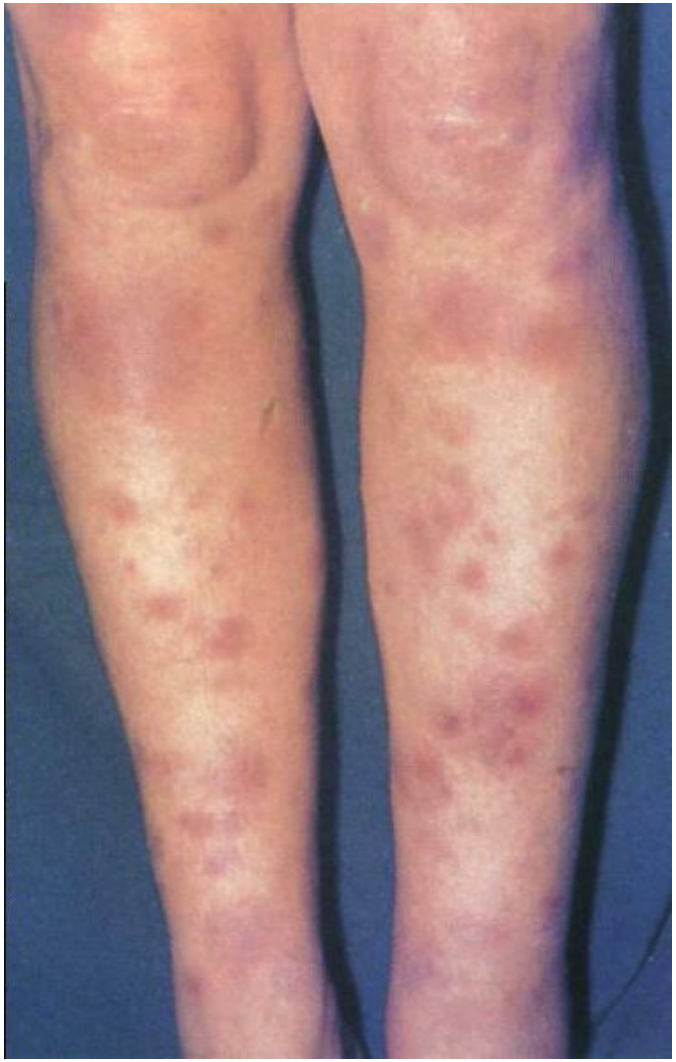
Topical therapy	Systemic therapy	Refractory PG
Sodium cromoglyate / Local injections of triamcinolone acetonide	Prednisone Cyclosporine Sulfa drugs	Infliximab

ERYTHEMA NODOSUM

- Upto 11% of cases
- UC > CD
- Women - three to six times
- Peak age - 20 and 30 years
- Often are associated with exacerbations of the bowel disease

Angelo V. Marzano, MD,* Alessandro Borghi, MD et al
Inflamm Bowel Dis Volume 20, Number 1, January 2014

- Sudden onset
- Multiple, bilateral, symmetric
- Red, warm, and painful nodules about 2 cm in diameter.
- Most commonly on shins
- Can occur on the calves, trunk, and face



- Systemic symptoms such as fever, malaise, and joint pain often occur.
- The typical course lasts for three to six weeks
- Neither ulceration nor scarring occurs in EN.

Diagnosis

- Clinical
- Avoid Biopsy - scarring

Management

- In most cases, EN is self limiting
- Resolves in three to six weeks without scar formation

Management

- Control of the IBD (Usually will resolve)
- Supportive treatment includes leg elevation, support stockings, and bed rest
- NSAIDs
- Systemic corticosteroids

Hepatobiliary disease

- **Primary sclerosing cholangitis (PSC)**
- Pericholangitis
- Steatosis
- Chronic hepatitis
- Cirrhosis,
- Gallstone formation

Primary sclerosing cholangitis (PSC)

- Asymptomatic elevation of LFT's
- Later jaundice
- MRCP
- ERCP – to dialate stricture
- UDCA- 20 mg/kg /bw
- CCA/CA colon

Thank you