IBD associated arthritis

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Classification criteria for CD-SpA adapted from the Assessment of SpondyloArthritis international Society (ASAS) criteria [14, 15]

Axial CD-SpA	Peripheral CD-SpA
Inflammatory back pain[a] in a patient with CD	Arthritis and/or dactylitis and/or enthesitis in a patient with CD
AND	AND
Sacroiliitis on imaging[b]	Exclusion of other specific forms of inflammatory joint disease
OR	
HLA B-27 antigen positivity	

CD Crohn's disease, *CD-SpA* Crohn's disease associated spondyloarthritis, *SpA* spondyloarthritis

[a]Insidious onset, chronic back/buttock pain with morning stiffness lasting $\geq$ 30 min, improvement with activity and nocturnal exacerbation

[b]Active inflammation on MRI highly suggestive of sacroiliitis OR definite radiographic sacroiliitis according to modified New York criteria

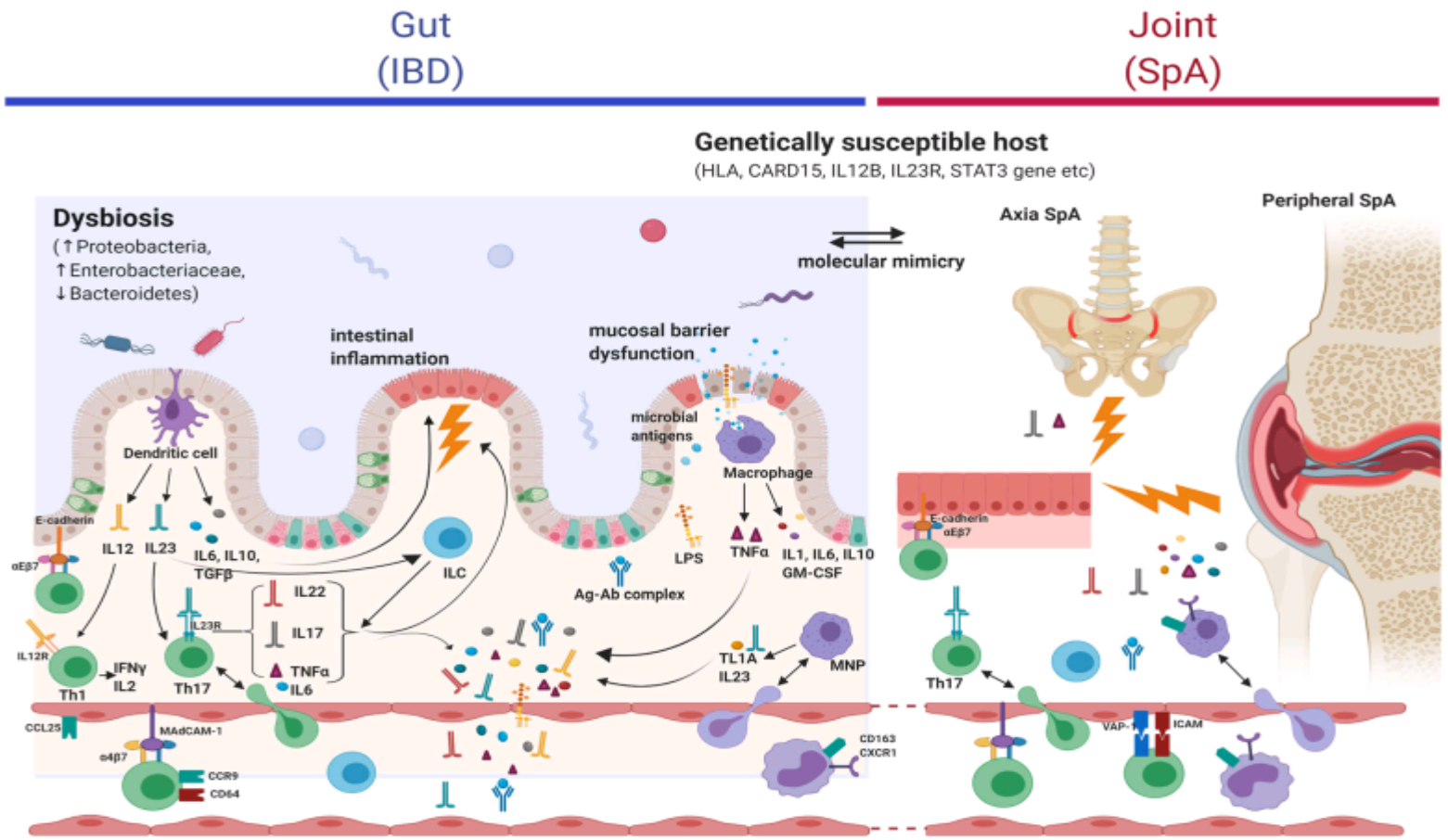
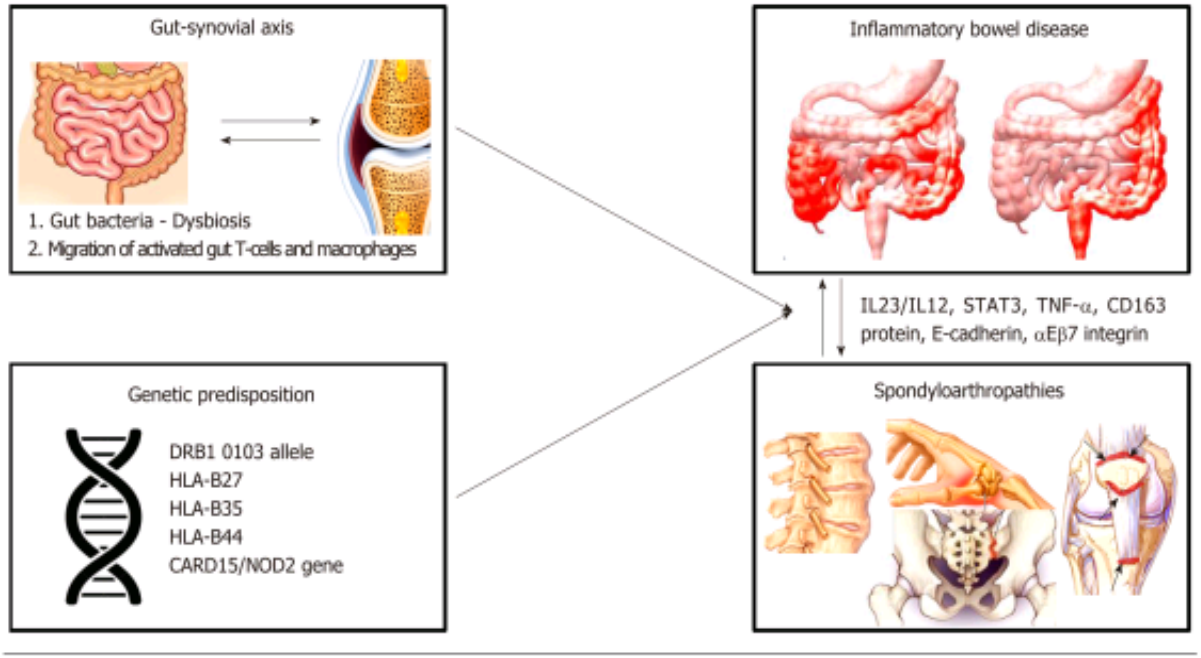


Fig. 1 Pathogenic mechanisms of Crohn's-associated spondyloarthritis. *Ag-Ab* antigen–antibody complex, *CARD15* Caspase recruitment domain-containing protein 15, *CD* Crohn's disease, *CD-SpA* Crohn's disease associated spondyloarthritis, *GM-CSF* granulocyte monocyte colony stimulating factor, *HLA* human leukocyte antigen, *IBD* inflammatory bowel disease, *IL* Interleukin, *ILC* innate lymphoid cell, *IFN* interferon, *LPS* lipopolysaccharide, *MNP* mono-nuclear phagocytes, *SpA* spondyloarthritis, *TNF* tumor necrosis factor, *Th* helper T cells. Genetic susceptibility: presence of HLA genes (B27, B35, B44) and polymorphisms in IL-23R, IL-12B, STAT3, and CARD9, CARD15 genes increase the susceptibility of host to both IBD and SpA. Intestinal dysbiosis: abundance of *Proteobacteria, Enterobacteriaceae, Ruminococcus gnavus* and a reduction in Bacteroidetes in patients with CD-SpA. Additionally, abundance of *Dialister, R. gnavus, Prevotella* (axial SpA) seen in SpA. Molecular mimicry: cross reactivity between peptide sequences common between enteric bacteria and host HLA. Autoimmune gut inflammation in CD triggered by genetic and environmental factors leading to activation of IL23-IL17 axis and intestinal phagocytic cells. Extension of immune response from gut to joint could occur through: Molecular mimicry; Trafficking of activated immune cells (T cells, macrophages, innate lymphoid cells) facilitated by: ectopic expression of gut-specific chemokines (CCL25), adhesion molecules (MAdCAM, ICAM, E-cadherin) and integrins (α4β7, αEβ7) in the joint; binding to non-gut-specific adhesion molecules (VAP-1) and chemokine receptors (CXCR3, CCR5); Intestinal mucosal barrier dysfunction and translocation of microbial antigens/products (LPS); Increased inflammatory mediators and proinflammatory cytokines (IL-6, TNFα, IFNγ,) in serum; Circulating autoantibodies with epitopes shared between the gut and joint



Pathogenic mechanisms linking gut and joint inflammation. The pathogenic link between spondyloarthropathies (SpAs) and inflammatory bowel disease (IBD) involves the so-called "gut-synovial axis" hypothesis. Various environ mental (gut bacteria-dysbiosis) and host factors (migration of activated gut-T cells and macrophages) leading to initiation of inflammation in genetically predisposed individuals may act as triggers of inflammatory responses against gut and joints components. IBD patients carrying specific human leukocyte antigens (HLA) alleles (such as DRB1 0103 allele, HLA-B27, HLA-B35, HLA-B44) and mutations of the CARD15/NOD2 gene are at higher risk of developing SpAs. Recently, up-regulation of adhesion molecules (E-cadherin, αEβ7 integrin), increased levels of pro-inflammatory cytokines (tumor necrosis factor-α), macrophages expressing CD163 protein, interleukin (IL)-12/IL-23 signaling pathway and signal transducer and activator of transcription 3 protein have also been implicated in the pathophysiology of SpAs in IBD patients. IL: Interleukin; STAT: Signal transducer and activator of transcription; TNF: Tumor necrosis factor; HLA: Human leukocyte antigen; CARD15: Caspase recruitment domain-containing protein 15; NOD: Nucleotide-binding oligomerization domain-containing protein 2.

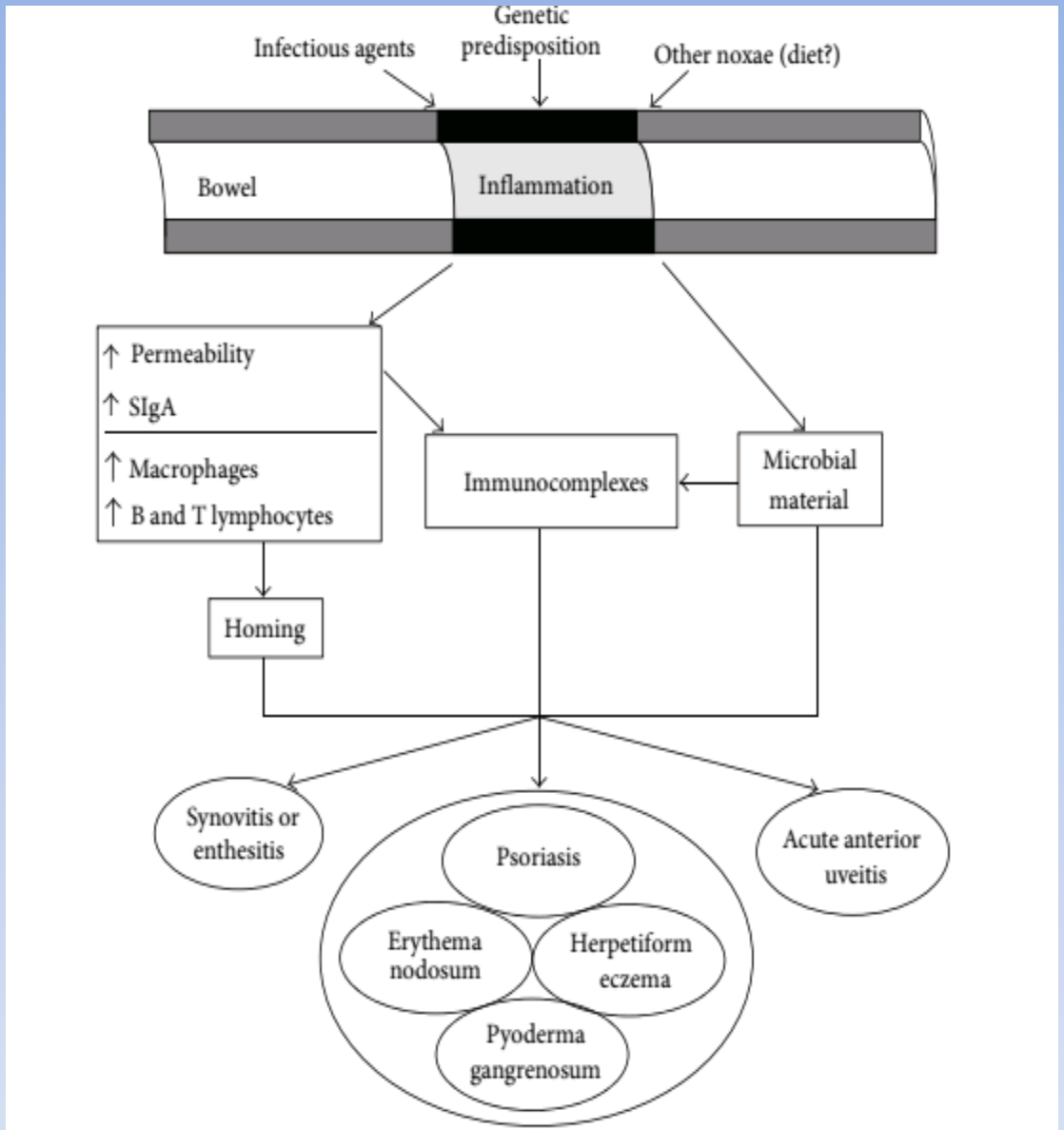


FIGURE 1: The bowel component in the pathogenesis of seronegative spondyloarthritis.

Classification and features of articular involvement subsets in inflammatory bowel disease (IBD).

Peripheral			Axial	
Type 1	Type 2	Type 3	Isolated sacroiliitis	Spondylitis
(i) Pauciarticular (less than 5 joints) (ii) Asymmetric involvement (iii) Acute, self-limiting attack (<10 weeks) (iv) Usually coincides with relapse of IBD (v) Strongly associated with other extra-intestinal manifestations (vi) Lower limbs more affected (vii) Associated with HLA DRB1, B35, B27	(i) Polyarticular (5 or more joints) (ii) Symptoms persist for months or even years (iii) May be erosive (iv) Runs a course independent of IBD (v) Affects both large and small joints (vi) Strongly associated with uveitis (vii) Associated with HLA B44	(i) Both axial and peripheral involvement	(i) Asymptomatic (ii) Usually non progressive disease	(i) Usually precede the onset of IBD (ii) Runs a course independent of IBD (iii) Clinical course is similar to idiopathic ankylosing spondylitis (iv) Disease progression leads to increasing immobility and ankylosing (v) Associated with uveitis (vi) Strongly associated with HLA B27

Axial arthritis (sacroiliitis and spondylitis) in inflammatory bowel disease (IBD) has the following characteristics:

- **Insidious onset of low back pain, especially in younger persons**
- **Morning stiffness**
- **Exacerbated by prolonged sitting or standing**
- **Improved by moderate activity**
- **More common in Crohn disease (CD) than in ulcerative colitis (UC) [5]**
- **Independent of GI symptoms**

Peripheral arthritis in IBD demonstrates the following characteristics:

- **Nondeforming and nonerosive**
- **More common in CD with colonic involvement than in UC**
- **May precede intestinal involvement, but usually concomitant or subsequent to bowel disease, as late as 10 years following the diagnosis**
- **Type 1 (pauciarticular [< 5 joints]) [7] - Acute, self-limiting attacks, lasting less than 10 weeks; asymmetrical and affecting large joints, such as the knees, hips and shoulders; strong correlation to IBD activity, most frequently with extensive UC or colonic involvement in CD; associated with other extraintestinal manifestations of IBD**
- **Type 2 (polyarticular [>5 joints]) [7] - Chronic, lasting months to years; more likely symmetrical, affecting**

Enthesitis affects the following parts of the body:

- **Heel - Insertion of the Achilles tendon and plantar fascia**
- **Knee - Tibial tuberosity, patella**
- **Others - Buttocks, foot**

Extra-articular IBD demonstrates the following characteristics:

Intestinal - Abdominal pain, weight loss, diarrhea, and hematochezia
Skin - Pyoderma gangrenosum (in UC), erythema nodosum (in CD)
Oral - Aphthous ulcers (in UC, CD)
Ocular - Uveitis, anterior, nongranulomatous
Systemic low-grade fever, secondary amyloidosis (in CD)

Intestinal bypass arthritis demonstrates the following traits:

- **Triggered following a procedure for morbid obesity (jejunocolostomy or jejunoileostomy) - The proposed mechanism is bacterial overgrowth in the bypassed bowel, which causes inflammation and synthesis of immune complexes**
- **Arthritis - Develops in 20-80% of patients 2-30 months after surgery and is chronic in 25% of cases**
- **Polyarthritis - May occur**
- **Dermatitis - Associated in 66-80% of cases**
- **Reversal of procedure produces permanent remission of symptoms**

Celiac sprue demonstrates the following characteristics:

- **Gluten-sensitive enteropathy**
- **Arthritis uncommon**
- **May precede diagnosis of celiac disease**
- **Lumbar spine, hips, knees, shoulders**
- **Usually symmetrical**
- **Improves with gluten-free diet**

Collagenous and lymphocytic colitis can be characterized as follows:

- **Unknown cause**
- **Linear deposition of collagen in the subepithelial layer of the colon**
- **Watery diarrhea and colicky abdominal pain**
- **Peripheral arthritis of hands and wrists - May precede GI symptoms by years (10% of cases)**
- **Arthritis improved by nonsteroidal anti-inflammatory drugs (NSAIDs)**

Whipple disease demonstrates the following characteristics:

- **Rare, multisystemic**
- **Caused by infection with Tropheryma whippleii**
- **Most common in middle-aged men**
- **Diarrhea, weight loss, and malabsorption**
- **Migratory polyarthritis in as many as 90% of cases, which may precede GI symptoms by years**
- **Sacroiliitis - Occasional**
- **Diagnosis via small-bowel biopsy**
- **Symptoms improved by prolonged courses of antibiotics - Eg, penicillin, tetracycline, erythromycin**

Assessment of Spondyloarthritis International Society Classification criteria for axial spondyloarthropathy and peripheral spondyloarthropathy

Axial Spondyloarthropathy

Patients with back pain ≥ 3 months and age at onset <45 years

Sacroiliitis on imaging[1] plus ≥ 1 **Spondyloarthropahty feature** (Imaging arm)	OR	*HLA-B27 plus* ≥ *2 other* **Spondyloarthropahty features** (Clinical arm)
	Spondyloarthropahty features	
	Inflammatory back pain	
	Arthritis	
	Enthesitis (heel)	
	Uveitis	
	Dactylitis	
	Psoriasis	
	Crohn's Disease/Ulcerative colitis	
	Good response to NSAIDs	
	Family history of spondyloarthropahty	
	HLA-B27	
	Elevated CRP	

Peripheral Spondyloarthropathy

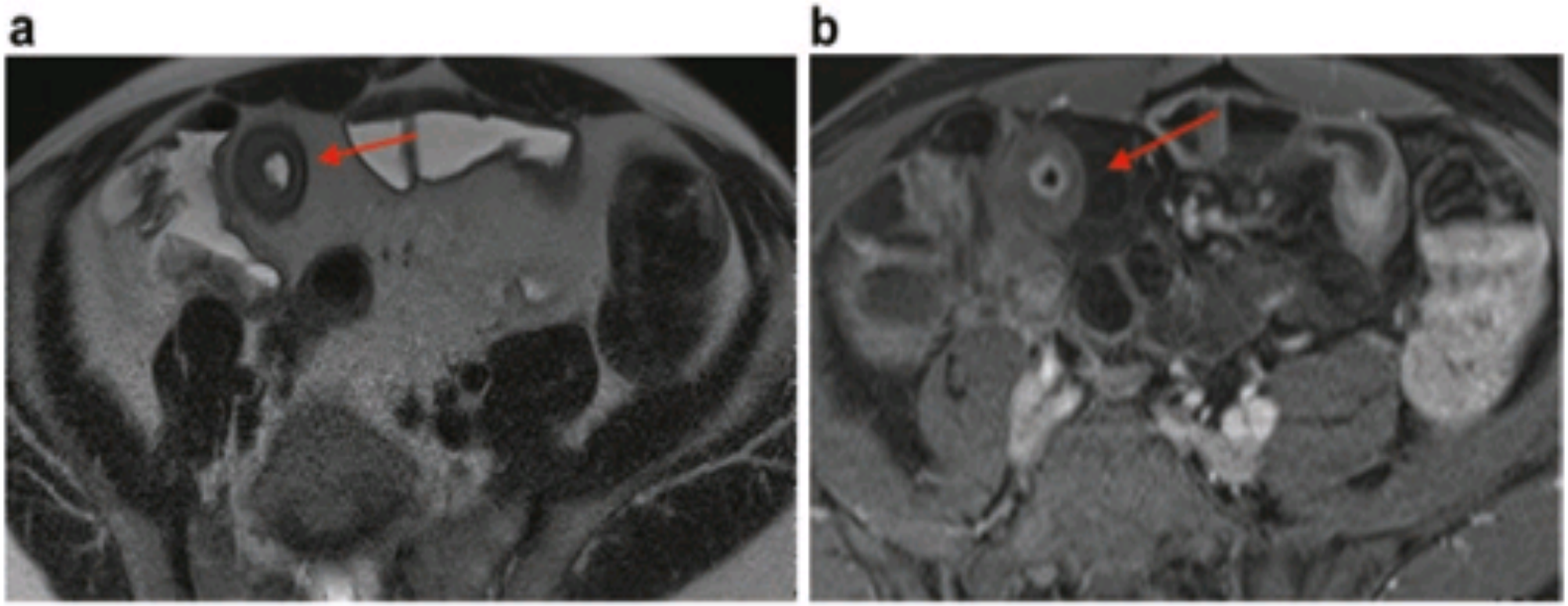
Arthritis OR Dactylitis OR Enthesitis[2]

PLUS

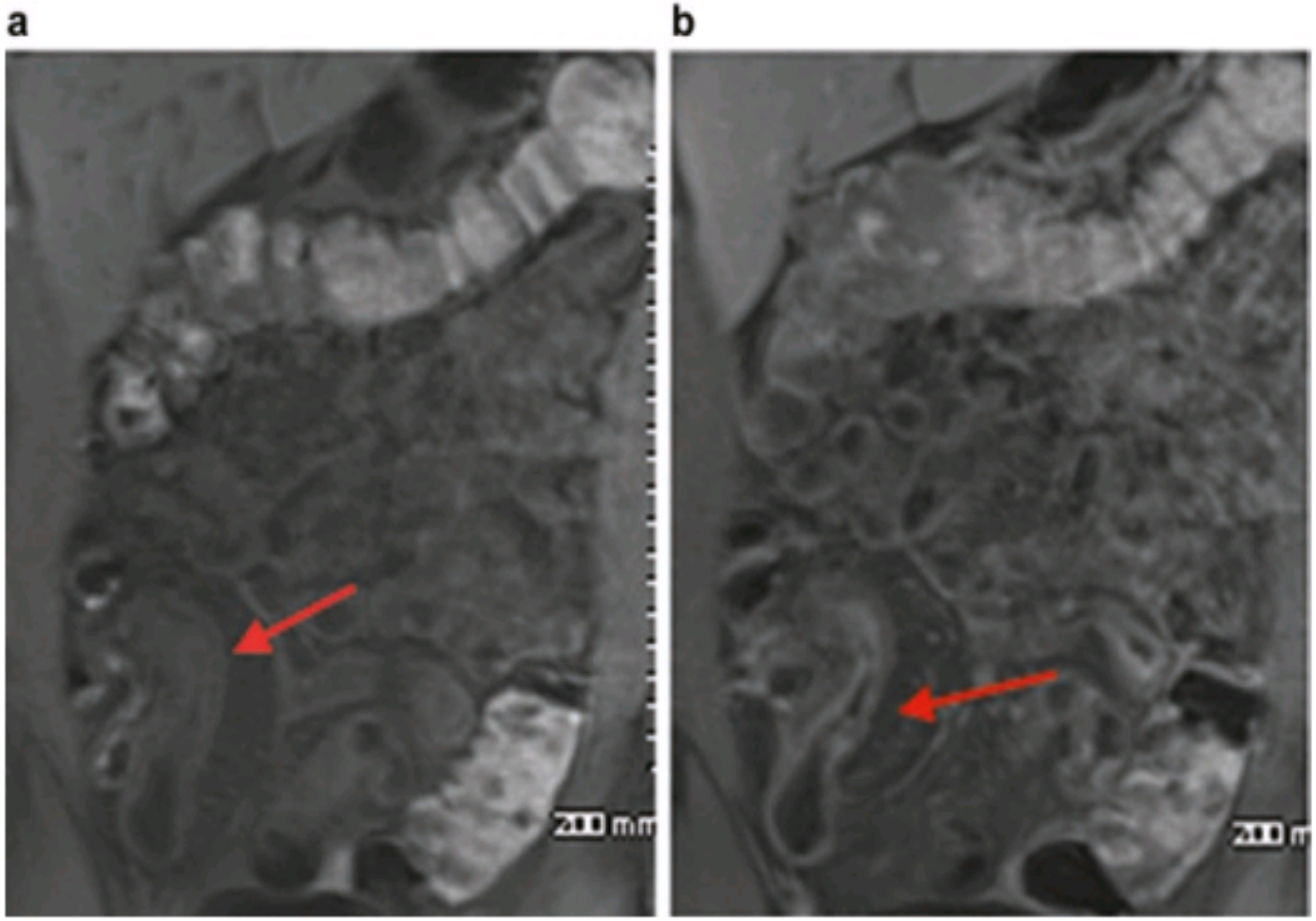
≥ 1		≥ 2
Uveitis		Arthritis
Psoriasis		Enthesitis
Inflammatory bowel disease	OR	Dactylitis
Preceding infection		IBP (past)
HLA-B27		Family history of Spondyloarthropahty
Sacroiliitis on imaging		

ASAS (ASAS, Assessment of Spondyloarthritis international Society) classification criteria for axial Spondyloarthropathy (axSpA) and peripheral Spondyloarthropathy (peripheral SpA).
[1]Definite radiographic sacroiliitis according to the modified New York criteria or positive sacroiliac magnetic resonance imaging.
[2]Without current back pain. NSAIDS: Non-steroidal anti-inflammatories; HLA: Human leukocyte antigen; CRP: C-reactive protein; IBP: Inflammatory back pain (3,4).

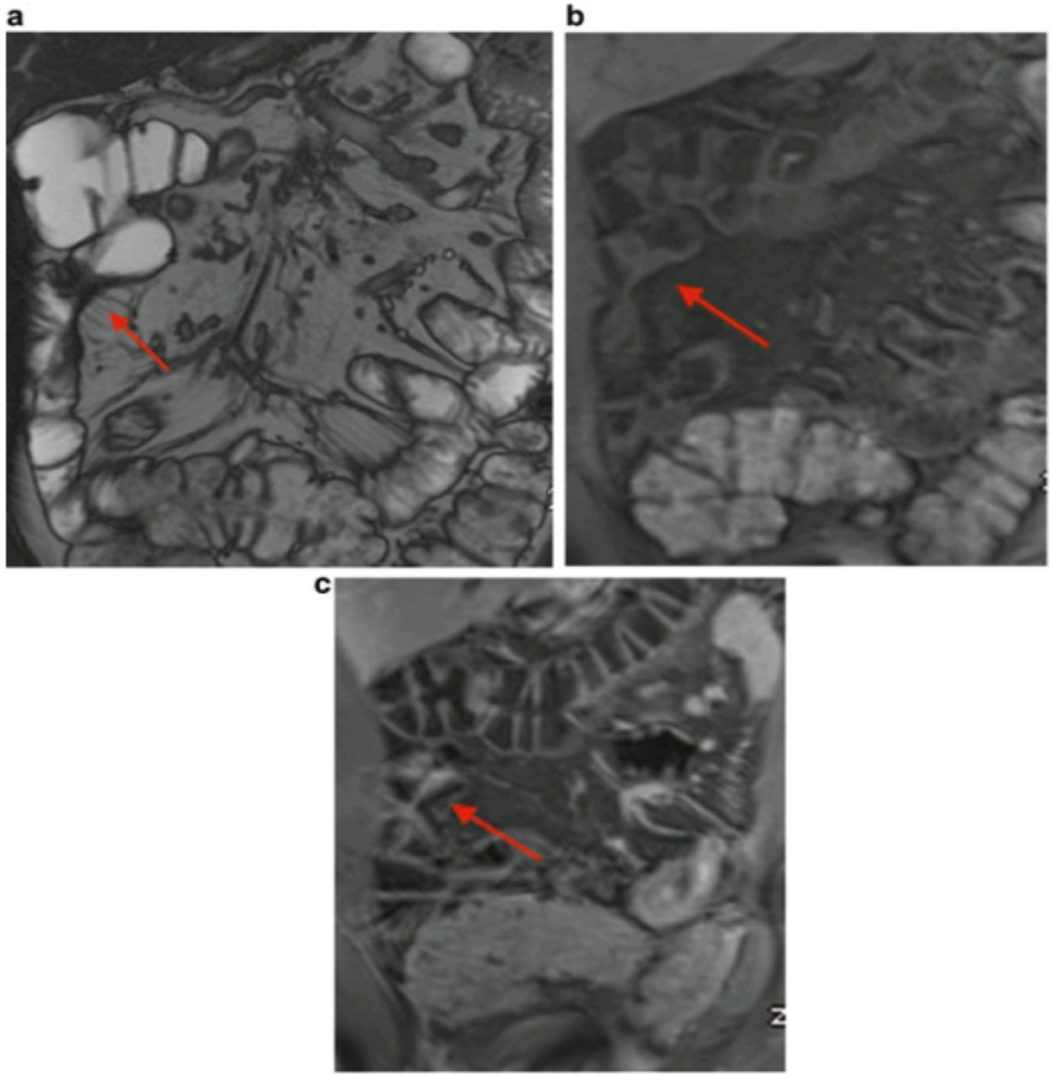
suggested to link these two entities.



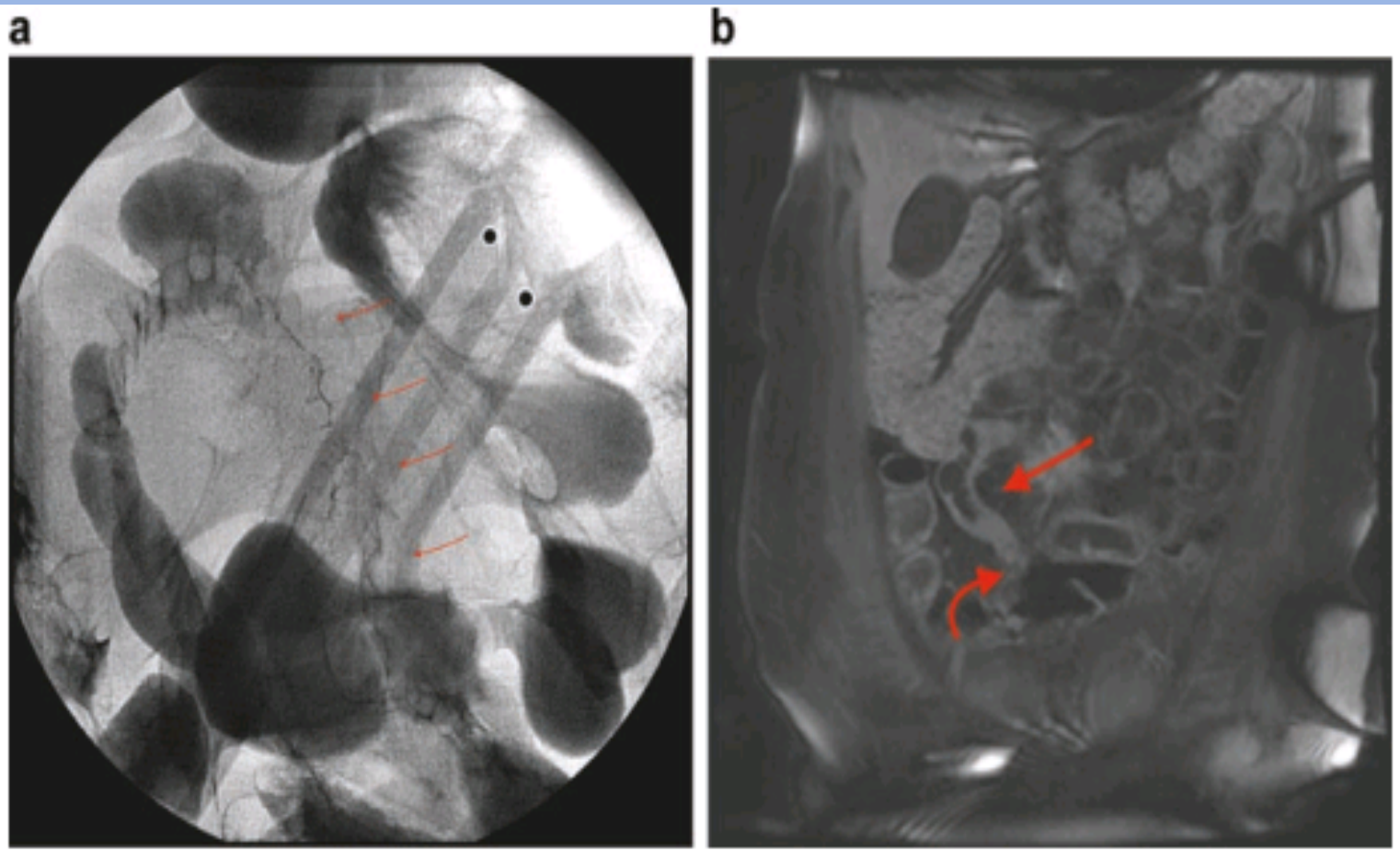
(**a**) Axial half-Fourier acquisition single-shot turbo spin-echo sequence demonstrates abnormal T2 signal within the bowel wall (*arrow*) signifying underlying mural edema. (**b**) Early (70 s) post-contrast T1-weighted image demonstrates marked wall thickening within the abnormal small bowel loop (*arrow*). We can identify the stratified wall enhancement consisting of the strongly enhancing mucosa, a poorly enhancing edematous submucosa, and an enhancing serosa



(**a**) Coronal noncontrast T1-weighted image demonstrates an abnormally thickened segment of terminal ileum (*arrow*). (**b**) Coronal T1-weighted image obtained at 70 s demonstrates a stratified enhancement pattern of the actively inflamed bowel wall



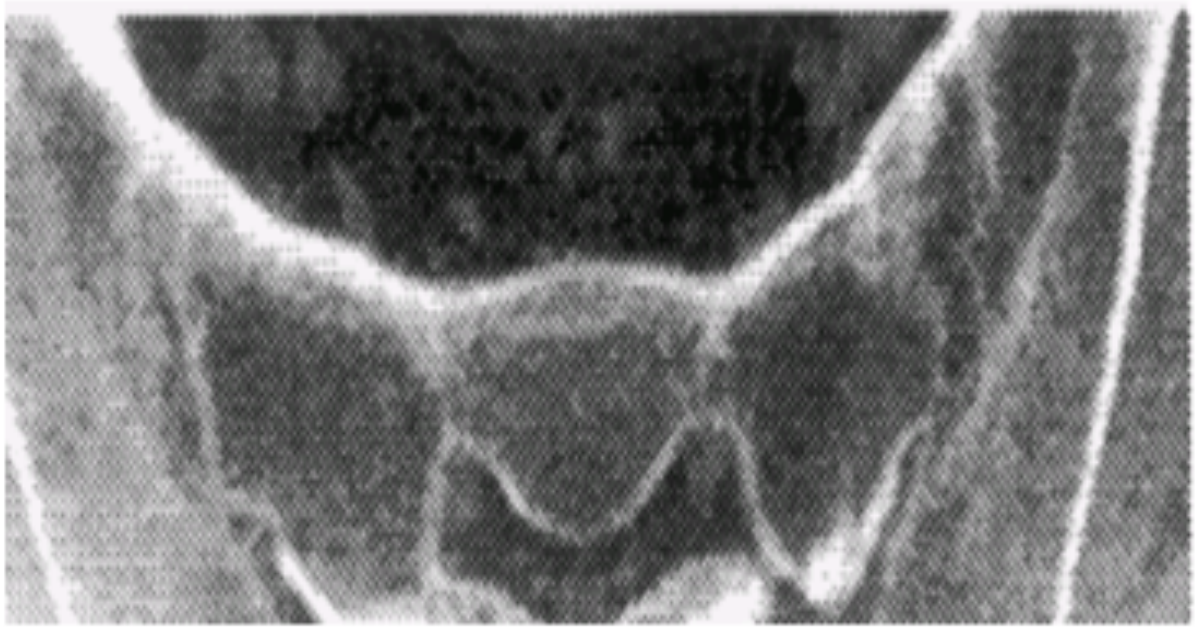
(**a**) Coronal fast imaging with steady-state free precession demonstrates low T2 signal within the wall of a short segment chronic stricture involving distal ileum consistent with underlying fibrosis. (**b**) Coronal noncontrast T1-weighted image shows mild wall thickening of the same segment consistent with chronic disease. (**c**) Coronal post-contrast T1-weighted image demonstrates homogeneous enhancement within the abnormal strictured segment consistent with fibrosis. Note the absence of stratified enhancement which would suggest active inflammation



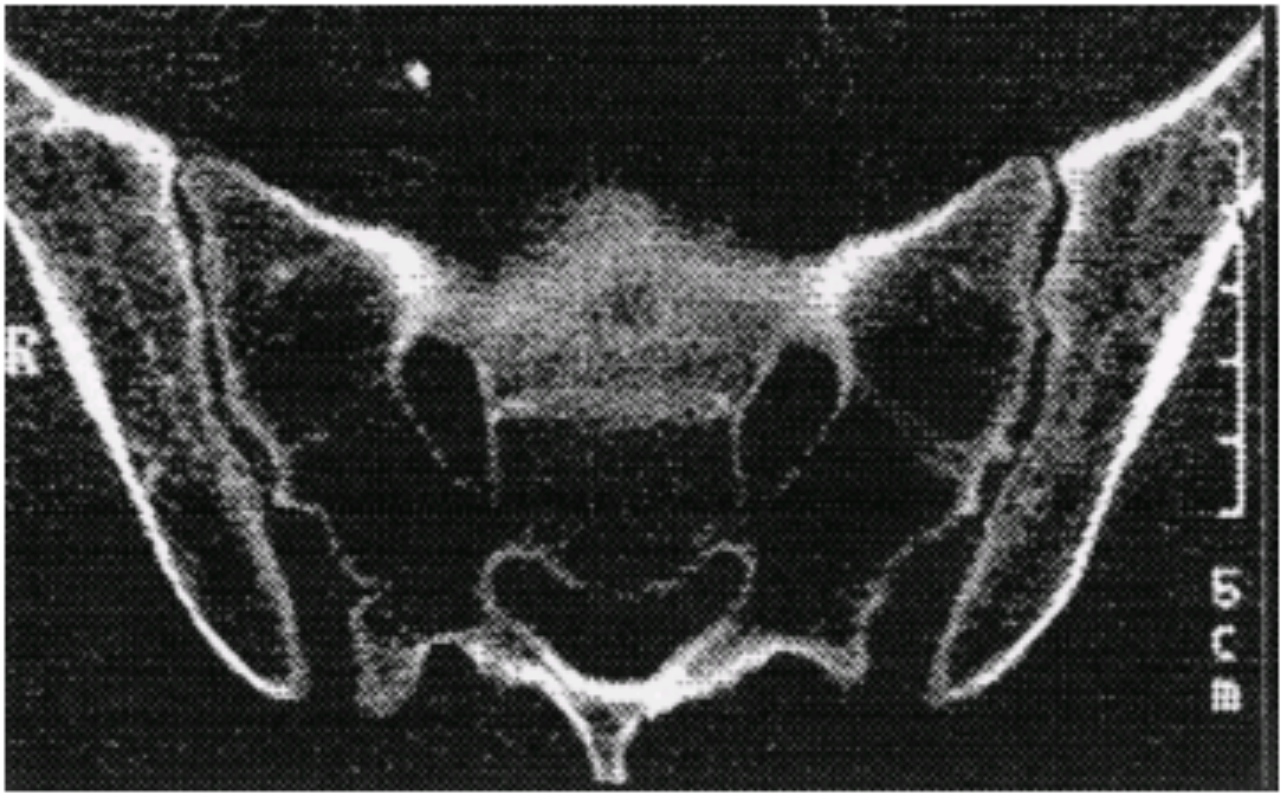
Axial (**a**) and coronal (**b**) post-contrast CTE images demonstrate abnormal mural thickening and stratification of a segment of distal ileum (*arrows*) in a patient with active inflammation and IBD

HRCT categories in sacroileitis

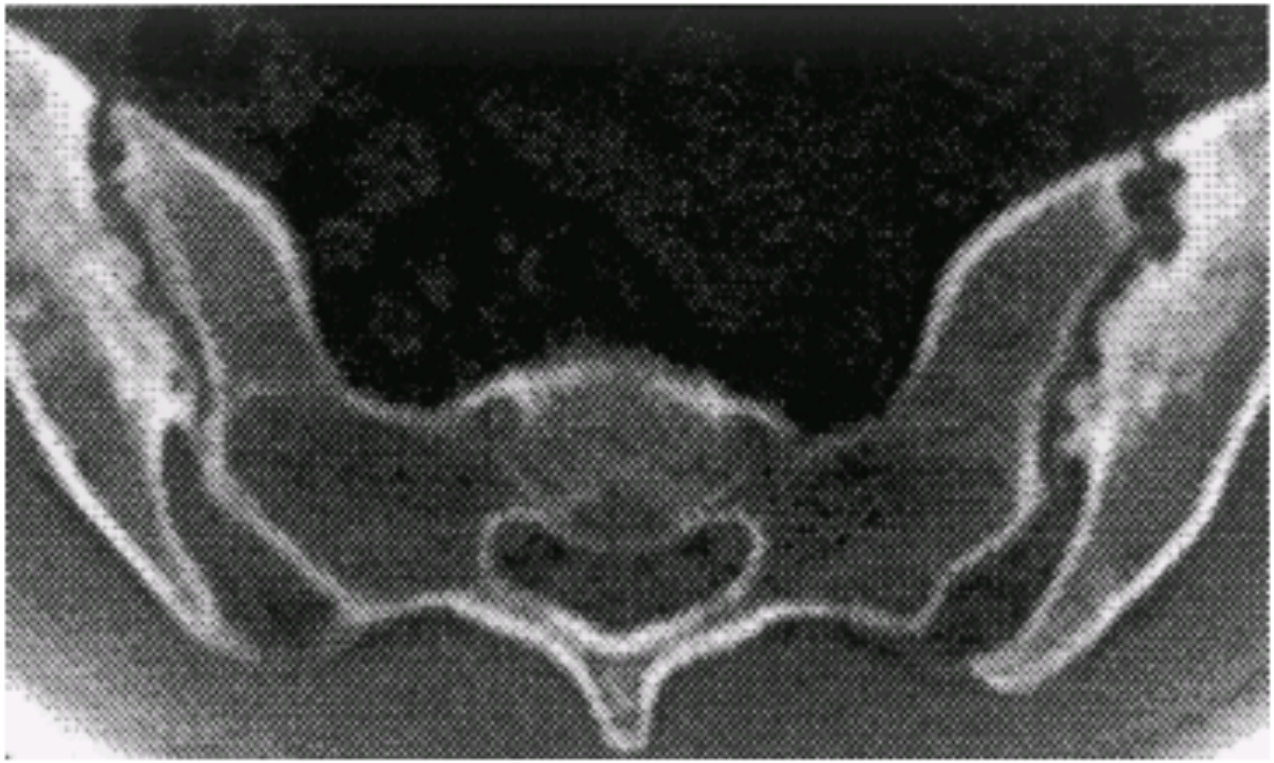
I (A)	SIJ > 4 mm
I (B)	SIJ < 2 mm
II (A)	Contour irregularities
II (B)	Erosion (early iliac, later sacral side)
III (A)	Subchondral sclerosis (osteitis)
III (B)	'Spur formation' (enchondral ossification)
IV (A)	Transartikular bony bridges
IV (B)	Ankylosis (synchondrosis)



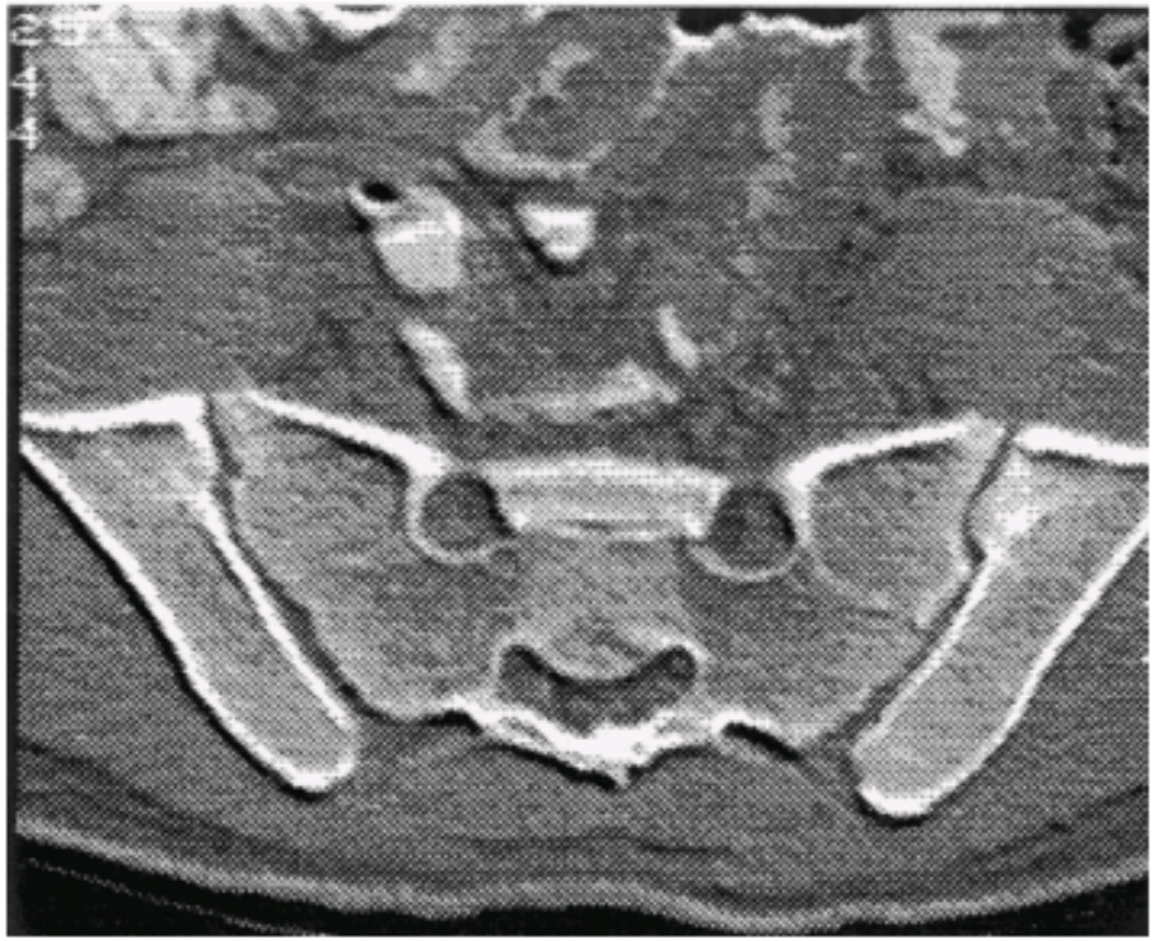
Complete bony ankylosis in case of AS. The HRCT visualises irregular dilatation of the joint space behind the ankylosing new bone formation (St. IV.B.).



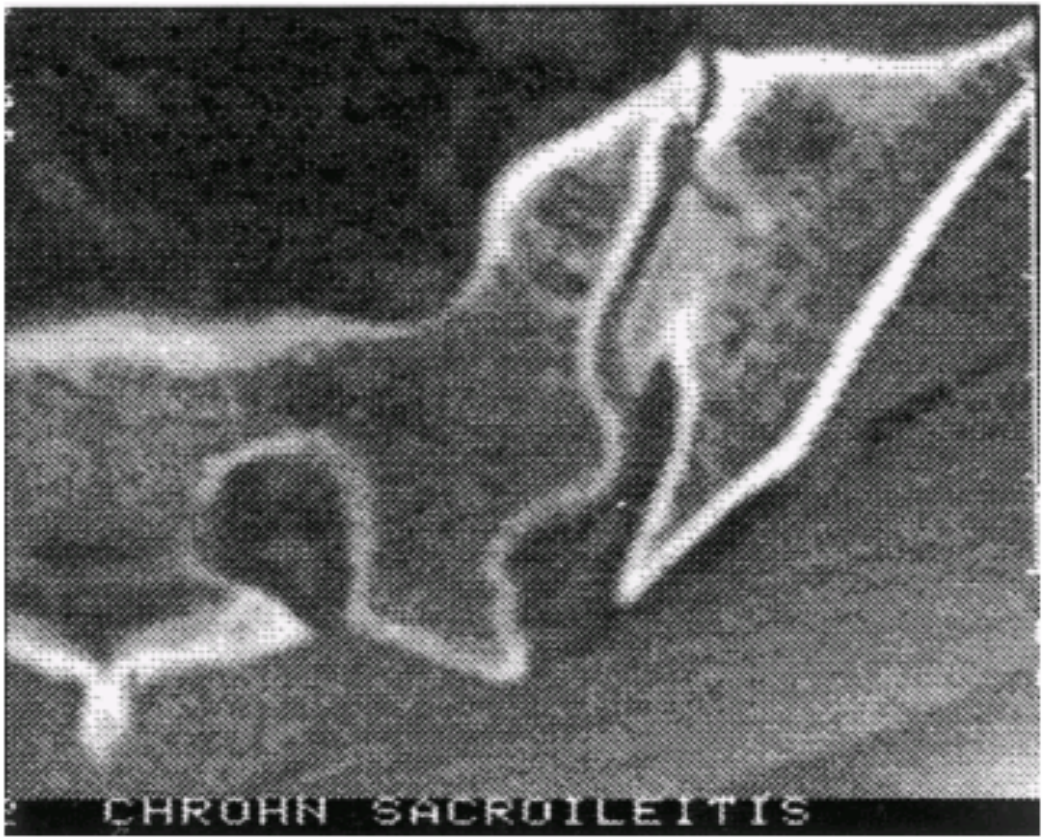
Bilateral irregularity of the SIJ space in CD. Solitary erosion is evident on the right side on the posterior area of the synovial portion of the iliac side of the SIJ (St. II.B.).



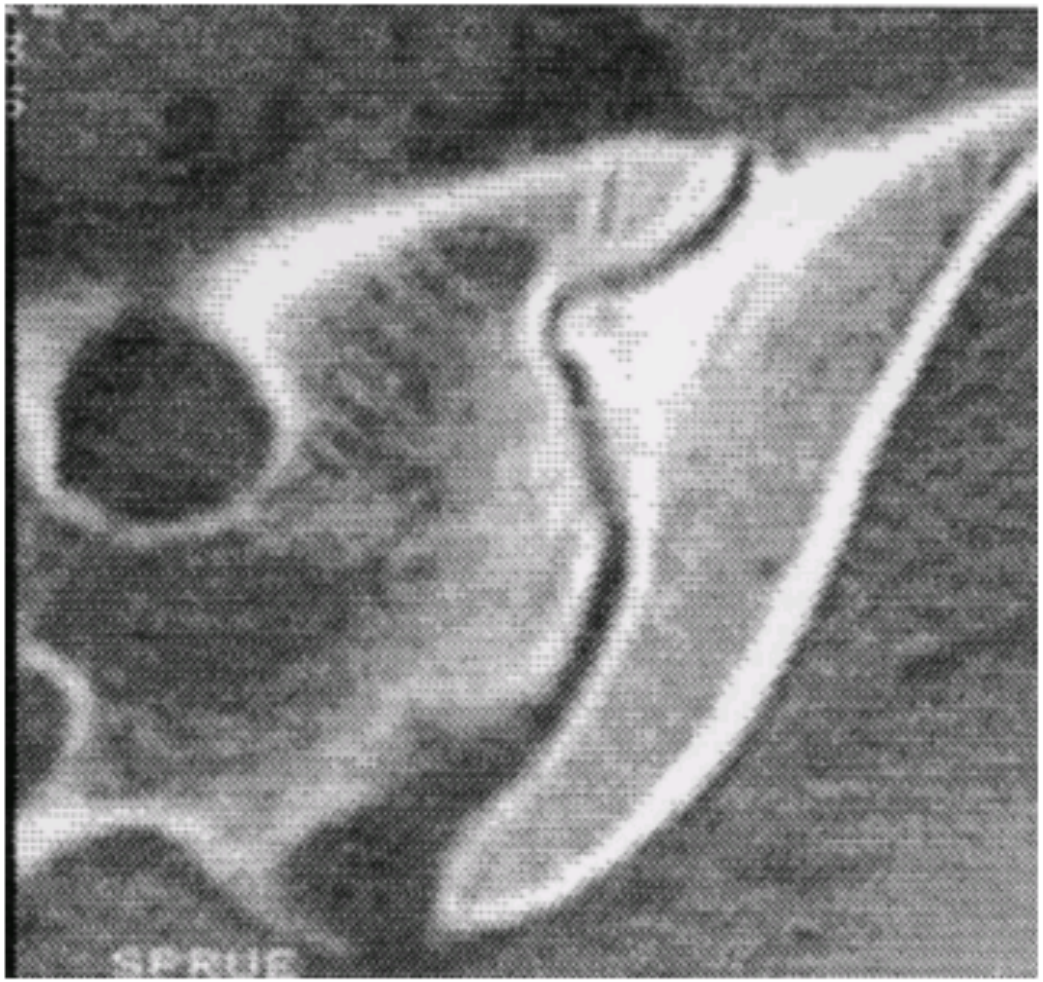
Late onset AS with multiple erosive lesions. SIJ space narrowing and dilatation, sclerosis behind the erosions are well delineated. Some spur formation is already evident (St. III.B.).



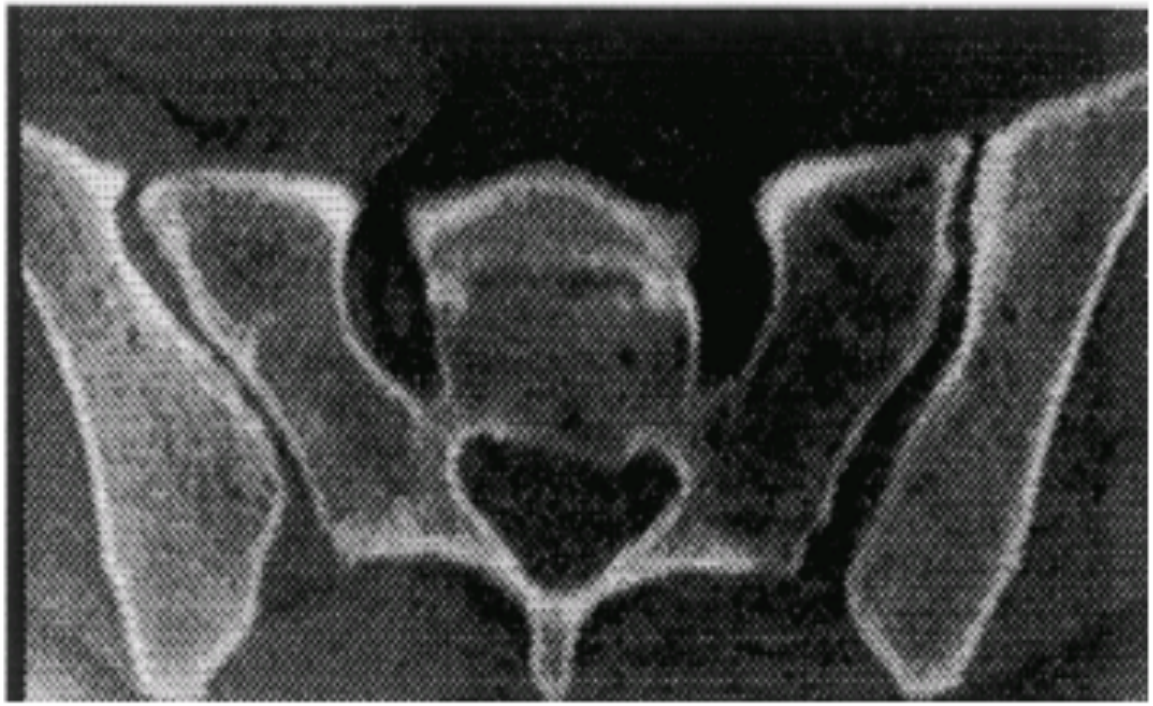
Unilateral solitary deep erosion in Crohn's disease on the sacral surface of the SIJ (St. II.B.). See AgAb scintigraphy in the Nuclear Medicine article of this issue (Fig. No 2 there).



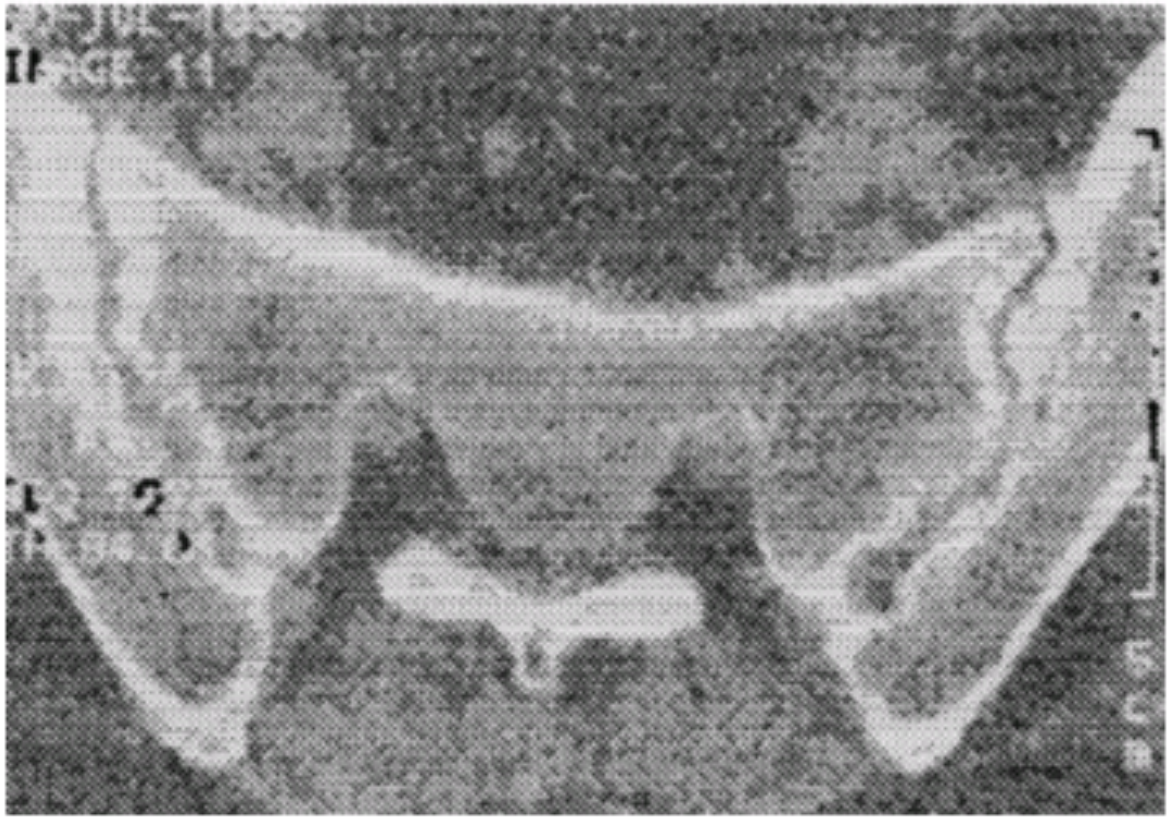
. Focal dilation of the SIJ, plus unusual (8 mm) deep "fjord"-like solitary erosion, not seen in other conditions, except CD. This erosion is much deeper than the cartilage itself, and involves the bone deeper, than the usual subchondral erosive lesions in general. A real extraintestinal CD manifestation: granulomatous inflammation (St. III.A.).



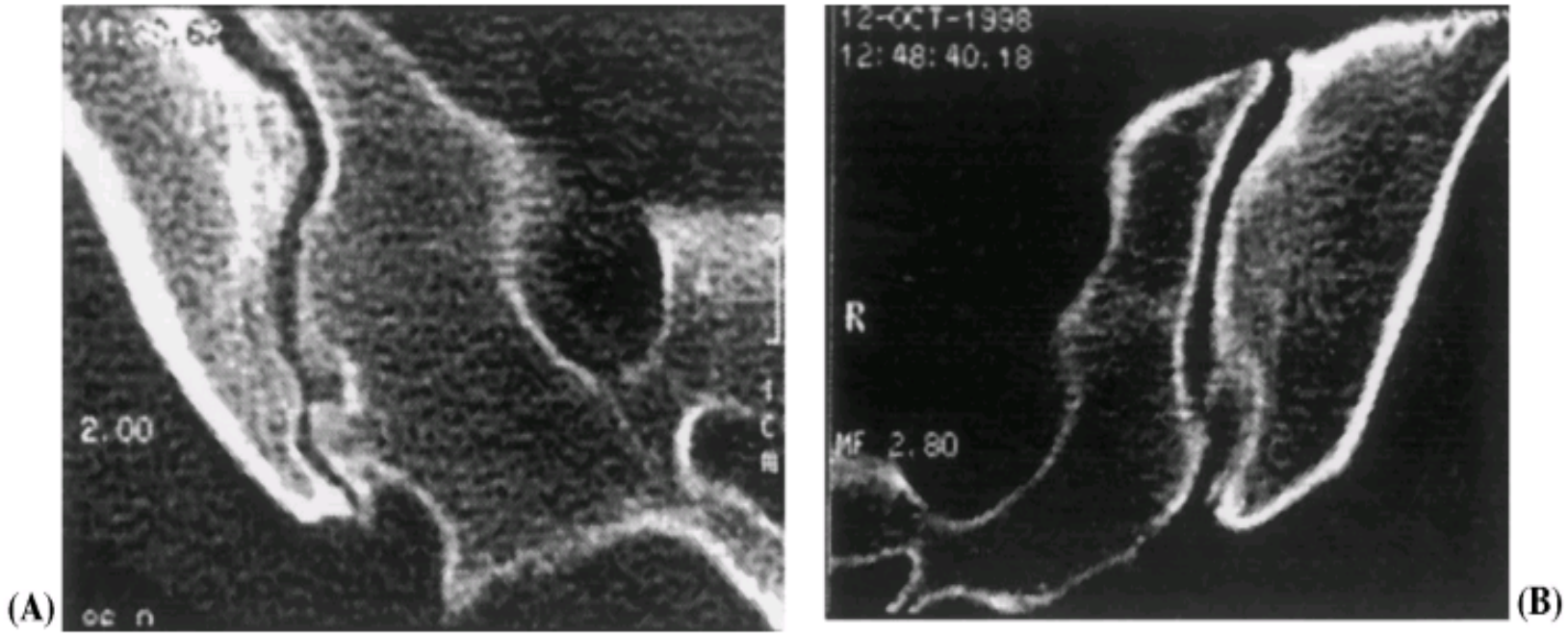
Early contour irregularity in the middle portion of the SIJ. Erosion is not yet observed (St. II.A.).



Early sacroileitis in Crohn's disease. No erosions observed yet, but the irregularity of the SIJ space is evident on the right side: dilatation of the joint space (St. I.A.) and narrowing (St. I.B.).

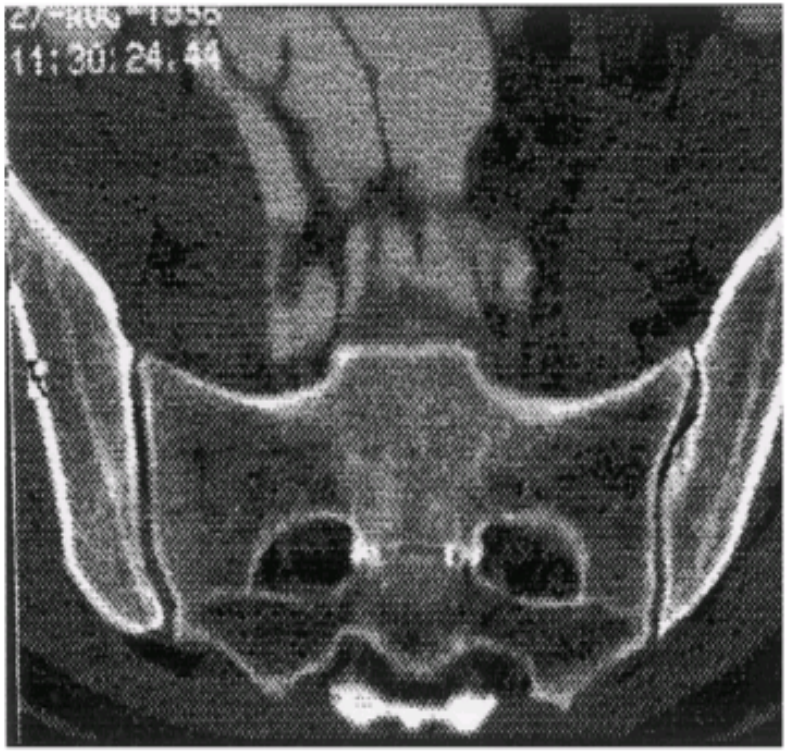


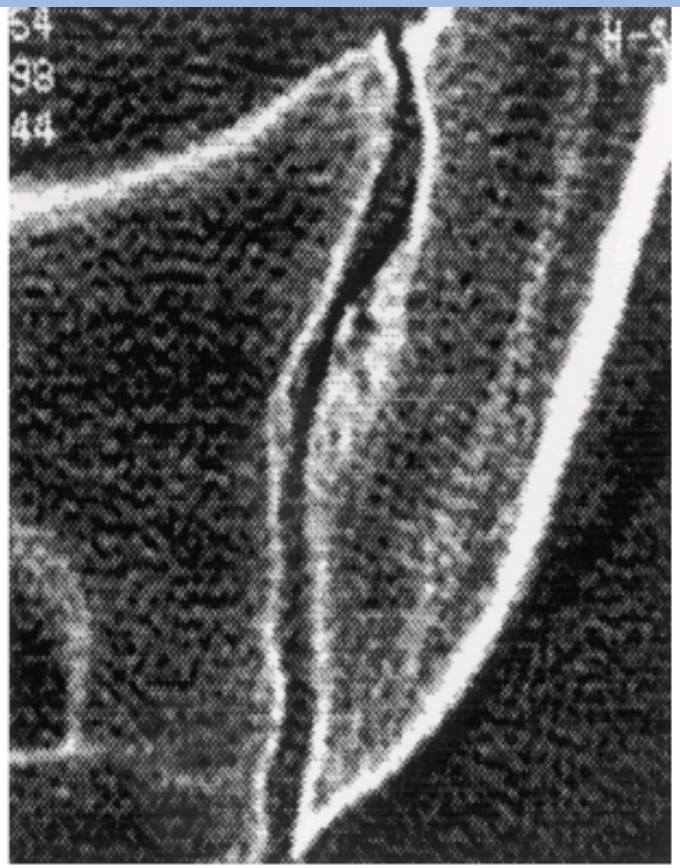
Bilateral multiple erosions in UC patient. Some deep erosions with subchondral sclerosis and calcifications in the non-synovial portion of the SIJ are characteristic.



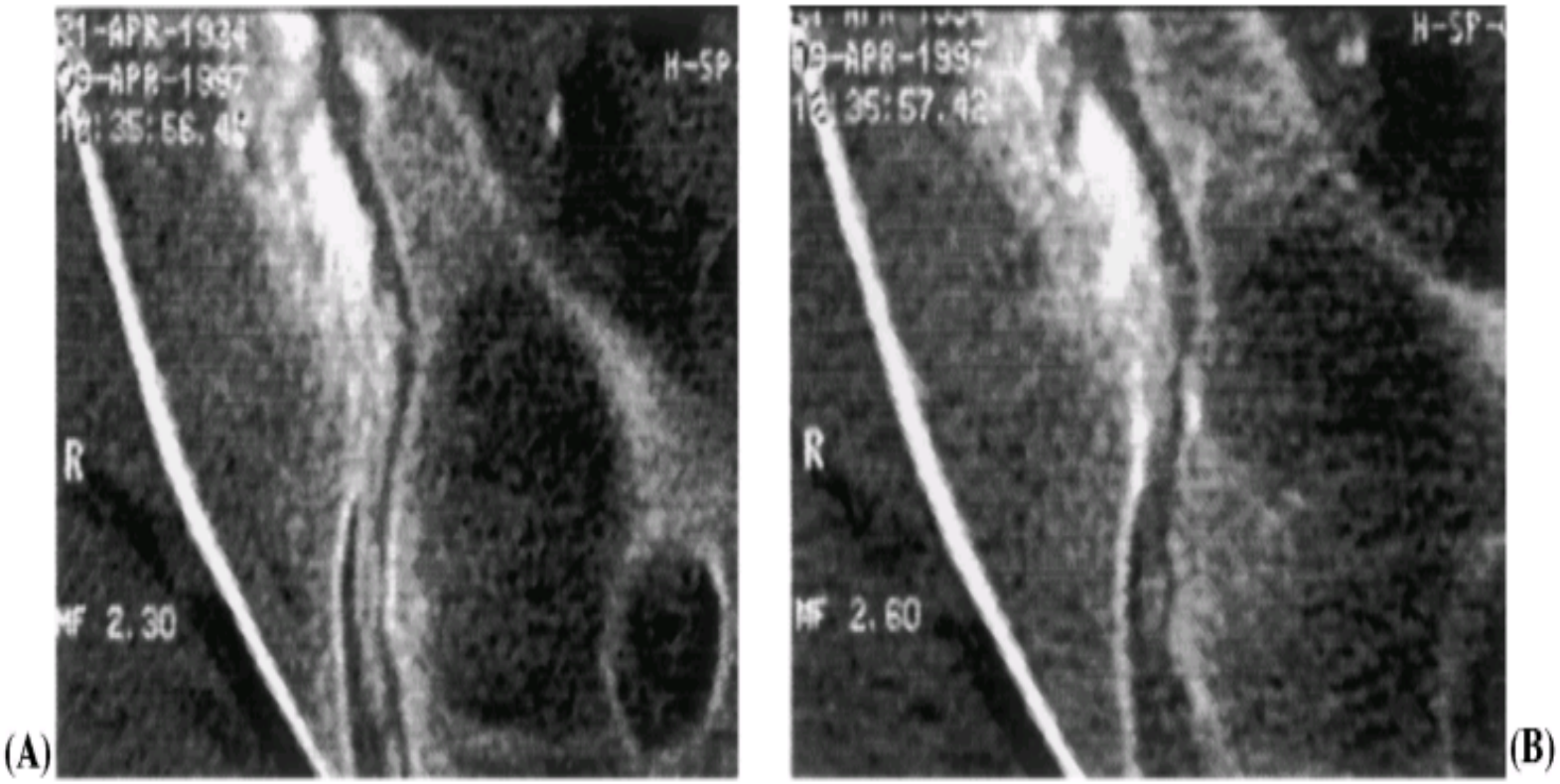
(A) (B)

Left side of the same patient with bilateral SIJ involvement. Intraarticular bony spur (IV.A) and adjacent erosion was detected in the left SIJ, with posterior ligamental calcification.



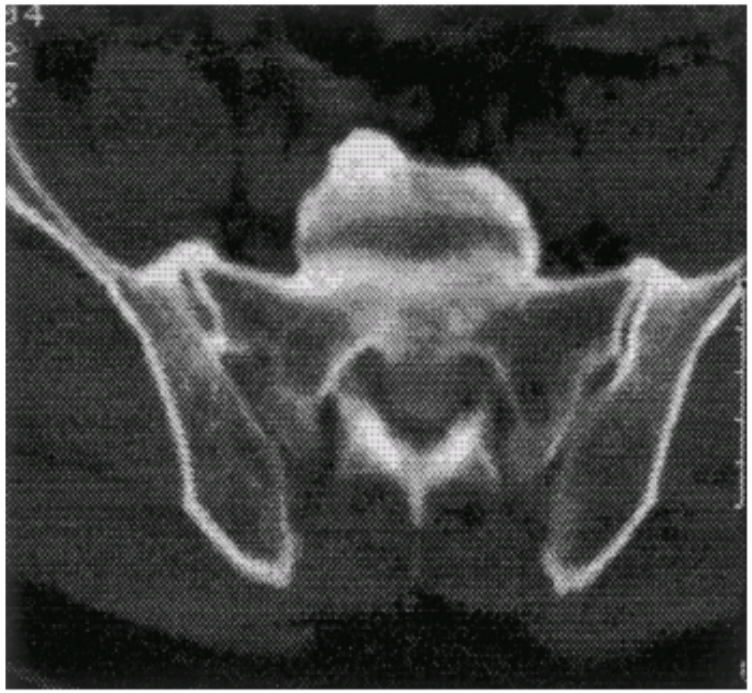


Specific CD related erosion, not seen in any other SNSA sacroileitis. The solitary erosion has a very special osteochondritis dissecans-like morphology in three layers: centrally sclerotic portion, surrounded with "crescent sign" and asteroid lines into the deep sclerotic bone structure.

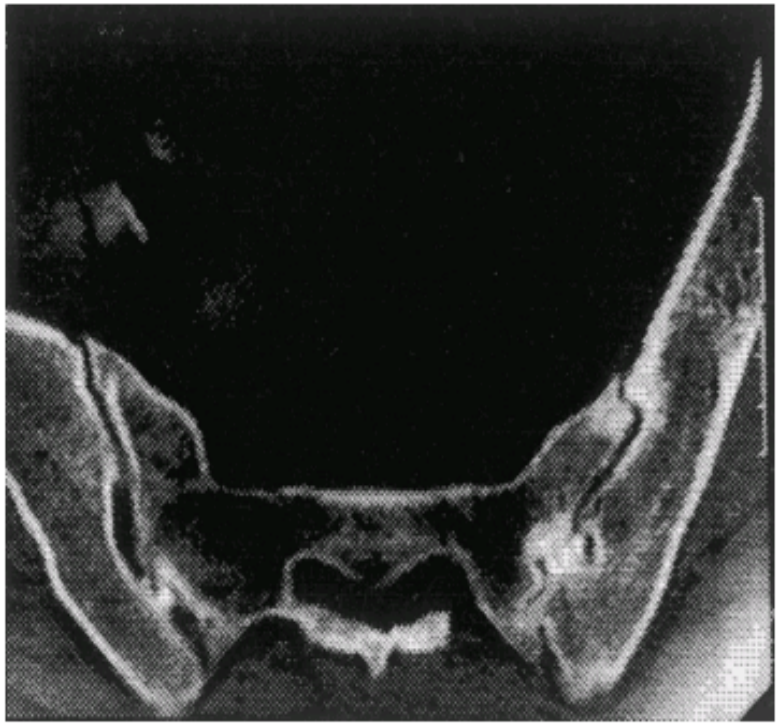


(A) (B)

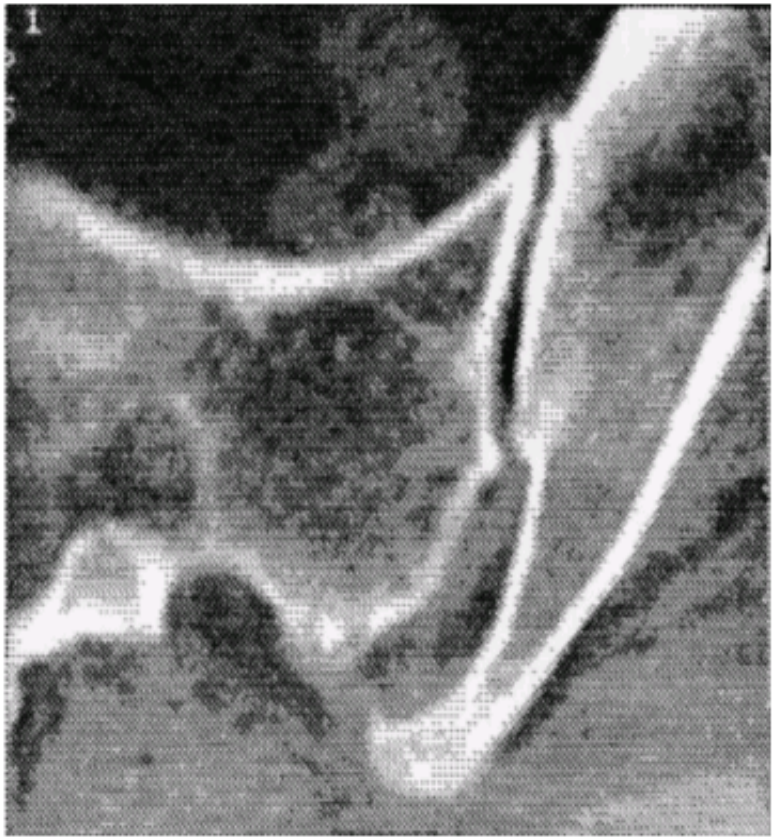
(A) Multiple deep erosions with sclerosis in CD patient (St. II.B.). Additional ligamental calcification is evident in the posterior (non-synovial) portion of the SIJ. (B) Other scan of the same patient. Osteochondritis dissecans-like lesion with three layers (see details above).



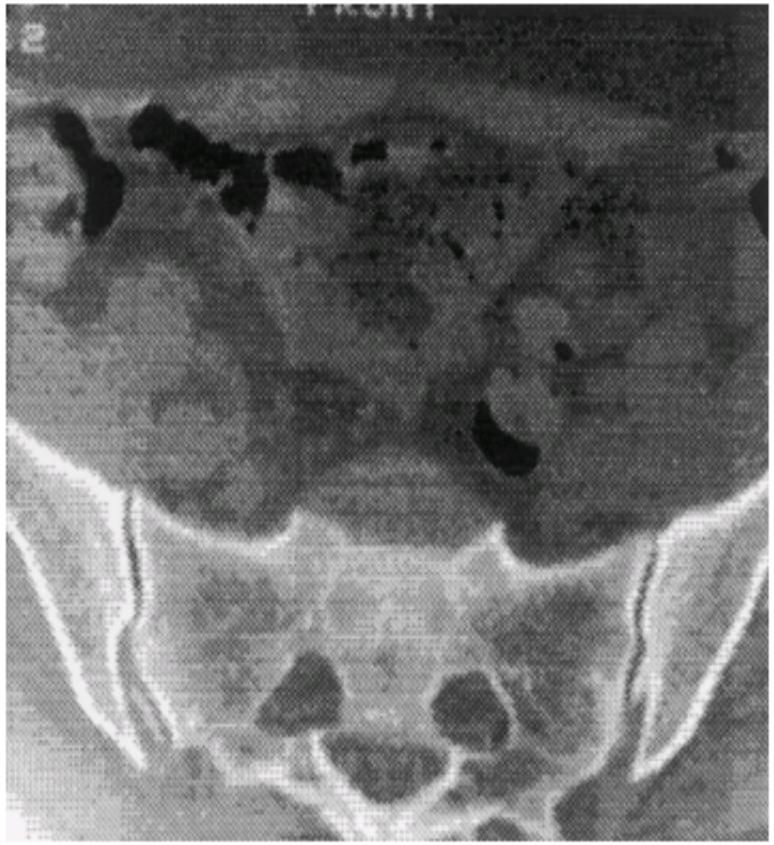
Extraarticular calcification in the capsule of the synovial joint. Normal SIJ. DISH patient.



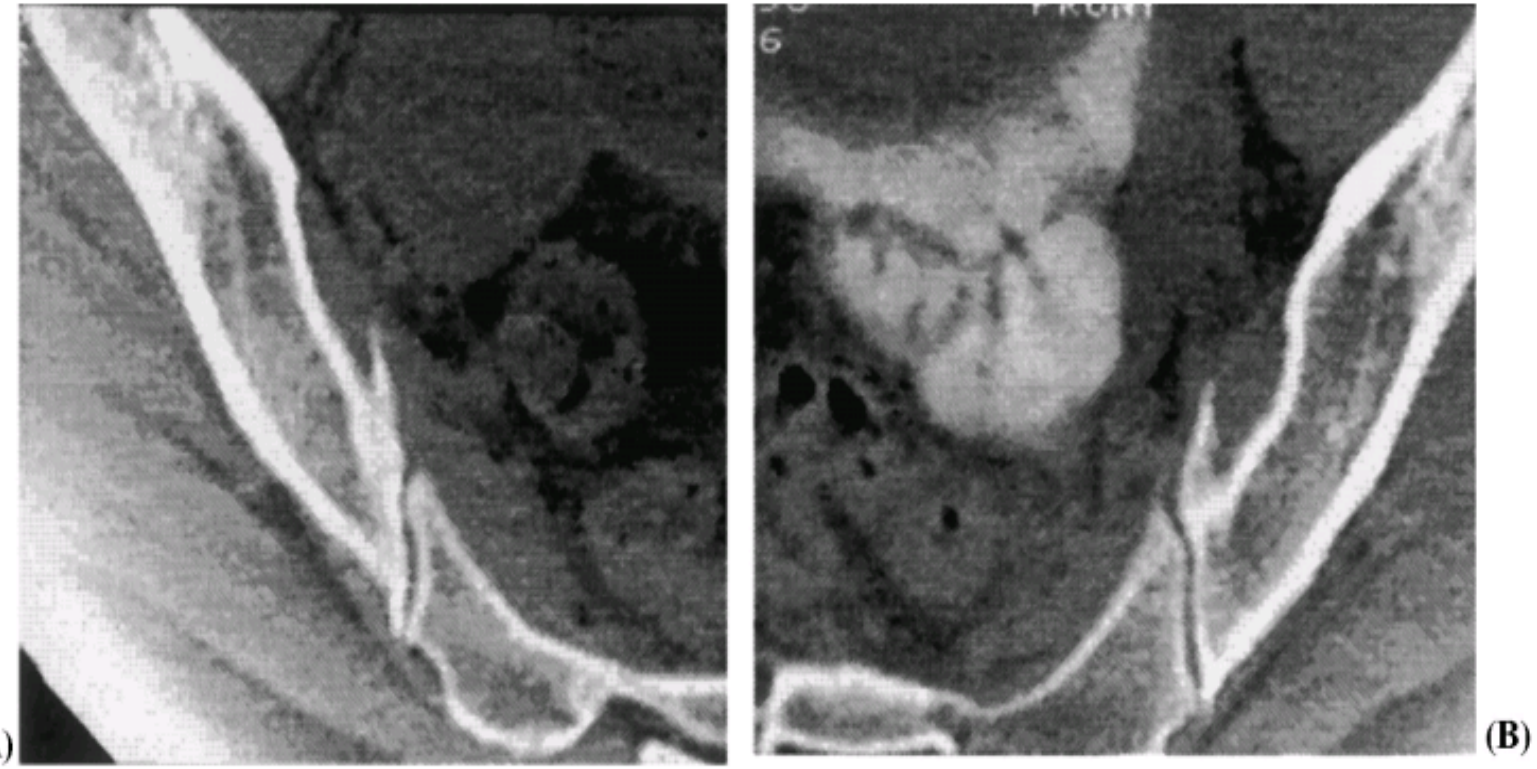
Intraarticular calcifications combined with deep erosions. CD patient.



Intraarticular "vacuum-phenomena". Degenerative diseases.



Spruce syndrome. Calcification in the ligamental portion of the SIJ, no erosion.



(A) Extraarticular calcification in the sacrotuberous ligament. Normal SIJ. DISH patient. (B) Extraarticular calcification in the sacrotuberous ligament. Normal SIJ. DISH patient.

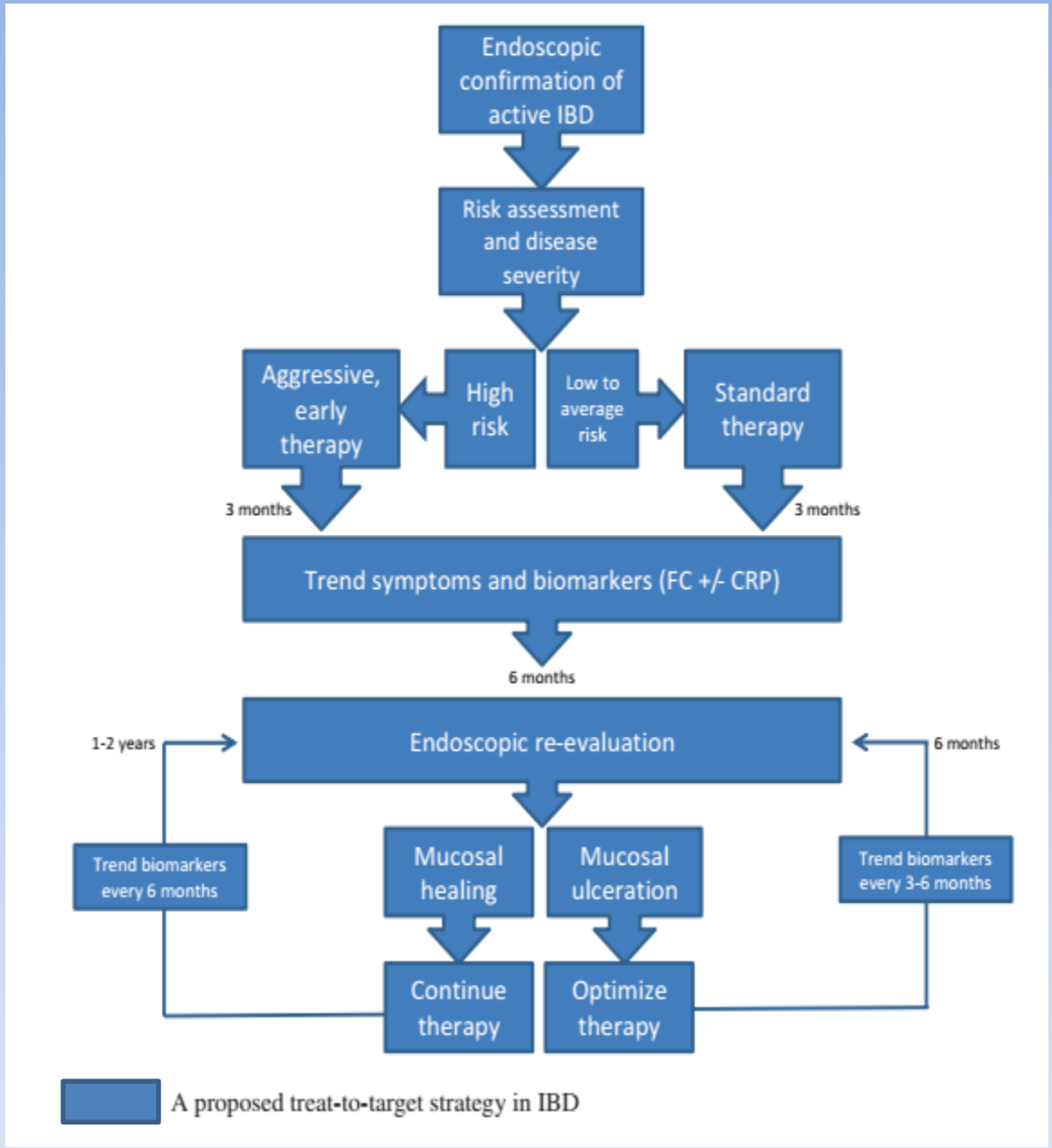
Foods of concern for ostomy patients

Foods that may cause blockages	Gas-producing foods	Odor-producing foods
Raw cabbage	Broccoli	Broccoli
Chinese vegetables	Garlic	Garlic
Corn	Onion	Onion
Raw celery	Eggs	Eggs
Mushrooms	Fish	Fish
Coconut	Cabbage	Cabbage
Apple peel	Brussel sprouts	Brussel sprouts
Tomatoes	Legumes	Asparagus
Popcorn	Cauliflower	Cauliflower
Dried fruits	Carbonated beverages	Baked beans
Nuts		Strong cheese
Grapes		
Oranges		
Pineapple		
Bean sprouts		

Therapy of arthritis associated with inflammatory bowel disease (IBD).

Axial involvement and active IBD	Axial involvement and IBD in remission	Peripheral involvement and IBD	Peripheral involvement and IBD in remission
Physical activity	Physical activity	Local (type 1) or systemic (type 2) steroids	Local (type 1) or systemic (type 2) steroids
TNF-α inhibitors	NSAIDs/COXIBs	Sulfasalazine	NSAIDs/COXIBs
	TNF-α inhibitors	TNF-α inhibitors	Sulfasalazine
			TNF-α inhibitors

COXIBs, selective inhibitors of COX-2; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumour necrosis factor.



A proposed treat-to-target strategy in IBD

. When to start treatment with TNF-α inhibitors.

Axial involvement	Persistently high disease activity (BASDAI >4)
	Failure at least two NSAIDs
Peripheral involvement	Failure of local or systemic steroids
	Failure of DMARDs
Enthesitis/dactylitis	In severe case or after failure of traditional therapy.
Poor prognostic factor risk	High CRP/ESR bone edema at MRI
Active inflammatory bowel disease	Moderate or severe form in case of fail to respond at least one DMARDs
Inflammatory bowel disease complicated by abdominal abscess or stricture	Abdominal surgery before starting TNF-α inhibitors

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NSAIDS, nonsteroidal anti-inflammatory drug; TNF, tumour necrosis factor.

Pharmacologic treatments for CD-SpA

Axial CD-SpA	Peripheral CD-SpA
Currently approved therapies	
Short term NSAIDs if CD is in remission[a]	Short term NSAIDs if CD is in remission[a]
Anti-TNFα therapy:	Local steroid injection for pauciarticular or short-term oral steroid for polyarticular peripheral SpA
Infliximab	Sulfasalazine
Adalimumab	Methotrexate
Certolizumab pegol	Anti-TNFα therapy: Infliximab, adalimumab, certolizumab pegol
No IL12/23 inhibitor therapy is proven beneficial in axial SpA	Anti IL12/23: Ustekinumab
Other therapies under investigation/development	
Selective JAK-1 inhibitor: Upadacitinib and filgotinib (successful phase 2 trials in AS, PsA and CD; positive results in phase 3 trial of upadacitinib in PsA. Ongoing phase 3 trial in CD)	
α4β7 anti-integrin: vedolizumab	
Approved for treatment of moderate-to-severe CD. Based on recent a systematic review, may be effective in preventing onset of arthritis in CD, however, may not be effective in improving co-existing arthritis	
Therapies under investigation:	
S1P1 receptor modulator—ozanimod, etrasimod	
Anti-TNF like cytokine 1A (anti-TL1A) therapy	
Fecal microbiota transplant	
Combination biologic therapy (combining two or more biologics with different mechanism of action)	

CD Crohn's disease, *CD-SpA* Crohn's disease associated spondyloarthritis, *IL* interleukin, *JAK* Janus kinase, *PsA* psoriatic arthritis, *S1P1* Sphingosine 1-phosphate-1, *SpA* spondyloarthritis, *TNFα* tumor necrosis factor-alpha

[a]Typically < 15 days and should be avoided in active IBD

TEACHING POINTS

- **NSAIDs and anti-IL-17 drugs**, while useful in **SpA**, must be used with considerable **caution in patients with IBD**.
- In consideration of the **high CV risk among IBD patients**, common cardiovascular drugs (**statins and angiotensin-converting enzyme inhibitors**) may have dual potential for **preventing or treating coronary artery disease** and **controlling inflammatory bowel disease**
- Advances in the understanding of the **molecular basis of CD and UC** have led to the development of promising **new biologic therapies**, which will likely be studied further both as **monotherapeutic agents**, and for use in combination with **immunomodulators.**
- Imaging-specific findings are important, and for infectious sacroiliitis, **periarticular muscle edema is an important predictor**, with this sole finding demonstrating an accuracy of **85% in distinguishing between infectious sacroiliitis and spondyloarthritic sacroiliitis**.