Axial and Peripheral SpA: A Rheumatic Duet

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Information

- This scientific session is sponsored by Novartis Medical Affairs; and
- For any questions, please see Novartis associates here in the room or at Booth 26

Learning Objectives

1. Recognize that spondyloarthritis (SpA) is a spectrum of disease consisting of axial and peripheral subtypes
2. Differentiate SpA from other rheumatic diseases by highlighting enthesitis, bone erosion, and osteoproliferation
3. Identify the features of axial and peripheral SpA in patients to aid earlier diagnosis
4. Explore sex differences in axial spondyloarthritis (axSpA) disease presentation

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Disclosures for Grace Wright, MD, PhD

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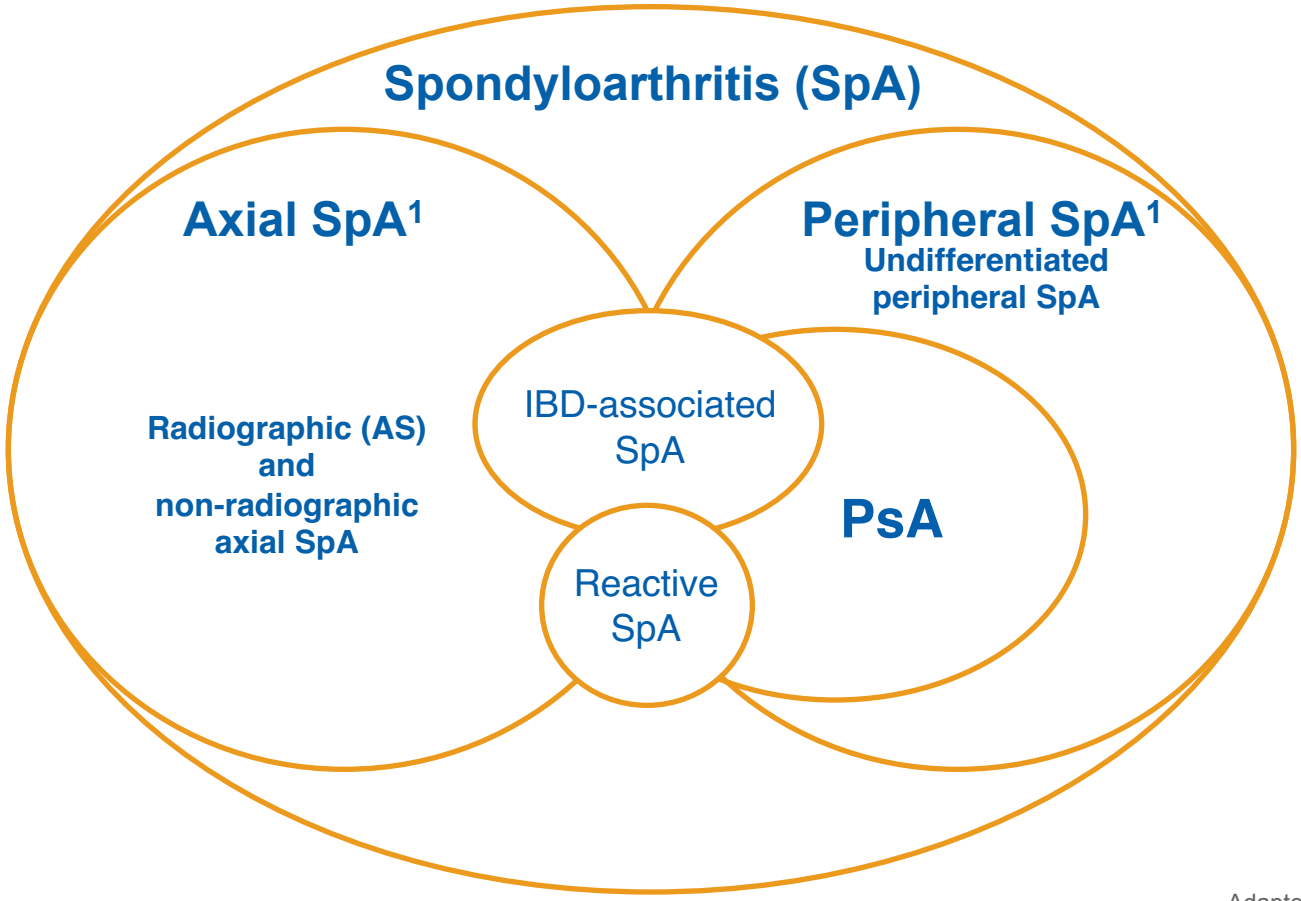
The spondyloarthritis (SpA) spectrum is comprised of axial and peripheral subtypes

Spondyloarthritis (SpA) is a group of diseases with many subtypes



Adapted with permission from Raychaudhuri SP, et al.

AS = ankylosing spondylitis; AxSpA = axial spondyloarthritis; IBD-SpA = inflammatory bowel disease and spondyloarthritis; SpA = spondyloarthritis; AS = ankylosing spondylitis; IBD = inflammatory bowel disease; PsA = psoriatic arthritis; nr-AxSpA = non-radiographic axial spondyloarthritis; PsA = psoriatic arthritis; ReA = reactive arthritis; SpA = spondyloarthritis.

1. Raychaudhuri SP, Deodhar A. *J Autoimmun*. 2014;48-49:128-133.

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Is SpA a spectrum of diseases or one heterogenous disease?

REPORT

"Seronegative spondyloarthropathies: to lump or split?"

P Nash, P J Mease, J Braun, D van der Heijde

Ann Rheum Dis 2005;64(Suppl II):ii9–ii 13. doi: 10.1136/ard.2004.033654

"Moll et al initially included Whipple's disease in their classification—a disease, which when studied as ***its own entity rather than "lumped" in a group***, has had its aetiological agent defined allowing appropriate therapy and cure. We would like to agree…"[1]

SpA = spondyloarthritis.

1. Nash P et al. *Ann Rheum Dis.* 2005;64(Suppl II):ii9-ii13.

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Is SpA a spectrum of diseases or one heterogenous disease?

REVIEW

"Are Spondylarthritides Related but Distinct Conditions or a Single Disease With a Heterogenous Phenotype?"

D Baetan, M Breban, R Lories, G Schett, J Sieper[1]

"The available evidence suggests a common pathophysiologic foundation for SpA as a whole and thereby supports the concept that ***SpA is a single disease with a heterogeneous phenotype***. However, this conclusion is tempered by the facts that our understanding of the cellular and molecular pathways driving SpA pathogenesis are still very incomplete…"[1]

SpA = spondyloarthritis.

1. Baeten D et al. *Arthritis Rheum*. 2013;65(1):12-20.

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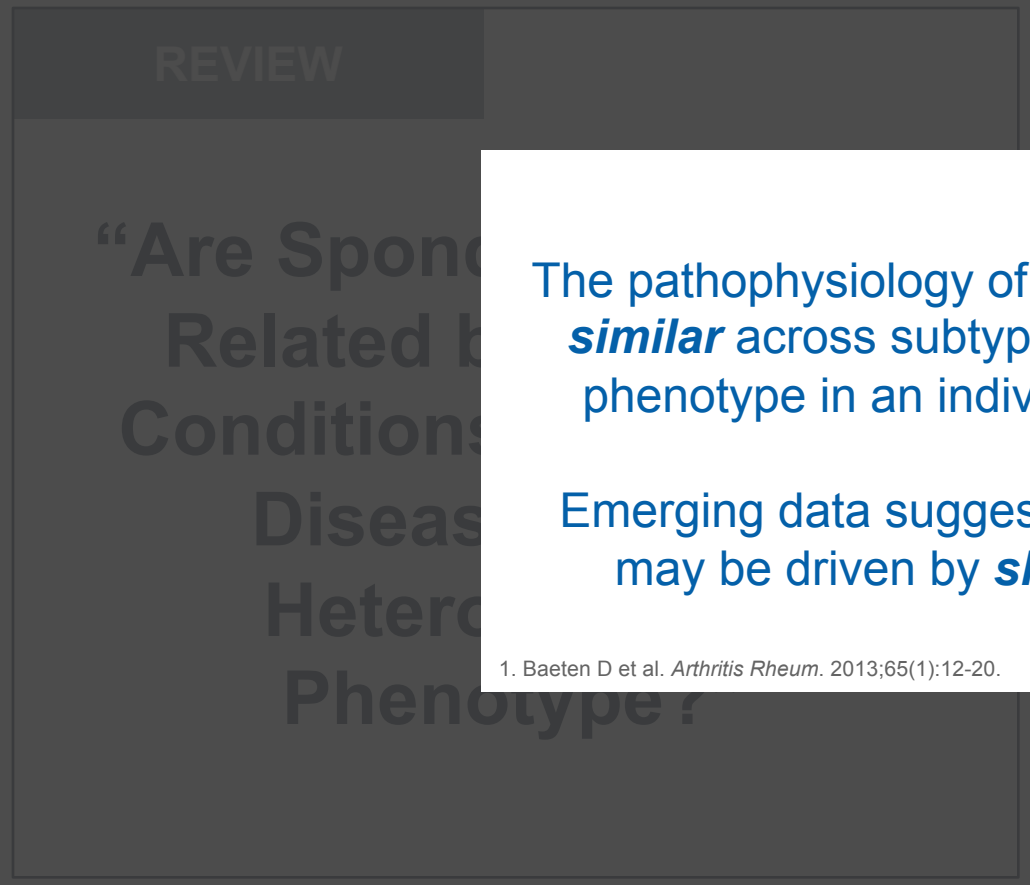
Is SpA a spectrum of diseases or one heterogenous disease?



The pathophysiology of articular ***manifestations is largely similar*** across subtypes, but what determines the exact phenotype in an individual patient remains ***unknown***.[1]

Emerging data suggest that axial and peripheral disease may be driven by ***slightly different mechanisms***.[1]

1. Baeten D et al. *Arthritis Rheum*. 2013;65(1):12-20.

ests a common
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pt that ***SpA is a erogeneous*** conclusion is
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SpA = spondyloarthritis

1. Baeten D et al. *Arthritis Rheum*. 2013;65(1):12-20.

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How common is SpA?

National Arthritis Data Workgroup (2005 US Census data)[1]

Disease	Prevalence in US adults
RA	1.3 million (0.6%)
SpA	0.6 million to 2.4 million (0.3 to 1.3%)

The prevalence of SpA is comparable or higher than that of RA, yet it remains less known.[2,5]

Subtype (criteria)	Prevalence in US adults
SpA, 2009-2010 (Amor)[2]	0.9%
SpA, 2009-2010 (ESSG)[2]	1.4%
axSpA, 2010 (ASAS)[3]	0.7%
PsA (various)[4]	0.06 to 0.25%

AxSpA = axial spondyloarthritis; SpA = spondyloarthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; US = United States.

1. Helmick CG et al. *Arthritis Rheum.* 2008;58:15-25. 2. Reveille JD et al. *Arthritis Care Res (Hoboken).* 2012;64:905-910. 3. Strand V et al. *Arthritis Care Res.* 2013;65:1299-1306; 4. Ogdie A, Weiss P. *Rheum Dis Clin North Am.* 2015;41:545-568. 5. Spondylitis Association of America. https://www.spondylitis.org/. Accessed May 12, 2019.

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How does SpA affect patients?

SpA occurs in young adults at the peak of their productive lifespan[1]

Associated with burden in:[1]

DAILY LIVING

49%

report disability[1,a]

HEALTH-RELATED QUALITY OF LIFE

EMPLOYMENT

36%

Experienced limitations hindering development/career[1,a]

+

21%

changed, left, or lost their job due to SpA[1,a]

WORK PRODUCTIVITY

HOURS

of work lost over the last 7 days were greater due to SpA than other reasons[1,a,b]

SpA = spondyloarthritis.

a. Data from the 2013 ATLANTIS survey of 770 respondents from 17 regions in Italy. b. Other reasons included vacation or family commitments.

1. Ramonda R et al. *Arthritis Res Ther.* 2016;18:78.

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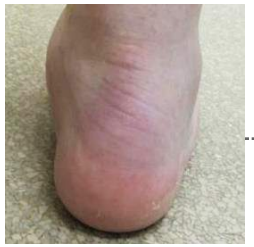
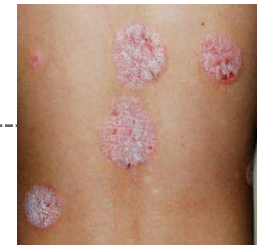
What are the distinguishing features of SpA?



Permission granted by ACR.[13]

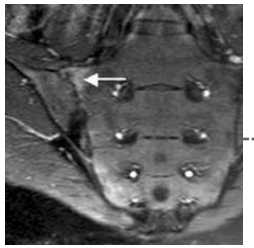
Enthesitis[3,7]

PsO[4,7]



Permission granted by Elsevier.[4]

Bone Formation[12]

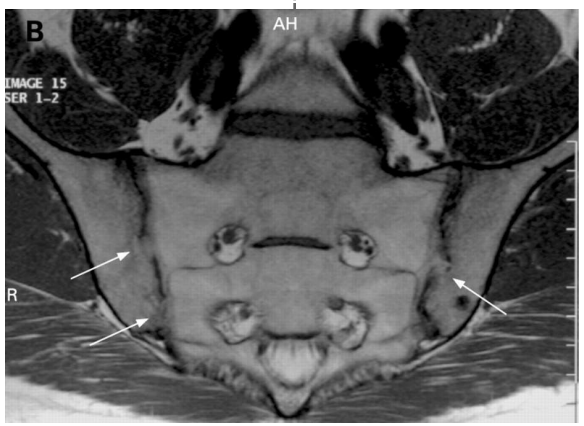


Permission granted by McQueen F, et al.[8]

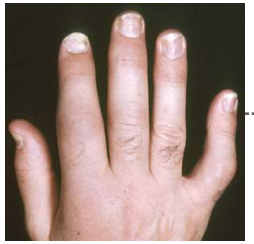
Axial disease[1,7]

Uveitis[6,7]

Permission granted by AAO.[11]



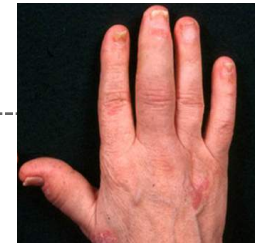
Permission granted by Sieper J et al.[12]



Permission granted by ACR.[9]

Peripheral arthritis[2,7]

Dactylitis[5,7]



Permission granted by ASAS.[10]

SpA = spondyloarthritis. 1. Watad A et al. *Front Immunol.* 2018;9:2668. 2. McGonagle D et al. *Arthritis Rheum.* 1998;41:694-700. 3. McGonagle D et al. *Curr Opin Rheumatol.* 1999;11:244-250. 4. Van de Kerkhoff P, Nestlé F. Psoriasis. In: Bolognia JL et al, ed. *Dermatology*. 3rd ed. Saunders, an Imprint of Elsevier; 2012: Chapter 8. 5. Tan AL et al. *Ann Rheum Dis* 2015;74:185-189. 6. Muñoz-Fernández S et al. *Arthritis Rheum.* 2009;60:1985-1990. 7. Calabresi E et al. *Clin Exp Rheumatol*. 2019 Mar-Apr;37(2):167-178. 8. McQueen F et al. *Arthritis Res Ther.* 2006;8:207. 9. American College of Rheumatology. http://images.rheumatology.org/bp/#/search?=psoriatic%20arthritis&filters=%257B%257D. Accessed July 17, 2019. 10. Assessment of SpondyloArthritis international Society (ASAS). http://slides.asas-group.org/app/slides/search?q=dactylitis&submit=. Accessed July 17, 2019. 11. American Academy of Ophthalmology. What Is Uveitis? https://www.aao.org/eye-health/diseases/what-is-uveitis. Accessed July 17, 2019. 12. Sieper J et al. *Ann Rheum Dis.* 2009;68(Suppl II):ii1-ii44 13. American College of Rheumatology. http://images.rheumatology.org/bp/#/search/?q=enthesitis&filters=%257B%257D. Accessed July 17, 2019.

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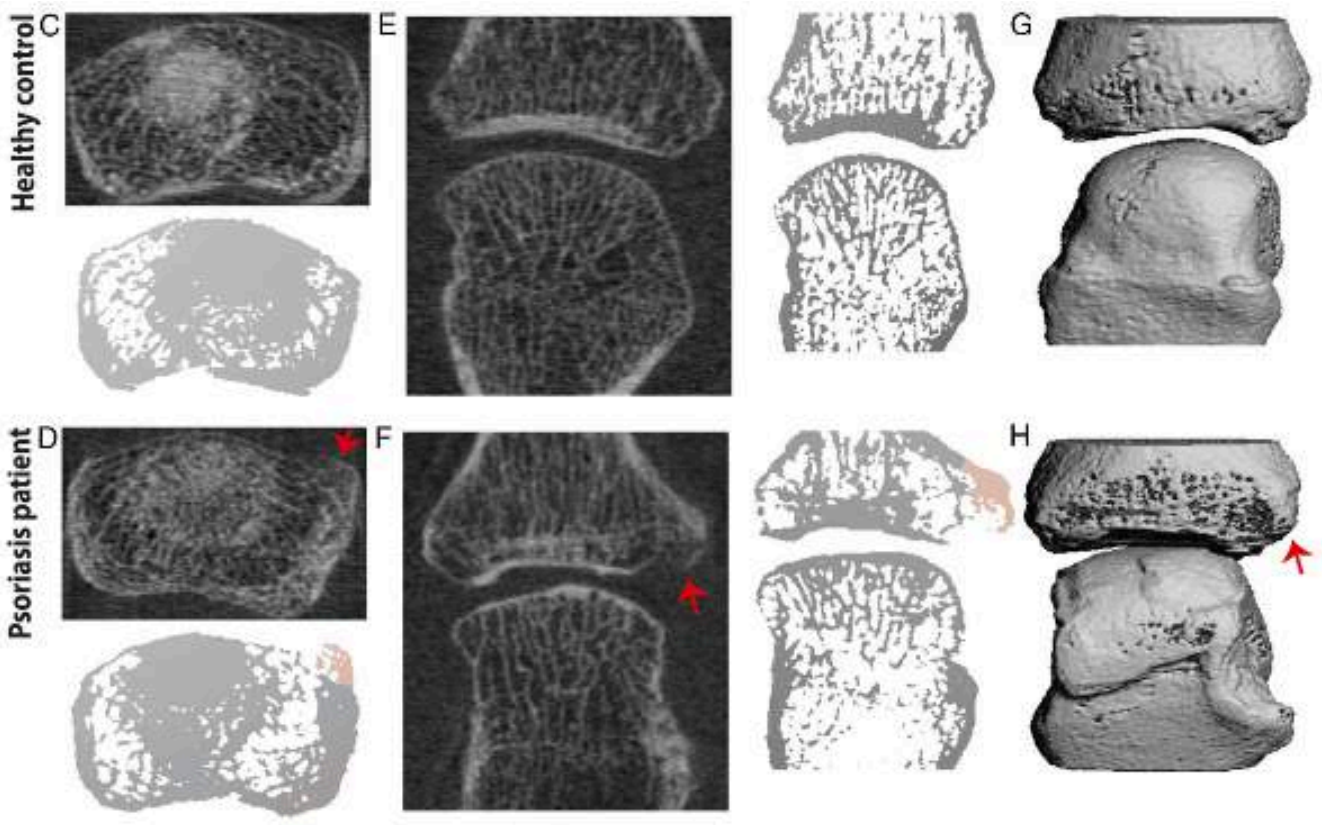
Enthesitis is an important early feature in SpA



Permission granted by Simon D, et al.[1]

One of the first signs of musculoskeletal involvement in patients with psoriasis (before joint involvement) is enthesophyte formation in the peripheral joints (indicated by red arrows), indicating that enthesitis may be an important early feature in psoriatic disease.[1,2]

SpA = spondyloarthritis.

1. Simon D, et al. *Ann Rheum Dis.* 2016;75:660-666
2. Schett G, et al. *Nat Rev Rheumatol.* 2017;13:731-741.

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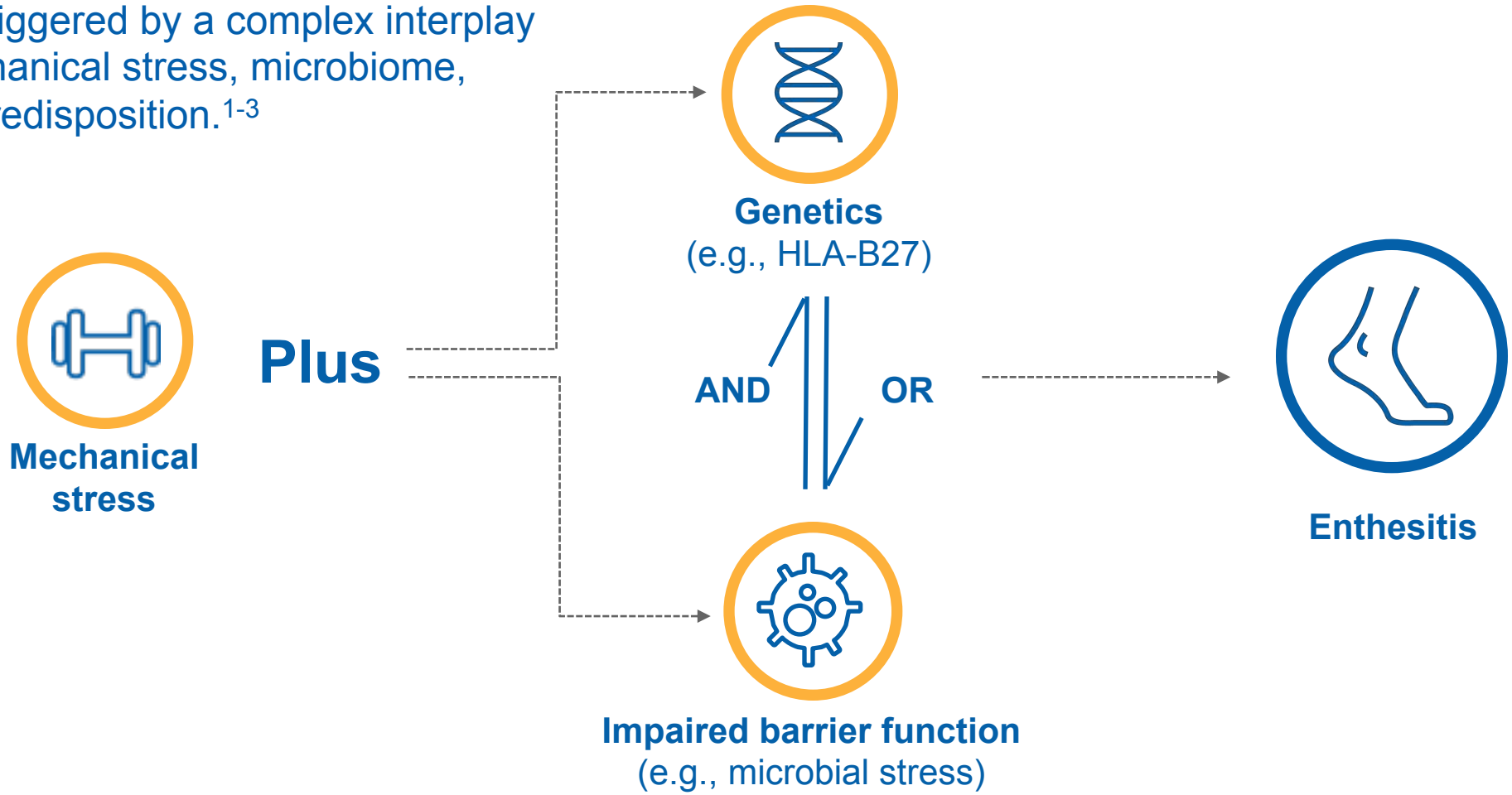
Mechanical stress is a key trigger for enthesitis

Enthesitis is triggered by a complex interplay between mechanical stress, microbiome, and genetic predisposition.[1-3]



HLA-B27 = Human leukocyte antigen B27.

1. Kehl AS, et al. *Arthritis Rheumatol.* 2016;68:312–22. 2. Sieper J, Poddubnyy D. *Lancet.* 2017;90:73–84. 3. McGonagle D, Benjamin M. *Topical Reviews.* 2009;4:1–6.

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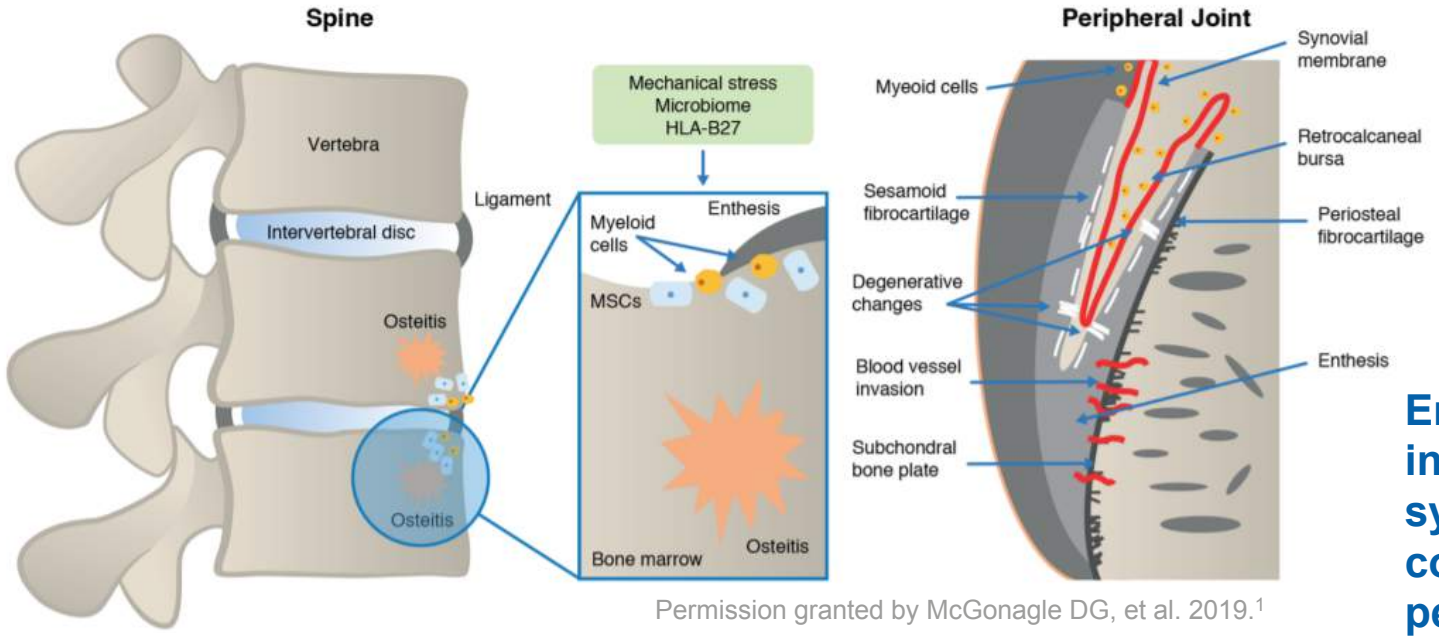
Anatomic differences between spinal and peripheral entheses

There may be anatomical and immunological differences between axial and peripheral enthesitis and downstream disease manifestations[1]

Peri-entheseal osteitis in the spine



Permission granted by McGonagle DG, et al. 2019.[1]

Entheseal soft tissue inflammation or synovio-entheseal complex disease in peripheral enthesitis

1. McGonagle DG, et al. *Ann Rheum Dis*. 2019 Jul 5. pii: annrheumdis-2019-215356.

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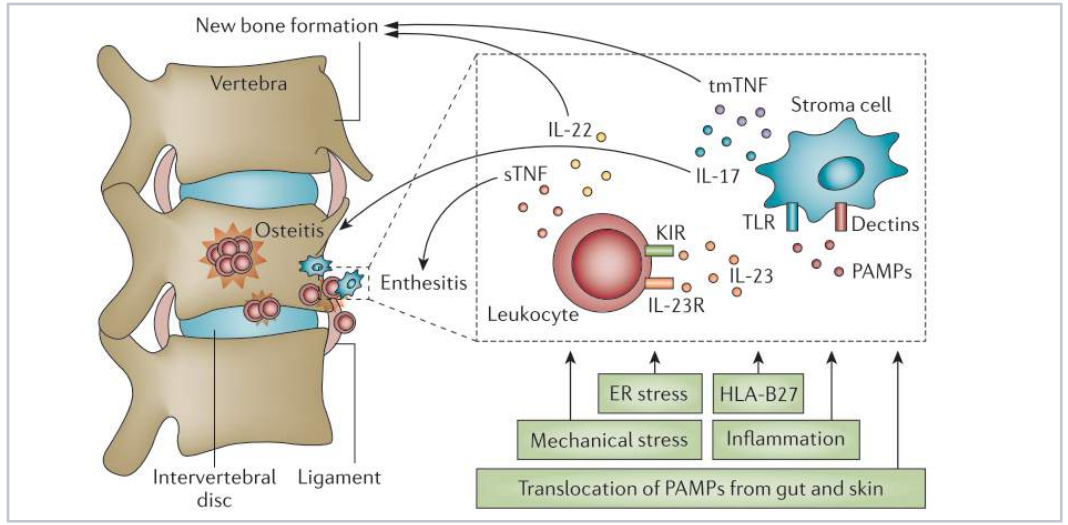
Inflammation in axial and peripheral entheses

Axial enthesitis



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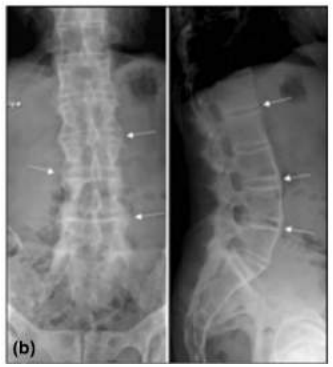
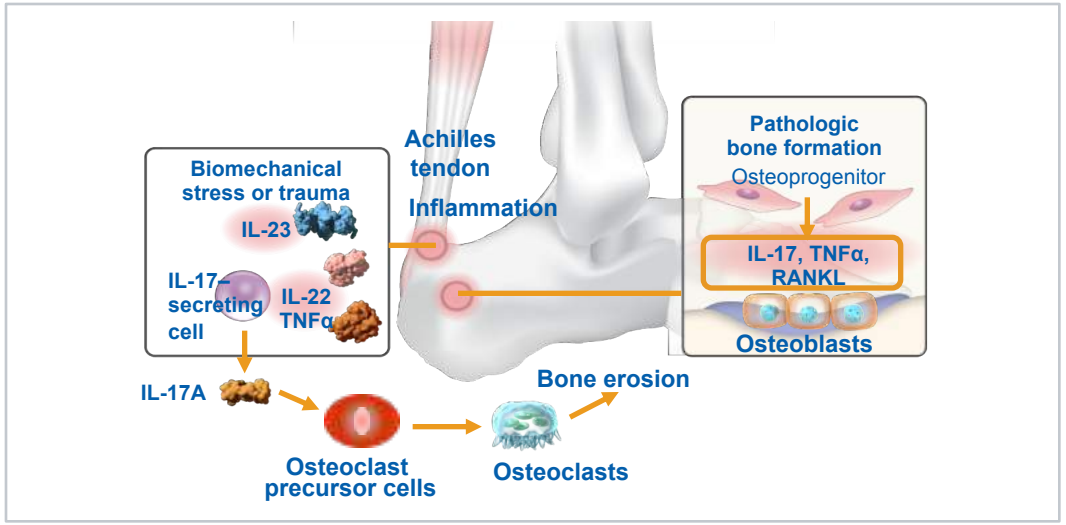
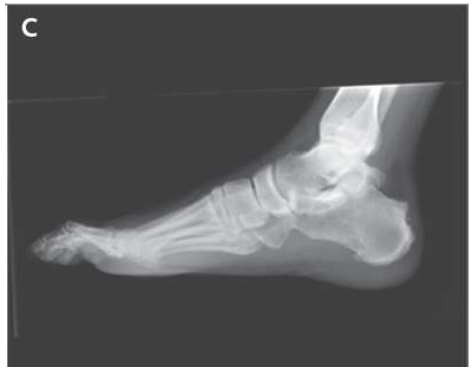


Permission granted by Van Mechelen M et al.[2]

Peripheral enthesitis



Permission granted by Ritchlin CT et al.[3]



Permission granted by Ritchlin CT et al.[3]

1. Sieper J et al. *Nat Rev Dis Primers*. 2015;1:15013. 2. Van Mechelen M et al. *Calcif Tissue Int*. 2018 May;102(5):547-558. 3. Ritchlin CT, et al. *N Engl J Med*. 2017;376:957-970

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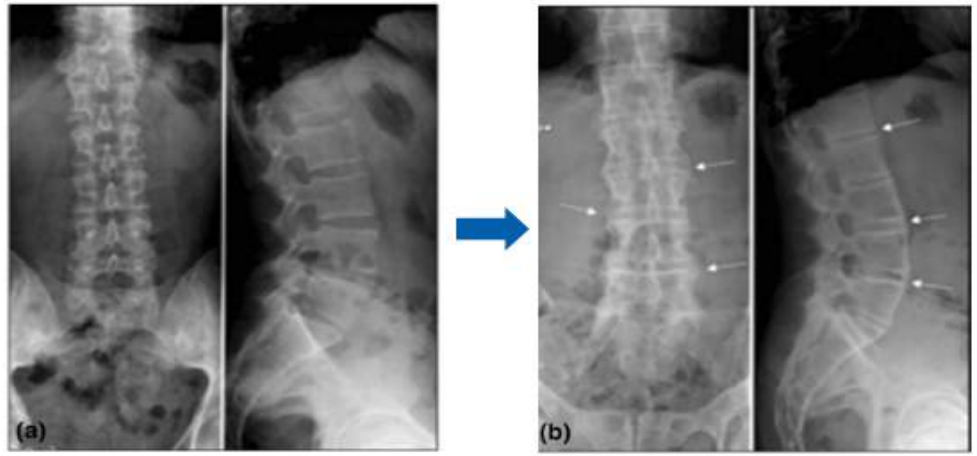
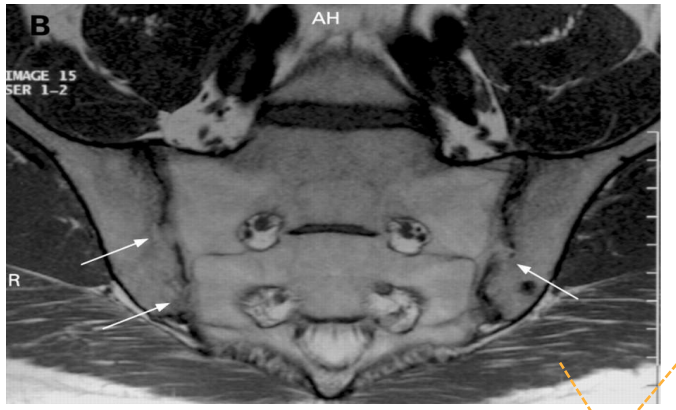
Bone remodeling is tightly linked to enthesitis



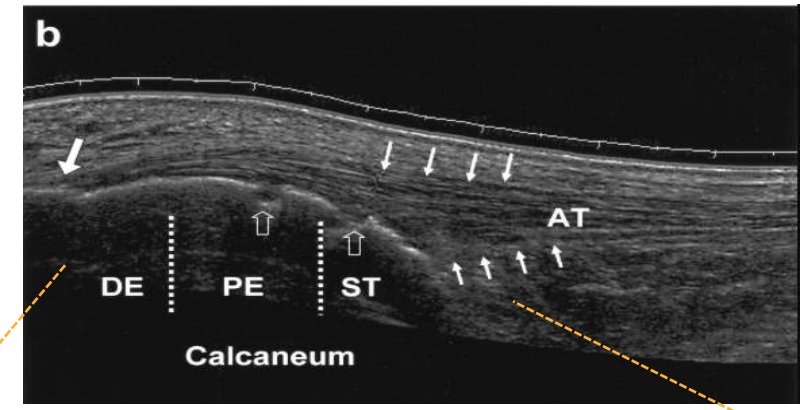
Permission granted by Van Mechelen M et al.[3]

Permission granted by Van Mechelen M et al.[3]

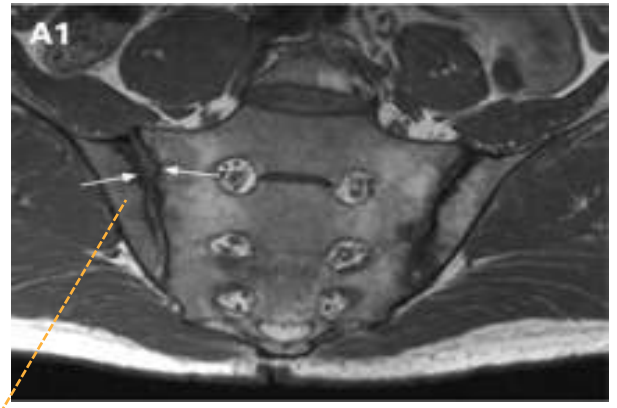
- Structural changes in SpA are unique and severe
- Skeletal damage is a consequence of bone destruction and aberrant bone formation originating from the entheses and can lead to total ankylosis or “bamboo spine”[3]



Permission granted by Sieper J et al.[1]



Permission granted by McGonagle D et al.[2]



Permission granted by Sieper J et al.[1]

Bone formation

Bone erosion

1. Sieper J et al. *Ann Rheum Dis*. 2009;68(Suppl II):ii1-ii44. 2. McGonagle D et al. *Arthritis Rheum*. 2008;58:2694-2699 3. Van Mechelen M, et al. *Calcif Tissue Int*. 2018;102(5):547-558.

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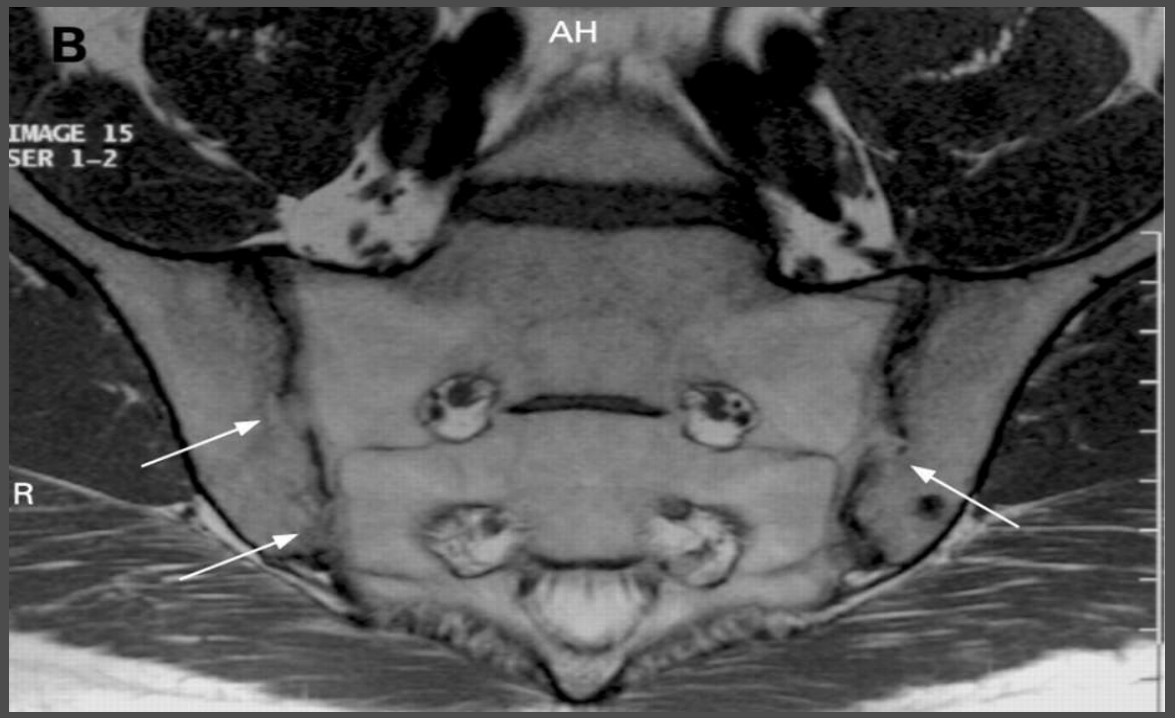
Bone remodeling is tightly linked to enthesitis



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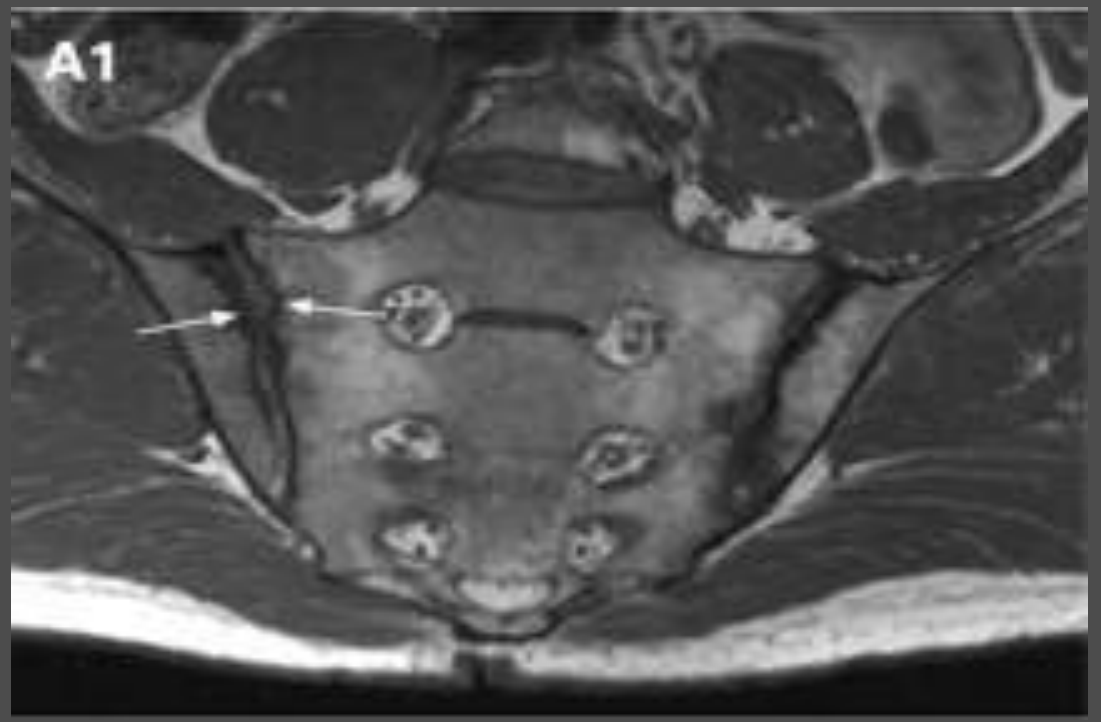

Permission granted by Sieper J et al.[1]

Bone erosion

1. Sieper J et al. *Ann Rheum Dis*. 2009;68(Suppl II):ii1-ii44. 2. McGonagle D et al. *Arthritis Rheum*. 2008;58:2694-2699 3. Van Mechelen M et al. *Calcif Tissue Int*. 2018 May;102(5):547-558

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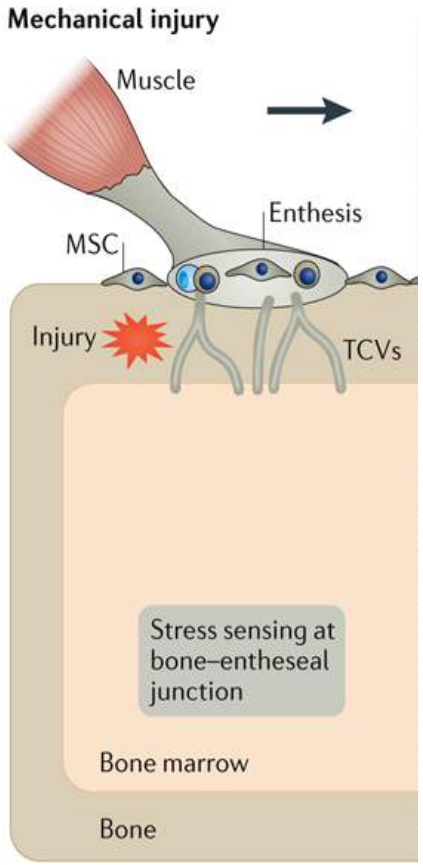
Entheseal inflammation is closely linked to osteitis and new bone formation



Permission granted by Schett G, et al.[1]

- Extensive transcortical microvessels (TCVs) enable communication between the bone marrow and the enthesis[1]
- TCVs become widened following stress/injury, leading to efflux of immune cells from the bone marrow into the enthesis[1]

MSC = mesenchymal stem cell; PsA = psoriatic arthritis; TCV = transcortical microvessels.

1. Schett G, et al. *Nat Rev Rheumatol.* 2017;13:731-741.

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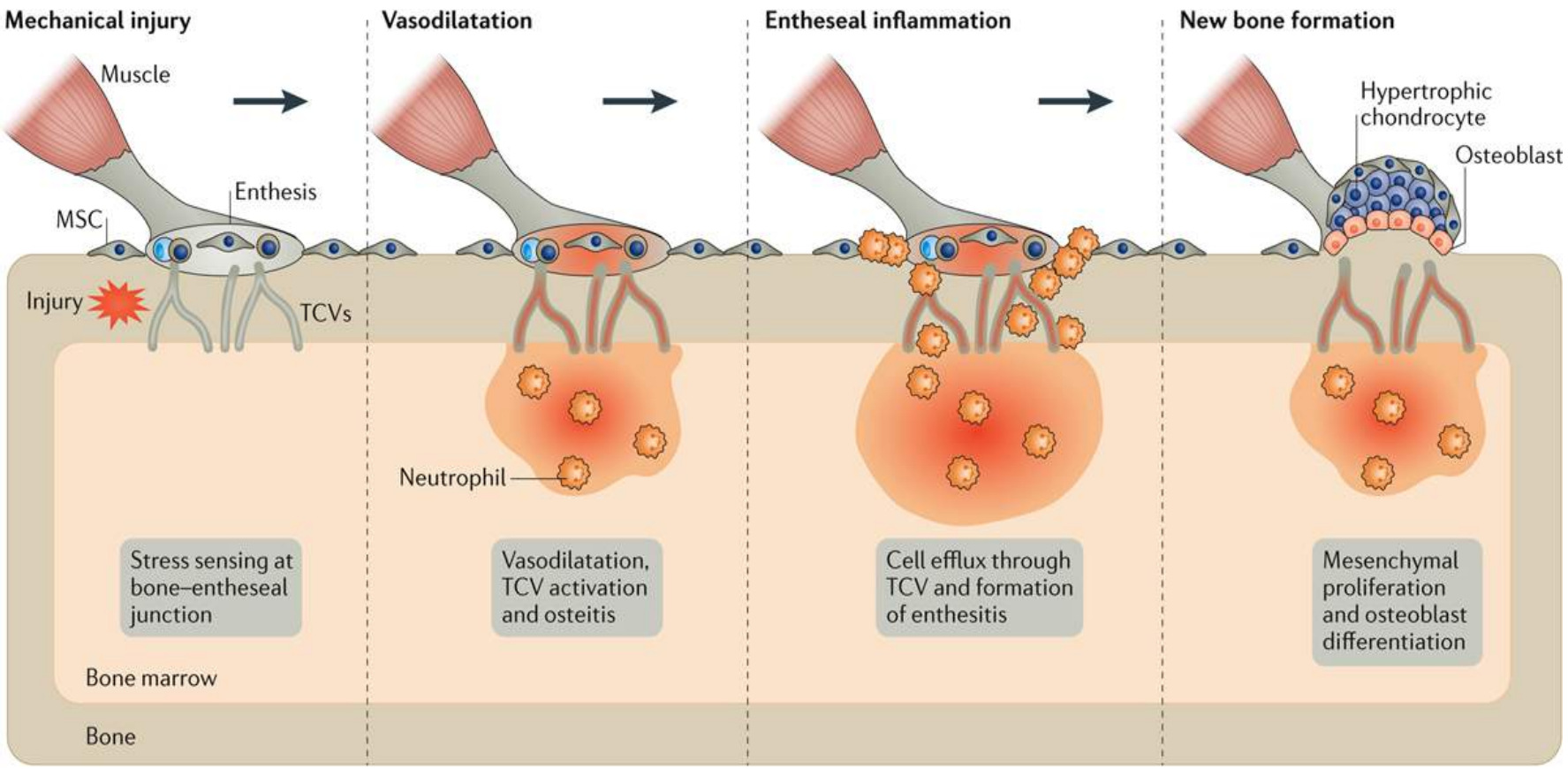
Entheseal inflammation is closely linked to osteitis and new bone formation



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Entheseal inflammation is closely linked to osteitis and new bone formation

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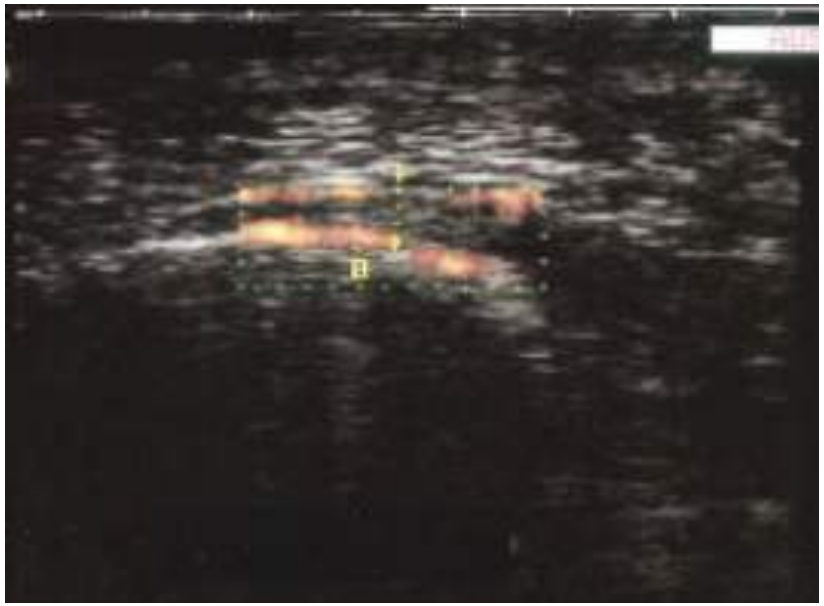

Permission granted by D'Agostino MA et al.[1]

Abnormal vascularization at the cortical junction of a SpA patient with plantar fascia enthesitis[1]

1. D'Agostino MA et al. *Arthritis Rheum*. 2003;48:523-533.

MSC = mesenchymal stem cell; PsA = psoriatic arthritis; TCV = transcortical microvessels.

1. Schett G, et al. *Nat Rev Rheumatol*. 2017;13:731-741.

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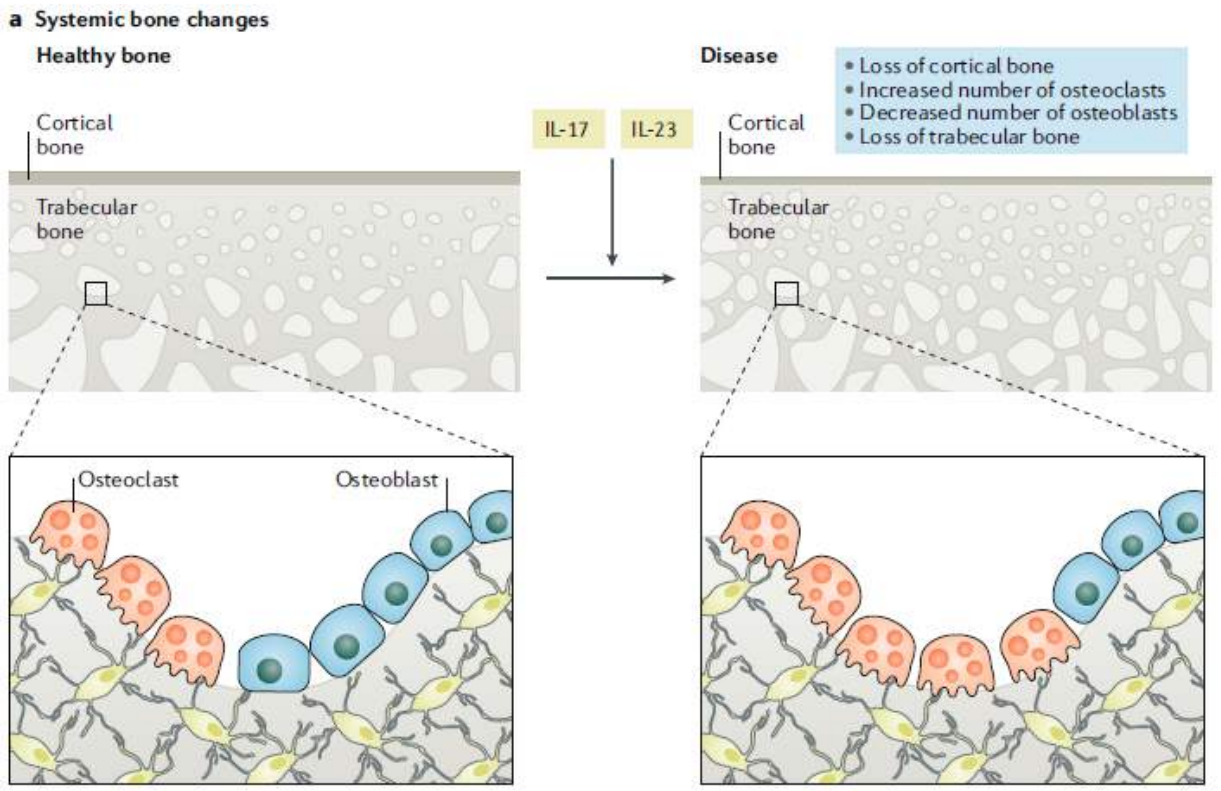
Systemic bone erosion in SpA

- Increased bone resorption and decreased bone formation leads to bone loss[1]
- Premature systemic bone loss; trabecular and cortical bone are lost, resulting in osteopenia and/or osteoporosis[2]



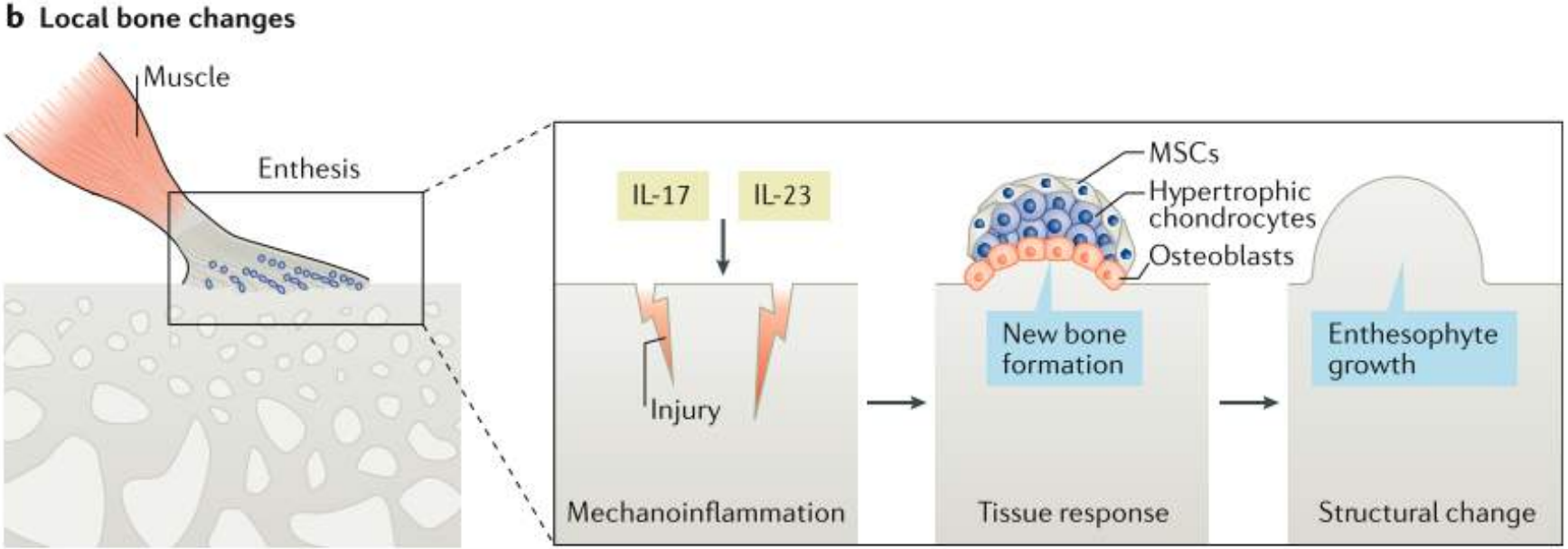
Permission granted by Gravallese EM, et al.[2]

SpA = spondyloarthritis; IL = interleukin.

1. Teitelbaum SL, Ross FP. *Nat Rev Genet.* 2003;4:638-649. 2. Gravallese EM et al. *Nat Rev Rheumatol*. 2018 Nov;14(11):631-640

IL-17 and IL-23 initiate entheseal inflammation and new bone formation

- Bone formation tends to be localized at entheseal sites[1]
- Resembles a response-to-injury process; a cartilage scaffold is formed and remodeled into bone[1]



Permission granted by Gravallese EM, et al.[1]

IL = interleukin; MSC = mesenchymal stem cell.

1. Gravallese EM et al. *Nat Rev Rheumatol*. 2018 Nov;14(11):631-640

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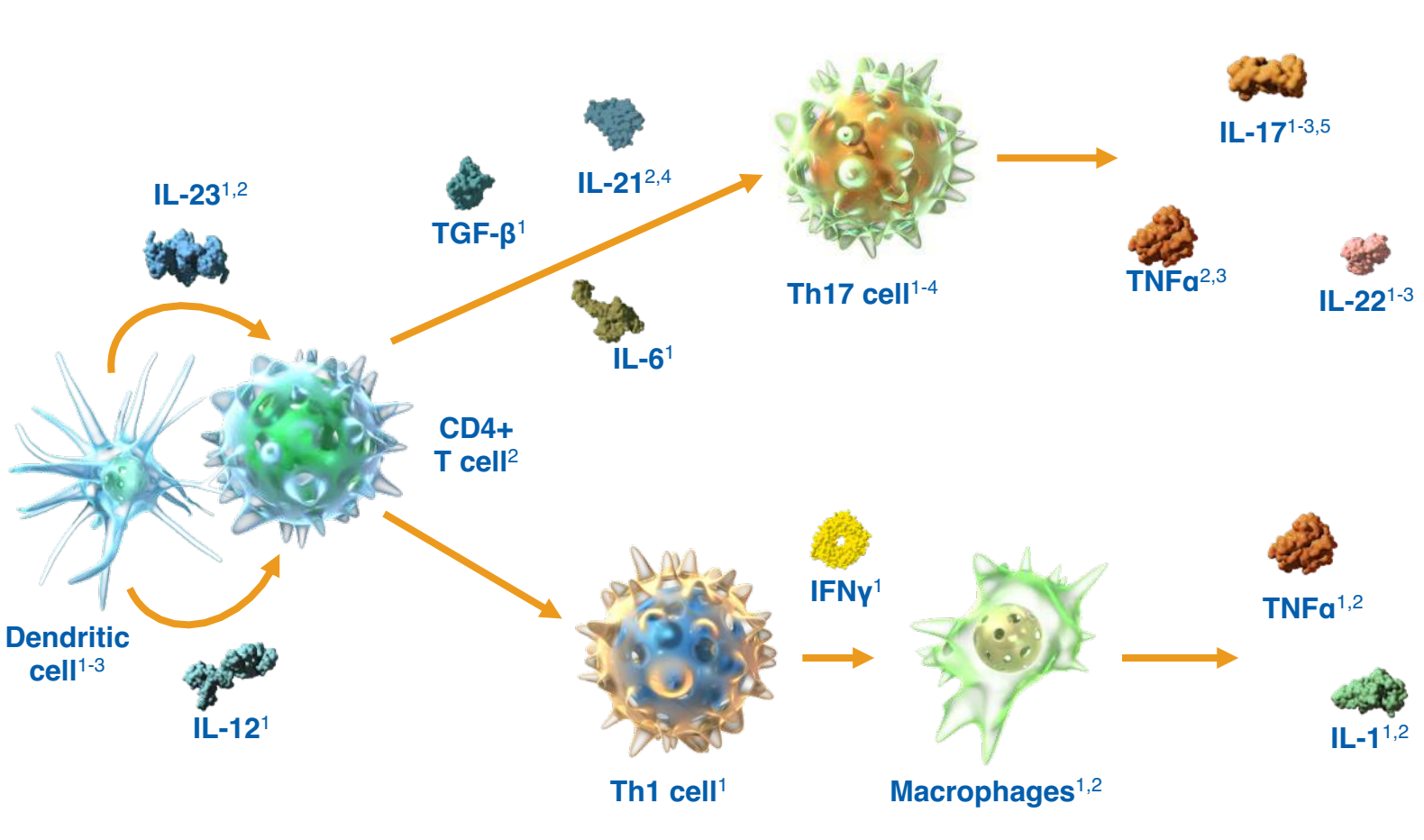
Proinflammatory immune cells produce cytokines that contribute to clinical manifestations of SpA[1-5]



- Enthesitis[3]
- Synovitis[3]
- Osteoproliferation[3]
- Bone erosion[1,2]
- Cartilage destruction[1,2]
- Cutaneous lesions[5]

SpA = spondyloarthritis; CD = cluster of differentiation; IFNγ = interferon gamma; IL = interleukin; TGF-β = transforming growth factor β; Th cell = T helper cell; TNFα = tumor necrosis factor-α.

1. Raychaudhuri SP. *Clin Rev Allergy Immunol*. 2013;44:183-193; 2. Miossec P, Kolls JK. *Nat Rev Drug Discov*. 2012;11:763-776;
3. Smith JA, Colbert RA. *Arthritis Rheumatol*. 2014;66:231-241; 4. Palmer MT, Weaver CT. *Nature*. 2007;448:416-418. 5. Suzuki E et al. *Autoimmun Rev*. 2014;13:496-502.

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Discussion

1. How often do you see enthesitis in your practice?

2. Is enthesitis the first inflammatory lesion you observe in SpA?

Axial and Peripheral Manifestations of PsA

Undiagnosed PsA is prevalent among patients with PsO

PREPARE Study (Prevalence of PsA in Adults With PsO: An Estimate From Dermatology Practice)[1]

Patients with PsO in dermatologists' offices (N=949)

Rheumatologists examined patients using:

- Medical history
- Physical examination
- Laboratory test findings

30% of patients (n=285) received a clinical diagnosis of PsA

41% (n=117) of patients had not previously been diagnosed with PsA

Patients with PsO also showed a higher prevalence of enthesopathy, which may be an early sign of PsA[2]

Dermatologists can play an important role in screening patients with PsO for early signs of PsA and actively monitoring for signs of joint or arthritic involvement[3]

PsA = psoriatic arthritis; PsO = psoriasis.

PREPARE, Prevalence of Psoriatic Arthritis in Adults With Psoriasis: An Estimate From Dermatology Practice.

1. Mease PJ et al. *J Am Acad Dermatol*. 2014;71(4):649-655. 2. Naredo E et al. *Rheumatology*. 2011;50:1838-1848. 3. Mease PJ, Armstrong A. *Drugs*. 2014;74(4):423-441.

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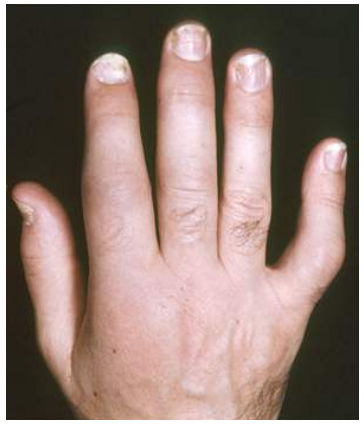
Various clinical manifestations of PsA

Patients with PsA face a multifaceted disease involving multiple clinical domains[1]

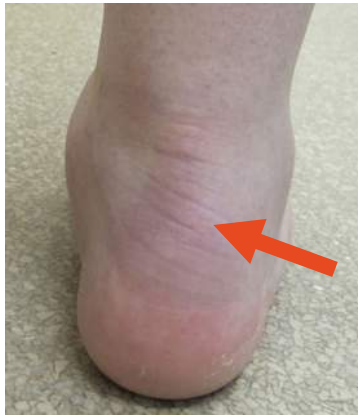
Peripheral arthritis[2]



Permission granted by ACR.[2]

96%[8]

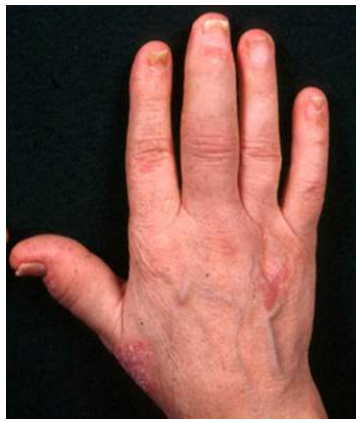
Enthesitis[3]



Permission granted by ACR.[3]

30% to 50%[8]

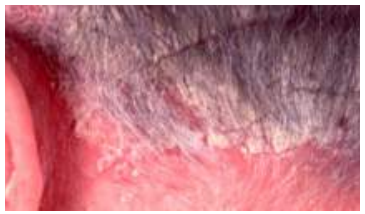
Dactylitis[4]

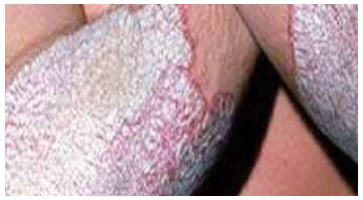


Permission granted by ASAS.[4]

40% to 50%[8]

Skin[5,6]





Permissions granted by Wozel G et al.[5] and Menter A, et al[6]

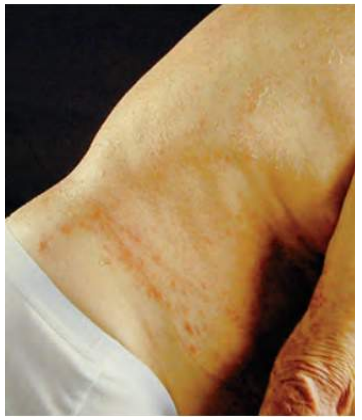
100%[8]

Nails[7]

Permission granted by Manhart R et al.[7]

>80%[8]

Axial disease[8]



Permission granted by Ritchlin CT et al.[8]

25 to 70%[9]

PsA = psoriatic arthritis.

1. Coates LC, et al. *Arthritis Rheumatol*. 2016;68:1060-1071;
2. American College of Rheumatology. http://images.rheumatology.org/bp/#/search?q=psoriatic%20arthritis&filters=%257B%257D. Accessed July 17, 2019;
3. American College of Rheumatology. http://images.rheumatology.org/bp/#/search/?q=enthesitis&filters=%257B%257D. Accessed July 17, 2019;
4. Assessment of SpondyloArthritis international Society (ASAS). http://slides.asas-group.org/app/slides/search?q=dactylitis&submit=. Accessed July 17, 2019;
5. Wozel G. *Clin Dermatol*. 2008;26:448-459; 6. Menter A, et al. *J Am Acad Dermatol*. 2011;65:137-174; 7. Manhart R, Rich P. *Clin Exp Rheumatol*. 2015;33(suppl 93):S7-S13;
8. Ritchlin CT et al. *N Engl J Med*. 2017;376:957-970. 9. Gladman DD. *Curr Rheumatol Rep*. 2007;9:455-460.

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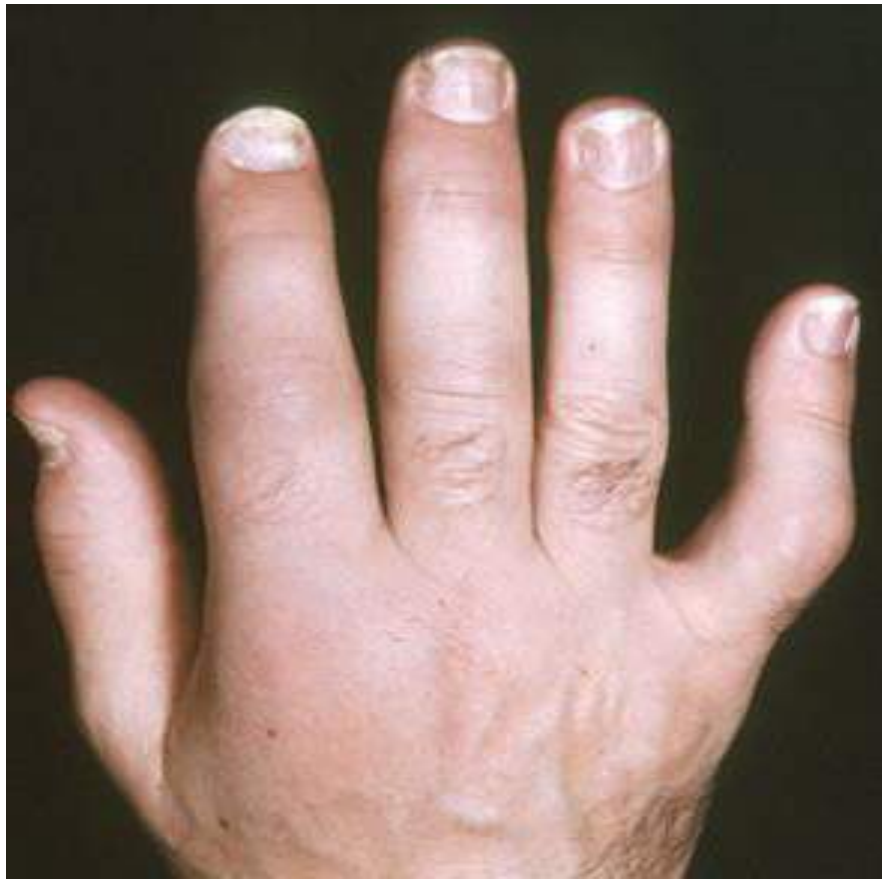
Peripheral arthritis in PsA

Presentation

- Involves the peripheral joints: elbows, wrists, hands, and feet[1,2]
- Leads to joint erosion, joint space narrowing, bony proliferation, osteolysis, and synovitis[3]
- Ranges from none through to monoarthritis, to oligoarthritis (≤4 joints), to polyarticular (>4 joints) destructive erosive arthritis[1,2]

Patient impact

- Pain and irreversible deformities can result in loss of function[2]
- Damage is progressive in majority of patients[4]
  - Median of 0.42 peripheral joints/year (range: 0-7.2)[4]



Permission granted by ACR.[5]

PsA = psoriatic arthritis.

1. Her M, Kavanaugh A. *Expert Rev Clin Immunol*. 2014;10:1241-1254; 2. Acosta Felquer ML, FitzGerald O. *Clin Exp Rheumatol*. 2015;33:S26-S30;
3. Gottlieb A et al. *J Am Acad Dermatol*. 2008;58:851-864; 4. McHugh NJ et al. *Rheumatology (Oxford)*. 2003;42:778-783; 5. American College of Rheumatology. http://images.rheumatology.org/bp/#/search?q=psoriatic%20arthritis&filters=%257B%257D. Accessed July 17, 2019.

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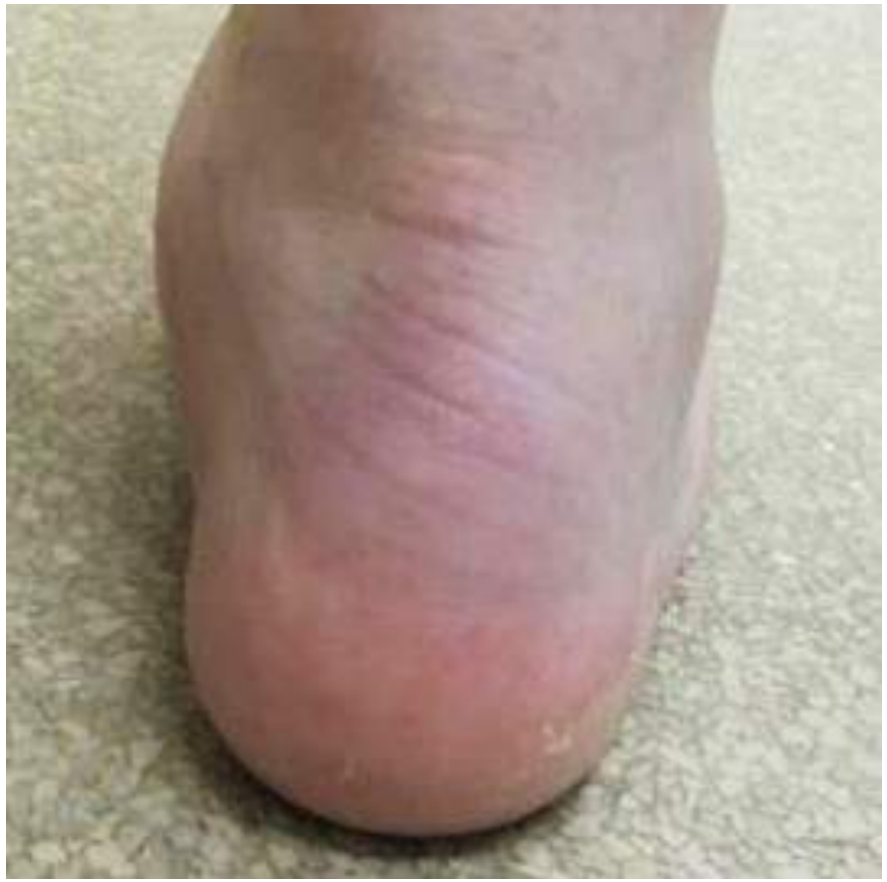
Enthesitis

Presentation

- Characterized by pain and swelling at the site of tendon and ligament insertion into the bone[1-3]
- Common sites: Achilles tendon, plantar fascia, and greater trochanter[4]
- Reported to occur in 35% to 50% of patients with PsA[5]

Patient impact

- PsA patients with enthesitis face a greater burden than those without enthesitis, reporting greater pain, fatigue, and impairment of work and activity[6]



Permission granted by ACR.[7]

PsA = psoriatic arthritis.

1. McGonagle D et al. *Arthritis Rheum*. 2007;56:2482-2491; 2. Benjamin M et al. *Arthritis Rheum*. 2004;50:3306-3313; 3. Lories RJ, McInnes IB. *Nat Med*. 2012;18:1018-1019;
4. Liu JT et al. *World J Orthop*. 2014;5:537-543; 5. Kaeley GS et al. *Semin Arthritis Rheum*. 2018;48:35-43; 6. Mease PJ et al. *Arthritis Care Res (Hoboken)*. 2017;69:1692-1699;
7. American College of Rheumatology. http://images.rheumatology.org/bp/#/search/?q=enthesitis&filters=%257B%257D. Accessed July 17, 2019.

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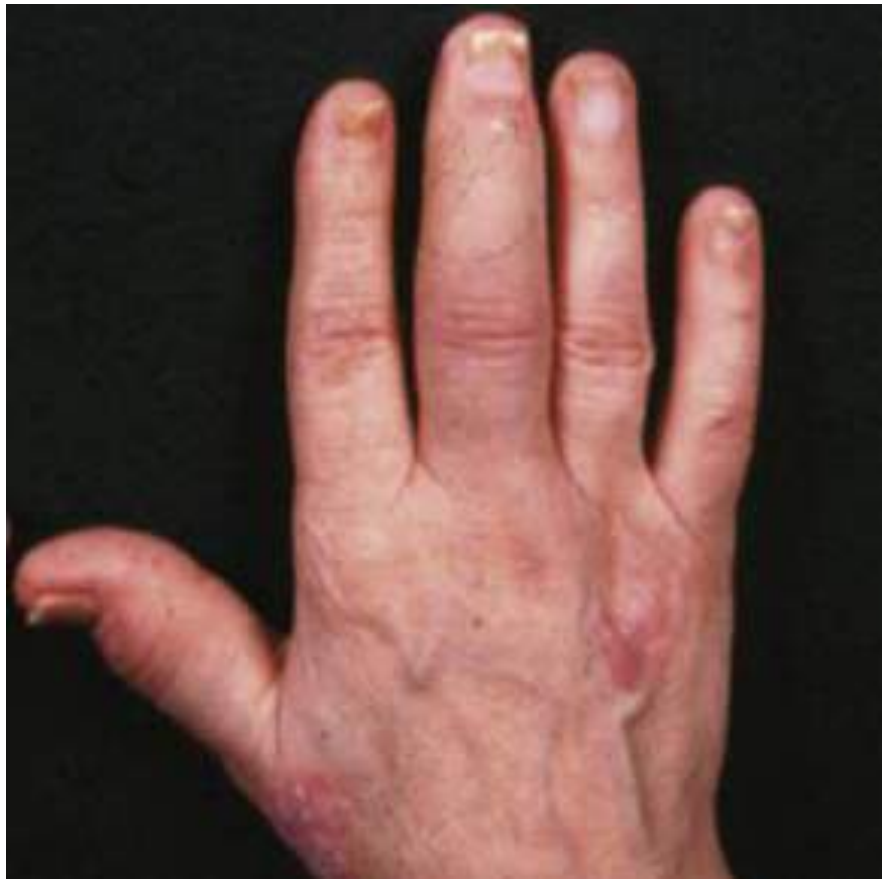
Dactylitis

Presentation

- Diffuse swelling of the entire finger or toe (sausage digit)[1,2]
  - Swelling can be acute (inflammation/pain) or chronic (without inflammation)[3]
- Associated with erosive joint damage[3]
- 32%-48% of patients with PsA have dactylitis[5]
  - 50% of patients have multiple digits involved simultaneously[5]

Patient impact

- Fatigue, pain, and swelling impairs work and non-work activities[4]
- Morbidity related to dactylitis increases with time[5]



Permission granted by ASAS.[6]

PsA = psoriatic arthritis.

1. Her M, Kavanaugh A. *Expert Rev Clin Immunol*. 2014;10:1241-1254; 2. Gladman DD et al. *J Rheumatol*. 2013;40:1357-1359; 3. Brockbank JE et al. *Ann Rheum Dis*. 2005;64:188-189; 4. Mease PJ et al. *Arthritis Care Res*. 2017;69:1692-1699; 5. Liu JT et al. *World J Orthop*. 2014;5:537–543; 6. Assessment of SpondyloArthritis international Society (ASAS). http://slides.asas-group.org/app/slides/search?q=dactylitis&submit=. Accessed July 17, 2019.

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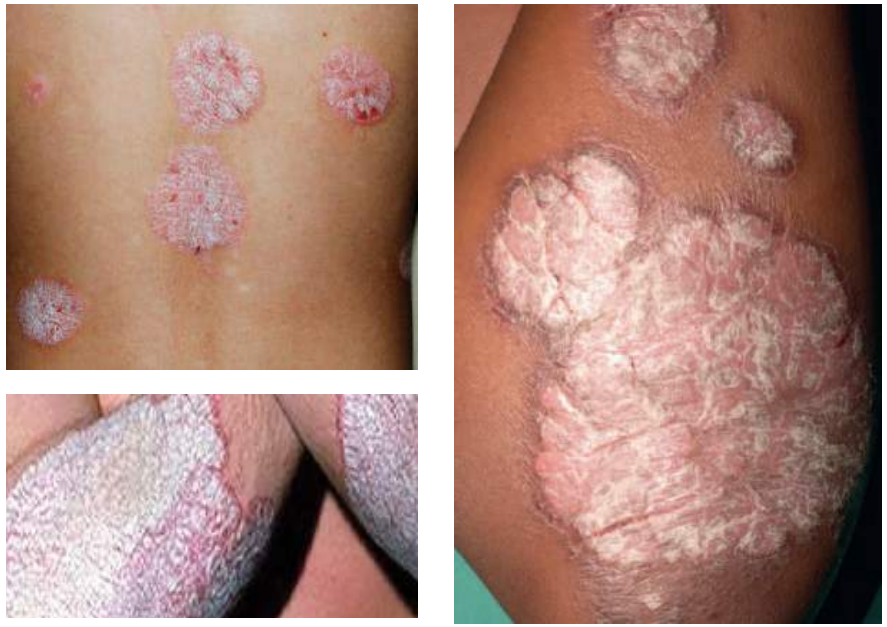
Skin

Presentation

- Papules, patches, and plaques, sharply marginated with silvery buildup of dead skin cells (scales)[1]
- Common sites: scalp, nails, trunk, elbows, and knees[2]
- All patients with PsA have PsO[2]
  - ~10%-37% of PsO patients develop PsA, which may precede skin disease in some cases[3]

Patient impact

- Even moderate amounts of psoriatic skin involvement are associated with a greater disease burden of PsA, with greater reported pain, fatigue, and higher HAQ scores[3]



Permissions granted by Van de Kerkhof P, Nestlé F. Psoriasis. In: Bolognia JL et al, ed. Dermatology. 3rd ed. Saunders, an Imprint of Elsevier; 2012: Chapter 8[4] and Menter A, et al[5]

HAQ = Health Assessment Questionnaire; PsA = psoriatic arthritis; PsO = psoriasis.

1. Nestle FO et al. *N Engl J Med*. 2009;361:496-509; 2. Lee S et al. *P T*. 2010;35:680-689; 3. Mease PJ et al. *J Rheumatol*. 2017;44;1151-1158. 4. Van de Kerkhof P, Nestlé F. Psoriasis. In: Bolognia JL et al, ed. *Dermatology*. Based on: 3rd ed. Saunders, an Imprint of Elsevier; 2012: Chapter 8. https://www.elsevier.com/books/dermatology-2-volume-set/bolognia/978-0-7234-3571-6. Accessed Aug 14, 2019. 5. Menter A, et al. *J Am Acad Dermatol*. 2011;65:137-174.

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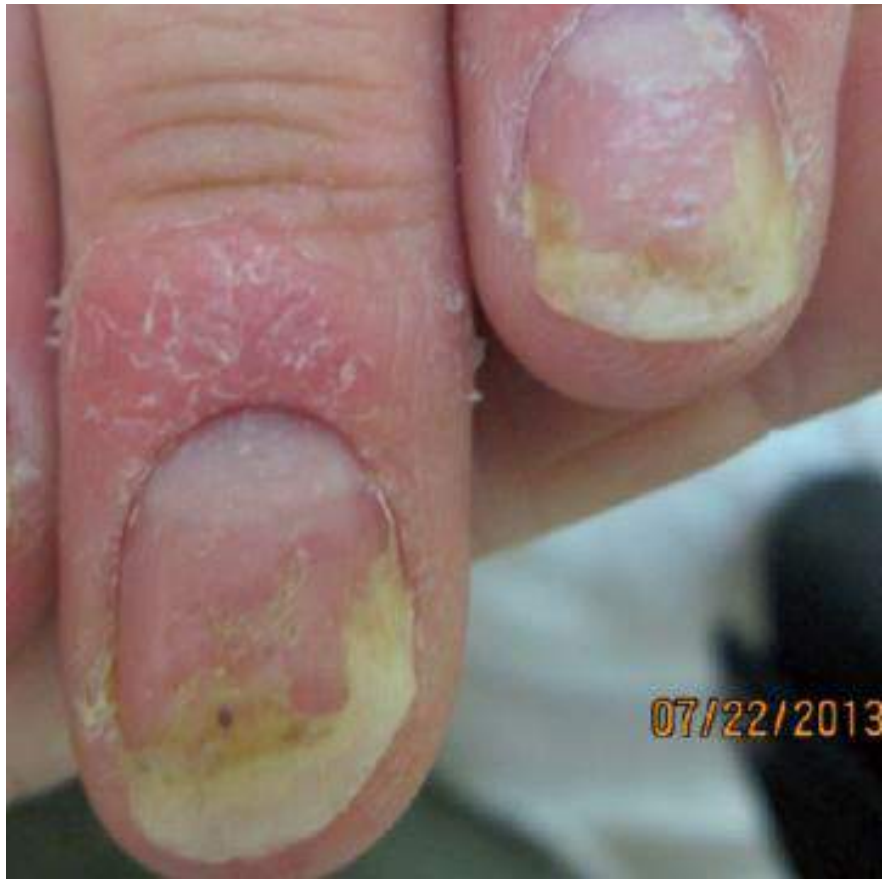
Nail

Presentation

- Pitting, discoloration, crumbling, nail bed separation, changes in nail shape/thickness, horizontal lines[1]
- Affects ~ 80% of PsA patients due to close association between DIP joints and nail matrix[2]

Patient impact

- Associated with discomfort and pain[2]
- Can lead to functional impairment and psychological stress[2]



Permission granted by Manhart R et al.[7]

DIP = distal interphalangeal; PsA = psoriatic arthritis.

1. Yamamoto Y. *Open Access Rheumatol*. 2015;7:55–62; 2. Sobolewski P et al. *Reumatologia*. 2017;55:131-135; 3. Manhart R, Rich P. *Clin Exp Rheumatol*. 2015;33(suppl 93):S7-S13.

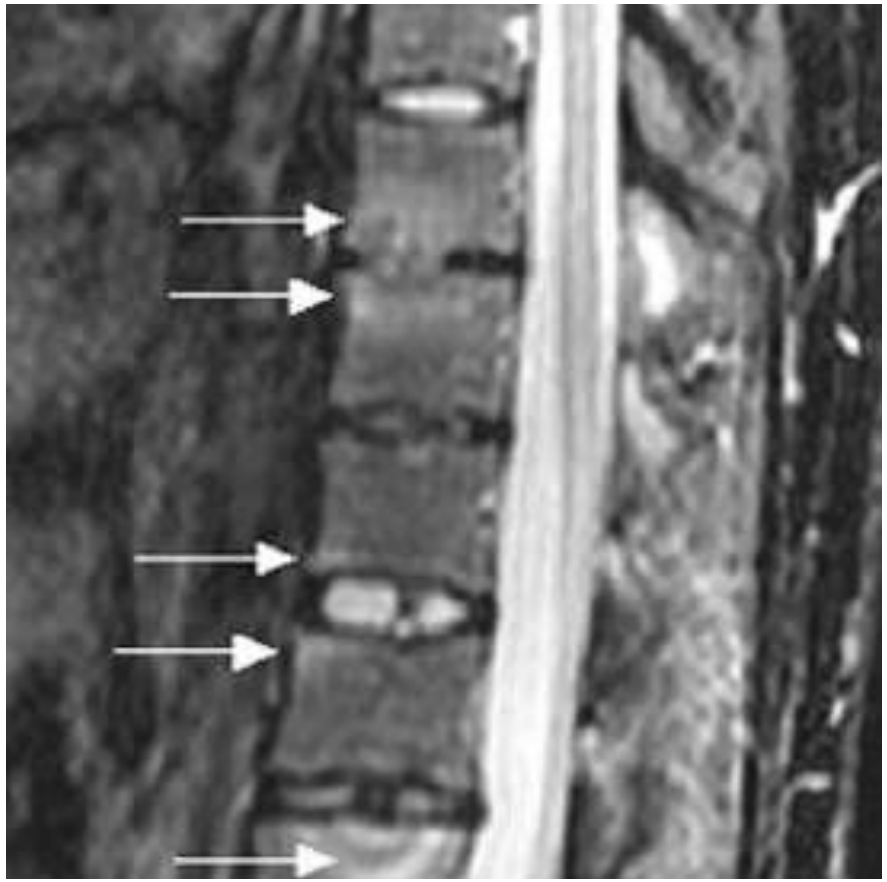
Axial disease

Presentation

- Inflammation in the axial skeleton
- Back pain, stiffness, restriction in spinal mobility, sacroiliitis, spondylitis, and syndesmophyte formation[1,2]
- Prevalence of axial PsA ranges from 25% to 75% of patients with PsA; may be asymptomatic[3,4,6]

Patient impact

- PsA patients with axial involvement had a higher likelihood of higher disease activity and worse quality of life compared to those with mainly peripheral involvement in PsA.[5]



Permission granted by McQueen F, et al[7]

PsA = psoriatic arthritis.

1. Baraliakos X et al. *Clin Exp Rheumatol*. 2015;33:S31-S35; 2. Nash P. *J Rheumatol*. 2014;41:2286-2289; 3. Ogdie A, Weiss P. *Rheum Dis Clin North Am*. 2015;41:545-568; 4. Gladman DD. *Curr Rheumatol Rep*. 2007;9:455-460; 5. Zink A et al. *J Rheumatol*. 2006;33:86-90; 6. Mease PJ, et al. *J Rheumatol*. 2018;45(10):1389-1396; 7. McQueen F, et al. *Arthritis Res Ther*. 2006;8:207.

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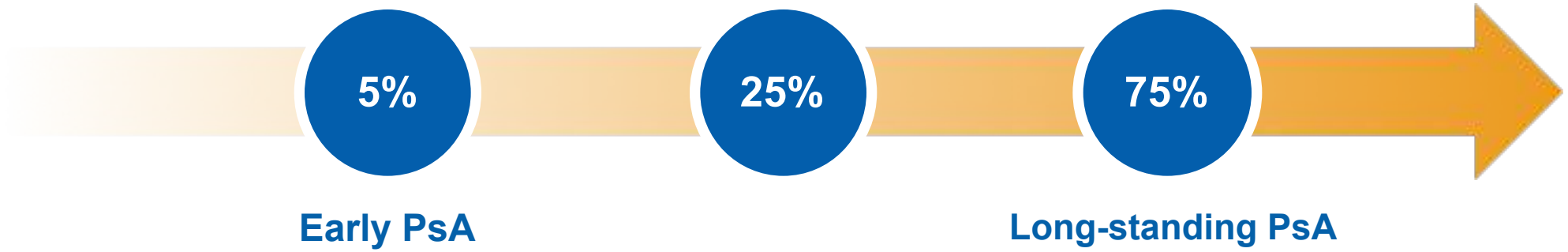
Axial involvement in PsA is prevalent

- 2-5% of patients with PsA have solely axial disease[1]
- 15% of patients with PsA who did not have axial involvement at presentation developed axial PsA during 10 years of follow-up[2]
- Increased risk of developing axial disease at an early stage:[1]
  - 40-50% of patients with PsA are HLA-B27 positive[3]
  - Presence of radiographic damage to peripheral joints
  - Increased ESR

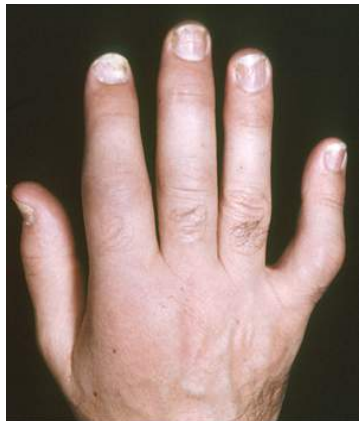


PsA = psoriatic arthritis; ESR = erythrocyte sedimentation rate; HLA-B27 = human leukocyte antigen B27.

1. Feld J, et al. *Nat Rev Rheumatol* 2018;14:363-71. 2. Chandran V, et al. *J Rheumatol* 2010;37:809-15. 3. Ritchlin CT et al. *N Engl J Med.* 2017;376:957-970.

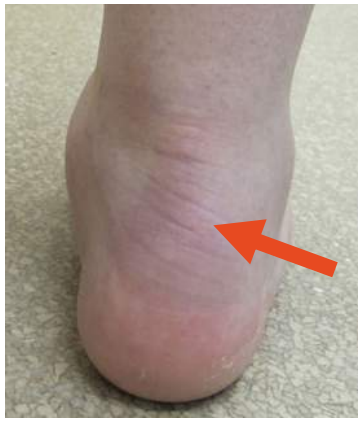
PsA is a multifaceted disease involving multiple clinical domains

Peripheral arthritis[2]



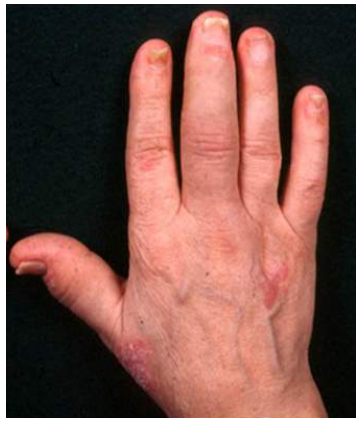
Permission granted by ACR.[2]

Enthesitis[3]



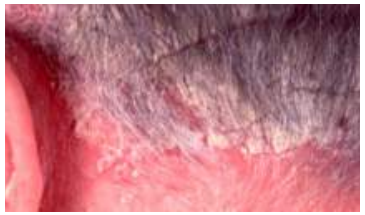
Permission granted by ACR.[3]

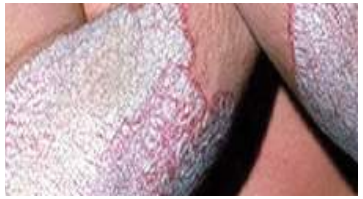
Dactylitis[4]



Permission granted by ASAS.[4]

Skin[5,6]



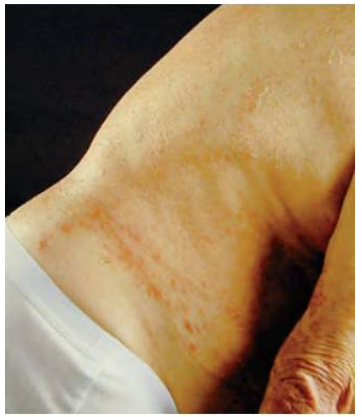


Permissions granted by Wozel G et al.[5] and Menter A, et al[6]

Nails[7]

Permission granted by Manhart R et al.[7]

Axial disease[8]



Permission granted by Ritchlin CT et al.[8]

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1. Coates LC, et al. *Arthritis Rheumatol*. 2016;68:1060-1071;
2. American College of Rheumatology. http://images.rheumatology.org/bp/#/search?q=psoriatic%20arthritis&filters=%257B%257D. Accessed July 17, 2019;
3. American College of Rheumatology. http://images.rheumatology.org/bp/#/search/?q=enthesitis&filters=%257B%257D. Accessed July 17, 2019;
4. Assessment of SpondyloArthritis international Society (ASAS). http://slides.asas-group.org/app/slides/search?q=dactylitis&submit=. Accessed July 17, 2019;
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7. Manhart R, Rich P. *Clin Exp Rheumatol*. 2015;33(suppl 93):S7-S13; 8. Ritchlin CT et al. *N Engl J Med*. 2017;376:957-970.

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Discussion

1. How often are PsA patients with solely axial pain misdiagnosed with fibromyalgia?

2. How frequently are PsA patients with solely peripheral manifestations misdiagnosed with osteoarthritis?

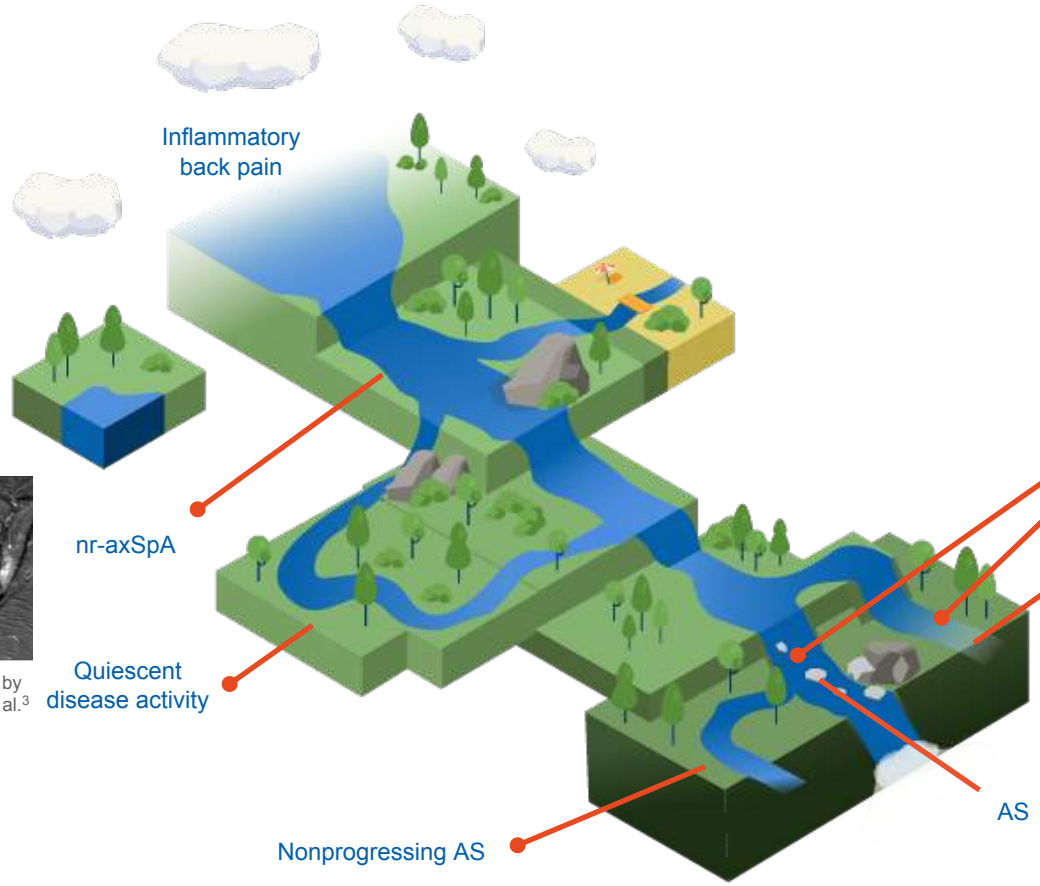
Axial and Peripheral Manifestations of axSpA

Disclosures for Reeti Joshi, MD

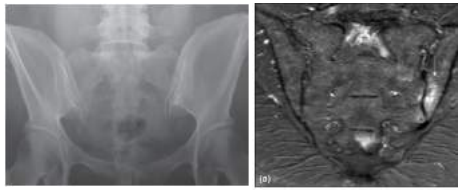
- Reeti Joshi has received consulting and speaker fees from AbbVie, Celgene, Novartis, Sanofi Genzyme and UCB. She is also adjunct faculty at Baylor College of Medicine, Houston.

- This is a non-CME, unbranded, disease state presentation developed by Dr. Joshi and sponsored by Novartis Pharmaceuticals Corporation.

Natural history of axSpA includes radiographic (AS) and nr-axSpA



Adapted with permission from Garg N, et al.[1]

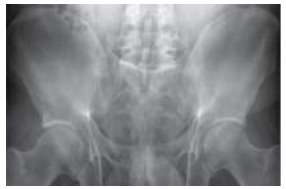


Permission granted by Sieper J et al.[4]

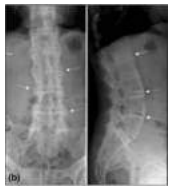
Permission granted by Van Mechelen M et al.[3]

The terms AS and nr-axSpA are distinguished by the degree of "radiographic sacroiliitis" assessed by conventional radiography[2]

These terms should only be used for classification of patients with axSpA and not as separate diagnoses[2]



Permission granted by Sieper J et al.[4]



Permission granted by Van Mechelen M et al.[3]

axSpA = axial spondyloarthritis; nr-axSpA = nonradiographic axial spondyloarthritis; AS = ankylosing spondylitis.

1. Garg N et al. *Best Pract Res Clin Rheumatol*. 2014;28(5):663-672. 2. Deodhar A et al. *Ann Rheum Dis*. 2016;75(5):791-794. 3. Van Mechelen M, et al. *Calcif Tissue Int*. 2018;102(5):547-558.
4. Sieper J, et al. *Lancet*. 2017;390(10089):73-84.

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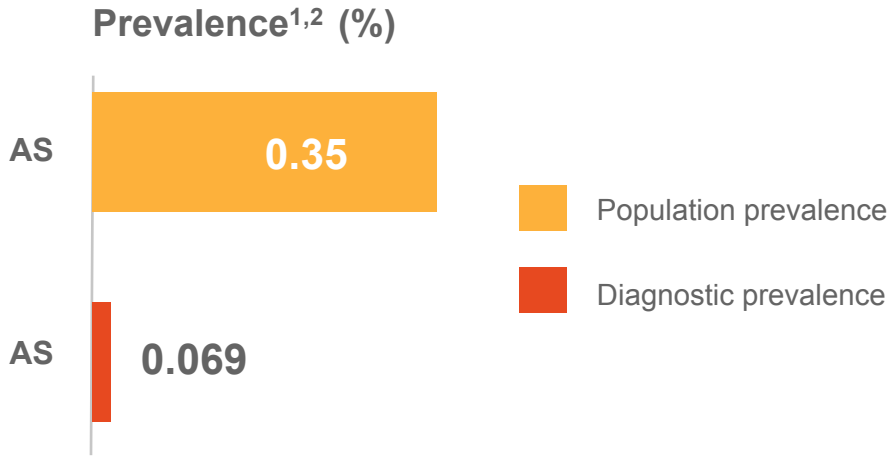
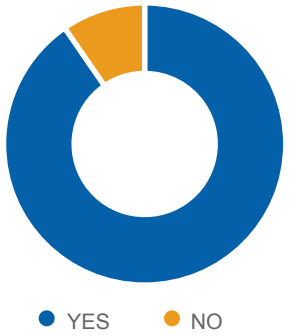
Is axSpA underdiagnosed?



- Axial spondyloarthritis usually starts in the third decade of life with a male to female ratio of:[4]
  - 2-3:1 for AS
  - 1:1 for nr-axSpA
- Proportion of nr-axSpA and AS patients are largely similar[5]

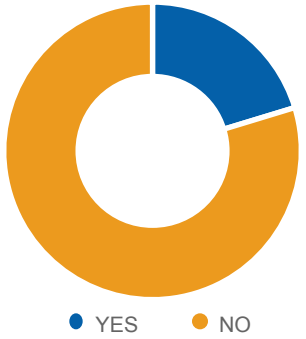
Many patients with axSpA are misdiagnosed with RA

Morning stiffness and joint involvement are common between the two[3]



Morning Stiffness

Reported in **90.4%** of patients diagnosed with axSpA, with duration ≥ 30 minutes in 76% of patients[3]



≥ 1 Swollen Joints

observed in **20.3%** of patients with axSpA[3]

axSpA = axial spondyloarthritis; nr-axSpA = nonradiographic axial spondyloarthritis; AS = ankylosing spondylitis; RA = rheumatoid arthritis.

1. Strand V et al. *Arthritis Care Res*. 2013;65:1299-1306. 2. MarketScan data, 2017. State level prevalence of RA, PsA, and AS by gender. 3. Mease P et al. Arthritis Care Res. 2018;70:1661-1670.
4. Sieper J, Poddubnyy D. *Lancet*. 2017;390:73-84. 5. Baraliakos X, et al. *RMD Open*. 2015;1:e000053

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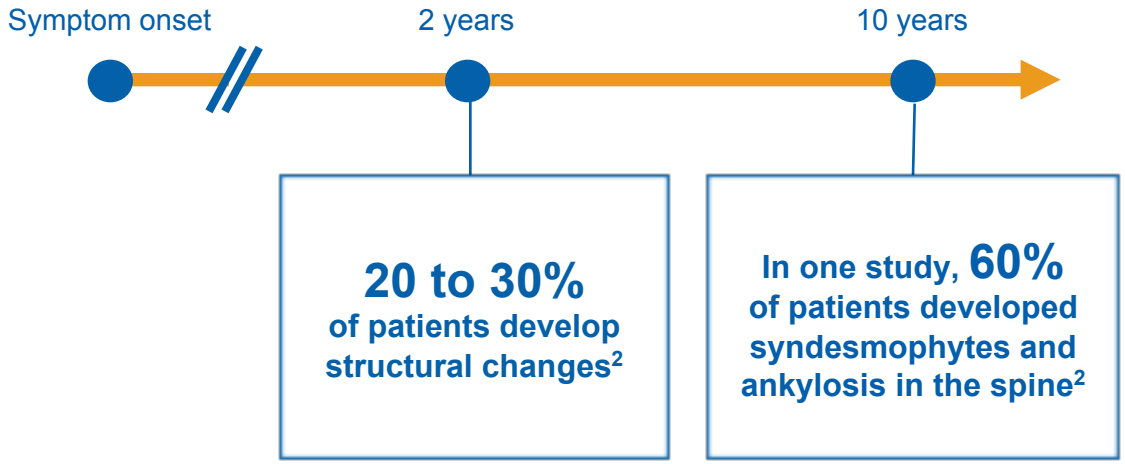
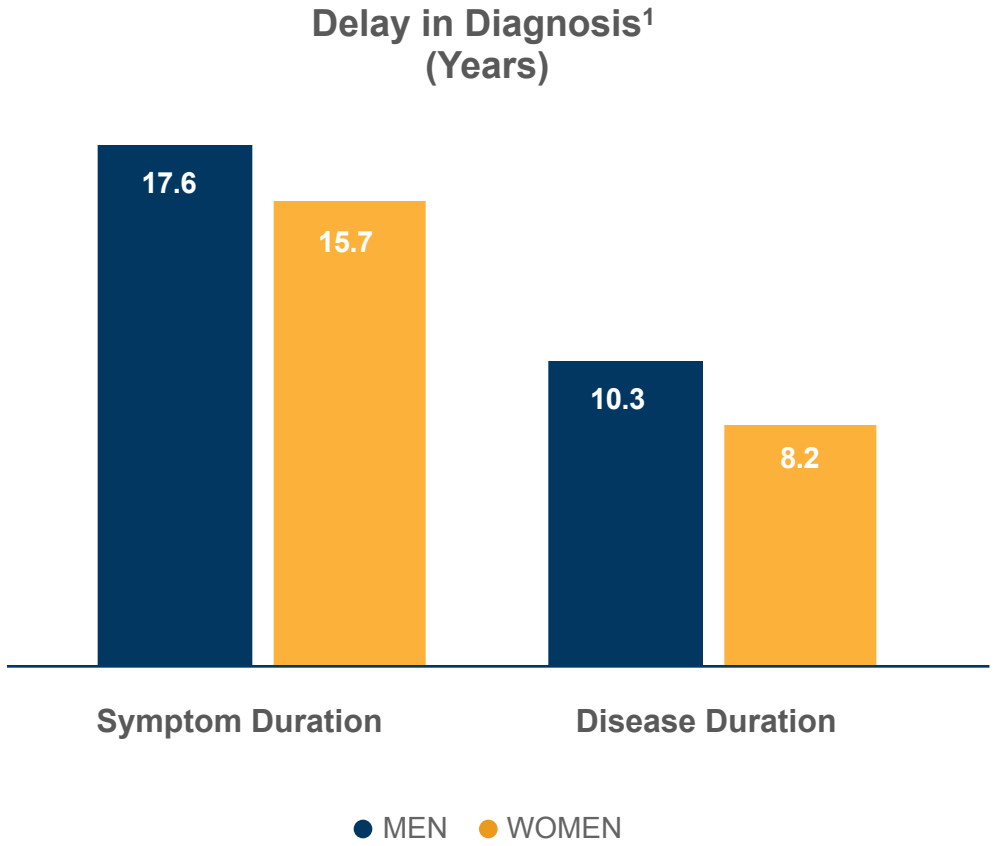
Patients with axSpA experience a delay between symptom onset and diagnosis

- Delays in diagnosis of axSpA result in prolonged pain, stiffness, fatigue, decreased mobility, irreversible new bone formation, loss of spinal function, and reduced QoL[3]





axSpA = axial spondyloarthritis; QoL = quality of life.

1. Liu M. Corrona final report with gender stratification. 2019. 2. Sieper J et al. *Nat Rev Dis Primers.* 2015;1:15013. 3. Danve A et al. *Clin Rheumatol.* 2019;38:625-634.

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Features of axSpA

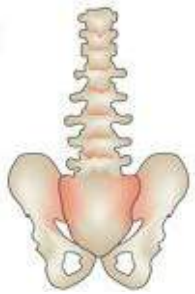
Chronic back pain (> 3 months)

- **Mechanical**
- **Inflammatory**

Presence of other SpA features[1,2]

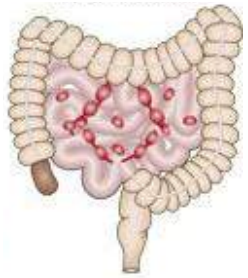

Psoriasis


Uveitis


Sacroiliitis and spondylitis


Peripheral joint involvement (oligo)arthritis


Enthesitis


Inflammatory bowel disease


Good response to NSAIDs


Positive family history

Adapted with permission from Rosenbaum JT, et al[1]

axSpA, axial spondyloarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis.

1. Rosenbaum JT, Rosenzweig HL. *Nat Rev Rheumatol.* 2012;8:249-250. 2. Rudwaleit M, et al. *Ann Rheum Dis.* 2009;68:777-783.

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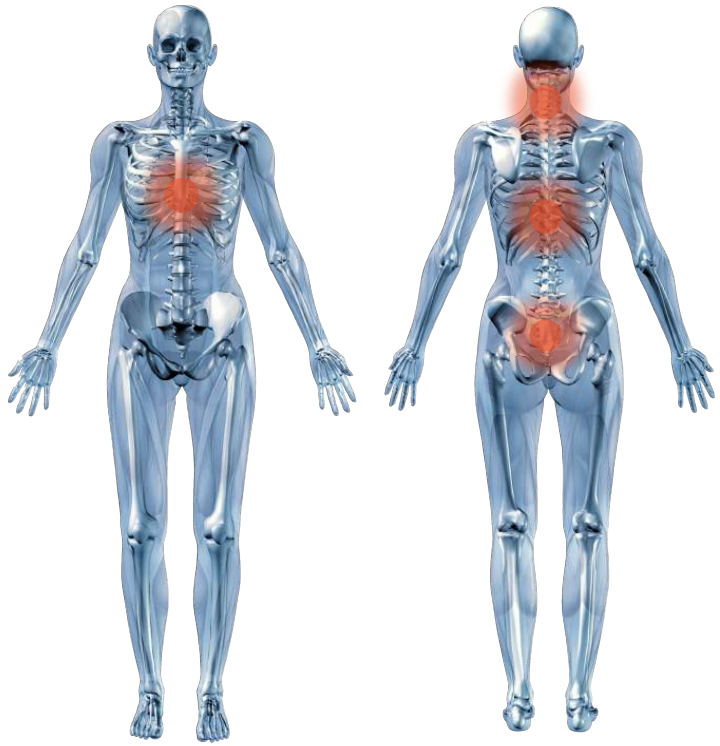
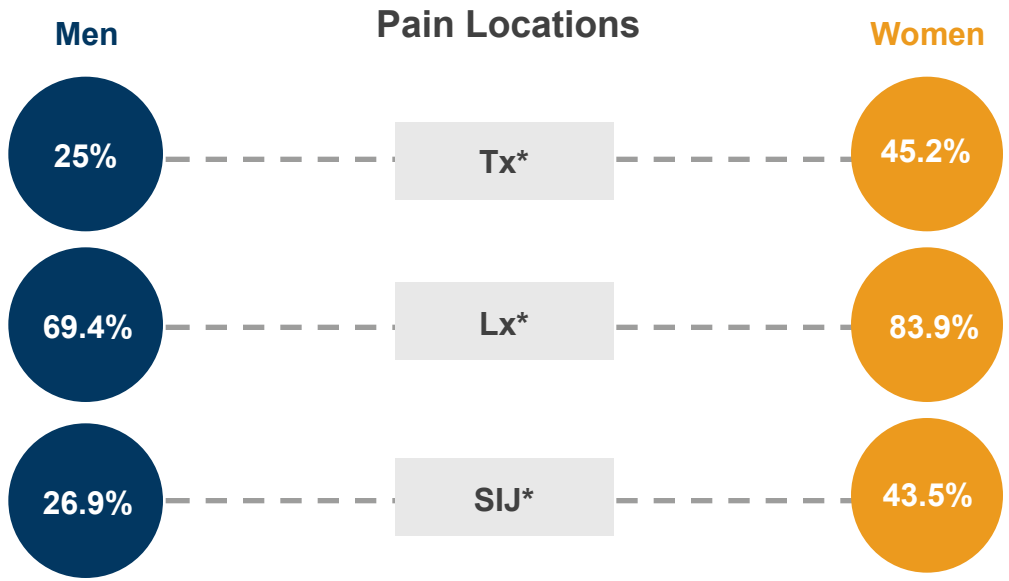
axSpA patients can present symptoms across different axial sites

- The most typical symptom of axSpA is IBP[1]
- Thoracic spine, cervical spine, and chest can also be affected[1]



Female patients present IBP at a lower frequency[2]
73 vs 89% (F vs. M)



Axial pain in thoracic, lumbar, and SIJ tends to be more common in women[3]

F = female; IBP = Inflammatory back pain; Lx = lumbar; M = male; SIJ = sacroiliac joint; Tx = thoracic.
* Denotes significant difference between the sexes

1. Taurog JD et al. *N Engl J Med*. 2016;374:2563-2574. 2. Slodobin G, et al. *Clin Rheumatol*. 2011 Aug;30(8):1075-80. 3. Swinnen TW et al. *Arthritis Res Ther*. 2018;20:156.

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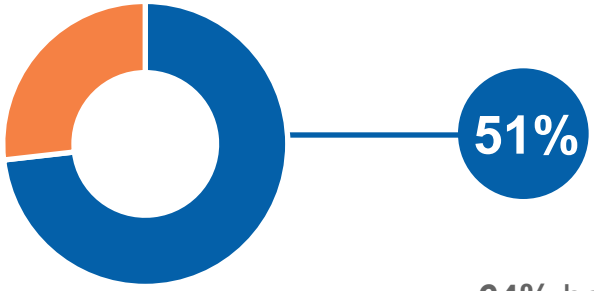
axSpA patients can present symptoms across the body including peripheral sites

- Peripheral manifestations—arthritis and enthesitis—can occur at any time in the course of the disease[1]
  - Predominantly lower limbs, asymmetrically
  - Dactylitis is less frequent but may also occur

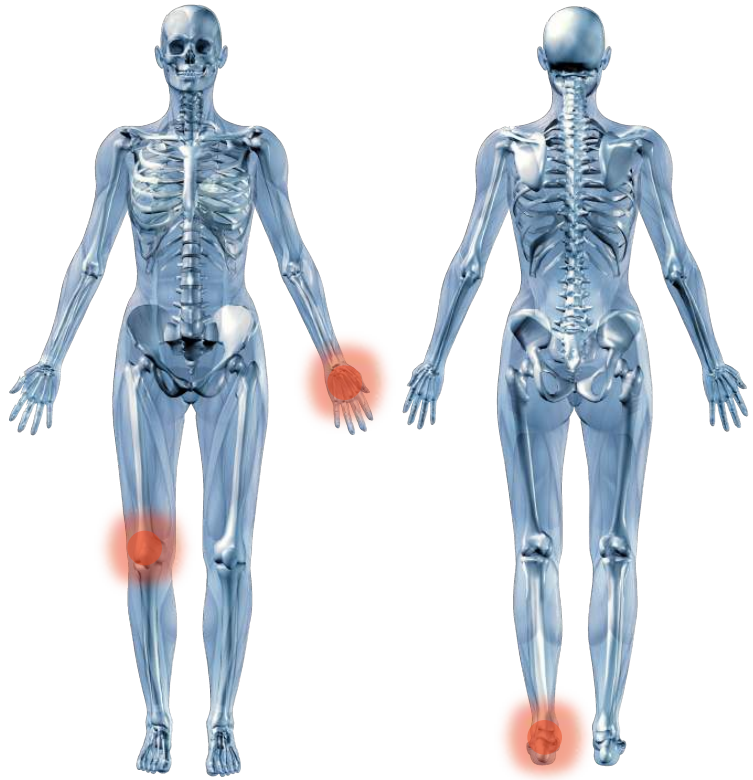
SpA diagnosis by ASAS criteria[2]



- Axial Cohort (73.2%)
- Peripheral Cohort (26.8%)

51% **of patients diagnosed using axial criteria also met the peripheral criteria**

- **64%** had history/presence of peripheral arthritis
- **62%** had history/presence of enthesitis
- **8%** had history/presence of dactylitis



Enthesitis is more common and severe in females[3,4]
67.9% vs 41.1% (F vs. M)

axSpA = axial spondyloarthritis; SpA = spondyloarthritis; ASAS = assessment of spondyloarthritis international society; F = female; M = male.

1. Taurog JD et al. *N Engl J Med*. 2016;374:2563-2574. 2. de Winter JJ et al. *RMD Open*. 2019;5:e000802. 3. Rusman T et al. *Curr Rheumatol Rep*. 2018; 20(6):35.
4. Landi M et al. *Medicine (Baltimore)*. 2016 Dec; 95(51):e5652.

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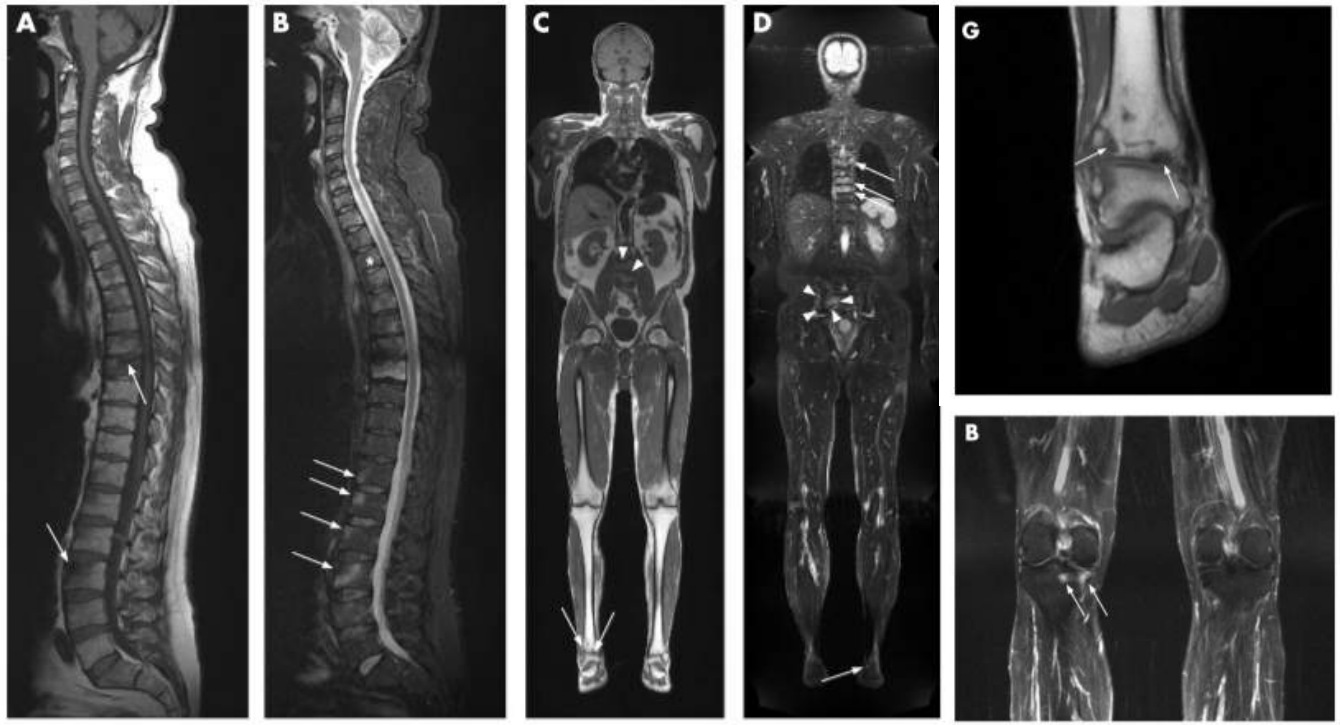
axSpA tends to affect the lower extremities

- In a whole-body MRI study of axSpA, inflammatory lesions were most often present in the lower thoracic, lumbar spine, and lower extremities[1]
- Enthesitis primarily affects the lower limbs, which are exposed to higher mechanical forces than the upper limbs[1,2]



Permission granted by Althoff CE, et al.[3]

axSpA = axial spondyloarthritis; MRI = magnetic resonance imaging.

1. Althoff CE, et al. *Ann Rheum Dis*. 2013 Jun;72(6):967-73. 2. Schett G, et al. *Nat Rev Rheumatol*. 2017;13:731-741. 3. Althoff CE, et al. *Ann Rheum Dis*. 2007 Jul;66(7):983-5.

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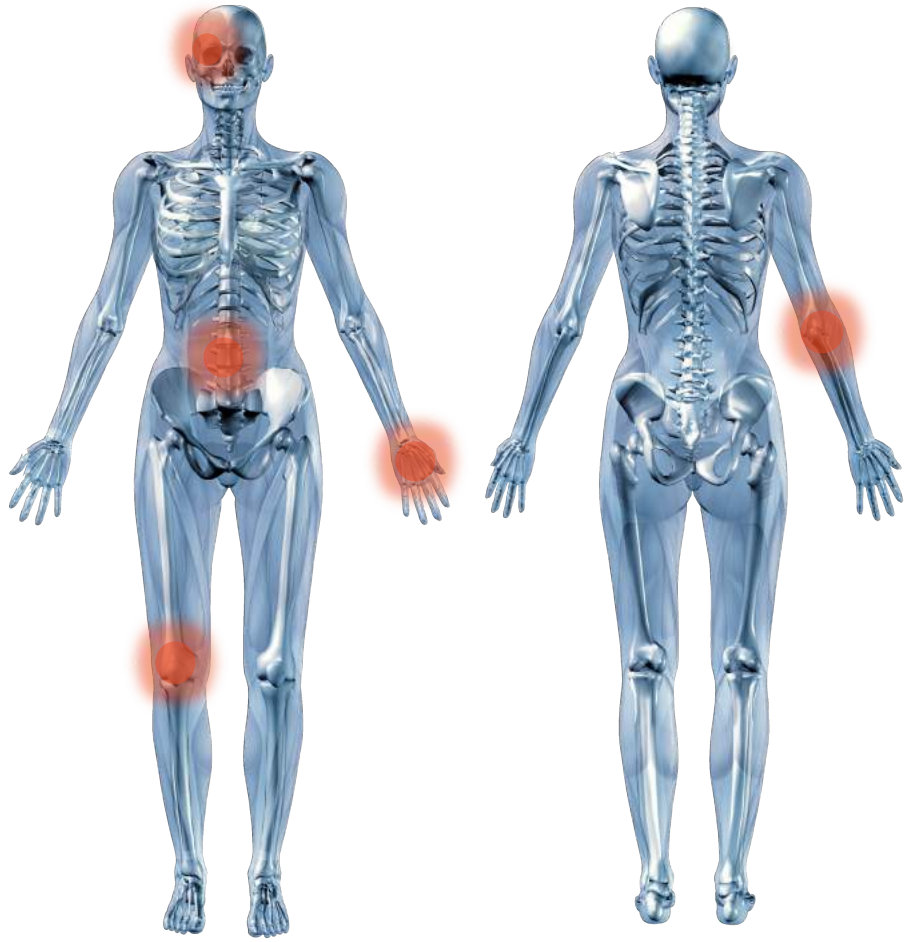
axSpA patients can present symptoms across the body including peripheral sites

- Extra-articular involvement includes:[1]
  - Uveitis
    - Typically acute anterior, limited in duration, unilateral, and frequently alternating between eyes
  - Psoriasis
  - IBD



axSpA = axial spondyloarthritis; IBD = inflammatory bowel disease.

1. Taurog JD et al. *N Engl J Med.* 2016;374:2563-2574.

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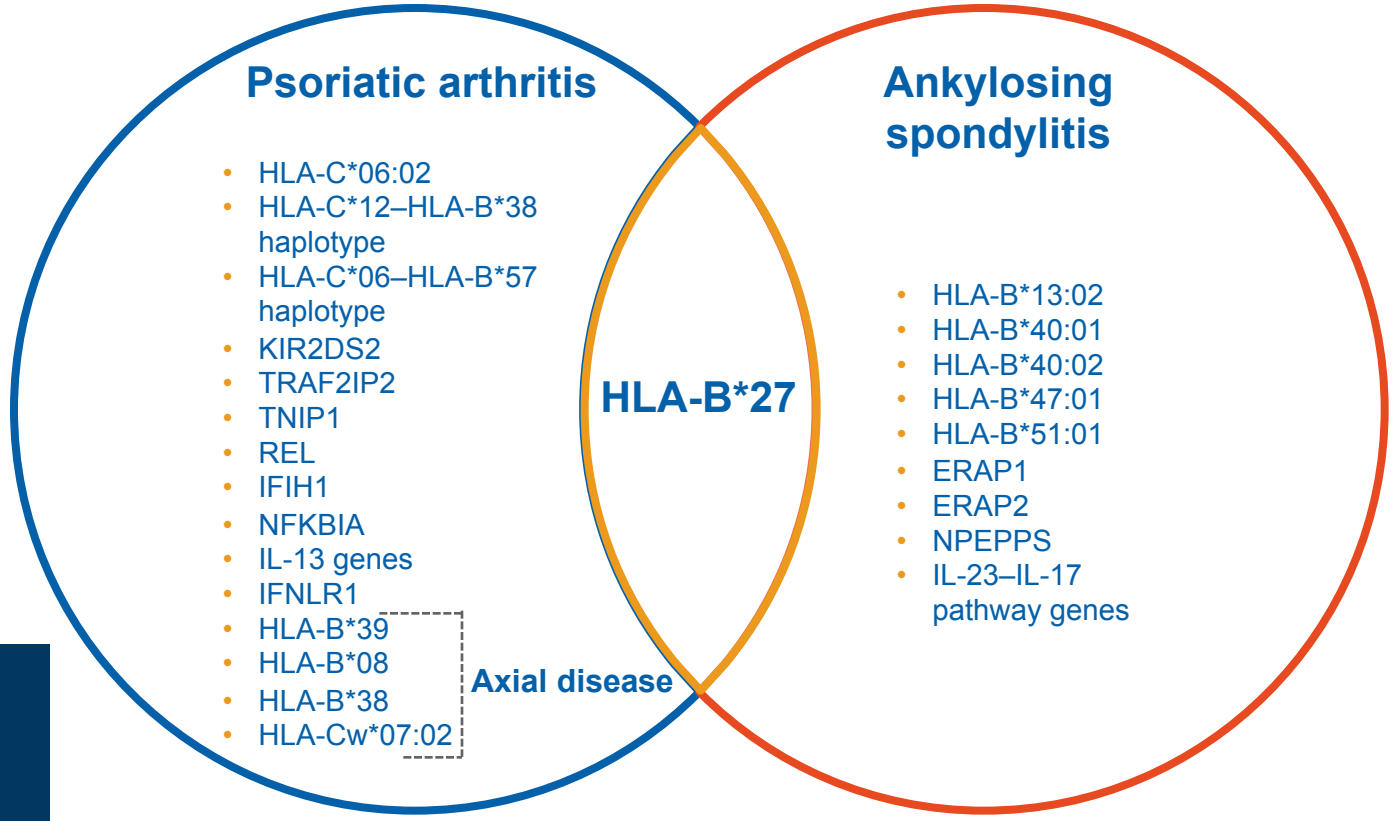
Genetic susceptibility in PsA and AS

- Axial disease in PsA is more commonly associated with other HLA genes than with HLA-B27[1]
- HLA-B27 positivity
  - 83-90% of patients with AS[2,3]
  - 74-86% of patients with nr-axSpA[4-6]
  - Disease occurs 5 years earlier in HLA-B27(+) patients than in those who are HLA-B27(-)[7]

HLA-B27 positivity is more common in male axSpA patients[8]

- 80% vs. 60% **(M vs. F)**

HLA-B27 is commonly associated with PsA and AS[1]



AS = ankylosing spondylitis; F = female; HLA = human leukocyte antigen; HLA-B27 = human leukocyte antigen B27, M = male; nr-axSpA = nonradiographic axial spondyloarthritis; PsA = psoriatic arthritis.

1. Feld J et al. *Nat Rev Rheumatol*. 2018 Jun;14(6):363-371. 2. Ritchlin CT et al. *N Engl J Med*. 2017;376:957-970. 3. Londono J, et al. *BMJ Open*. 2015; 5(11): e009092.
4. Baraliakos X, et al 2015 RMD Open. 2015 Aug 15;1(Suppl 1):e000053 5. Kiltz U, et al. *Arthritis Care Res (Hoboken)*. 2012 Sep;64(9):1415-22.
6. Rudwaleit M, et al. *Arthritis Rheum*. 2009 Mar;60(3):717-27. 7. Jaakkola E et al. *Ann Rheum Dis*. 2006;65:775-780. 8. Ortolan A, et al. *Arthritis Res Ther*. 2018;20(1):1-8.

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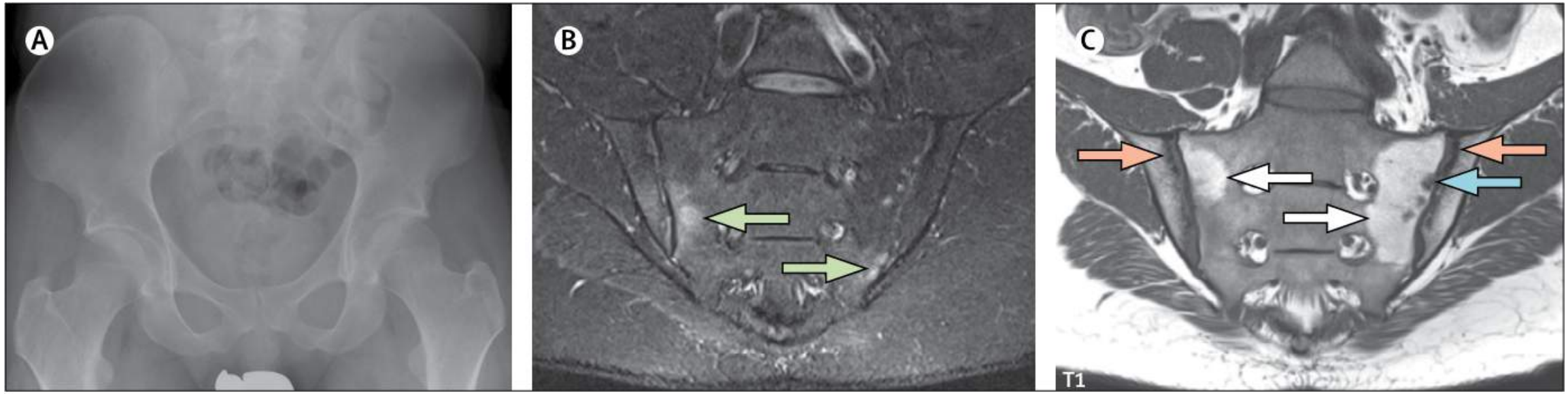
Imaging of the SI joint is critical for accurate and early diagnosis of axSpA



Permission granted by Sieper J, et al.[1]

- Radiography of the SI joints is recommended as the first imaging method to diagnose sacroiliitis[1]
- Limitations:[1]
  - Structural changes may take months to years to occur
  - Interpretation is challenging

- MRI of the SI joint is required for normal or ambiguous radiographic results in the context of a possible diagnosis of axSpA[1]

- Early non-radiographic stage may demonstrate normal radiography[2]
- MRI can detect acute inflammatory changes (bone marrow edema) in the absence of radiographic sacroiliitis[2]

axSpA = axial spondyloarthritis; SI = sacroiliac; MRI = magnetic resonance imaging.

1. Sieper J, Poddubnyy D. *Lancet*. 2017;390:73-84. 2. Rudwaleit M, et al. *Arthritis Rheum*. 2005 Apr;52(4):1000-8.

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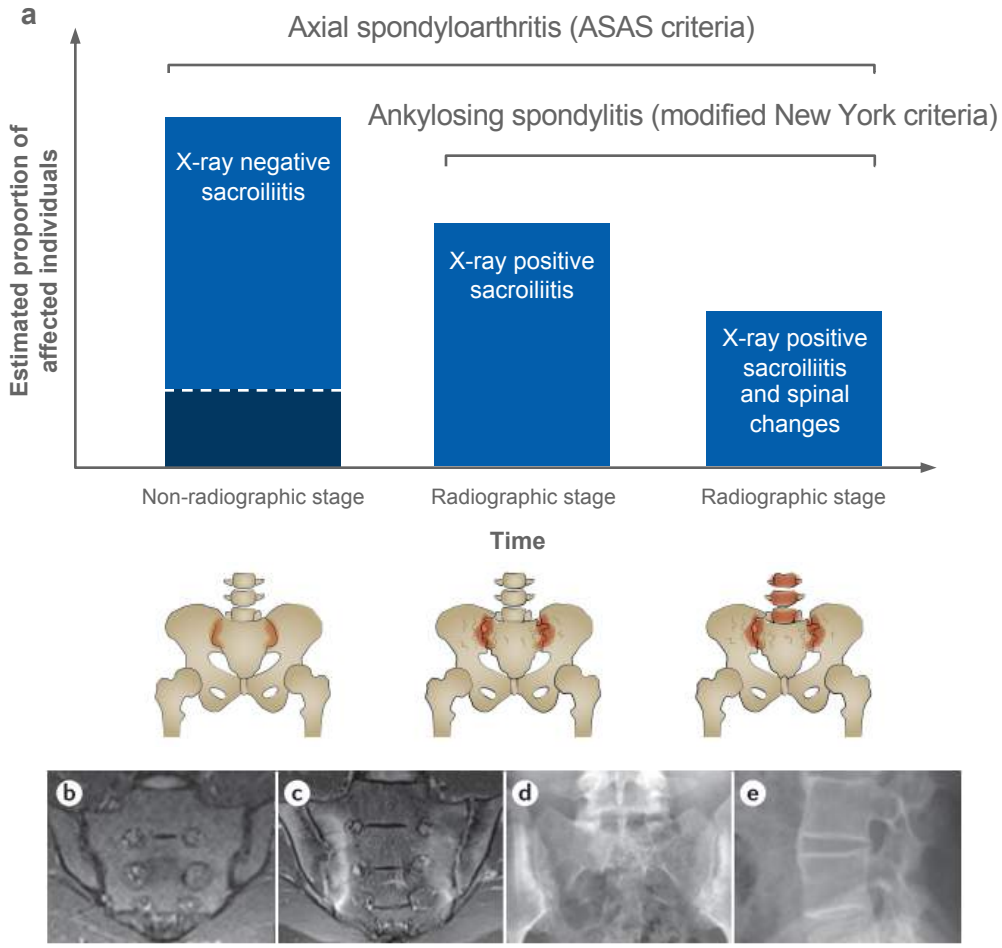
Radiographic distinction between nr-axSpA and AS

- The subgroups of axSpA - nr-axSpA and AS - are differentiated by the presence of structural change in the sacroiliac spine[1]
- Out of a cohort of patients who met ASAS criteria for axSpA, ratio of patients with AS to those with nr-axSpA is 1:1[2]



Adapted with permission from Sieper J, et al.[1]

Females have slower progression of radiographic damage[3,4]

- Less thoracic and lumbar spine radiographic severity
- Lower BASRI scores

axSpA = axial spondyloarthritis; nr-axSpA = nonradiographic axial spondyloarthritis; AS = ankylosing spondylitis; ASAS = assessment of spondyloarthritis international society; BASRI = bath ankylosing spondylitis radiology index.

1. Sieper J et al. *Nat Rev Dis Primers.* 2015;1:15013; 2. Strand V et al. *Arthritis Care Res.* 2013;65:1299-1306. 3. Rusman T, et al. *Curr Rheumatol Rep*. 2018; 20(6):35.
4. Lee W, et al. *Ann Rheum Dis*. 2007 May; 66(5): 633–638.

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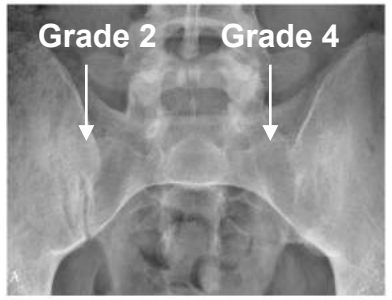
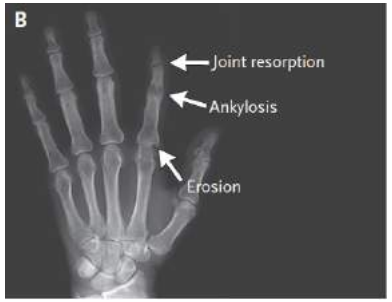
Radiographic changes in PsA and axSpA

- Symmetric lesions are characteristic for axSpA, while unilateral, asymmetric sacroiliitis point to other forms of SpA – most commonly psoriatic arthritis[2,4]
- Asymmetric distribution of syndesmophytes is more common in cases of PsA[3]
- Severity of radiographic axial disease may be greater in AS than PsA[5]

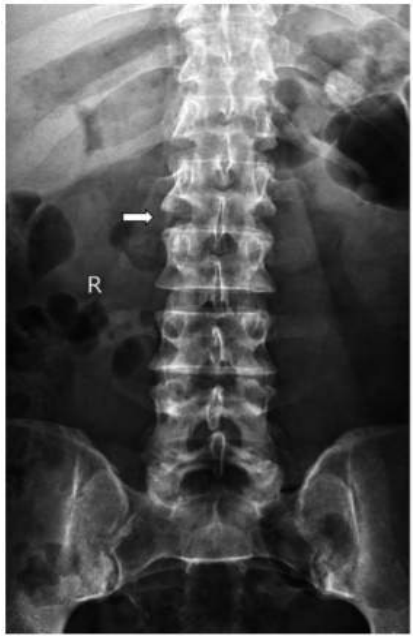
PsA



Permission granted by Sudoł-Szopińska I, et al[2]

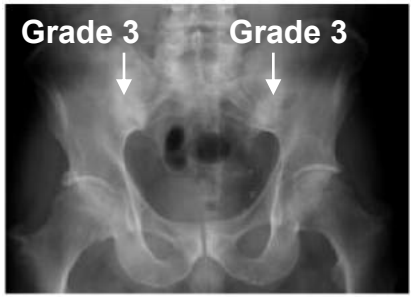


Permission granted by Ritchlin CT, et al.[6]

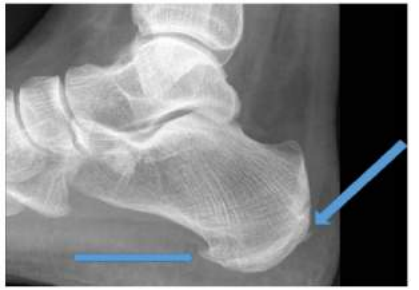


Permission granted by Baraliakos X, et al[3]

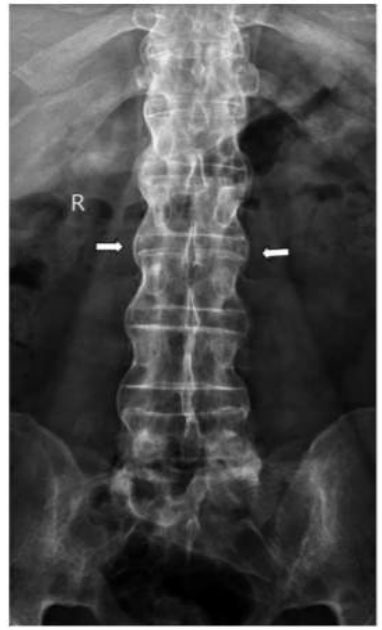
axSpA



Permission granted by Sieper J, et al et al[1]



Permission granted by D'Agostino MA, et al.[7]



Permission granted by Baraliakos X, et al[3]

PsA = psoriatic arthritis; axSpA = axial spondyloarthritis.

1. Sieper J, et al. *Ann Rheum Dis*. 2002;61(Supplement 3):8iii-18. 2. Sudoł-Szopińska I, et al. *J Ultrason*. 2016;16(64):65-77. 3. Baraliakos X, et al. *Clin Exp Rheumatol*. 2015;33(7):31-35.
4. Feld J et al. *Nat Rev Rheumatol*. 2018;14:363-371. 5. Jadon DR, et al. *Ann Rheum Dis*. 2017;76:701–707. 6. Ritchlin CT, et al. *N Engl J Med*. 2017;376:957-970.
7. D'Agostino MA, et al. *Rheum Dis Clin North Am*. 2016 Nov;42(4):679-693

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Women have a unique presentation and burden of disease

More diagnosis delay[1]

Poorer quality of life[8]

Less likely to have children than women in the general population[2]

Misdiagnoses of fibromyalgia and psychosomatic disorder[7]

More pronounced enthesitis, disease severity, and peripheral symptoms[3-6]

Lower inflammatory markers despite comparable or higher disease severity score[6]

1. Jovani V, et al. *J Rheumatol.* 2017;44:174-183. 2. Sieper J et al. *Nat Rev Dis Primers.* 2015;1:15013. 3. Shahlaee A, et al. *Clin Rheumatol.* 2015;34:285-293. 4. Ibn Yacoub Y, et al. *Clin Rheumatol.* 2012;31:293-297. 5. de Carvalho HM, et al. *Clin Rheumatol.* 2012;31:687-695. 6. van der Horst-Bruinsma IE, et al. *Ann Rheum Dis.* 2013;72:1221-1224. 7. Ogdie A, et al. EULAR 2018. Poster FRI0180. 8. Webers C, et al. *Rheumatology (Oxford).* 2016;55:419-428.

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axSpA has a significant patient burden

- Patients with axSpA have **poorer QoL** than the general population[1]
- Patients with axSpA are more likely to be **unmarried or divorced**[1]
- Patients with axSpA are more than twice as likely to be **too disabled to work** as the general population[1]
- Scores of disease status correlate with **anxiety, depression,** and **health status**[1]
- High costs due to **functional disability** and **disease management**[2]

axSpA = axial spondyloarthritis; QoL = quality of life.

1. Sieper J et al. *Nat Rev Dis Primers*. 2015;1:15013. 2. Ward MM. *Arthritis Rheum*. 2002;46(1):223-231.

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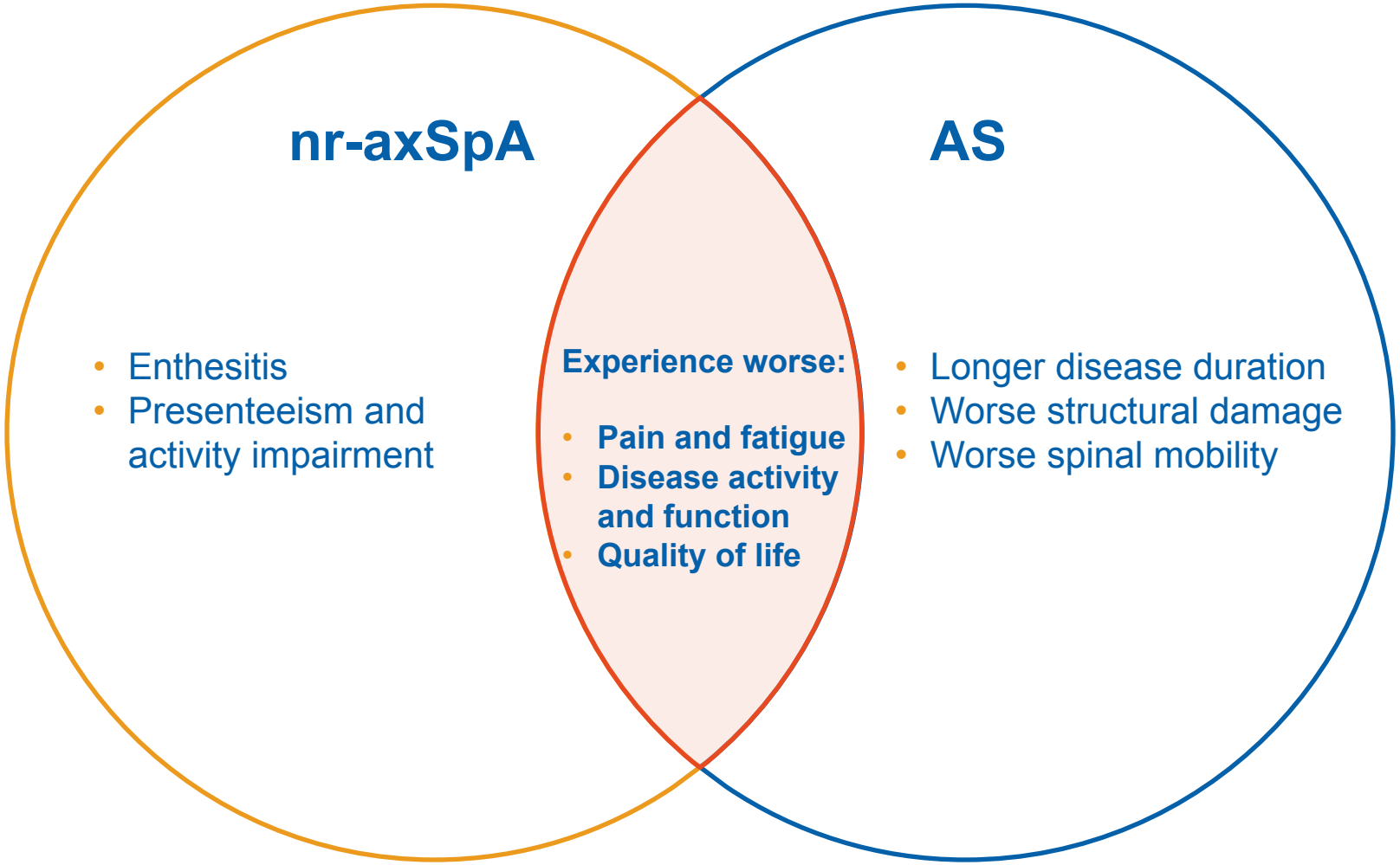
nr-axSpA patients share a comparable degree of disease burden with AS patients



nr-axSpA = nonradiographic axial spondyloarthritis; AS = ankylosing spondylitis.

Mease PJ et al. *Arthritis Care Res.* 2018;70:1661-1670.

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Peripheral disease manifestations contribute significantly to disease activity

	Purely axial disease	Peripheral and axial disease
Patient's global assessment	52	61
Physician's global assessment	44	53
Disease activity (BASDAI)	4.4	5.4
Disease activity (ASDAS-CRP)	2.6	3.0

BASDAI = bath ankylosing spondylitis disease activity index; ASDAS = ankylosing spondylitis disease activity score; CRP = C-reactive protein.

de Winter JJ et al. *RMD Open.* 2019;5:e000802.

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Discussion

1. How do female axSpA patients present differently compared to men?

2. What imaging modalities do you use in your axSpA patients to help in diagnosis, prognosis, and disease management?

3. How often are axSpA patients with peripheral disease presentation misdiagnosed?

Peripheral and axial spondyloarthritis share many similar features

		Peripheral	Axial
Pathophysiology	**IL-17**	Important[6,7]	Important[6]
	IL-23	Involved[6]	Less involved[6]
	TNF	Important[6,7]	Important[6]
	HLA-B27 positivity	Sometimes present • 40-50% of patients with PsA[1]	Common • 83-90% AS patients[1,2] • 74-86% nr-axSpA patients[3-5]
Bone changes	**Bone marrow edema**	Present[9]	Present[8]
	Bone erosion	Hallmark[8,9]	Hallmark[8]
	Bone formation	Hallmark[9]	Hallmark[8]

IL = interleukin; TNF = tumor necrosis factor; HLA = human leukocyte antigen; AS = ankylosing spondylitis; nr-axSpA = nonradiographic axial spondyloarthritis; PsA = psoriatic arthritis.

1. Ritchlin CT et al. *N Engl J Med.* 2017;376:957-970. 2. Londono J, et al. *BMJ Open*. 2015; 5(11): e009092. 3. Baraliakos X, et al 2015 RMD Open. 2015 Aug 15;1(Suppl 1):e000053. 4. Kiltz U, et al. *Arthritis Care Res (Hoboken)*. 2012 Sep;64(9):1415-22. 5. Rudwaleit M, et al. *Arthritis Rheum*. 2009 Mar;60(3):717-27. 6. McGonagle DG, et al. *Ann Rheum Dis*. 2019 Jul 5. pii: annrheumdis-2019-215356. 7. Raychaudhuri SP. *Clin Rev Allergy Immunol*. 2013;44(2):183-193. 8. Van Mechelen M et al. *Calcif Tissue Int*. 2018;102(5):547-558. 9. Ritchlin CT, et al. *N Engl J Med*. 2017;376(10):957-970.

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Peripheral and axial spondyloarthritis share many similar features

		Peripheral	Axial
Axial manifestations	**Sacroiliitis**	Common[1]	Hallmark[2]
	Spondylitis	Common[1,4]	Hallmark[2]
Peripheral manifestations	**Peripheral arthritis**	Hallmark[1]	Common[2,3]
	Enthesitis	Common[1,4]	Common[2,3]
	Dactylitis	Common[1,4]	Sometimes present[3]
Extra-articular manifestations	**Psoriasis**	Hallmark[1]	Sometimes present[2,3]
	Uveitis	Sometimes present[1]	Sometimes present[2,3]
	IBD	Sometimes present[1]	Sometimes present[2,3]

IBD = inflammatory bowel disease

1. Ritchlin CT, et al. *N Engl J Med*. 2017;376(10):957-970. 2. Sieper J, et al. *Nat Rev Dis Prim*. 2015;1(1):15013. 3. Sieper J, Poddubnyy D. *Lancet*. 2017;390(10089):73-84.
4. Ogdie A, Weiss P. *Rheum Dis Clin North Am*. 2015;41:545-568.

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Key differences in axial and peripheral SpA

	Peripheral SpA	Axial SpA
Age of onset[1]	Mid to late 30s	Early 20s
Severity and pain[1]	Less	More
Sacroiliitis[2]	Less symmetrical	More symmetrical
Syndesmophytes[1]	Less symmetrical	More symmetrical

SpA = spondyloarthritis.

1. Ritchlin CT, et al. *N Engl J Med.* 2017;376:957-970. 2. Feld J, et al. *Nat Rev Rheumatol.* 2018;14:363-371.

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Conclusion

1. SpA is a spectrum of disease that contains both axial and peripheral symptoms
2. Enthesitis and new bone formation are unique features of SpA
3. Axial and peripheral SpA share many common features as well as some key differences
4. Sex distinctions of axSpA are present across facets of the disease

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Thank you for attending!

Let us know what you thought of this symposium

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