Review Article

Spectrum of Spondyloarthritis

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Abstract

Spondyloarthritis (SpA) comprises a group of related diseases which share similar pathogenesis and clinical manifestations. Although the occurrence of SpA spectrum disorders has been known for some time, it was only in the latter half of the twentieth century that the concept of SpA was formally defined. Advances in radiography and magnetic resonance imaging techniques have led to the development of classification criteria which have aided early diagnosis and effective management. This narrative review summaries the latest developments in our understanding of the concept of SpA.

Key Words: *Ankylosing spondylitis, axial spondyloarthritis, human leucocyte antigen-B27, nonradiographic axial spondyloarthritis, peripheral spondyloarthritis, psoriatic arthritis, reactive arthritis*

Introduction

The concept of spondyloarthritis (SpA) and related conditions was first defined by Wright and Moll in 1976.[1] Our understanding of the SpA spectrum disorders has advanced significantly in the last decade, largely due to the availability of magnetic resonance imaging (MRI) and publication of the Assessment of Spondyloarthritis International Society (ASAS) classification criteria.[2,3] SpA is an "umbrella term" for a heterogeneous group of diseases with shared genetic predisposition, pathogenic mechanisms, and clinical manifestations. Sacroiliitis, peripheral arthritis, enthesitis, dactylitis and extra-articular manifestations (EAMs) including acute anterior uveitis (AAU), psoriasis (Pso), and inflammatory bowel diseases (IBDs) are prototypical manifestations of SpA. Late recognition of these features in the disease course contributes to delayed diagnosis, resulting in worse functional outcomes, spinal and peripheral joint damage, and an attenuated response to biological therapy.[4]

Pathogenesis of Spondyloarthritis

The pathological hallmarks of SpA are enthesitis and osteitis, and there is a strong genetic association with inheritance of the human leukocyte antigen (HLA)-B27 gene, an allele of the major histocompatibility (MHC) gene complex. HLA-B27 is a surface antigen encoded by the B-locus of MHC class I gene (class I HLA in humans). The prevalence of HLA-B27 in the general population is approximately 6%–10%; however, it is present in between 74% and 89% of SpA patients – the highest association being in ankylosing spondylitis (AS).[5] The function of MHC class I molecules is to present endogenous peptides to the cytotoxic CD8+ T-cell through T-cell receptors on the cell surface. Dysregulation of antigen presentation through HLA-B27 leads to impaired T-cell responses, alteration of regulatory T-cell function, and enhanced apoptotic death. Immune dysregulation at entheseal and intestinal barrier membranes is considered to be the primary site of activation of the immune cascade. In a mouse model, it has been shown that entheseal CD4+ and CD8+ T-cells, in association with interleukin (IL)-23, produce pro-inflammatory cytokines including IL-17. These along with non-MHC dysfunctions of molecules such as endoplasmic reticulum aminopeptidase (ERAP)-1 result in pro-inflammatory cytokines generation, leading to enthesopathy, joint erosions, and osteoproliferation.[5,6]

Spectrum of Spondyloarthritis

SpA encompasses the following disorders [Figure 1]:

- Axial SpA (AS [also known as radiographic SpA] and nonradiographic SpA)

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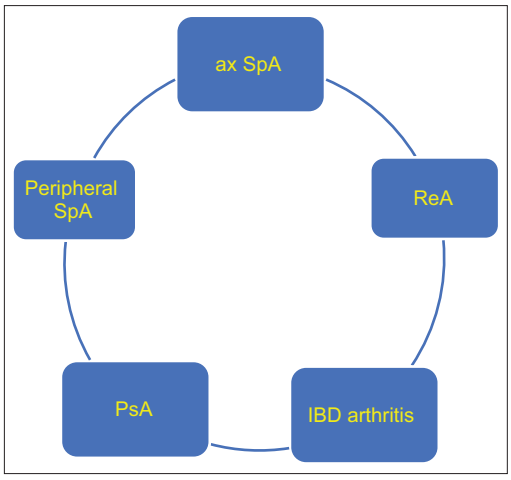

Figure 1: Unified concept of spondyloarthritis

- Psoriatic arthritis
- IBD-related arthritis
- Reactive arthritis (ReA)
- Peripheral SpA.

There may be patient subsets who cannot be clearly categorized within this spectrum. These patients might be early in the course of disease evolution and develop a typical spectrum in later years. However, some patients remain unclassifiable and therefore may be labeled as undifferentiated SpA.

Axial Spondyloarthritis

The term axial spondyloarthritis (axSpA) comprises a heterogeneous group of diseases with AS as its prototype but also includes nonradiographic axSpA (nr-axSpA). Patients with axSpA typically describe inflammatory back pain (IBP) which is usually characterized by at least four of the following features: age of onset <45 years; duration >3 months; morning back stiffness ≥30 min and pain which improves with exercise but not with rest; and second half of nighttime awakening due to back pain and alternating buttock pain.[7]

The diagnosis of AS requires an evidence of bilateral grade 2 or unilateral grade 3 or 4 sacroiliitis on radiograph.[8] We know that the disease starts long before structural changes including sclerosis, erosions, and ankylosis is visible on radiographs of the spine and sacroiliac joints. Our understanding of axSpA has improved significantly in the past two decades, driven by advances in imaging, development of new classification criteria, and the availability of new effective biological therapies. It has long been recognized that there are a cohort of patients with the AS clinical phenotype, but in whom radiographs may be normal, resulting in a considerably delayed or incorrect diagnosis.[9] In 2009, the concept of nr-axSpA was proposed by ASAS, enabling patients to be classified with axSpA without the requirement for X-ray evidence of structural damage.[2] Utilizing these criteria, patients can be classified utilizing MRI and/or a number of clinical criteria if they are positive for HLA-B27. Although these classification criteria were originally intended for epidemiology and clinical research purposes, they facilitate earlier diagnosis and inform treatment decisions [Figure 2]. Research during the past two decades has repeatedly validated the concept of nr-axSpA as a part of the SpA spectrum, and it can be expected that between 23% and 80% patients may have nr-axSpA at the time of new diagnosis of axSpA.[8] Similarly, radiographic sacroiliitis may be present in 20%–30% axSpA at the time of diagnosis with 2–3 years of symptoms.[10]

Comparison between AS and nr-axSpA is discussed in Table 1.[11,12] AS is more common in men and more strongly associated with HLA-B-27. Not all patients with nr-axSpA progress to AS. It is been postulated that about 10% of nr-axSpA patients, diagnosed by clinical and radiographical criteria, will progress into radiographic axSpA within 2 years.[12] The presence of a raised baseline CRP and active sacroiliitis on MRI increases this risk. This suggests that the progression from the nonradiographic phase to radiographic is not linear or indeed inevitable.[12]

Peripheral musculoskeletal manifestations include arthritis, enthesitis, and dactylitis. Peripheral arthritis predominantly involves the lower limb joints: ankles, hips, and knees; however, the shoulders and sternoclavicular joints can also be affected. In a meta-analysis of eight studies of axSpA patients, the pooled prevalences of peripheral arthritis, enthesitis, and dactylitis were 29.7%, 28.8%, and 6%, respectively, and occurrence was similar in AS and nr-axSpA.[11] In the DESIR cohort, the presence of AAU, smoking, and HLA-B27 positivity was associated with less peripheral arthritis among patients with axSpA.[12] Common sites of entheseal inflammation include the Achilles tendon, plantar fascia, lateral and medial epicondyles, shoulders, iliac crest, costochondral joints, costovertebral joints, and vertebras. Dactylitis is present in approximately 6% of axSpA patients.[11]

AAU, Pso, and IBD are referred to as EAM of SpA. The occurrence of EAMs is influenced by genetic predisposition and environmental factors. AAU is the most common EAM of axSpA and its prevalence increases with disease duration. Undiagnosed AAU can cause visual loss in SpA patients. The prevalence of AAU is higher in AS (23.0%) than nr-axSpA (15.9%); however, other peripheral articular and EAMs were similar in AS and nr-axSpA.[11,13] AAU can also be seen in with PsA (7%–19%) and IBD (2%).[14] Approximately 50% of AAU patients are HLA-B27 positive, and unilateral uveitis is the more common presentation.[14] Increased expression of HLA-B27 and vascular adhesion molecules on uveal connective tissues, mechanical stress on intraocular entheses, endoplasmic reticulum dysregulation, and increased propensity to infections are a few of the proposed mechanisms for AAU in SpA.[14]

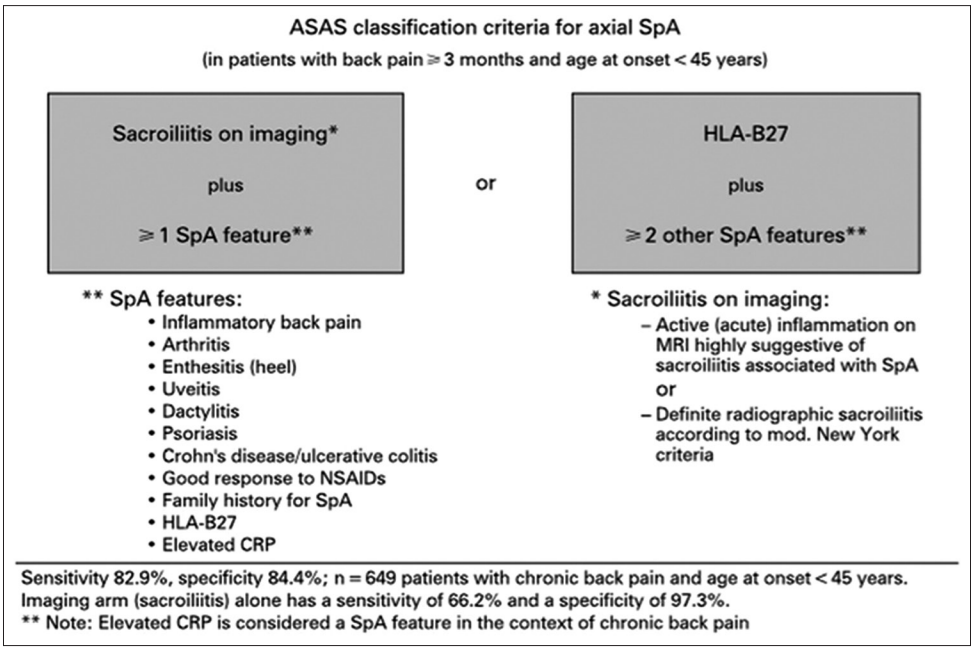

Figure 2: Assessment of Spondyloarthritis International Society Classification Criteria for axial spondyloarthritis

Table 1: Comparison between nonradiographic axial spondyloarthritis and ankylosing spondylitis

	nr-axSpA	AS
Age on onset (years)	<45	<45
Gender	Male ≤female	Male >female
HLA B27 positive prevalence	75%-85%	85%-95%
Axial symptoms	Inflammatory back pain most common	Inflammatory back pain most common
Articular symptoms	Oligoarthritis, lower limb large joints	Oligoarthritis, lower limb large joints
Extra articular association (enthesitis, dactylitis, uveitis, IBD)	Similar to AS except uveitis which is slightly more prevalent in AS	
Severity on patient reported disease activity measurement tools (BASDAI, BASMI, ASDAS)	Similar to AS	
Laboratory investigations	CRP and ESR may be normal or slightly raised especially in active disease	CRP and ESR may be normal or slightly raised, especially in active disease
X-ray changes	No discernable sacroiliac or spondylitic changes	Unequivocal sacroiliitis with or without spondylitis with syndesmophytes, facet joint arthrotpathy, and calcification of the anterior longitudinal ligament
MRI changes	Bone marrow edema of sacroiliac joints with or without erosions on T2 STIR	Bone marrow edema of sacroiliac joints on T2 STIR, erosions with old fatty changes
Response to NSAIDS	Good	Good
Efficacy of biologics	Excellent response to TNFi and IL-17 inhibitors not approved	Excellent response to TNFi and IL-17 inhibitors

CRP: C-reactive protein, HLA: Human leukocyte antigen, MRI: Magnetic resonance imaging, NSAIDs: Nonsteroidal anti-inflammatory drugs, TNFi: Tumor necrosis factor inhibitors, IL-17 inhibitors: Interleukin 17 inhibitors, nr-axSpA: Nonradiographic axial pondyloarthritis, AS: Ankylosing spondylitis, IBD: Inflammatory bowel diseases, ESR: Erythrocyte sedimentation rate, STIR: Short-TI inversion recovery

Psoriatic Arthritis

Psoriatic arthritis was considered to be a subset of rheumatoid arthritis in the earlier part of the 20th century; however, epidemiological studies have shown that PsA is a distinct clinical entity. The American College of Rheumatology first included PsA in the classification of rheumatic diseases in 1963. In 1973, Moll and Wright described five clinical subtypes of PsA: predominant distal interphalangeal joint disease, asymmetrical oligoarthritis,

symmetrical polyarthritis (resembling rheumatoid arthritis in appearance), spondylitis, and arthritis mutilans. They also proposed criteria for establishing a diagnosis of PsA, based on the presence of inflammatory arthritis in a Pso patient who had a negative rheumatoid factor.[15] Although these criteria were capable of recognizing PsA in patients with established Pso and arthritis, this classification of PsA could exclude patients with Pso and predominant enthesitis and dactylitis. In 2006, an international collaborative effort led to the development off the CASPAR criteria, which are highly sensitive (91.4%) and highly specific (98.7%) for a diagnosis of PsA [Table 2].[16] PsA is associated with class I MHC alleles. The IL-17/23 and tumor necrosis factor pathways play a key role in pathogenesis. HLA-B*08, B*27, B*38, and B*39 have been associated with PsA. The prevalence of HLA-B27 in PsA is between 45% and 50%.[17-19]

Peripheral arthritis is more common in PsA with axial involvement than in AS.[20,21] Enthesitis can manifest in approximately 80% of PsA patients. Dactylitis is seen in up to 30% and is most common in the toes but can occur in any digit. Between 30% and 50% of patients have oligoarthritis, and in approximately 15% of cases, arthritis can precede Pso.[17,18] Younger age of disease onset, male, HLA-B27 positivity, nail dystrophy, raised inflammatory markers, and peripheral joint damage are risk factors for the development of axial disease in PsA patients.[19] Axial involvement in PsA has long been recognized and manifests on MRI and/or X-ray as sacroiliitis and/or spinal involvement. Typical spinal lesions include vertebral corner lesions, squaring of vertebrae, sclerosis, syndesmophytes (marginal and para-marginal), discitis, facet joint arthritis, atlantoaxial subluxation, and paravertebral ossification.[20,21]

IBP is reported in 15%–19% of PsA cohorts and about one-third of patients with PsA may have asymptomatic sacroiliitis on imaging which is more common in women.[20] The presence of HLA-B27 in PsA is associated with bilateral sacroiliitis and AS like vertebral changes. However, there are some significant radiographic differences in spinal disease between axSpA and PsA. Psoriatic sacroiliitis is asymmetrical/unilateral; syndesmophytes are less common but bulkier, may not exactly follow the course of the anterior longitudinal ligament and affect vertebrae intermittently rather than in a stepwise fashion. Due to less apophyseal joint involvement, spinal movements are less restricted in PsA.[20,21] This information suggests that axial PsA is a different disease than AS with Pso.[21]

Reactive Arthritis

ReA is defined as arthritis developing after extra-articular infection where a pathogen cannot be isolated from the affected joints. ReA is characterized by asymmetrical oligoarthritis, predominantly affecting the lower limb joints, unilateral or bilateral sacroiliitis, dactylitis, and enthesitis. The characteristic EAMs are elucidated in Table 3. Reiter's syndrome is a variant of ReA, first described by Hans Reiter as a triad of oligoarthritis, urethritis, and conjunctivitis in a young officer with "treponema arthritides."[22] Aphthous ulcers in the mouth, erythema nodosum, conjunctivitis, and keratoderma blennorrhagica are EAMs associated with ReA. Keratoderma blennorrhagica, a distinctive skin rash presents on the soles and palms, is the characteristic dermatological manifestation of ReA. Clinically and histopathologically, the rash is similar to Pso. In uncircumcised males, circinate balanitis may also be seen on the glans penis.[23]

Often, it can be difficult to differentiate ReA from other members of the SpA spectrum; however, early recognition of the association with recent genitourinary or gastrointestinal infections in ReA usually helps to establish the correct diagnosis. Diarrhea or urethritis for at least 1-day, 3 days to 6 weeks prior to arthritis development is considered significant.[23] The infection activates the local immune response at the site (synovial membranes). The main bacteria involved are Campylobacter, Chlamydia, Salmonella, Shigella, and Yersinia [Table 4]. Although causative bacteria are not cultured from the joints, lipopolysachhride and heat shock protein antigens from the enteric bacterial membrane coating have been found in the affected joints of ReA patients. Chlamydial DNA has also been found from synovial fluids of ReA patients' posturethrogenital infections.[23]

The prevalence of ReA in HLA-B27 positive patients is five times higher than the general population, and in HLA-B27

Table 2: CASPER criteria

CASPAR clasification criteria (a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following five categories)	
1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis	2 points
Current psoriasis	2 point
A personal history of psoriasis	1 point
A family history of psoriasis	1 point
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis	1 point
3. A negative test result for rheumatoid factor	1 point
4. Current dactylitis or a history of dactylitis recorded by a rheumatologist	1 point
5. Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	1 point

Table 3: Clinical manifestations of reactive arthritis

Articular: Mono/oligoarthrits, unilateral/bilateral sacroiliitis, spondylitis, enthesitis, dactylitis
Extra-articular: Conjunctivitis, iritis, scleritis, diarrhoea, urethritis, prostatitis, haemorrhagic cystitis, cervicitis, keratoderma blennorrhagica , circinate balanitis, oral ulcers, hyperkeratotic nails, erythema nodosum

positive relatives of ReA patients, the prevalence is another ten times higher.[24] Poststreptococcal, Lyme, and viral arthritis are different entities, not HLA-B27 associated, and should be described as distinct entities under the general heading of infection-related arthritis.[23]

Inflammatory Bowel Disease-Related Arthritis

The prevalence of asymptomatic sacroiliitis in IBD (Crohn's diseases and ulcerative colitis) is between 11% and 52%, and approximately 10% of patients develop typical AS.[25] Conversely, approximately 6.5% of AS patients can develop IBD as an EAMs.[26] IBD-related arthritis is more common in Crohn's disease, and usually, its course is independent of IBD disease activity status. The pathogenesis of IBD related arthritis is a complex interaction between host genetic predisposition (HLA B27, ERAP1, and other non-MHC factors), and the gut microbiome leading to decreased T_{reg} cells and activation of T helper 17 cells and the IL-17/23 pathway.[25,26] Increased intestinal permeability and immune cell migration with activated intestinal lymphocytes mediating peripheral synovitis are other proposed models of the gut-joint inflammatory axis. This is the subject of considerable ongoing research.[14,26]

Arthropathy in IBD is divided into peripheral and axial arthritis. Peripheral arthritis can be oligo-articular (<5 joints) asymmetrical arthritis (Type 1) involving the large joints of upper and lower limbs or bilaterally symmetrical small joint arthritis (>5 joints, Type 2). The Type 1 arthritis is usually transient, migratory, and self-limiting without deformity in 6–10 weeks. Type 2 arthritis can be symptomatic for months to years.[26] Other SpA features including enthesitis and dactylitis can be seen in 2%–10% of IBD patients.[14] Axial disease can present as IBP, isolated sacroiliitis, or AS.[25]

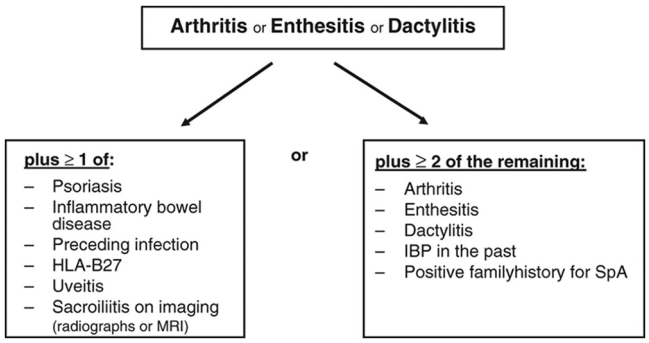

Figure 3: Classification of peripheral spondyloarthritis

Table 4: Causative organisms associated with reactive arthritis

Gastrointestinal pathogens
Salmonella species
Campylobacter jejuni and *Campylobacter coli*
Yersinia enterocolitica and *Yersinia pseudotuberculosis*, *Shigella flexneri*; less commonly, *Shigella sonnei* or *Shigella dysenteriae*, clostridium difficile
Genitourinary pathogens: *Chlamydia trachomatis*, *Mycoplasma* species
Respiratory pathogens: *Chlamydia pneumoniae*

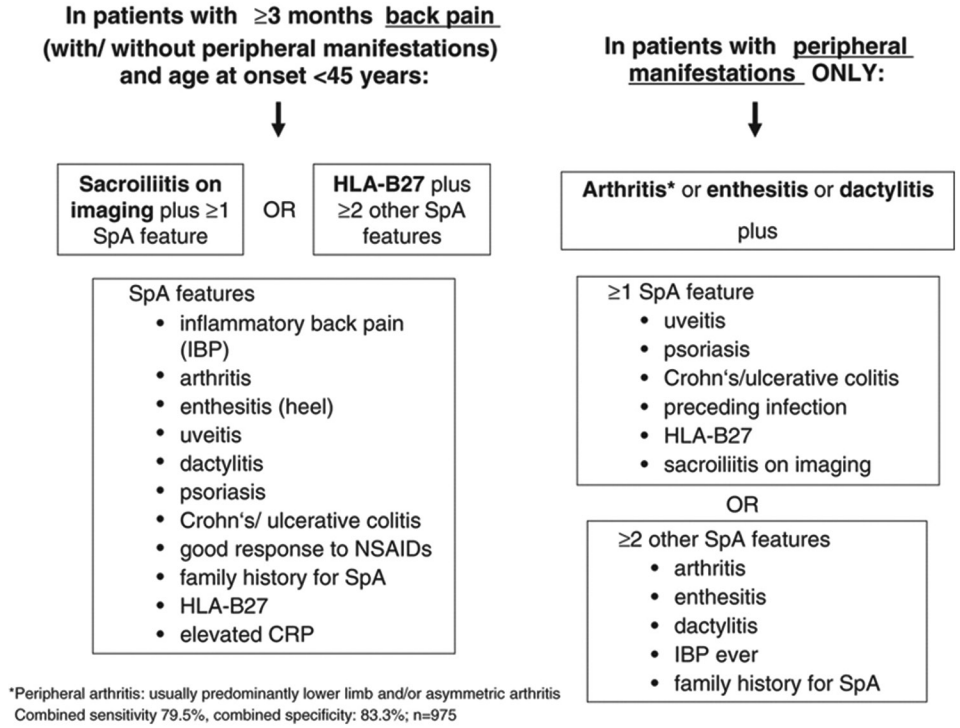

Figure 4: Axial spondyloarthritis vs peripheral spondyloarthritis

Peripheral Spondyloarthritis

Patients having predominant asymmetrical lower limb arthritis or enthesitis or dactylitis who do not fulfil criteria of any of the other SpA spectrum of diseases can be classified as peripheral SpA in the presence of other pertinent SpA features [Figure 3].[3] The presence of Pso, absence of HLA-B27, and older age were associated with more peripheral SpA.[27] It is important to understand that patients with predominant axial involvement (AS and nr-axSpA) with few peripheral features should not be categorized as peripheral SpA [Figure 4]. It should be emphasized that classification criteria are intended to increase the homogeneity of patient cohorts in clinical trials and epidemiology studies. There may be considerable overlap of peripheral SpA with other SpA spectrum conditions in real-life scenarios. In those situations, authors recommend modifying management strategies according to the manifestations present at the time of clinical review.

Conclusion

Recent research has improved our understanding of SpA spectrum disorders. The insight into immunopathogenic mechanisms and the development of validated disease classification criteria have facilitated a successful clinical trial program, which has helped establish new and effective therapies. There is an urgent need to increase awareness of SpA spectrum disorders among primary care physicians and other medical specialties to shorten the time to diagnosis and allow access to effective therapy.

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Conflicts of interest

There are no conflicts of interest.

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