Pathogenesis and Diagnosis of Psoriatic Arthritis

Lisa Anggriani Susanto[1], Arief Nurudhin[1,2]*

Affiliation:
1. Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia, 57126
2. Department of Internal Medicine, Dr. Moewardi General Hospital, Surakarta, Indonesia, 57126

*Correspondence: Arief Nurudhi, ariefnurudhin@staff.uns.ac.id, Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

ABSTRACT

Introduction: Psoriatic arthritis (PsA) is a chronic, heterogeneous inflammatory disease closely associated with psoriasis of the skin and nails. Its clinical manifestations are diverse, involving peripheral joints, the axial skeleton, entheses (sites where tendons or ligaments attach to bone), and various extra-articular sites, making its diagnosis a significant clinical challenge.

Methods: This is a narrative review of recent literature focusing on the complex pathogenesis and evolving diagnostic strategies for PsA. The review synthesizes information on genetic, immunological, and environmental factors, as well as the role of modern imaging and laboratory findings in accurate diagnosis.

Results: The pathogenesis of PsA arises from a complex interplay of genetic predisposition (such as HLA-B27), immunological pathways, and environmental triggers like mechanical stress and infections. The activation of both the innate and adaptive immune systems, particularly the IL-23/IL-17 axis, is central to driving the chronic inflammation and joint damage characteristic of the disease. Diagnosing PsA is often difficult due to its overlapping features with other inflammatory arthritides. The Classification Criteria for Psoriatic Arthritis (CASPAR) are widely used and incorporate evidence of psoriasis, specific patterns of joint involvement, dactylitis, and characteristic radiological changes. Imaging modalities are crucial for an early and accurate diagnosis: conventional radiography detects classic erosions and new bone formation, ultrasonography is sensitive for evaluating synovitis and enthesitis, and MRI is excellent for identifying early inflammatory changes in both axial and peripheral joints. Laboratory tests, such as a negative rheumatoid factor and anti-CCP, are key to differentiating PsA from rheumatoid arthritis.

Conclusions: A comprehensive understanding of the pathogenesis and diagnostic strategies for PsA is essential for early recognition, which is critical for preventing disease progression and selecting the most appropriate therapy. This review highlights current insights that can serve as a foundation for improved clinical practice in managing this complex disease.

Keywords: Psoriatic Arthritis; Pathogenesis; Diagnosis; CASPAR; Inflammation

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, heterogeneous inflammatory arthritis associated with psoriasis [1, 2]. While it most commonly develops in individuals with pre-existing skin disease, up to 15% of patients experience arthritic symptoms before any skin manifestations appear, creating a significant diagnostic challenge [3]. The disease affects approximately 30% of patients with psoriasis and is characterized by a wide array of musculoskeletal features, including peripheral arthritis, axial disease, enthesitis, and dactylitis [4]. Beyond the joints, PsA is a systemic disease associated with a higher burden of comorbidities, including cardiovascular disease, metabolic syndrome, and inflammatory bowel disease, which can affect disease activity, quality of life, and overall mortality [5, 6]. The pathogenesis is understood to be a complex interplay between a strong genetic predisposition, particularly involving the HLA region, and environmental triggers that activate both innate and adaptive immune pathways, with the IL-23/IL-17 axis playing a central role [7, 8].

Despite significant advances in understanding PsA, a critical gap remains in the early and accurate diagnosis of the disease. The clinical heterogeneity of PsA means its symptoms can overlap with other conditions like rheumatoid arthritis and osteoarthritis, leading to diagnostic delays that can last for years [9]. This delay is problematic, as early intervention is crucial to prevent irreversible joint damage and long-term disability [10]. While classification criteria such as CASPAR have improved diagnostic accuracy in clinical studies, their sensitivity in very early disease may be limited, as characteristic radiologic features may not yet be present [11]. This gap highlights the urgent need for better screening tools and validated biomarkers to identify psoriasis patients who are at high risk of transitioning to PsA, thereby allowing for earlier intervention during a potential "pre-clinical" phase [12].

This review aims to provide a comprehensive overview of current understanding of the pathogenesis of psoriatic arthritis and to detail evolving diagnostic approaches, from clinical criteria to the roles of advanced imaging and novel biomarkers.

METHODS

This is a narrative review of recent literature focusing on the pathogenesis and diagnosis of psoriatic arthritis (PsA). Information was synthesized from a range of sources, including rheumatology textbooks, clinical guidelines, and peer-reviewed journal articles, to provide a comprehensive overview of the topic. The review details the complex interplay among genetic, immunological, and environmental factors that contribute to disease development, with a specific focus on the central role of the IL-23/IL-17 axis in driving chronic inflammation. For diagnostic purposes, the synthesis emphasizes the clinical utility and limitations of the Classification Criteria for Psoriatic Arthritis (CASPAR) and details the roles of various imaging modalities—including conventional radiography, ultrasonography, and MRI—in identifying the characteristic features of PsA. The methodology involved a comprehensive summary of current insights to provide a foundation for improved clinical practice in the diagnosis of PsA

RESULTS

The literature review reveals that psoriatic arthritis (PsA) is a complex inflammatory disease resulting from interactions among genetic, environmental, and immunological factors. Its diagnosis is challenging due to clinical heterogeneity and overlap with other arthritides, necessitating a multi-faceted approach that combines clinical evaluation, laboratory tests, and advanced imaging.

Pathogenesis of Psoriatic Arthritis

The development of PsA is a multi-step process involving genetic predisposition, environmental triggers, and a subsequent immune response.

- Genetic Factors: A strong genetic contribution to PsA has been identified, involving both HLA and non-HLA gene regions. While the HLA-C*06:02 allele is strongly associated with cutaneous psoriasis, its frequency is lower in patients with PsA. Conversely, HLA class I molecules, particularly HLA-B27, are linked to PsA, especially axial disease. Non-HLA genes implicated in PsA susceptibility are involved in key immune signaling pathways, such as those encoding for IL-12B, IL-23R, and TRAF3IP2, which are crucial components of the IL-17 pathway.

- Environmental Triggers: Environmental factors are believed to initiate the disease in genetically susceptible individuals. These triggers include mechanical stress or trauma to entheseal sites (a "deep" Koebner phenomenon), which can initiate a local inflammatory response. Obesity is a significant risk factor, potentially through increased biomechanical load and the pro-inflammatory state associated with excess adipose tissue. Infections, such as those caused by Streptococcus or HIV, have also been implicated in triggering or exacerbating the disease.

- Immunological Pathways: The core of PsA pathogenesis is the dysregulation of both innate and adaptive immunity, with the IL-23/IL-17 axis identified as a central pathway. Environmental triggers activate innate immune cells, such as dendritic cells and macrophages, which produce cytokines like IL-23. IL-23 drives the differentiation and activation of T helper 17 (Th17) cells and other immune cells, leading to the production of pro-inflammatory cytokines, including IL-17, IL-22, and TNF-α. These cytokines promote chronic inflammation in the synovium, entheses, skin, and nails, leading to synovitis, enthesitis, bone erosion, and new bone formation. CD8+ T cells are also found to be clonally expanded in the synovial tissue of PsA patients, suggesting their key role in joint-specific inflammation.

Diagnosis of Psoriatic Arthritis

The diagnosis of PsA relies on a combination of clinical features, laboratory results, and imaging, with the CASPAR criteria being the most widely used classification tool.

- Clinical Presentation: PsA is clinically heterogeneous. While skin or nail psoriasis is present in most patients and often precedes arthritis, it can be subtle or "hidden" in locations like the scalp, umbilicus, or intergluteal cleft. Musculoskeletal manifestations include:

- Peripheral Arthritis: Can be mono-, oligo-, or polyarticular and is often asymmetrical. Involvement of the distal interphalangeal (DIP) joints is a characteristic feature.

- Dactylitis: Diffuse swelling of an entire digit ("sausage digit"), observed in 12-39% of patients.

- Enthesitis: Inflammation at the sites of tendon or ligament insertion into bone, a hallmark of PsA, is seen in up to 67% of patients at diagnosis.

- Axial Disease: Spondylitis and/or sacroiliitis, which can affect up to 70% of patients with long-standing disease.

- Laboratory Findings: There are no specific diagnostic blood tests for PsA. Patients are typically negative for rheumatoid factor (RF) and anti-citrullinated peptide (anti-CCP) antibodies, which helps differentiate PsA from rheumatoid arthritis. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be elevated but can be normal even in patients with active disease.

- Imaging Modalities: Imaging is crucial for confirming the diagnosis, assessing disease activity, and monitoring structural damage.

- Radiography: While often normal in early disease, conventional X-rays are useful for identifying characteristic features in established PsA, such as erosive arthritis combined with new bone formation (osteoproliferation), joint space narrowing, and the classic "pencil-in-cup" deformity in severe cases.

- Ultrasonography (USG): USG with power Doppler is a highly sensitive and accessible tool for detecting early signs of inflammation, including synovitis, tenosynovitis, and enthesitis, often before they are clinically apparent.
- Magnetic Resonance Imaging (MRI): MRI is the most sensitive technique for detecting early inflammatory changes like bone marrow edema (osteitis), synovitis, and sacroiliitis, particularly in the axial skeleton.
- Classification Criteria: The CASPAR (Classification Criteria for Psoriatic Arthritis) criteria are used to classify patients with PsA in clinical research and practice. A patient is classified as having PsA if they have inflammatory articular disease (joint, spine, or entheseal) and a score of ≥3 points from the following categories: current psoriasis (2 points) or a personal/family history of psoriasis (1 point); psoriatic nail dystrophy (1 point); a negative test for RF (1 point); current or a history of dactylitis (1 point); and radiological evidence of juxta-articular new bone formation (1 point).

DISCUSSION

The understanding and management of psoriatic arthritis (PsA) have undergone a profound transformation over the past decade, moving from a field constrained by diagnostic ambiguity and limited therapeutic options to one characterized by sophisticated pathogenic insights and a growing arsenal of targeted treatments [1, 2]. This review synthesizes the current knowledge on the pathogenesis and diagnosis of PsA, revealing a complex interplay of factors that drive the disease and the evolving strategies clinicians employ to identify it early. The discussion centers on the challenges posed by the disease's heterogeneity, the critical importance of early diagnosis for preventing irreversible damage, and the paradigm shift in diagnostic approaches from simple clinical observation to a multimodal assessment that incorporates advanced imaging and a deeper understanding of its immunological underpinnings [8, 20].
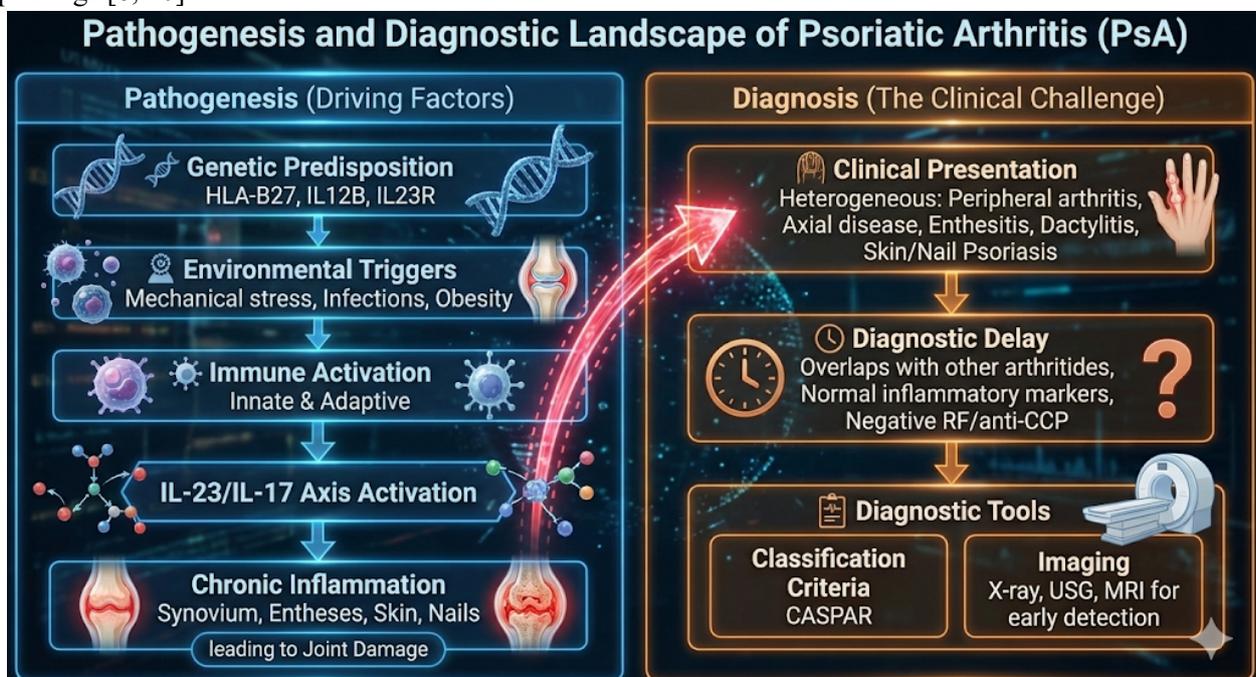

Figure 1. Integrated overview of the pathogenesis and diagnostic strategy for Psoriatic Arthritis (PsA).

The development of PsA is driven by a complex interplay between genetic predisposition (e.g., HLA-B27, IL12B, IL23R) and environmental triggers such as mechanical stress or infection, which activate innate and adaptive immune responses. Central to this pathogenesis is the dysregulation of the IL-23/IL-17 axis, leading to the

production of pro-inflammatory cytokines that cause synovitis, enthesitis, and bone erosion. Diagnosing this heterogeneous condition requires a multifaceted approach, as clinical presentation varies widely and specific serological markers, such as RF and anti-CCP, are typically absent. Consequently, diagnosis relies on the CASPAR classification criteria and the utilization of advanced imaging modalities—specifically ultrasonography and MRI—to detect early inflammatory changes and structural damage that conventional radiography may miss

A central theme in the modern understanding of PsA is the recognition of its profound heterogeneity, not just in its clinical presentation but also in its underlying genetic and immunological drivers [28, 31]. The disease is no longer viewed as a simple variant of rheumatoid arthritis with associated skin disease but as a distinct entity within the spondyloarthritis family, characterized by a unique combination of articular and extra-articular manifestations [29]. The pathogenesis is a classic example of a complex autoimmune disease, arising from a convergence of strong genetic predispositions, environmental triggers, and subsequent immune dysregulation [20]. Genetic studies have been instrumental in dissecting this complexity, identifying key susceptibility loci both within and outside the HLA region [13, 22]. While the association with HLA-B27 is well-established, particularly for axial disease, research has uncovered a more intricate genetic architecture involving alleles that regulate crucial immune pathways, most notably the IL-23/IL-17 axis [23, 26]. The identification of risk variants in genes such as IL12B, IL23R, and TRAF3IP2 has provided a molecular roadmap of the disease, directly implicating this cytokine pathway as a central driver of the chronic inflammation seen in the skin, entheses, and synovium [20, 26]. This genetic framework helps explain why environmental factors like mechanical stress (the "deep Koebner" phenomenon at entheseal sites), infections, and dysbiosis of the gut microbiome can precipitate disease in susceptible individuals by activating these pre-programmed inflammatory pathways [29, 30, 33]. This complex pathogenesis underscores why PsA can manifest in such diverse ways, from oligoarticular arthritis to destructive arthritis mutilans, and why a "one-size-fits-all" approach to treatment is often inadequate [44].

The greatest clinical challenge in PsA remains the significant delay in diagnosis that many patients experience [9]. The period between the onset of musculoskeletal symptoms and a definitive PsA diagnosis can be several years, a critical window during which irreversible joint damage can occur [10]. This delay is multifactorial, stemming from the disease's heterogeneous presentation, its symptomatic overlap with more common conditions like osteoarthritis and rheumatoid arthritis, and the frequent absence of specific serological markers [48]. For instance, inflammatory markers such as CRP may be normal in a substantial portion of patients with clinically active disease, and the hallmark autoantibodies of rheumatoid arthritis (RF and anti-CCP) are typically negative, removing a key diagnostic clue used in other arthritides [47]. This diagnostic gap has driven the evolution of classification criteria and the integration of advanced imaging into the diagnostic process. The CASPAR (Classification Criteria for Psoriatic Arthritis) criteria, developed in 2006, were a major step forward, providing a sensitive and specific tool for classifying PsA in clinical trials and practice [42]. By incorporating not just arthritis and psoriasis but also key features like dactylitis, enthesitis, nail dystrophy, and characteristic radiological findings, CASPAR allows for the classification of patients even in the absence of current skin psoriasis or in the presence of a positive RF [45].

However, the limitations of CASPAR in very early disease, where structural damage may not yet be radiographically visible, have highlighted the indispensable role of advanced imaging techniques [41, 52]. Musculoskeletal ultrasonography with power Doppler has emerged as a powerful, accessible, and non-invasive tool for the early detection of subclinical inflammation [57]. It is highly sensitive for identifying synovitis, tenosynovitis, and, crucially, enthesitis—the inflammation at tendon and ligament insertions that is considered a hallmark lesion of PsA [29]. The detection of sonographic enthesitis in psoriasis patients with arthralgia may be a key predictor for the future development of clinical PsA, offering a potential window for early intervention [58]. Similarly, MRI has proven superior for detecting early inflammatory changes such as bone marrow edema (osteitis) and sacroiliitis, particularly in patients with axial symptoms, long before any changes are visible on plain radiographs [56]. The ability of these imaging modalities to visualize inflammation at a subclinical level is shifting

the diagnostic paradigm towards a "pre-clinical" phase of PsA, where intervention might prevent the transition from psoriasis to established arthritis [14, 55]. This concept is supported by the "treat-to-target" strategy validated in the TICOPA trial, which demonstrated that aggressive management aimed at achieving minimal disease activity leads to significantly better outcomes, reinforcing the critical need for early and accurate diagnosis [47].

Looking forward, the future of PsA diagnosis and management will likely move towards a more personalized or "precision medicine" approach [34]. While the current diagnostic toolkit is powerful, it still falls short of predicting which psoriasis patient will develop arthritis, what disease course an individual will follow, or who will respond best to a specific therapy. The identification of reliable biomarkers remains a "holy grail" in the field [59]. Research into serum markers like COMP and MMP-3, which reflect cartilage and synovial turnover, and inflammatory mediators like CXCL10 has shown promise, but none have yet been validated for widespread clinical use [39, 60]. A deeper understanding of the distinct cellular signatures in different tissue domains—for example, the role of tissue-resident memory CD8+ T cells in the skin and synovium—may pave the way for biomarkers that can not only diagnose but also phenotype patients to guide therapeutic choices [35, 36, 54]. Ultimately, the goal is to move beyond the current classification criteria towards a truly diagnostic and prognostic framework. This will require a multi-pronged strategy that integrates clinical expertise with advanced imaging and novel molecular biomarkers to identify PsA at its earliest stages, allowing for timely intervention that can halt its progression, prevent long-term disability, and preserve quality of life for patients living with this complex and challenging disease.

CONCLUSIONS

Psoriatic arthritis is a complex, systemic, and heterogeneous disease involving a wide range of tissues and clinical domains. Advances have been made in understanding its pathogenesis, developing effective and safe treatments, and utilizing imaging to accurately diagnose and monitor disease progression. By recognizing the risk factors and key indicators of progression from psoriasis to psoriatic arthritis, clinicians can play a crucial role in early diagnosis and treatment. A comprehensive understanding of the underlying mechanisms and modern diagnostic approaches is essential for preventing irreversible structural damage and selecting appropriate therapies, which can ultimately improve clinical practice and patient outcomes.

Author Contributions

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Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article as it is a narrative review of existing literature. All data discussed are sourced from previously published studies, which are cited in the reference section.

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Conflicts of Interest

The authors declare no conflict of interest

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