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An overview of psoriatic arthritis,pathogenesis and management

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Abstract

Psoriatic arthritis (PsA) is a complex inflammatory disease with heterogeneous clinical features, which complicates psoriasis in 30% of patients. The pathogenesis of PsA is complex and multifaceted, with an interplay of genetic predisposition, triggering environmental factors, and activation of the innate and adaptive immune system, although autoinflammation has also been implicated. There are no diagnostic criteria or tests available. Diagnosis is most commonly made by identifying inflammatory musculoskeletal features in joints, entheses or the spine in the presence of skin and/or nail psoriasis and in the usual absence of rheumatoid factor and anti-cyclic citrullinated peptide. Early diagnosis is important to prevent long term functional disability and to ensure optimal management of arthritis and key comorbidities. Management involves the use of non-steroidal anti-inflammatory drugs, conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), biological agents, targeted DMARDs, and supportive measures, depending on clinical presentation and disease severity. The advancements of pathogenesis and innovations of therapies in PSA accelerates the progress of PSA treatments.

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1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory heterogenous disease characterized by the involvement of different domains including the skin, nails, peripheral joints, digits, entheses, axial skeleton, eyes, and bowel [1]. PsA is associated with poor health-related quality of life, and more active disease leads to progressive joint damage, higher mortality, and limitations in the activities of daily living. The clinical burden increases direct costs through the use of care resources and indirect costs through disability and lost productivity. Delay in diagnosis and treatment are associated with damage progression and poorer quality of life [2]. .Therefore, timely identification of PsA and early initiation of treatment play a key role in improving long-term outcomes, as does the need to improve the information provided to patients with respect to their treatment options [3].

1.1. Epidemiology

Globally, reported prevalence of PsA ranges from 0.3% to 1% with no gender predilection. In Egypt, prevalence of PsA was found to be 30%, with a mean age of 45 years. Further, psoriasis preceded onset of PsA in 76% of patients, arthritis began before psoriasis in10% of individuals, and both psoriasis and arthritis coincided in 13% of patients [4].

1.2. Etiopathogenesis

The pathogenesis of PsA is complex and not fully understood but is thought to result from a combination of genetic, immune, and environmental factors, such as infections, microbiota (dysbiosis), obesity, biomechanical stress, or smoking could initiates a chronic inflammatory process primarily involving joints and skin, producing the IL-23, a central cytokine in the pathogenesis of psoriatic arthritis and psoriasis. Macrophages and dendritic cells produce IL-23 which stimulate T cells. This stimulation produces the IL-17, IL-22, and TNF-alpha, which promote inflammation, bone loss with erosions, and osteoproliferation [5].

1.3. Genetic susceptibility

Heredity plays a particularly strong role in the development of PsA. It was found that, HLA-B27 antigen involvement is more common in patients with involvement of spine and sacroiliac joints, whereas HLA-DR4 association is more common in an erosive subgroup and HLA-DR7 in cases with involved DIP joints. Moreover, lymphocytic infiltrates and neoangiogenesis, synoviocyte activation, and the release of proinflammatory cytokines, particularly tumor necrosis factor-α (TNF-α), characterize synovitis, similar to rheumatoid arthritis [6].

1.4. Interleukin 23/Th17 pathway

IL-23 found to be fundamentally important in pathogenesis and mainly synthesized by dendritic cells of dermis and macrophages, is main trigger for IL-17 production in skin, initiating skin inflammation and acanthosis [7].

1.5. Obesity

Adipose tissue is metabolically active and produces a chronic low grade inflammation in obese individuals. Adipokines promote proinflammatory cytokines (interleukin-1α (IL-1α), IL-12, tumor necrosis factor alpha (TNFα), IL-17, and IL-6) and suppresses anti-inflammatory cytokines (i.e., transforming growth factor (TGFβ), IL-10) [8].

1.6. Trauma

It has been reported that patients with psoriasis exposed to trauma, especially bone and joint trauma, had an increased risk of PsA compared with controls [9].

1.7. Infection

Studies have suggested a role of infection in triggering PsA, in particular association between streptococcal infection and guttate psoriasis well established. In addition, psoriasis and PsA also occur more commonly and severely in individuals with HIV infection, targets CD4+ T cells but not CD8+ T cells, than in general population [10].

1.8. Microbiome and Dysbiosis

The bacterial association network in psoriatic non-lesional skin are more similar to psoriatic lesions than to healthy skin, suggesting an underlying dysbiotic process in the cutaneous surface of patients with psoriatic disease, even in the absence of clinically evident lesions [11].

1.9. Alcohol

Alcohol aggravate production of pro inflammatory cytokines, increase lymphocyte proliferation activation [12].

1.10. Smoking

Smoking has been positively associated with the risk of psoriasis and PsA. It causes an increase in inflammatory sytokines which are involved in causing PsA. Individuals who have smoked for longer and consume more cigarettes per day tend to develop more severe PsA [13].

2. Pathology

1) Skin

Pathophysiology of psoriasis involves infiltration of skin by activated T cells which stimulate the proliferation of keratinocytes. This dysregulation in keratinocyte turnover results in the formation of thick plaques [14].

2) Nails

Nail psoriasis is often associated with an inflammation at the insertion points of the tendons and ligaments giving rise to the enthesitis. The nail and joint disease may be linked to the tissue-specific factors, including the tissue biomechanical stressing and the microtrauma that lead to activation of aberrant innate immune responses [15].

3) Enthesis

Patients with PsA seem to have a different threshold to mechanical stress, which may be genetically determined. Hence patients with psoriatic disease respond pathologically with inflammation after being exposed to physiological mechanical stress. Activation of pro-inflammatory mediators such as IL-17 and TNF-α as well as influx of innate immune cells are key events in development of enthesitis in PsA [16].

4) Dactylitis

The finger joints move in the flexion and extension planes, the flexor tendons move within pulleys, thus creating a ‘functional enthesis’ with subsequent inflammation that can be diffuse along most parts or whole of finger, resulting in characteristic ‘sausage’ swelling of dactylitis [17].

5) Synovium

Chronic synovitis in PSA characterized by hyperplasia of fibroblast-like synoviocytes in intimal lining layer, inflammatory infiltrates of synovial sublining, and neo-angiogenesis phenomena. Analysis of PsA synovial membrane has shown presence of different types of immune cells [18].

6) Altered Bone Remodeling

Pathological bone remodeling in PsA arises from a dramatic alteration in the tightly regulated bone homeostatic pathways. This promote release cytokines and other factors in inflamed synovial tissues [19].

3. Clinical Features of Psoriatic Arthritis

There are no diagnostic criteria or testing for PsA. Inflammatory musculoskeletal characteristics in the joints, entheses, or spine are most typically identified in the presence of skin and/or nail psoriasis, and in the absence of rheumatoid factor and anticyclic citrullinated peptid [20].

A) Articular Manifestations

a) Peripheral PsA

Distinctive features of joint involvement in PsA, particularly in an early disease state, include inflammatory asymmetric monoarticular to oligoarticular distribution, possible spondylitis including sacroiliitis, and distal small-joint inflammation in hands and feet [21]. Majority of patients with the PsA experience peripheral joint involvement, and approximately 25–70% of patients have axial involvement depending on definition of the axial disease applied. In more severe cases erosive arthritis leads to arthritis mutilans [22].

b) Axial PsA

Axial arthritis can be an indicator of higher disease severity. It is associated with a particularly high incidence of sacroiliitis, which can present as bilateral and symmetrical [23]. An early manifestation of theaxial involvement associated with the PsA is the formation of the asymmetric syndesmophytes and paraspinal ossifications. Spondylitis and sacroiliitis can be detected in imaging modalities such as the MRI to identify bone marrow edema [24].

B) Extra- Articular Manifestations

1- Enthesitis

Enthesitis can present before arthritis symptoms in patients with PsA and may be only musculoskeletal manifestation in early PsA [25]. Most frequent areas of enthesitis are insertion sites of plantar fascia, Achilles tendon, lateral epicondyle of elbow, and ligament attachments at knee

[26]. Several clinical enthesitis scoring systems have been used such as Mander Enthesitis Index (MEI), The Leeds enthesitis index (LEI) and The Spondyloarthritis Research Consortium of Canada (SPARCC) index [27-28].

2- Dactylitis

Dactylitis presents as diffuse digit swelling of a finger or toe accompanied by redness of skin, and pain. It can be an indicator of disease severity. It usually is asymmetrical. It affects right more than left side, involves the feet more than hands, and often affects the multiple digits simultaneously [29].

3- Skin Manifestations

Skin psoriasis is a prerequisite for diagnosis of psoriatic arthritis. Psoriasis presents as well-defined erythematous plaques covered with silvery scales commonly over scalp, and extensors of extremity, particularly over knees, elbows, and lumbosacral region. It can present with different morphology e.g. plaque, guttate, erythrodermic, pustular and inverse [30]. Plaque psoriasis, the most common form of disease, affects approx. 80% to 90% of patients with psoriasispresents as erythematous plaques with silvery scales most commonly over extensors of extremities [31].

4- Nail changes

Nail psoriasis is strongly associated with cutaneous psoriasis and psoriatic arthritis. The common clinical manifestations of nail psoriasis are nail Pitting, subungual hyperkeratosis, the onycholysis, and the oil drop discoloration [32].

5-Arthritis mutilans

Arthritis mutilans often called resorptive arthritis, is most severe and rare form of psoriatic arthritis, affecting only about 5-16% of patients. It characterized by severe osteolysis of peripheral joints, often resulting in the shortening of digits and the opera glass hand deformity. It primarily affects the joints of hands and feet, causing the severe functional impairment [33].

6- Uveitis

Uveitis, an inflammatory disorder of the mid-portion of the eye, is considered a relatively rare but very serious ocular complication of psoriasis. The presence of uveitis in the context of psoriasis has been estimated to occur in 7–20% of the psoriasis cases. This incidence tends to be higher in patients suffering from psoriatic arthritis. Psoriatic uveitis is usually bilateral, chronic, and severe [34].

7- Inflammatory bowel disease

Amongst patients with SpA, IBD is common .Patients with PsO, PsA and AS have a 1–4 fold increased risk of IBD compared to the general population .IBD is also more common in patients with axial-PsA than in those with peripheral-only PsA [35].

C- Other Extra-articular Manifestations

1) Cardiovascular Affection

PsA is associated with a 55% increased risk of developing cardiovascular diseases (CVD), such as ischemic heart disease, cerebrovascular disease, and congestive heart failure [36].

2) Metabolic disease

PsA is associated with an increased prevalence of obesity, hypertension, dyslipidemia and insulin resistance (metabolic syndrome) [37].

3) Hyperuricemia

PsA patients might present higher serum levels of uric acid and that hyperuricemia might affect severity of clinical manifestations and degree of inflammation in PsA patients [38].

4. Diagnosis of Psoriatic Arthritis

4.1. Classification Criteria

Diagnosis of PSA depends mainly on CASPAR Criteria. The CASPAR criteria consist of confirmed inflammatory articular disease (joint, spine, or entheseal) with at least 3 points from the following features: current psoriasis (assigned a score of 2 points), a history of psoriasis or a family history of psoriasis (unless current psoriasis is present, assigned a score of 1 point), the dactylitis (present or past assigned a score of 1 point), psoriatic nail dystrophy (present or past assigned a score of 1 point), negative rheumatoid factor by any method except latex test(assigned a score of 1 point), and juxtaarticular new bone formation (hands or feet radiographs assigned a score of 1 point) [39].

4.2. Laboratory Indications

There are no laboratory tests specifically for psoriatic arthritis. As in most inflammatory diseases, acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated. However, a normal ESR and CRP should not be used to rule out a diagnosis of psoriatic arthritis, as these levels are increased in only about 40% of patients. Rheumatoid factor and anti-cyclic citrullinated peptide antibodies are classically considered absent in psoriatic arthritis [40].

4.3. Imaging Modalities

Radiographic changes show some characteristic patterns in psoriatic arthritis: erosive changes, gross joint destruction, joint space narrowing, and “pencil-in-cup” deformity [41]. Musculoskeletal ultrasound (MSUS) and MRI are more sensitive than plain radiography for detecting early joint inflammation, damage, and axial changes, including sacroiliitis [42].

4.4. Differential Diagnosis of PSA

Definitive diagnosis of PsA is further complicated by several arthritic conditions with similar clinical presentations. PsA is can be misdiagnosed for rheumatoid arthritis (RA) or osteoarthritis (OA) .PsA include asymmetric monoarticular to oligoarticular distribution, possible spondylitis including sacroiliitis,absence of rheumatoid factor, and distal small-joint inflammation in the hands and feet but RA includes symmetric and poly articular distribution, proximal hand and foot involvement, more tender and swollen joints, presence of rheumatoid factor and absence of sacroiliitis [21]. PSA and RA can present at any age, but peak age of onset is between ages 30 and 50 years. OA is the most common non-inflammatory arthritic condition strongly associated with aging, and symptoms arise from deterioration of joint cartilage, which can cause changes in the bone and connective tissues of the joints [43].

We should differentiate PsA from gout. Gout is caused by monosodium urate crystal deposition. It presents as an acute, selflimiting inflammatory monoarthritis that affects the joints of especially the first metatarsophalangeal joint [44]. Radiograph show punched-out or rat-bite erosions with overhanging edges and sclerotic margins [45].

4.5. Psoriatic Arthritis Assessment

Disease activity in Psoriatic Arthritis (DAPSA) is based on four pillars: number of tender joints (0 – 68), number of swollen joints (0 – 66), Creactive protein (CRP) (mg/l), patient assessment of disease activity and pain. To determine disease activity, the following values apply: 0 - 4 remission, 5 - 14 low disease activity, 15 - 28 moderate disease activity, >28 high disease activity [46].

4.6. Assessment of skin severity

Psoriasis severity was measured by the Psoriasis Area and Severity Index (PASI) and patients were categorized based on PASI. Both intensity and extent (BSA) of the psoriatic plaques are calculated separately for four anatomical regions (head, trunk, upper and lower extremities) by the physician. The intensity of erythema, desquamation and induration is rated on a 5-point scale with 0 indicating no involvement, 1 slight, 2 moderate, 3 severe and 4 very severe characteristics. The percentage of involvement of the four anatomical regions is assigned a numerical value of 0–6 with 0 indicating no involvement, 1 = 1–9%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89% and 6 = 90–100% BSA involvement. When calculating the PASI, the four anatomical regions are evaluated according to their proportion of the whole integument. The PASI score varies from 0 to 72. Higher scores indicate severer conditions [47].

4.7. EULAR recommendations for the management of psoriatic arthritis

The updated EULAR recommendations comprise 7 overarching principles and 12 recommendations, and provide a treatment strategy for pharmacological therapies [48].

Recommendation 1: Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy.

Recommendation 2: Non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.

Recommendation 3: Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose.

Recommendation 4: In patients with polyarthritis, a csDMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement.

Recommendation 5: In patients with mono arthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a csDMARD should be considered.

Recommendation 6: In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.

Recommendation 7: In patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a JAK inhibitor may be considered.

Recommendation 8: In patients with mild disease and an inadequate response to at least one csDMARD, in whom neither a bDMARD nor a JAK inhibitor is appropriate, a PDE4 inhibitor may be considered.

Recommendation 9: In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered.

Recommendation 10: In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice a TNF inhibitor is; when there is relevant skin involvement, IL-17 inhibitor may be preferred.

Recommendation 11: In patients who fail to respond adequately to, or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered, including one switch within a class.

Recommendation 12: In patients in sustained remission, cautious tapering of DMARDs may be considered.

4.8. Prognosis

Psoriatic arthritis is considered an aggressive disease with the potential for significant morbidity and poor quality of life in patients. Some features are harbingers of a severe disease course and poor prognosis. These include a large number of actively inflamed joints or poly articular presentation, elevated erythrocyte sedimentation rate, clinical or radiographic damage, loss of function, and diminished quality of life [49].

4.9. Complications

Once considered a mild disease, psoriatic arthritis is now considered a debilitating disease requiring targeted treatment with frequent monitoring and follow-up care. Complete symptomatic relief is achievable, but most patients continue to have the persistent inflammatory disease. Patients with uveitis will require the evaluation and treatment by an ophthalmologist. Patients with the psoriatic arthritis have an increased prevalence of the comorbidities, including metabolic syndrome, obesity, diabetes mellitus, hyperlipidemia, the hypertension, and the cardiovascular disease [50].

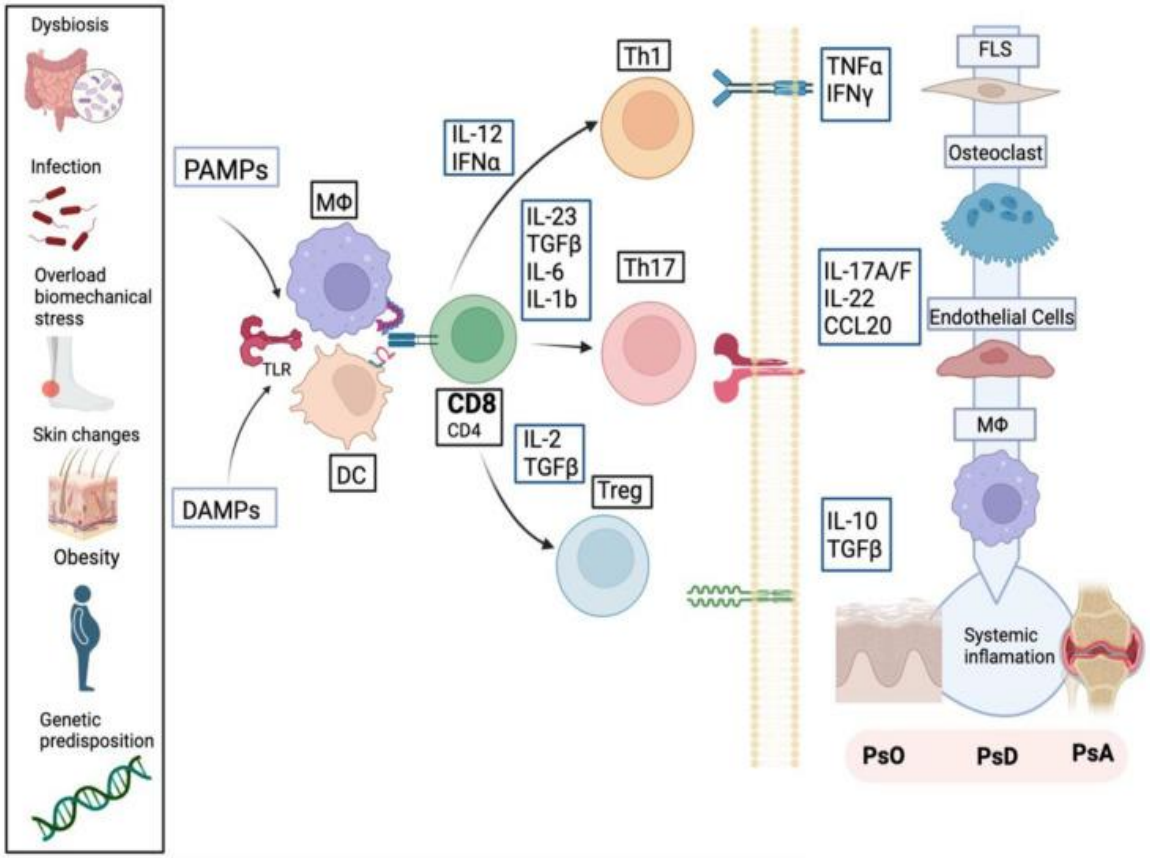

Figure (1): The integration of genetic predisposition, environmental triggers, and proinflammatory cytokines is represented. DAMPS (Damage-associated molecular pattern), PAMPs (Pathogen-associated molecular patterns), DC (dendritic cells), MΦ (Macrophages), CD8 (CD8 T lymphocyte), CD4 (CD4 T lymphocyte), Th1 (T helper 1 cells), Th17 (T helper 17 cells), Treg (T regulatory), FLS (synovial fibroblast), PsD (psoriatic disease), PsO (psoriasis) [5].

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