Seminars in Arthritis and Rheumatism 43 (2013) 325–334

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Enthesitis in psoriatic arthritis

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ARTICLE INFO

Keywords:
Assessment
Dactylitis
Enthesitis
Magnetic resonance imaging
Psoriatic arthritis
Psoriasis
TNFα inhibitors
Ultrasonography
Treatment

ABSTRACT

Objectives: It is increasingly recognized that enthesitis in patients with psoriatic arthritis (PsA) is of clinical importance. We review data on the detection, assessment, and treatment of enthesitis and its related dactylitis in PsA.
Methods: We searched Pubmed with the search terms psoriatic arthritis or psoriasis in combination with enthesitis, enthesopathy, and treatment, or enthesitis in combination with imaging.
Results: One hundred fifty-seven papers were selected. Enthesitis occurs frequently in PsA and may be asymptomatic or painful. It can also affect patient's function and quality of life. New imaging modalities, such as ultrasonography and magnetic resonance imaging, have revealed that enthesitis may be the initial osteoarticular inflammatory site in patients with PsA. Enthesitis indices have been developed and should be incorporated in clinical trials. Dactylitis, a characteristic and frequent manifestation of PsA can be tender or not tender and is prognostic of disease progression. Treatment of enthesitis includes non-steroidal anti-inflammatory drugs, classical DMARDs, and adjunctive local steroid injections. In inadequate response, TNFα inhibitors are used.
Conclusions: Enthesitis and dactylitis are important manifestations of PsA, and their evaluation is increasingly used in drug trials and clinical practice.

Introduction

Psoriatic arthritis (PsA) develops in 8%–48% of patients with psoriasis [1–3]. The incidence of PsA in patients with psoriasis is 1.87 cases/100 patients per year [4]. Psoriasis itself is a common disease affecting 2% of the general population [5]. PsA has been defined for many years as an inflammatory arthritis in individuals with psoriasis and no serum rheumatoid factor [6]. However, arthritis develops before psoriasis in 6%–18% of cases, with an average 7 years before psoriasis [7,8]. In addition, PsA is a heterogeneous disease affecting, apart from skin and nails, peripheral joints, the axial skeleton, entheses, synovial sheaths of tendons, and eyes [9,10]. Each clinical manifestation can occur for a long time in isolation [11].

Inflammation of enthesis, called enthesitis, is an inflammatory osteoarticular component of the classification criteria for PsA and spondyloarthritis (SpA) in general. The CASPAR (Classification Criteria for Psoriatic Arthritis) criteria, the most widely used criteria with the highest sensitivity, classified PsA as the presence of an inflammatory articular disease (joint, spine, or entheseal) plus a score of at least 3 of the following categories (each with a score 1, except current psoriasis that scores 2): current psoriasis, a history of psoriasis, a family history of psoriasis, dactylitis (swelling of an entire digit, present or past), radiographic evidence of juxta-articular bone formation, and typical nail dystrophy [12,13]. The European Spondyloarthropathy Study Group preliminary criteria for SpA [14] and the new Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA and peripheral SpA also include enthesitis [15,16]. In fact, enthesitis is one of three entry criteria for peripheral SpA.

Enthesitis is characteristic of SpA and can affect the quality of life of patients negatively [17]. Some investigators suggest that enthesis is the initial site of inflammation in SpA in general and PsA in particular [18]. Therefore, enthesitis is an important inflammatory osteoarticular manifestation of PsA. The aim of this review is to describe clinical manifestations, assessment, and treatment of enthesitis and its related dactylitis in PsA. We also include recent existing development on pathogenesis.

Materials and methods

We searched for original articles and review articles in Pubmed using the term psoriatic arthritis or psoriasis in combination with

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http://dx.doi.org/10.1016/j.semarthrit.2013.04.005

enthesitis, enthesopathy, or treatment. We also searched using the terms enthesitis and imaging. In addition, we had a large collection of original articles on PsA, ankylosing spondylitis (AS), and SpA.

Results

We reviewed over 250 articles. Non-English language articles, meeting reports, opinion articles, and articles on treatment with no reference to enthesitis or dactylitis were excluded. In the final list, we included 112 original articles, 28 reviews, 9 guidelines, 4 editorials, 3 letters to the editor, and 1 case series.

Enthesis and enthesitis

Enthesis is a Greek word for the insertion of tendons, ligaments, and joint capsule fibers into bone. Entheses are numerous in axial and appendicular skeleton and can be classified as fibrous and fibrocartilaginous according to tissue present at the skeletal attachment site [19]. At the fibrocartilaginous entheses, cortical bone is extremely thin or absent, and tendons/ligaments are directly connected to underlying bony trabecular network and bone marrow spaces. Bone microdamage and vascular invasion are frequently detected at entheses [20].

Enthesis is not just the focal attachment to bone. For example, in the Achilles tendon, the whole structure includes the junction point (the enthesis itself), the periosteal and sesamoid fibrocartilages, the retrocalcaneal bursa, and the tip of Kager's fat pad. The enthesis is in close proximity to synovium with a synovial membrane covering the tip of the fat pad. These structures that are related in anatomical, functional, and physiological ways can perform as one entity, the "synovio-entheseal complex," and frequently (82%) exist at many entheseal sites [20,21]. At entheseal sites in normal mice, there are double-negative T cells expressing interleukin-23 receptor (IL-23R)(CD3+CD4−CD8−IL23R+ cells) [22].

Macrophages and lymphocytes are present at the insertion sites and synovial sites of synovial–entheseal complex in ethesitis [20] The chronic inflammation of enthesis usually causes cystic and erosive changes in the bone where the tendon inserts to, followed by periosteal changes, formation of spurs, sub-periosteal new bone, and syndesmophytes. Therefore, enthesitis encompasses inflammatory changes and structural changes (enthesophytes, calcifications, and erosions). Enthesopathy is a general term and includes enthesitis, metabolic disease, mechanical lesions, and degenerative lesions [19,23].

Pathogenetic relevance of enthesitis to PsA

The pathogenesis of PsA is not known. One model suggests that T-cell response to a common skin and synovial membrane antigen drives the inflammation in this disease [24]. The association of enthesitis with HLA-DR17 is in line with this concept [25]. Another model suggests that enthesis may be the initial site that drives innate immune response [26]. The synovial–entheseal complex, due to mechanical stress, is prone to microdamage, and this triggers innate immune inflammation that spreads to adjacent synovium [26]. At the entheses, there are degenerative changes, including clusters of hypertrophied fibrocartilage cells and matrix fissuring. Microdamage or trauma may also be responsible for skin lesions in psoriasis, an example of Koebner phenomenon [27]. A spontaneous animal model of PsA (aging DBA/1 mice) supports the concept of enthesitis as triggering the innate immune response [28]. Dexamethasone or TNFα inhibitor treatment of this animal model reduced inflammation but did not affect ankylosis [29,30]. In another animal model, type II collagen antibody-induced arthritis in B10.RIII mice, enthesitis develops before arthritis and is driven by IL-23 [22]. Furthermore, in vivo over-expression of IL-23 alone is sufficient to induce enthesitis, psoriasis, and sacroiliitis in naive B10.RIII mice. CD3+CD4−CD8−IL23R+ native entheseal cells respond to IL-23 to produce IL-22, which induces osteoproliferation via STAT3 activation and inflammation at entheses [22].

Enthesis is also anatomically connected to nail. The extensor tendon not only attaches to the base of the terminal phalanx but also encloses the nail root and anchors the nail laterally [31]. Thus, the nail can be considered as an extension of the skin and enthesis and can explain the association of nail disease with arthritis of distal interphalangeal (DIP) joint in PsA.

Clinical manifestations of enthesitis

Enthesitis is more frequent in lower than upper extremities with Achilles and plantar enthesitis being the most frequent clinically. A small percentage (3.5%) of patients with PsA may have enthesitis alone and/or dactylitis for months to years [11].

Enthesitis may be asymptomatic or can cause pain. Pain is minimal to mediocre. It is most pronounced in lower extremities, particularly Achilles enthesis and plantar aponeurosis enthesis, where pain can be severe and disabling. US-detected quadricipital enthesitis is symptomatic in nearly half of PsA patients [32,33]. In heel enthesitis, pain is experienced briefly on weight bearing after a period of prolonged rest. There is tenderness on pressure over enthesis and occasionally soft tissue swelling. The latter is mostly visible in Achilles enthesitis, the humeral lateral epicondyle, and the patellar tendon. It should be mentioned that in pelvis and lower limbs of patients with seronegative SpA, clinical manifestations correlate poorly with radiological enthesopathy (calcifications, new bone formation, and/or erosions) [34].

Symptoms of enthesitis can mimic various conditions, as enthesopathy can be caused by metabolic, mechanical (including sports-related injury), and degenerative conditions [23,35–37] (Table 1). In most cases, enthesitis should be differentiated from fibromyalgia. In one study, the presence of ≥6 fibromyalgia-associated symptoms and ≥8 tender points was the best discriminating predictor of fibromyalgia [33]. Whole-body MRI may **also** be able to rule out fibromyalgia [38]. Entheseal pain may be attributed to arthritic pain and isolated enthesitis is often misdiagnosed as overuse-induced tendinitis. Enthesitis of the proximal insertion of deltoid is frequent in PsA (17%) and causes symptoms and signs very similar to those of impingement

Table 1
Conditions associated with enthesopathy

Rheumatic diseases
– SpA
– Osteoarthritis
– Rheumatoid arthritis
– Calcium pyrophosphate deposition disease
– Gout
Drugs
– Fluoroquinolones
– Retinoids
– Fluoride
Metabolic diseases
– Familial hypercholesterolemia
– Hyper(hypo)parathyroidism
– Hypothyroidism
– Acromegaly
– Hemochromatosis
– Diabetes mellitus