Differentiation Between Rheumatoid Arthritis and Psoriatic Arthritis in Early Stage Hand Arthritis

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Abstract

Arthrtis of the hand is commonly encountered. Numerous types of arthritis have been investigated and described in order to classify them into non-inflammatory arthritis (osteoarthritis) and inflammatory arthritis caused by crystal deposition (pseudogout, basic calcium phosphate disease, gout), by bacterial and viral infections (Staphylococcus aureus, Neisseria gonorrhea, complications of Lyme disease, Parvovirus, Enterovirus) or by autoimmune processes (RA , PsA , SLE). Differential diagnosis of hand arthritis is a challenge and represents the optimal medical approach. Certain features must be evaluated in order to make a differentiation. The distribution of synovitis is different in RA (symmetric, great, and small joints including wrist and elbow) than in ankylosing spondylitis (limited to small joints) and psoriatic arthropathy (asymmetric, including toes). Inflammation is more intense in RA than in osteoarthritis. Diagnosis of early seronegative rheumatoid arthritis may be challenging, with consequent possible diagnostic mistakes and inappropriate therapies. This is likely due to the absence of specific markers for seronegative RA, as well as the greater difficulty in classification of RA in early phase. Patients with seronegative RA experienced a delay in diagnosis, according to both the 1987 and 2010 classification criteria, as well as a delay in the initiation of DMARD therapy. Patients with seronegative RA were also less likely to attain remission, suggesting that the window of opportunity for intervention may be more frequently missed in this group. The main differential diagnosis of seronegative forms of early RA is early polyarticular psoriatic arthritis, whose recognition is also troublesome, especially when dealing with minimal or atypical cutaneous or nail lesions

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Introduction

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Differential diagnosis of hand arthritis is a challenge and represents the optimal medical approach. Certain features must be evaluated in order to make a differentiation. The distribution of synovitis is different in RA (symmetric, great, and small joints including wrist and elbow) than in ankylosing spondylitis (limited to small joints) and psoriatic arthropathy (asymmetric, including toes). Inflammation is more intense in RA than in osteoarthritis**(Wasserman ,2011).**

Diagnosis of early seronegative rheumatoid arthritis may be challenging, with consequent possible diagnostic mistakes and inappropriate therapies. This is likely due to the absence of specific markers for seronegative RA, as well as the greater difficulty in classification of RA in early phase **(Aletaha et al.,2010).**

Patients with seronegative RA experienced a delay in diagnosis, according to both the 1987 and 2010 classification criteria, as well as a delay in the initiation of DMARD therapy. Patients with seronegative RA were also less likely to attain remission, suggesting that the window of opportunity for intervention may be more frequently missed in this group**(Coffey ,et al., 2019).**

While typically considered having a less inflammatory and less destructive form of RA **(Rönnelid,et al.,2005),** seronegative patients require more clinical symptoms to be classified as having RA according to the 2010 ACR/EULAR criteria **(Aletaha,e al.,2010),** compared to seropositive patients, and may consequently be diagnosed later **(Nordberg,et al .,2017)** Since all patients benefit from early treatment, early diagnosis is critical also for seronegative patients **(Verschueren,et al.,2015).**

The main differential diagnosis of seronegative forms of early RA is early polyarticular psoriatic arthritis, whose recognition is also troublesome, especially when dealing with minimal or atypical cutaneous or nail lesions **(Zabotti et al., 2018).**

Hand in Rheumatoid Arthritis

Distribution and pattern

The hallmark of RA is chronic bilateral symmetric inflammatory arthritis (synovitis) involving the small joints of the hands and feet. More than 50% of the cases of RA have an insidious onset of the disease, while abrupt onset can be seen in up to 25% cases. Mono articular joint involvement especially that of larger joints such as knee or shoulder that eventually progresses to polyarticular involvement, has been seen. In the elderly population, the onset of RA may mimic symptoms of polymyalgia rheumatica with arthralgias, myalgias, and stiffness of the shoulders and hip girdles with elevated ESR and constitutional symptoms such as fever and fatigue. Rarely, extra-articular manifestations, especially rheumatoid nodulosis or interstitial lung disease in addition to seropositivity, can be the initial presenting feature of RA **(Mohammed et al., 2021).**

Regardless of the pattern of onset, most patients experience gradual progression of the disease if left untreated, although some patients may experience episodic/palindromic pattern or a brief self-remitting pattern. Although the severity of RA may fluctuate over time, spontaneous remission in RA is uncommon, especially if left untreated after the first 3-6 months **(Smolen et al., 2018).**

RA tends to involve small joints of bilateral upper and lower extremities. In the hands, the most commonly involved joints are the metacarpophalangeal (MCP) joints and the proximal interphalangeal (PIP) joints, especially the 2nd and 3rd MCP and PIP joints. Distal interphalangeal (DIP) joints are usually spared, and involvement of the 1st carpometacarpal joint is less common. In the feet, the most commonly involved joints are the metatarsophalangeal (MTP) joints. The involvement of the wrist, elbow, shoulder, knee has, and hip joints are also frequent. Axial involvement includes C1-C2 synovitis, erosion, and subluxation, although the rest of the spine and sacroiliac joints are spared **(Gulati et al., 2018).**

Prevalence

Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. In the early stages of rheumatoid arthritis (RA) involvement of the hand and wrist is commonly described, causing pain, limited range of motion and/or loss of muscle strength. Previ- ous studies have reported 28% hand involvement and 8% wrist involvement at the onset of the disease (1–3) **(Mohammed et al., 2021).**

First-degree relatives of individuals with RA are at 2- to 3-fold higher risk for the disease. Disease concordance in monozygotic twins is approximately 15-20%, suggesting that nongenetic factors play an important role. Because the worldwide frequency of RA is relatively constant, a ubiquitous infectious agent has been postulated to play an etiologic role. Women are affected by RA approximately 3 times more often than men are, but sex differences diminish in older age groups **(Hurnakova et al., 2019).**

Hand in Psoriatic arthritis (PsA)

Distribution and pattern

Psoriatic arthritis (PsA) is chronic inflammatory arthritis

associated with psoriasis (PsO) and found in about 20 to 30% of such patients. It shares many clinical features with other spondyloarthropathies and also rheumatoid arthritis (RA). It is usually seronegative, but a small percentage of patients may be positive for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP antibodies). The clinical manifestations are varied and can change over time, evolving from one articular pattern to another. There is a considerable financial and psychological burden associated with this disease **(Tiwari & Brent, . 2019).**

Dermatological features of psoriasis precede arthritis in ~65% (range 60-70%) whereas arthritic symptoms proceed dermatological features in 15-20%. There is a strong association with nail involvement, particularly for distal interphalangeal joint arthritis. It most commonly presents as an asymmetrical oligoarthritis with spondylitis common; oligoarthritis may progress to polyarthritis in the clinical course of the disease (**KOARADA & TASHIRO, . 2020).**

Clinically, peripheral arthritis is the most common manifestation of PsA there are no diagnostic markers for PsA. Therefore, clinical diagnosis of PsA is based on recognizing patterns of inflammatory joint involvement **(Acebes & Harvie, . 2015**). **Moll and Wright** recognized five subsets of PsA. Of these 5 subsets, the two most common are asymmetric oligoarthritis and symmetric polyarthritis. A "ray" pattern involving all three joints of affected digits has been described for the distribution of affected joints with other digits of the hand being less involved.

Asymmetric arthritis and the ray distribution are clinical features often used to distinguish PsA from rheumatoid arthritis (RA) **(Espinoza, . 2018)**. However, **Helliwell et al**. examined damage patterns seen over follow-up and demonstrated that the perceived difference in symmetry between PsA and RA is due to the higher number of joints generally being involved in RA**(Helliwell et al., 2000).**

Moreover, using data from patients registered with the Norfolk Arthritis Register, **Bukhari et al.** demonstrated that inflammatory polyarthritis is a symmetrical disease irrespective of rheumatoid factor status **(Bukhari et al., 2002).**The authors challenged the use of symmetry as an important feature in identifying subgroups of patients with inflammatory arthritis, such as RA and PsA. It is also possible that joint involvement in PsA can be described as a "row" pattern where all joints of a particular type (e.g., MCP) are involved.

However, apart from the attempt by Helliwell et al., as far as know there has not been an attempt to formally investigate whether the pattern of joint involvement in PsA is appropriately described as symmetric, ray, and/or row. Thus, the long-term issue of patterns in PsA has not been resolved and there is a need for additional clinical evidence for the presumed patterns including symmetry and ray distribution **(Chandran et al., 2018).**

Prevalence

Overall prevalence is ~0.5% (range 0.1-1%), however, it affects up to ~25% (range 6-41%) of patients with psoriasis. In contrast to many other arthropathies, there is no gender predilection in psoriatic arthritis. The median age of diagnosis is 48 years **(Tiwari & Brent,. 2019)**.

The onset of psoriatic arthritis is usually in the 30s and 40s and occurs about equally in males and females. In the majority of patients, the onset of skin disease precedes that of arthritis (68%), in about 15% of patients, the arthritic manifestations coincide with the skin disease, and in 17% of patients, arthritis occurs before the skin manifestations making the diagnosis more difficult. When examining the occurrence of psoriatic arthritis over time in a population of patients with psoriasis, the annual incidence of psoriatic arthritis was 1.9 to 2.7% per 100 patients with psoriatic arthritis. The cumulative incidence of psoriatic arthritis in patients with psoriasis was 1.7% at 5 years, 3.1% at 10 years, 5.1% at 20 years, and 20.5% at 30 years **(Eder et al., 2016).**

Clinical characteristics of RA and PsA

For RA, the American College of Rheumatology (ACR)/European League .Against Rheumatism classification criteria were designed for patient characterisation and use in clinical trials **(Janssen et al., 2015).**The key clinical characteristic is the confirmation of definite, persistent, clinical synovitis in at least one joint. The criteria include the number of joints involved, duration of symptoms, and the demonstration of serological markers and an elevated acute-phase reactant. For PsA, the Classification Criteria for Psoriatic Arthritis help categorise patients with inflammatory articular disease for clinical trials. Key clinical characteristics include a personal or family history of psoriasis, psoriatic nail dystrophy and dactylitis. Neither classification criteria should be confused as diagnostic criteria **(Merola et al., 2018).**

Joint involvement is predominantly symmetric in RA and often, but not always, asymmetric in PsA. In both RA and PsA, most patients have polyarthritis (≥5 involved joints), although joint involvement can be oligoarticular or polyarticular **(Veale & Fearon, . 2015).** Monoarticular disease is less common in PsA; however, 5%–10% of patients may present with isolated distal joint involvement. In PsA, prognosis worsens and symmetry of joint involvement tends to increase as the number of affected joints increases **(Gladman, . 2015).**

Typically, RA affects the shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, hip, knee, ankle and metatarsophalangeal joints. In PsA, the distal interphalangeal joints of the hands and feet, large joints of the lower extremities, the axial spine and sacroiliac joints are commonly affected; the metacarpophalangeal and metatarsophalangeal joints and wrist can be involved as well. PsA, rather than RA, is included in the spectrum of spondyloarthritis as PsA can affect the axial skeleton (eg, sacroiliac joints and spine). It is estimated that up to 50% of patients with PsA experience inflammation in the axial skeleton; axial involvement can be a differentiating feature of PsA because it is not present in RA other than cervical spine involvement, which has been reported in up to 80% of patients with RA **(Merola et al., 2018).**

Although TNF-α induces angiogenesis in both RA and PsA, differences in synovial vascularity can help differentiate the diseases. Both RA and PsA exhibit proliferation of endothelial cells, but topological differences in endothelial cells suggest differing pathological features.Among patients with knee synovitis, straight, branching vessels are observed in RA, and predominantly tortuous, bushy vessels are observed in PsA.These physiological differences may be caused by varied patterns of synovial cytokine expression as significantly higher levels of IL-1β, IL-2, IL-10 and IFN-γ are found in PsA synovial explants compared with RA synovial explants**(Veale & Fearon, . 2015).**

Enthesitis (inflammation of entheses at sites where ligaments or tendons insert into the bone) occurs in 35% of patients with PsA but is uncommon in patients with RA. Enthesitis is proposed to have a key role in the pathogenesis of PsA, and the presence of enthesitis can be particularly valuable in differentiating PsA from RA. The most common locations of enthesitis in patients with PsA are the insertion sites of the plantar fascia, the Achilles tendon and ligamentous attachments of the knee. In rare cases, enthesitis may be the only manifestation of PsA. Signs and symptoms of enthesitis can be non-specific and difficult to distinguish from other inflammatory conditions, particularly fibromyalgia, in the absence of other manifestations common to PsA **(Polachek et al., 2017).**

Dactylitis (inflammation of an entire digit) is a common manifestation of PsA that affects up to 50% of patients, compared with approximately 5% of patients with RA. Dactylitis may also occur in patients with other forms of spondyloarthritis, such as ankylosing spondylitis and reactive arthritis, but also occasionally in gout and sarcoidosis. However, dactylitis is a fairly specific sign of PsA that can aid in the differential diagnosis, especially when it is present along with enthesitis **(Gladman, . 2015).**

Nail dystrophy, which is characterised by onycholysis, pitting and hyperkeratosis, is an important clinical manifestation of PsA. In a prospective study characterising the clinical presentation of early PsA, 67% of patients had nail dystrophy; the incidence was higher (80%) in patients with distal interphalangeal joint involvement. The increased incidence of nail disease in patients with distal interphalangeal joint involvement has been attributed to the topographic association between the extensor tendon enthesis and the nail. Thus, the presence of nail lesions can be especially helpful in differentiating PsA from other forms of spondyloarthritis, RA, gout and osteoarthritis **(Merola et al., 2018).**

Ocular disorders are common extra-articular manifestations of RA and PsA. The most common ocular manifestation of RA is keratoconjunctivitis sicca, which affects approximately 18% of patients; other common eye disorders in patients with RA include episcleritis (5%) and scleritis (2%).Uveitis occurs in PsA, affecting approximately 7% of patients and is more common in women than men; the incidence is far higher in patients with axial disease and HLA-B27 positivity. In patients with PsA or inflammatory bowel disease, uveitis is typically bilateral with an insidious onset, affecting the anterior and intermediate layers of the eye **(Rosenbaum, . 2015).**

Cutaneous manifestations are common in both RA and PsA. The most common cutaneous features of RA include rheumatoid nodules, vasculitic skin lesions and granulomatous dermatoses **(Makol et al., 2014).** Current psoriasis is an important clinical finding in a patient with arthritis. Skin disease precedes the development of joint symptoms in 84% of patients with PsA, and up to 96% of patients with PsA have either current or previous psoriasis or family history of psoriasis. Compared with patients with psoriasis but without PsA, patients with PsA have more extensive psoriasis and higher rates of pustular and inverse psoriasis. In addition, patients with scalp psoriasis, inverse psoriasis and nail dystrophy are at increased risk for PsA. **(Shin et al., 2016).** It is important to remember that manifestations of psoriasis are not always overt, and patients with seronegative inflammatory arthritis should be evaluated for scalp, inverse, genital, palmoplantar and nail psoriasis. Furthermore, inverse psoriasis is traditionally under-recognised, and recent findings indicate a greater prevalence of inverse psoriasis than commonly appreciated. With such a thorough physical examination, many patients with 'seronegative' RA are correctly identified as actually having PsA **(Merola et al., 2018).**

Serological features of RA and PsA

RA is a seropositive arthropathy, with approximately 80% of patients having a positive test result for RF or CCP antibodies.CCP antibodies are a more specific marker for RA than RF, but both biomarkers are considered to be distinct and complementary predictors of disability and joint erosion **(Merola et al., 2016).**

In contrast, PsA is a seronegative inflammatory arthropathy. RF and CCP are absent in most patients with PsA, and if patients do have positive test findings for RF or CCP, the titres are usually low. In a study comparing patients with RA or PsA and controls, the mean RF and anti-CCP titre values were substantially higher in patients with RA compared with PsA (RF titre: 56 vs 11 U/mL; anti-CCP titre: 14 vs 2 U/mL). Titres in patients with PsA were similar to values in controls. **(Merola et al., 2016)**.Although the presence of serum RF or CCP antibodies is generally not used to exclude diagnosis of non-rheumatic diseases (eg, fungal infections), data suggest that at anti-CCP titre values ≥11.6 U/mL, it is highly probable that patients have RA rather than PsA. In both patients with RA and PsA, the presence of anti-CCP antibodies is associated with bone destruction, suggesting that the osteocatabolic effect of anti-CCP antibodies is not found only in RA as previously thought. **(Shen et al., 2015).**

C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are markers of acute-phase inflammatory responses in patients with RA and PsA, but more so in patients with RA. In a systematic literature review of RA disease activity parameters, ESR and CRP levels were a significant predictor of radiographic progression in most studies. The acute-phase response is correlated with synovial inflammation, radiographic disease progression and erosive joint damage. On average, patients with PsA have significantly lower CRP and ESR levels than patients with RA **(Merola et al., 2018).**

However, elevated ESR and CRP levels are significantly correlated with the number of swollen joints and with ultrasound abnormalities in PsA. ESR, in particular, is considered to be one of the best predictors of damage progression in PsA. It has been suggested that a low ESR is protective, while rates >15 mm/hour are associated with increased risk for mortalit **(Shen et al., 2015).** Changes in ESR and CRP correspond with clinical outcomes and can be used to track response to treatment **(Lindqvist et al., 2008).**

Increased ESR and CRP levels are markers of inflammation, but not necessarily just in RA. Other rheumatological diseases associated with elevated ESR and CRP levels include polymyalgia rheumatica, Sjögren's syndrome and ankylosing spondylitis **(Bitik et al., 2015).**

Evaluation

Radiography is a well-established examination for the evaluation of inflammatory arthritis and should be used as the primary tool owing to its accessibility and cost effectiveness. It has many advantages compared with other imaging modalities, such as the ability to image multiple joints simultaneously with minimum radiation exposure. Although detection and assessment of bone changes are the most important reasons for obtaining radiographs, bone changes only become apparent at a later stage in the disease course **(Coates and Helliwell, 2017)**.

However, owing to the delay in the patient's first visit to the rheumatologist from the time of symptom onset, which could range from several months to more than a year, there is a possibility that minor bone changes on the radiograph can be detected. Radiography can also be used for evaluation of soft-tissue changes such as swelling and calcification. Furthermore, radiography, which is the easiest imaging modality to perform, should be considered for joint assessment at regular follow-up for arthritis **(Colebatch et al., 2013)**.

US is the imaging modality of choice for evaluating arthritis, even if findings at radiography are unremarkable. For the detection of inflammatory lesions, US has a higher sensitivity than clinical assessment. Doppler US can depict increased blood flow in the joints and can help grade disease activity. As for bone erosion, several studies suggest that US could depict more erosions in RA when compared with radiography (**Bhasin and Cheung, 2015)**.

MRI is also superior to clinical examination in the detection of inflammatory lesions and has a higher sensitivity than radiography and US for detecting bone erosion. Coronal and axial T1-weighted images are preferred during the assessment of structural changes in peripheral joints **(Colebatch et al., 2013)**.

CT is an effective tool to assess calcification, sclerosis, and structural changes such as erosion and bone proliferation. CT has been regarded as the standard examination when evaluating structural changes. However, the utility of conventional CT in inflammatory arthritis is limited owing to the inability to delineate inflammatory lesions.

Recently, dual-energy CT has become available in clinical settings and has been applied to various clinical entities. By measuring the attenuation at different x-ray energy levels, dual-energy CT enables the identification of material composition (**Mohammed et al., 2018).**

Synovial fluid examination is one of the most important tests especially for the initial diagnosis of arthritis. Cell counts and differentials, crystal evaluation under polarized

light microscopy, bacterial/acid-fast bacilli/fungal cultures and Lyme's DNA PCR shall be performed on the synovial fluid as appropriate **(Bhattacharjee et al., 2016).**

Degenerative arthritis is usually associated with cell counts of less than 2,000 cells/mm3 while in inflammatory arthritis, cell counts are usually more than 5,000 cells/mm3 and may be as high as 50,000 cells/mm3. More than 50,000 cells/mm3 cells and/or more than 90% neutrophils in synovial fluid analysis shall raise suspicion of septic arthritis, although this can also be seen in the setting of acute gout or pseudogout **(Tekeoğlu et al., 2016).**

A synovial biopsy is rarely performed but can be considered especially in cases of monoarthritis where other modalities have failed to provide a diagnosis **(Coiffier et al., 2018).**

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