Clinical manifestations and diagnosis of RA and psoriatic arthritis: distinct and complex disease entities Part 2

PATRICIA MINNOCK, RGN, FFN RCSI, BSC, MSC, PHDADVANCED NURSE PRACTITIONER (RHEUMATOLOGY), RHEUMATOLOGY REHABILITATION, OUR LADY'S HOSPICE AND CARE SERVICES, HAROLD'S CROSS, DUBLIN

This update on inflammatory arthritis (IA) reviews the clinical manifestations and diagnosis of the separate disease entities of rheumatoid arthritis (RA) and psoriatic arthritis (PsA), multifactorial diseases with common and distinct features. RA is regarded as the index disease of the IA[1] while PsA was originally seen as an atypical variant of RA before gaining its own unique identity.[2]

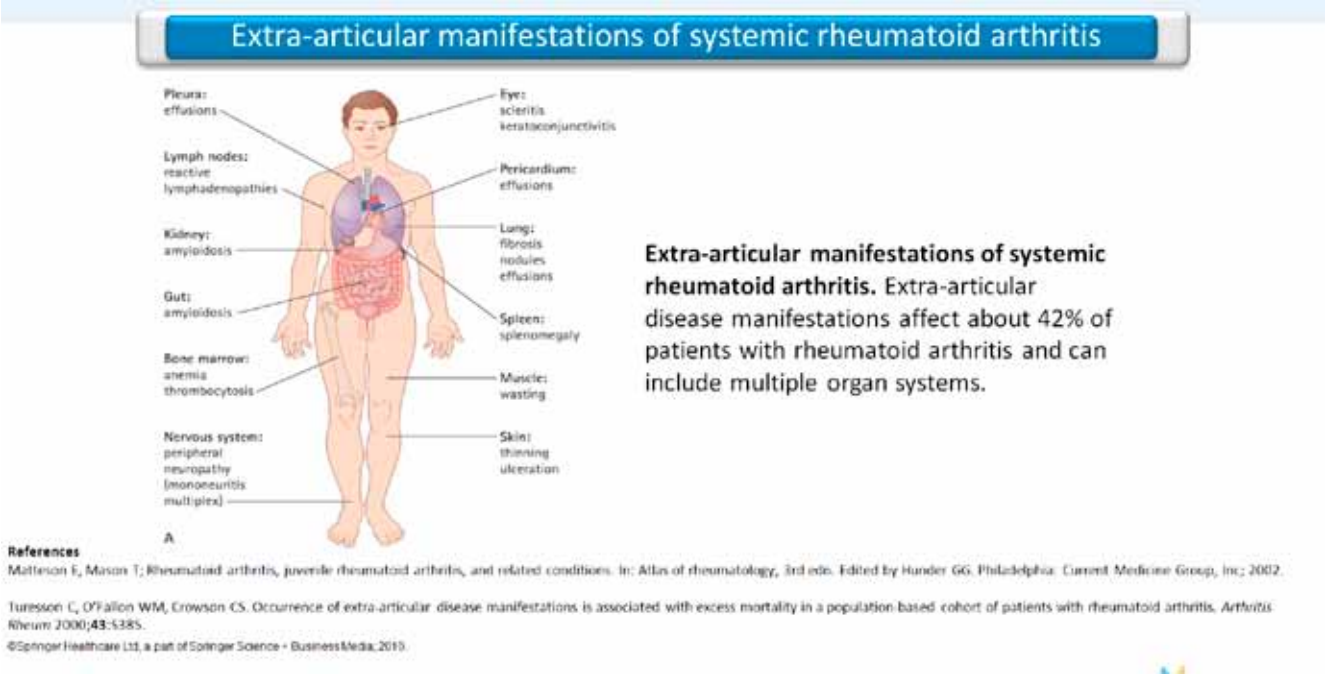
Clinical signs of RA

The key signs of early IA joint disease in RA include swelling, tenderness, warmth, and painful movement;[3] joint tenderness is the most sensitive physical sign.[4] The joints most often involved early in the disease are the small joints of the hands and feet, commonly in symmetrical distribution, with gradual progression to the larger joints of the upper and lower limbs. Tendon sheath synovitis, predominately affecting the flexor tendon sheath of the hands, is another common finding.[5] The degree of joint swelling evident may not correlate with the amount of active synovitis or pain expressed by the patient. Joint swelling may be peri-articular or intra-articular, the latter is associated with the presence of a joint effusion.[3,6]

Articular features of RA

The usual pattern of joint distribution or involvement includes the proximal interphalangeal joints (PIP) and the metacarpophalangeal joints (MCP) joints of the hands, wrists, elbows, shoulders, knees, ankles, subtalar, and metatarsophalangeal (MTP) joints of the feet. The cervical spine is the only characteristic axial location, with atlantoaxial subluxation a known complication,[7] and tempromandibular joints are frequently involved.[3] The radiographic hallmarks of chronic synovitis include periarticular osteoporosis, focal bone erosions at the joint margins and loss of joint space.[8] Inadequately treated articular inflammation can lead to progressive weakening or destruction of collateral structures, including the associated joint ligaments, tendons, cartilage,

Figure 1: Extra-articular manifestations of systemic rheumatoid arthritis



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and bone. In addition, the pain associated with ongoing synovitis frequently leads to decreased range of movement at the affected joints. Initially, it is inflammation, and subsequently the progressive joint destruction, evident on x-ray, that drives disability in RA.[9] It is estimated that 90% of patients with RA become disabled within 20 years of disease onset.[8]

While the recognised classic presentation of RA is a symmetric polyarthropathy of the small joint of the hands and feet it may also present with an extra-articular or non-articular presentation, such as a local bursitis, tenosynovitis, carpal tunnel syndrome, or a symmetric presentation with a diffuse polyarthralgia or polymyalgia.[3]

Extra-articular features of RA

Extra-articular features of RA affect over 40% of patients, and involve multiple organ systems (Figure 1). One of the most common extra-articular manifestations is the development of subcutaneous rheumatoid nodules. This feature, found in about 30% of patients with RA, is usually associated with the presence of a high titre rheumatoid factor (RF) antibody[3] Rheumatoid nodules are regarded as a cardinal diagnostic feature, they have been shown to be a marker for more severe disease but often appear late in the disease. Studies show a two to fourfold increase in mortality in patients with extra-articular manifestations, such as rheumatoid nodules.[10,11] Early presence of rheumatoid nodules is regarded as a predictor of more severe extra-articular manifestations. The many and varied extra-articular manifestations occur in a small but important subset of patients with RA 10 (Figure 1).

Table 1: Possible extra-articular and systemic manifestations of RA

General Fever Lymphadenopathy Anorexia/Weight loss Fatigue[12-17]	**Cardiac** Pericarditis Myocarditis Nodules on valves Ischaemic heart disease[18-23]
Dermatological Palmar erythema Subcutaneous nodules Vasculitis (leukocytoclastic) (nailfold infracts) Digital ulceration; Leg ulceration Raynaud's phenomenon[3,10-12,24-26]	**Neuromuscular** Entrapment neuropathy Peripheral neuropathy Mononeuritis multiplex Cervical myopathy Steroid mypopathy[8,12,27]
Ocular Episcleritis Scleritis Choroid and retinal nodules Sjogrens syndrome (keratoconjunctivitis sicca) (10-35%) Steroid related cataracts Drug induced retinopathies[3,28]	**Hematological/ Biochemistry** Normocytic hypochromic anemia Thrombocytosis Felty's syndrome Lymphomas Serology: Positive for rheumatoid factor and anti-CCP antibodies (30%)[11,29-34]
Pulmonary Pleuritis Pulmonary nodules Interstitial lung disease Bronchiolitis obliterans[3,28,35]	**Renal** Drug induced renal toxicity Renal vasculitis Glomerulonephritis Amyloidosis[18]
Hepatic Elevated liver enzymes Drug induced hepatotoxicity[12,36,37]	**Others** Hodgkin disease Non-Hodgkin lymphoma and Squamous cell skin cancer Osteoporosis[32,38]

Systemic extra-articular features of RA

Systemic features of RA also referred to as constitutional or extra-articular manifestations, such as fatigue, fever, anorexia and weight loss, may occur early in the course of the disease. In some cases these features persist, and can predominate the articular symptoms. Elderly patients in particular may present with polymyalgias (pain in several muscle groups), polyarthralgias (pain in several joints simultaneously), and profound fatigue.[3] Laboratory indicators of systemic involvement in RA include elevated acute-phase reactants; erythrocyte sedimentation count (ESR); C-reactive protein (CRP); anaemia; thrombocytopenia; elevation of certain liver function tests.[12] These multi-system features found in a small but important subset of patients,[10] presented in Figure 1 are summarised in Table 1. When present these can confound the correct diagnosis of this disease that has no single diagnostic pathognomonic feature. (Table 1)

Clinical signs of PsA

Clinical signs of PsA are similar to those of RA. These key signs of an early inflammatory joint disease include swelling, tenderness, warmth, and painful movement. It is recognised that the associated joint tenderness found in PsA is less than that found with RA.[39] Clinical signs peculiar to PsA include psoriasis, nail changes such as nail pitting – small indentations in the nail, and onycholysis (separation of the nail from the nail bed), tendonitis and dactylitis. The range of signs and symptoms can vary from patient to patient dependant on both the variety and severity of presentation.

Articular features of PsA

PsA is a heterogeneous condition; patients may present with any combination of diverse features at different stages of their disease. Five classic presentations of joint involvement are described[40] (Table 2).

Table 2: Five classic presentations of joint involvement in PsA

1	Inflammatory distal interphalangeal (DIP) joint involvement
2	Peripheral polyarthritis: often symmetrical as seen in RA
3	Spondyloarthropathy: spondylitis and sacro-ilitis (spinal and sacro-iliac joint inflammation)
4	Asymmetrical, oligoarthritis (involvement of four joints or less)
5	Arthritis mutilans: characterised by destruction and 'telescoping' of the fingers

Extra-articular features of PsA

Any of these aforementioned presentations may be accompanied by the most frequently described extra-articular manifestations of psoriatic arthritis listed in Table 3.[2] Unlike RA, PsA is not a multisystem disorder, the predominant extra-articular manifestations include, psoriasis, dactylitis, enthesitis and nail lesions.[2,41]

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Table 3: Extra articular and systemic features of PsA

1	Any form of psoriasis (or a personal or family history of psoriasis)
2	Dactylitis – sausage shaped digits (inflammation of a finger or toe)
3	Enthesitis: (inflammation of the entheses i.e the sites where tendons or ligaments insert into bone)
4	Tenosynovitis (tendon sheath inflammation)
5	Features common to the spondyloarthropathies: mucous membrane lesions, ocular lesions (conjunctivitis, iritis, uveitis), urethritis, colitis, aortic root dilatation, HLA-B27 association

It is noteworthy that fatigue is seldom listed as either an extra articular or systemic feature of PsA. More commonly it is referred to as a symptom or a comorbidity[42] of this disease entity. Its recognition as an important feature of PsA is recent.[43,44] It is acknowledged that fatigue is often underrated by treating physicians.[45]

Diagnosing RA and PsA

Distinguishing a chronic illness such as RA from other self-limiting conditions can be difficult. There are no early onset disease specific features; the characteristic hallmarks of the disease develop over time. A salient characteristic of RA is its chronic and enduring nature; therefore it is not unusual that the diagnosis of RA is delayed for months or even years. With the lack of a disease-specific feature or test the diagnosis of RA remains a composite of clinical and investigational features.[46]

The study of PsA has lagged behind other inflammatory arthropathies; it still lacks universal agreement on diagnostic criteria and therefore can pose a diagnostic challenge for physicians.[47, 48] Recognised experts in the field have been known to disagree when a diagnosis involves cases lacking characteristic clinical features[49]. A typical challenging diagnostic case might be a patient with a seronegative symmetrical polyarthritis and psoriasis. Similar to RA there is no clinical, radiological, or immunological feature that is pathognomonic of PsA.

Laboratory investigations: markers of inflammation

Laboratory measures or markers of a biological activity within the body such as inflammation, that indirectly measure a disease state, are known as surrogate measures. Inflammation is a biological activity; in RA and PsA this is prolonged, and disproportional.[8] Therefore, measures of inflammation, called acute-phase reactants, are used as surrogate markers of this inflammatory process. The most widely used biological markers to establish the presence of inflammation and disease activity in RA and PsA include laboratory blood measurement such as: – an elevated ESR, CRP, and fibrinogen; elevated liver enzymes, specifically serum aspartate aminotransferase (AST) and alkaline phosphatase; a fall in serum albumin level; anaemia of chronic disease, and hypoalbuminaemia.[8]

Clinical diagnosis

There is no one clinical, radiological, or immunological feature that is pathognomonic of RA or PsA, therefore, the diagnosis is largely clinical, made by recognising the pattern of signs and symptoms. Diagnosis of an early IA is dependent on good history taking skills and physical examination rather than on any special investigations.[3,17,50] The standard procedure for diagnosis includes documentation of history and pattern of

Table 5: Clinical and investigational diagnostic features of PsA

Standard procedures for diagnosis	presenting symptoms
History of pain/swelling, psoriasis	Asymmetrical joint pain, swelling, stiffness Variable clinical distribution – distal interphalyngeal (DIP), spinal, sacroiliac joints, asymmetrical oligoarthritis, symmetrical polyarthritis.[53] Fatigue[54,55] Established psoriasis (75%)
Physical examination	
Laboratory tests/ evidence: Elevated ESR, CRP[56]	
Rheumatoid factor negative, HLA-B27 association, Hyperuricaemia Hypercholesterolemia[47]	
Imaging evidence of damage/inflammation (radiography, MRI, ultrasonography)	Good response to anti-inflammatory drugs
Extra-articular disease and co-morbid conditions	
Physical signs	**Clinical features**
Evidence of synovitis-joint tenderness (positive squeeze test), joint swelling/effusions/warmth Asymmetrical joint involvement DIP joint involvement (40%)[57] Dactylitis (16-48%)[58] Enthesitis and Tenosynovitis Psoriasis[57] Nail changes (98%) Spondyloarthritis (>50%) Features common to the spondyloarthropathies: mucous membrane lesions, ocular lesions (conjunctivitis, iritis, uveitis), uretritis, colitis, aortic root dilatation[47,59]	Evidence of synovitis and psoriasis
	Inflammation (ESR/CRP)
	Rheumatoid factor negative HLA B27 positivity +/-
	X-ray evidence: including DIP joint involvement +/ – erosive changes, asymmetric distribution, involvement of entheseal sites with proliferative new bone formation e.g plantar fascia, tendo-Achilles insertion, osteolysis of phalanx, periostitis of metacarpals and metatarsals MRI/Ultrasound abnormalities Systemic features: fatigue, fever, weight loss.

Table 4: Clinical and investigational diagnostic features of rheumatoid arthritis4

Standard procedures for diagnosis	Presenting symptoms	
History of swelling/pain	Joint pain	
Physical examination	Joint swelling:	Small joints, symmetrical
Laboratory tests: elevated ESR, CRP	Joint stiffness	
Laboratory evidence of specific auto-antibodies (rheumatoid factor and anti-CCP)[34]	Difficulty making a fist, especially on waking	
Imaging evidence of damage/inflammation (radiography, MRI, ultrasonography)	Fatigue	
Extra-articular disease and co-morbid conditions	Good response to anti-inflammatory drugs	
Physical Signs	**Clinical Features**	
Evidence of synovitis	Evidence of synovitis	
Joint tenderness (positive squeeze test)	Inflammation (ESR/CRP)	
Joint swelling/effusions/warmth	Serological abnormalities	
Symmetrical involvement	Rheumatoid factor, anti CCP auto antibodies	
Nodules (occasionally)	X-ray evidence (joint space increased due to effusion, soft tissue swelling, periarticular osteoporosis, characteristic erosions) MRI/Ultrasound abnormalities	
	Systemic features: fatigue, fever, weight loss	

joint swelling and pain, physical examination, laboratory tests for measures of inflammation such as ESR and CRP; evidence of specific auto antibodies, such as RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies:[33,51] radiographic imaging of affected joints, and presence of extra-articular disease and co-morbid conditions.[4,17]

The composite clinical and investigational features of RA summarised in Table 4, provide a framework for diagnosis, and for monitoring and management of the course of this chronic rheumatic autoimmune disease. A history indicative of RA includes prolonged early morning stiffness that improves with activity, polyarthritis, polyarthralgia (pain in many joints), and fatigue. Examination findings consistent with a diagnosis of RA include symmetric polyarthritis and rheumatoid nodules. Radiographic changes include periarticular osteopenia, joint space loss, and erosions. Although most serology studies are neither sensitive nor specific for RA they help exclude mimics of RA and confirm the presence of inflammation.[4]

The standard procedure for diagnosing PsA includes documentation of history and pattern of articular and extra-articular features, physical examination, and laboratory testing to establish markers of inflammation,[47] and serological status of RF. The majority of cases will be RF negative on serology (90-95%).[47,52] The composite clinical and investigational features of PsA are summarised in Table 5. These provide a framework for diagnosis and for monitoring and management of the course of this distinct disease entity. Patients with PsA usually present with the typical hallmarks of an inflammatory arthritis; joint pain, swelling, erythema and varying degrees of joint stiffness, fatigue, impaired function, other defining features of this disease entity including enthesitis, dactylitis, psoriasis, nail changes, distal interphalangeal involvement, and iritis[2,39,40,48]

Subsequent review will provide an update management of these similar yet distinct disease entities.

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