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TOPIC REVIEW: Diagnostic work-up of early rheumatoid arthritis in the foot and ankle patient

by Megan L. Wilder, DPM[1]; Casey C. Ebert, DPM[2]; Craig E. Clifford, DPM[3]

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Rheumatoid arthritis is a chronic, progressive disease that affects the synovial membranes of joints, and leads to bone and cartilage destruction of both small and large joints in the upper and lower extremities. Foot and ankle specialists may be the first providers to recognize symptoms at their earliest stages. As first line providers a good understanding of the disease and its classification criteria is imperative. Diagnostic work-up requires patient history, physical examination, imaging modalities, and laboratory markers. A literature review and review of updated diagnostic criteria are presented.

Key words: Rheumatoid arthritis, diagnostic criteria, inflammatory synovitis, DMARD

Rheumatoid arthritis (RA) is a chronic, progressive disease that preferentially affects the synovial membranes of joints and eventually leads to bone and cartilage destruction if not diagnosed and treated early in the disease process. This arthropathy affects both small and large joints in the upper and lower extremities. It affects 0.5%-1% of the population worldwide, with women being affected 2-3 times more frequently than men [1]. It can occur at any age but the peak incidence is seen in the fourth to sixth decades of life [2].

Foot and ankle specialists encounter many cases of arthritis at numerous sites and from varying etiologies (Table 1). In the acute onset of RA, the feet are involved in 15.7% of cases [3]. People affected with mild to moderate rheumatoid arthritis with foot involvement have marked reduction in mobility and functional capacity [4].

Address correspondence to: Megan Wilder, DPM; Franciscan Foot and Ankle Institute, Federal Way, WA, Email: MeganWilder@fhshealth.org

[1] Podiatric Medicine and Surgery Resident (Postgraduate Year 2), Franciscan Foot and Ankle Institute, Federal Way, WA
[2] Podiatric Medicine and Surgery Resident (Postgraduate Year 1), Franciscan Foot and Ankle Institute, Federal Way, WA
[3] Attending Staff, Franciscan Orthopedic Associates, Franciscan Medical Group, Federal Way, WA

Furthermore, in recent studies it has been shown that orthopedic joint replacement procedures are associated with increased mortality in this patient population. Fortunately, the rates of joint surgery for patients 10 years after RA incidence are declining. This decline is attributed in large part to improved treatments initiated earlier in the disease process [5].

Articular manifestations of RA might be reversible in the early stages of the disease. Persistent and uncontrolled synovitis leads to bone and cartilage destruction and irreversible tendon and ligament injuries. The average time for the first visit of RA patients with a rheumatologist is 17 months, and 19 months usually elapses before the first administration of disease-modifying antirheumatic drugs (DMARDs) [6]. Foot and ankle specialists may be the first providers to recognize RA symptoms at their earliest stages. Prompt referral has been shown to optimize treatment for the prevention of deleterious effects. As first line providers a good understanding of the disease and its classification criteria is imperative.

Disease Presentation

At first presentation a detailed history and physical is paramount in evaluation of RA as the list of differentials is extensive (Table 1).

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Differential Diagnoses of Arthritis	
Class	Differential Diagnoses
Infections	Viral (dengue, HIV, parvovirus, cytomegalovirus, hepatitis) **Bacterial** (N. gonorrhea, S. aureus) Microbacterial, Fungal
Spondyloarthritis	**Reactive arthritis** (Chlamydia, Salmonella, Shigella, Yersinia) **Ankylosing Spondylitis**, **Psoriatic Arthritis**, Enteropathic Arthritis
Systemic Rheumatic Diseases	**Rheumatoid Arthritis**, Systemic Lupus Erythematous, Polymyositis/Dermatomyositis, Systemic Sclerosis, Sjogren's Syndrome, Behcet's disease, Rheumatic Polymyalgia, Systemic Vasculitides
Microcrystalline Arthritis	**Gout**, Calcium Pyrophosphate Deposition Disease
Endocrine Diseases	Hypothyroidism, Hyperthyroidism
Neoplastic Diseases	Metastatic Neoplastic Disease, Lymphoma, Paraneoplastic Syndromes, and others
Others	**Osteoarthritis, Neuropathic,** Haemochromatosis, Amyloidosis, **Sarcoidosis**, Serum Sickness

Table 1 Differential diagnoses of arthritis. Bolded items demonstrate those joint disorders that are most commonly found in the foot and ankle. (Spraul G, Koenning G: A descriptive study of foot problems in children with juvenile rheumatoid arthritis. Arthritis Care Res 7(3):144-150, 1994.)

Patient History

Disease progression and symptomatology is important in differentiating RA from other conditions. Patients will often present with insidious onset of joint pain and swelling that cannot be attributed to other etiologies, such as trauma. Duration of symptoms greater than six weeks is more suggestive of RA rather than other more acute etiologies, such as infection. Increased symptom duration correlates to increased probability of RA diagnosis. It is essential to determine whether the complaints are generalized or regional, symmetric or asymmetric, and peripheral or central in nature. Most commonly RA will present as symmetric pain that progresses from peripheral joints to more centralized locations, although early findings may not display these expectations. Complaints of morning stiffness are useful in RA diagnosis, morning stiffness of greater than one hour being most predictable of RA diagnosis [7]. It is also common for symptoms to undergo cycles of exacerbation and remission [8].

A thorough patient history should identify potential risk factors of RA, both intrinsic and extrinsic. Revealing family history is crucial in the risk of RA as its genetic heritability is roughly 60% [9]. Additionally, evidence has revealed that a familial history of a multitude of other autoimmune diseases increases the risk of developing RA due to the genetic similarities within these conditions [10]. In both males and females, Stolt and colleagues [11] identified an increased risk of developing seropositive RA with long duration and moderate intensity of smoking, owing to overall increased cumulative dosing effect. This increased risk remained 10-19 years following smoking cessation, however, smoking cessation is encouraged. While alone it has not been associated with increased risk of developing RA, obesity has been linked to poorer prognosis and response to treatment modalities, therefore, it is suggested that patient's attempt weight loss to optimize treatment success [12].

Physical examination

A thorough lower extremity dermatological, neurological, vascular, and musculoskeletal examination is recommended as RA can affect various systems. Symptomatic joints should be evaluated for tenderness upon palpation, synovial thickening, effusion, erythema, decreased ROM/ankylosis, joint subluxation/dislocation, ligamentous and capsular laxity [13]. Extra-articular disease manifestations include rheumatoid nodules, synovitis, bursitis, tendinitis, fasciitis, neuritis, and vasculitis [14].

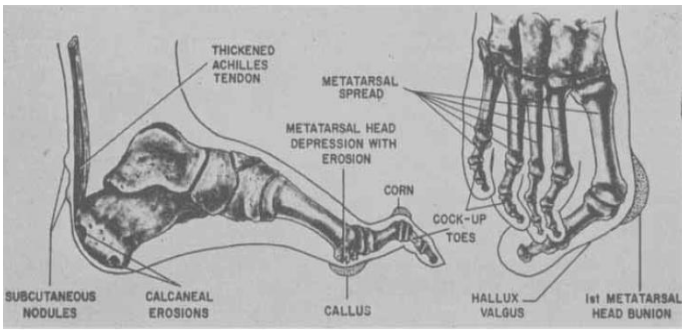

Figure 1 Common foot features of RA. (Calabro JJ. A critical evaluation of the diagnostic features of the feet in rheumatoid arthritis. Arthritis and Rheumatism, 5(1):19-29, 1962.)

Common foot features of RA are demonstrated in Figure 1 as described by Calabro in 1962 [15]. It is vital to recognize that the classic presentation of joint erosions and extra-articular disease manifestations such as rheumatoid nodules are most commonly seen in long standing disease and often are absent at earlier stages of disease.

Diagnostic Work-Up

Imaging modalities

Radiographs continue to be the mainstay of imaging for foot and ankle specialists. Classic radiographic signs of RA include bilateral involvement of the metatarsophalangeal joint (MTPJ), uniform joint space narrowing, medial erosions to forefoot joints (lateral of 5th MTPJ), fibular deviation of digits with subluxation and late stage dislocation (Figure 2).

In addition, osteopenia is a characteristic finding of RA if found in conjunction with erosions and joint space narrowing. Cyst or pseudocyst formations may occur as demonstrated by centralized geographic, subchondral lucencies. Ankylosis can also be demonstrated, most commonly to the tarsus. Erosions have also been described to the posterosuperior and inferior aspect of the calcaneus [8]. In later stages of disease classic radiographic signs will be displayed and will aid in differential diagnosis (Table 2).

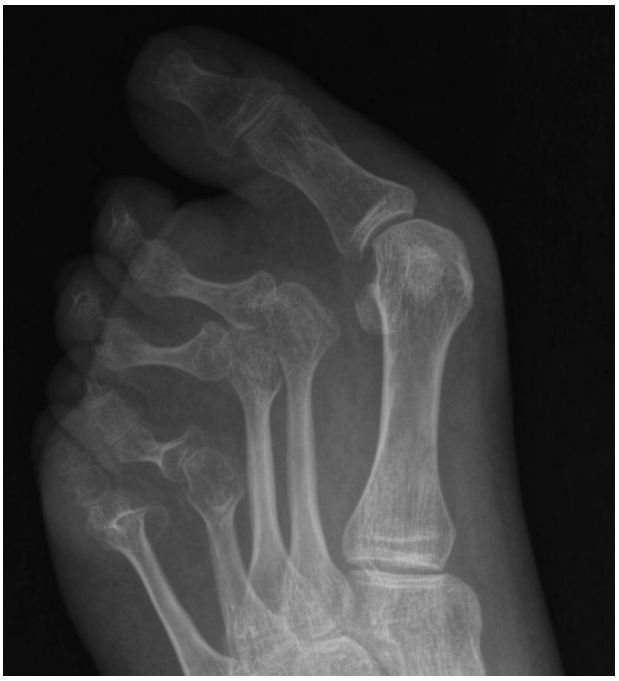

Figure 2 Classic radiographic features of rheumatoid arthritis of the forefoot.

Radiographs will no doubt drive conservative and surgical treatment options that will be managed by the foot and ankle specialist. However, MRI and ultrasound have been found to have increased sensitivity in identifying RA within the earlier stages of the disease prior to diagnosis or initiation of antirheumatic pharmacologic agents [16, 17]. In fact, Ostendorf et al found forefoot MRI was able to detect synovitis and bone edema in patients with early RA who had normal MRI findings of the hands [18].

Laboratory markers

In addition to clinical evaluation, the laboratory markers are key to diagnosis. Rheumatoid factor, cyclic citrullinated peptide antibodies, and inflammatory markers aid in diagnosing RA. Rheumatoid factor (RF) is found in approximately 70% of RA patients and is correlated with a poorer disease prognosis [19]. In the early stages of RA, 30-50% of patients test have a negative RF [20]. In addition, patients without RA might have a false positive reading as its prevalence increases with age and other medical conditions [21]. More recently, cyclic citrullinated peptide (CCP) antibodies have been shown to be the best diagnostic tool for RA.

Arthritis	Target Joints	Bone Production	Erosion	Joint Space	Soft Tissue Swelling	Soft tissue calcification /ossification	Positional Deformity	Bilateral
Osteoarthritis	1st MTPJ	Osteophyte; subchondral sclerosis	None-subchondral cyst may mimic	Nonuniform narrowing	None	Loose body	HAV	No (if post traumatic)
Rheumatoid	Lesser MTPJ's and hallux IPJ	None	Medial aspects (pannus)	Uniform narrowing	Not significant	None	Lateral Deviation/ Subluxation	Yes
Psoriatic	Lesser MTPJs and IPJs; varies	Periostitis, whiskering & ivory phalanx	Medial/ lateral/ central	Widening (relative)	Diffuse: Sausage Digit	None	Nothing specific	No
Gouty	1st MTPJ	Overhanging edge (Martel's Sign)	Medial and/or lateral margins	Normal	Lumpy-bumpy	Small, punctate calcifications	No	No
Neuropathic	Tarsal-metatarsal joints	Diffuse Sclerosis	Subchondral resorption	Narrowing or relative widening	Diffuse	Fragmenting of bone	Subluxation/dislocation	No

Table 2 Differential Diagnosis of joint disorders affecting the foot. (Christman RA. Foot and ankle radiology. 1st ed. London: Churchill Livingstone; 2003.)

1987 ACR Classification Criteria RA is defined by the presence of 4 or more criteria
Morning stiffness
Arthritis of 3 joint areas
Arthritis of the hands
Symmetric arthritis
Rheumatoid nodules
Serum Rheumatoid Factor
Radiographic Changes

Table 3 1987 ACR Classification Criteria. RA is defined by the presence of 4 or more criteria that must be present for greater than 6 weeks. (Arnett et al. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis and Rheumatism. 31(3) 315-323)

The sensitivity of CCP is similar to RF with its specificity being superior, at 70% and 95% respectively. CCP is detected very early in the course of RA therefore making it particularly useful in patients with early RA and negative RF serology [22]. General inflammatory markers are measured by erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP). Both levels being elevated in RA and may be linked to increased radiographic damage [23].

2010 ACR/EULAR Criteria		
	Criteria	Score
Joint Involvement	1 Large Joint	0
	2-10 Large Joints	1
	1-3 Small Joints	3
	>10 Joints (at least 1 small joint)	4
Serology	Negative RF and anti-CCP	0
	Low-Positive RF or anti-CCP	2
	High-Positive RF or anti-CCP	3
Acute-Phase Reactants	Normal CRP and ESR	0
	Abnormal CRP or ESR	1
Duration of Symptoms	<6 weeks	0
	≥6 weeks	1
***Total score of greater than 6 is classified as RA**		

Table 4 2010 ACR/EULAR Criteria. Applies to patients who have objective signs of unexplained synovitis in at least 1 joint. Sum of greater than 6 out of the total 10 suggests RA diagnosis. (Aletaha D et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010; 62:2569)

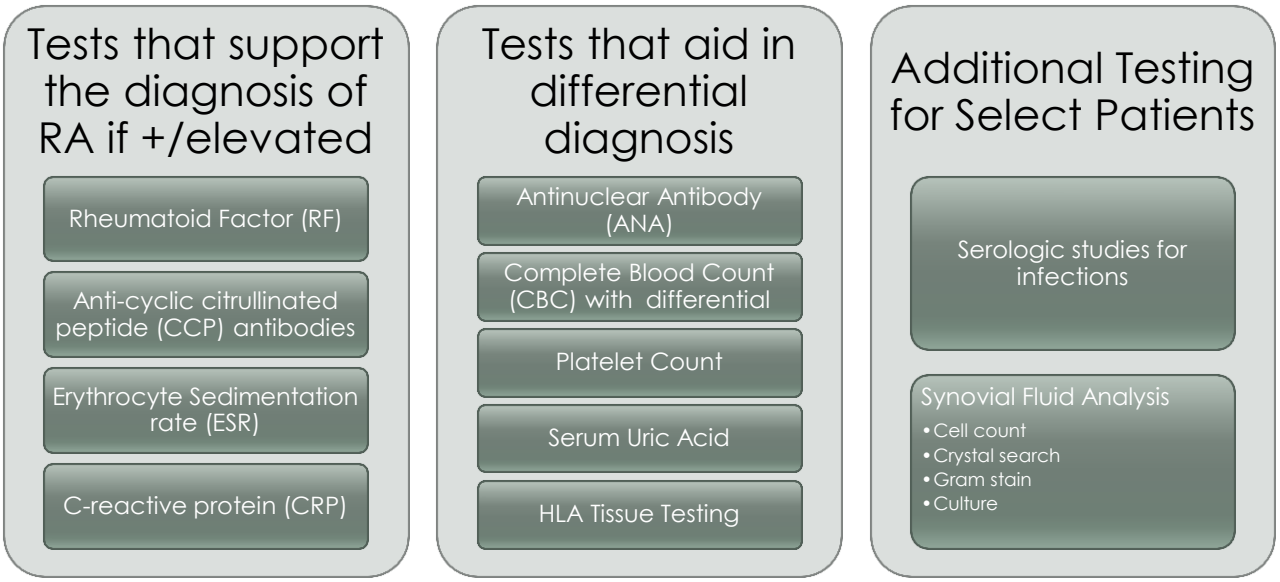

Figure 3 Laboratory work up for rheumatoid arthritis

Other laboratory values can aid in the differential diagnosis: CBC, BMP, ANA, and uric acid. A negative antinuclear antibody (ANA) test helps exclude SLE and other systemic rheumatic diseases (Figure 3). ANA can be positive in up to 30% of healthy people [24]. The CBC is often abnormal in RA, most commonly demonstrated by anemia and thrombocytosis consistent with chronic inflammation [25, 26]. Hyperuricemia may be indicative of gout with polyarticular gout infrequently mistaken for RA [27]. In patients with presentation less than 6 weeks it may be important to exclude an infectious etiology with serologic infectious disease workup and arthrocentesis [28].

Summary of ACR/EULAR Criteria

The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) task force developed an update to the 1987 ACR criteria (Table 3 and 4). The 1987 criteria has been criticized for its lack of sensitivity in detecting RA at early stages. The older criterion was devised to distinguish patients with established RA from patients with other rheumatic diseases. In contrast, the 2010 criteria focuses on screening patients with early onset of inflammatory synovitis [29]. This earlier detection will allow for risk stratification for treatment intervention with DMARDs. Early diagnosis of RA has become a priority for physicians in delaying later stages of disease. The early detection and treatment of RA may prevent disease progression and severe disease consequences. Early implementation of DMARDS demonstrates significant benefits in decreasing morbidity and mortality [30]. Recent advances in research have shown clinical and radiologic remission in patients that acquire RA diagnosis within 3 months of symptom onset and subsequent treatment of DMARD therapies. When treatment with DMARDs was began within the first 12 months the radiological progression was reduced at the 5-year follow up [31].

Conclusion

Although this diagnostic criterion was not designed as a referral tool for primary care physicians, awareness and education of PCPs and specialists needs to be raised. To assist in the referral process to rheumatologist specific information should be included. This has been shown to aid in effective triaging and thus decreased time to treatment implementation. The suggested information includes: number, pattern, and location of joint involvement; relevant imaging; and laboratory values [32]. With early identification and referral rheumatologists can effectively treat RA with DMARDs at the beginning stages of the disease. The foot and ankle specialists' role in early detection of RA will aid in improved clinical, radiographic, disability, and cost outcomes.

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