Rheumatoid Nodules

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KEYWORDS

• Rheumatoid nodules • Accelerated nodulosis • Palisading macrophages • Benign nodulosis • Methotrexate • Rheumatoid arthritis • Pulmonary rheumatoid nodules

KEY POINTS

- Rheumatoid nodules are the common extra-articular manifestation of rheumatoid arthritis (RA).
- Systemic RA medications are not proven therapy for rheumatoid nodules; paradoxically, methotrexate and possibly other systemic therapies can induce or exacerbate nodule formation.
- Regardless of location, rheumatoid nodules have a consistent histologic appearance with a central area of fibrinoid necrosis, surrounded by palisading macrophages that are $CD68^{+}$ and enclosed by a granulation layer.
- Subcutaneous nodules with typical clinical characteristics require neither biopsy for diagnosis nor specific treatment unless they are causing pain, interference in mechanical function, nerve compression, or other local phenomena.
- Pulmonary rheumatoid nodules require a more aggressive diagnostic evaluation to exclude malignancy, infection, or other causes of lung nodules.

INTRODUCTION

Rheumatoid nodules are the most common extra-articular manifestation of RA. RA is a chronic inflammatory arthritis that affects nearly 1.5 million adults in the United States[1] and 2 million in Europe.[2] It was traditionally a debilitating disease, but with advances in treatment, RA is now a manageable chronic disease state. The predominant feature of RA is synovial inflammation manifested as swelling and tenderness of small, medium, and large joints in a symmetric pattern, with a predilection for the smaller joints of the hands and feet.

RA is classified by the combined American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria (**Table 1**), which encompass joint swelling, elevated levels of serum rheumatoid factors (RFs) and anti–cyclic citrullinated peptide antibodies (anti-CCP), inflammatory markers, and symptom duration.[3] Prior classification criteria have included the presence of symmetric arthritis, rheumatoid nodules, and typical radiographic changes.

Patients with RA produce an array of auto-antibodies, including RF CCP. Although elevation of RF and CCP levels is not necessary for diagnosis, it helps to differentiate RA from other inflammatory arthropathies. In a 700-patient retrospective study, the sensitivity and specificity for anti-CCP was 74.0% and 94%, respectively, whereas RF had a sensitivity of 69.7% and specificity of 81%. Differences in specificity were largely due to the increased prevalence of RF in primary Sjögren syndrome, chronic viral hepatitis, and systemic lupus erythematosus (SLE).[4] Detection of antibody with anti-CCP2 antibody, the commonly used assay, resulted in improved sensitivity (64%–89%) and specificity (88%–99%). RF sensitivity ranged from 59% to 79% and specificity from 80% to 84% in the same groups.[5] Patients who meet classification criteria for RA as outlined in **Table 1**, but present without

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Table 1
ACR/EULAR classification criteria for rheumatoid arthritis

Criteria	Points
A. Joint Involvement	
1 Large joint	0
2–10 Large joints	1
1–3 Small joints	2
4–10 Small joints	3
>10 Joints (at least 1 small joint)	5
B. Serology	
Neg RF and neg CCP	0
Low pos RF or low pos CCP	2
High pos RF or high pos CCP	3
C. Acute phase reactant	
Normal CRP and ESR	0
Abnormal CRP or ESR	1
D. Duration of symptoms	
<6 wk	0
≥6 wk	1

Score of ≥6 is diagnostic criteria for rheumatoid arthritis.

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; neg, negative; pos, positive; RF, rheumatoid factor.

Adapted from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):2574; with permission.

RF or anti-CCP antibodies, and who do not fulfill criteria for other diseases are considered to have seronegative RA.

RA is a systemic disease with an array of extra-articular manifestations (**Box 1**) Extra-articular manifestation of the skin are common and usually occur in RF-positive patients and early in disease course.[6] The most frequent cutaneous manifestation is rheumatoid nodules. Other rare skin lesions include cutaneous ulcers from medium vasculitis, nail fold infarcts or palpable purpura from small vessel vasculitis, pyoderma gangrenosum, and granulomatous dermatitis.[7] The remainder of this article further defines the pathogenesis, histology, and treatment of rheumatoid nodules.

Box 1
Extra-articular manifestation of rheumatoid arthritis

Skin manifestations
- Rheumatoid nodules
- Rheumatoid small-vessel vasculitis
- Pyoderma gangrenosum

Ocular manifestations
- Keratoconjunctivitis sicca
- Episcleritis
- Scleritis
- Peripheral ulcerative keratitis

Pulmonary manifestations
- Interstitial lung disease
- Parenchymal pulmonary nodules
- Pulmonary effusion

Cardiac manifestations
- Pericarditis
- Myocarditis
- Increased cardiovascular disease

Renal manifestations
- Glomerulonephritis due to amyloid

Neurologic manifestations
- Peripheral neuropathy
- Mononeuritis multiplex
- Central nervous system vasculitis

Hematologic manifestations
- Felty syndrome
- Pancytopenia (in any combination)

Adapted from Cojocaru M, Cojocaru IM, Silosi I, et al. Extra-articular manifestations in rheumatoid arthritis. Maedica (Buchar) 2010; 5(4):286–91.

RHEUMATOID NODULES

Rheumatoid nodules are one of the most common extra-articular manifestations noted in RA. These nodules are usually encountered on extensor surfaces and areas of pressure or repetitive trauma, most notably the olecranon and dorsal aspect of the hand (**Fig. 1**). However, they can develop on any tendon/ligament-like structures such as the Achilles tendon and vocal cords. In bedbound patients, these nodules can also be seen on the occiput and ischium. The prevalence is estimated at 10%, although the 10-year occurrence rate in any single individual may be as high as 30% over 10 years.[8] The most common noncutaneous location for rheumatoid nodules is the lung (see section Systemic Location of Rheumatoid Nodules). Rarely rheumatoid nodules can be associated with other diseases such as rheumatic fever, and there are case reports of nodules in

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