Chapter 16
Nodules in Rheumatoid Arthritis

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Definition

The most common nodules in rheumatoid arthritis (RA) are rheumatoid nodules (RN). Approximately 1 in 4 patients with long-standing rheumatoid arthritis will have classic rheumatoid nodules over the extensor surfaces of joints such as the elbow, Achilles tendon, fingers, and pressure points [1], (Fig. 16.1). RN are part of the RA classification criterion and associated with seropositive disease [2]. They tend to be large, starting at a few millimeters but grow to several centimeters. They are often non-tender, firm, flesh-colored subcutaneous masses that may or may not be bound down to the underlying periosteum. In classic cases, a biopsy is not necessary for diagnosis. In atypical cases, however, a biopsy can be helpful. Rheumatoid nodules can occur in other tissues such as the eye, larynx, lung, and nervous system. Methotrexate therapy is associated with rheumatoid nodulosis with rapid onset of multiple smaller lesions over the hands. Less commonly, smaller papules and plaques, occasionally linear, with smooth, umbilicated, or crusted surfaces occur symmetrically over the joints or extensor surfaces in patients with RA or systemic lupus erythematosus (SLE) and on biopsy show palisaded neutrophilic and granulomatous dermatitis (PNGD) [3] (Fig. 16.2).

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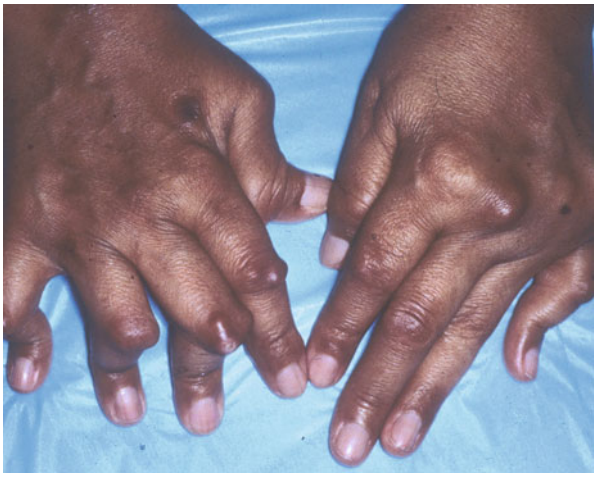

Fig. 16.1 Multiple rheumatoid nodules in a patient with advanced rheumatoid arthritis and destructive arthropathy of the hands

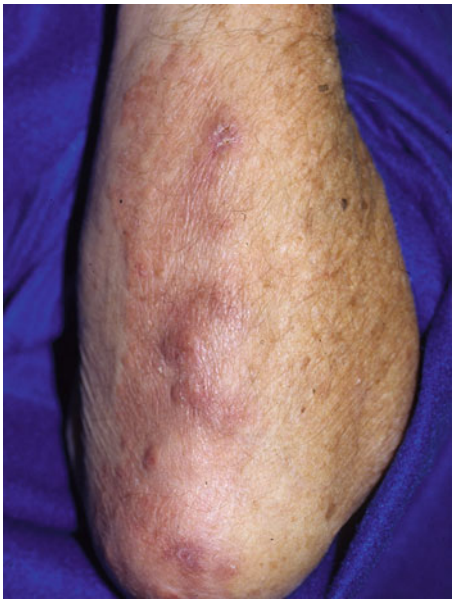

Fig. 16.2 Nodules and plaques of palisaded neutrophilic and granulomatous dermatitis in a somewhat linear configuration on the extensor forearm of a patient with rheumatoid arthritis

Differential Diagnosis

The differential diagnosis for rheumatoid nodules (RN) is broad [4, 5]. Acute rheumatic fever (ARF) is accompanied by subcutaneous nodules in 1 % of cases. ARF is associated with group A streptococcal pharyngitis. The location of the nodules over the olecranon and other joints is similar to rheumatoid nodules. Distinguishing features include that ARF nodules occur early in disease (first 1–3 weeks), tend to be

smaller in size, and resolve spontaneously. There are individuals who develop rheumatoid nodules in the absence of rheumatoid arthritis (RA); these are referred to as "benign nodules." Typically these occur in children on the scalp or posterior neck. Subcutaneous granuloma annulare is another entity that tends to occur in children or young adults and can present as subcutaneous nodules over joints. These have been referred as "pseudorheumatoid nodules." Calcinosis cutis forms whitish, rock hard subcutaneous nodules over joints and is more common in scleroderma and dermatomyositis than RA. The Gottron's papules of dermatomyositis occur over joints, but are violaceous and smaller than rheumatoid nodules. Tophi can mimic RN, but obviously occur in the setting of gout. Characteristic X-ray changes can be helpful to sort out the latter two entities. Multicentric reticulohistiocytosis occurs in middle-aged women, affects the skin and mucous membranes, and is associated with an erosive polyarthritis and increased risk of internal malignancy. There are multiple yellow-red papules that have a characteristic histology. A variety of xanthomas can occur as nodules over joints. They have a yellow-orange hue and are associated with abnormal lipids. Rheumatoid papules are distinctive because of their reddish-brown color, scale, and occurrence on the lower extremities. Approximately 10 % of SLE patients will have classic rheumatoid nodules that are clinically and histologically indistinguishable from nodules in an RA patient. Panniculitis typically affects larger areas of fat, is more amorphous than discrete nodules, and does not occur over joints. Similarly, medium vessel vasculitis such as polyarteritis nodosa typically occurs away from joints and may ulcerate, which RN do not. Infections tend to be more rapidly growing, tender, and may be associated with overlying erythema and suppurative ulceration. Urticaria is transient, and urticarial vasculitis is entirely macular without papules or nodules, so are easily distinguishable from RN.

Histologic Features

Rheumatoid nodules when well developed display a palisaded granulomatous pattern involving the deep dermis and/or subcutis, with a nodular infiltrate of histiocytes surrounding a homogeneous and eosinophilic zone containing altered collagen and typically fibrin centrally [6–8] (Fig. 16.3). Vasculitis may be evident in early lesions and fibrosis in late lesions. Deep granuloma annulare may present a similar pattern, but generally contains mucin in the centers of palisaded foci.

Palisaded neutrophilic and granulomatous dermatitis may present with a spectrum of histologic findings, depending on the age of the lesion [3, 6, 8]. Very early lesions display a pattern similar to urticaria, with a sparse infiltrate of neutrophils, eosinophils, and lymphocytes. Other lesions may contain leukocytoclastic vasculitic foci early in their evolution, with typical perivascular neutrophilic infiltrates with leukocytoclasis, and fibrin deposition within and surrounding vascular walls. Often, there is involvement of the deep dermis, and altered collagen may be present. Well-developed lesions also feature a palisaded to interstitial granulomatous pattern, but contain neutrophils and neutrophilic nuclear dust centrally as well as histiocytes at the periphery of such foci (Fig. 16.4). The infiltrate may form bands

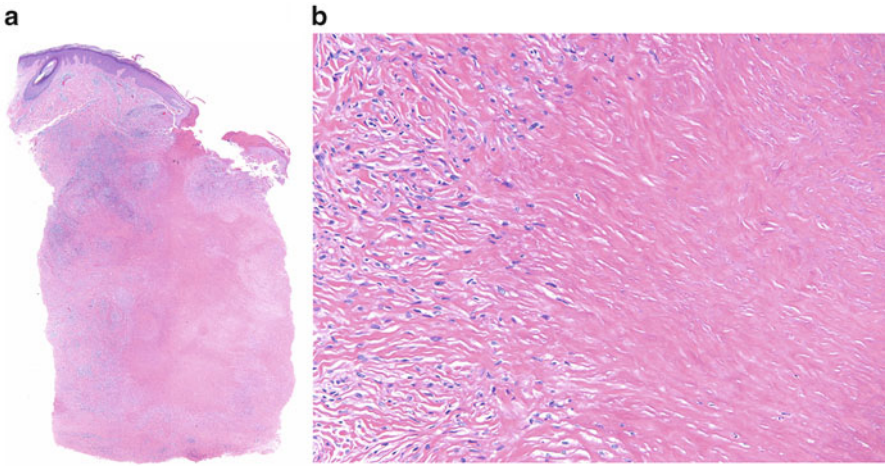

Fig. 16.3 Rheumatoid nodule: (**a**) large palisaded granulomata with an eosinophilic central zone at low magnification (40x); (**b**) palisaded histiocytes, and eosinophilic center, which contains fibrin and fibrosis typically, at higher magnification (200x)

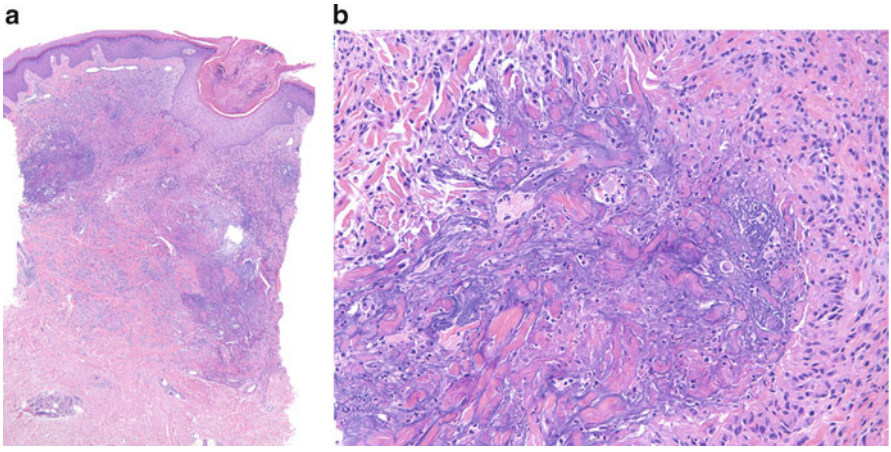

Fig. 16.4 Palisaded neutrophilic and granulomatous dermatitis: (**a**) a palisaded suppurative and granulomatous pattern at low magnification (40x); (**b**) neutrophils and altered basophilic and eosinophilic collagen at the centers of palisaded foci, with a rim of histiocytes at higher magnification (200x)

within the dermis and be "bottom-heavy," centered on the lower dermis. There is also altered basophilic degenerated collagenous material associated with the granulomas. Eosinophils may be present. Some histiocytes may have enlarged nuclei and mitotic figures may be present. The pattern is analogous to a so-called Churg-Strauss granuloma. In later lesions, fibrosis may supervene, with a palisaded infiltrate of histiocytes remaining, but a sparse neutrophilic component.

Classic Rheumatoid Nodules
No Biopsy Needed
Atypical Rheumatoid Nodules
Consider Biopsy
Atypical Location
Consider Biopsy if accessible
Papules vs Nodules
Biopsy to rule out PNGD or Gottron's Papules
Nodules in a Child without Arthritis
Consider Biopsy to rule out subcutaneous GA
Hard, Large Nodules
Consider X-Ray to rule out gout or calcinosis cutis
Yellow-Orange Color
Biopsy to rule out xanthoma
Open or Ulcerating
Culture/biopsy to rule out infection

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