

Rheumatoid Nodule

Vicente García-Patos, MD, PhD

Rheumatoid nodules are the most common extra-articular manifestation of rheumatoid arthritis. Dermatologist may be concerned with the diagnosis and management of rheumatoid nodules, although most patients will probably be under the care of a rheumatologist. This article focuses in clinical, pathogenic, diagnostic, and therapeutic aspects of rheumatoid nodules. Classic rheumatoid nodules commonly occur in genetically predisposed patients with severe, seropositive arthritis. However, they may appear in other clinical settings. Accelerated rheumatoid nodulosis, especially involving the hands, has been reported in patients receiving methotrexate, antitumor necrosis factor alpha biologic drugs or leflunomide therapy for rheumatoid arthritis. Rheumatoid nodulosis is characterized by multiple rheumatoid nodules, recurrent joint symptoms with minimal clinical or radiologic involvement, and a benign clinical course. Pseudorheumatoid nodules have been reported in healthy children. Although histologically almost indistinguishable from true rheumatoid nodules, some consider these lesions to be a form of deep granuloma annulare. *Semin Cutan Med Surg* 26:100-107 © 2007 Elsevier Inc. All rights reserved.

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Subcutaneous nodules are commonly found in patients with rheumatoid arthritis (RA) and occur as classic rheumatoid nodules (RNs), accelerated rheumatoid nodulosis, or rheumatoid nodulosis. When RNs coexist with chronic synovitis, the symptoms are pathognomonic for RA.¹⁻³

Classic Rheumatoid Nodules

Classic RNs occur in approximately 20% to 25% of patients with seropositive RA and are the most common extra-articular manifestation of RA.^{4,5} A much greater incidence (75%) is observed in those with RA-associated Felty syndrome.¹ RNs are relatively frequent in the white population and affect males more than females. Approximately 90% of patients with RA and subcutaneous nodules test positive for rheumatoid factor (RF), and approximately 40% of all RF-seropositive patients with RA have subcutaneous nodules, whereas only 6% involvement is seen in seronegative cases.⁶ In fact, the frequency of nodules correlates directly with FR titer, with more aggressive forms of the disease (joint erosions and

rheumatoid vasculitis) and less so with the actual severity of symptoms. It has been suggested that the presence of RNs often requires more aggressive treatment of the underlying RA to prevent sequelae, although nodular disease activity does not relate to RA disease progression or severity in all cases. Subcutaneous nodules also have been reported in 5% to 10% of children with juvenile RA.

Genetic Susceptibility

Genetics seems to play a role in the appearance of RNs. The HLA-DR4 haplotype (including the heterogeneous group of DRB1 alleles) is predictive of the risk of subcutaneous nodules in RA.⁷ RA patients with heterozygosity for HLADRB1 alleles, specifically *0401 with B1*0404/8 or *0101, are at high risk for nodular disease and even severe RA prognosis.⁸ Homozygosity for HLA-DRB1*0401 makes RA patients susceptible to major organ involvement.⁹ Those with HLA-DRw2 genetics, however, were observed to have fewer nodules and fewer RF titers.¹⁰

Clinical Manifestations

RNs generally develop as a later manifestation of active arthritic disease, although approximately 11% of RA patients have RNs at the time of the initial presentation of their rheumatologic symptoms or even can form before joint disease.

Department of Dermatology, Hospital Universitario Vall d'Hebron, Professor of Dermatology, Universidad Autónoma de Barcelona, Barcelona, Spain.

Address reprint requests to Vicente García-Patos, MD, PhD, Hospital Universitario Vall d'Hebron, Escuela de Enfermería, 2ª planta, Pº Vall d'Hebron 119-129, 08035 Barcelona, Spain. E-mail: vicente.briones@terra.es



Figure 1 Rheumatoid nodules on the elbow.

Nodules are skin colored, can be solitary or multiple, and their size ranges from 2 millimeters to more than 5 cm in diameter. Rarely, RNs can be linear.^{1,11,12} They are firm, nontender, and movable within the subcutaneous tissue; however, they could also be attached to underlying structures such as the periosteum, tendons, or bursae. Those found on the palms or soles may feel uncomfortable, although most are painless.¹

Most RNs are found on areas prone to mild repetitive traumas, such as bony prominences, extensor surfaces, or adjacent to joints. RNs have a predilection for the elbows (Fig. 1) and fingers. They are most frequently found on extensor surfaces of the proximal forearm, metacarpophalangeal, and proximal interphalangeal joints (Fig. 2), occiput, back, and heel. Other involved areas include sacral prominences, scalp, ischial tuberosities, joints in the foot, the Achilles tendons, pinnae of the ears, sacrum, penis, and vulva.^{13,14} Bedridden or wheelchair patients may develop lesions on the buttocks and lumbosacral area, whereas patients who wear eyeglasses can present with nodules on the bridge of the nose.¹

Occasionally, atypical internal sites for RNs include lung, which can be colonized with aspergillus,¹⁵ pleura,¹⁶ pericardium, peritoneum, tendons, synovium, bones,¹⁷ sclera,



Figure 2 Severely affected joints of a patient with rheumatoid arthritis with overlying rheumatoid nodules.

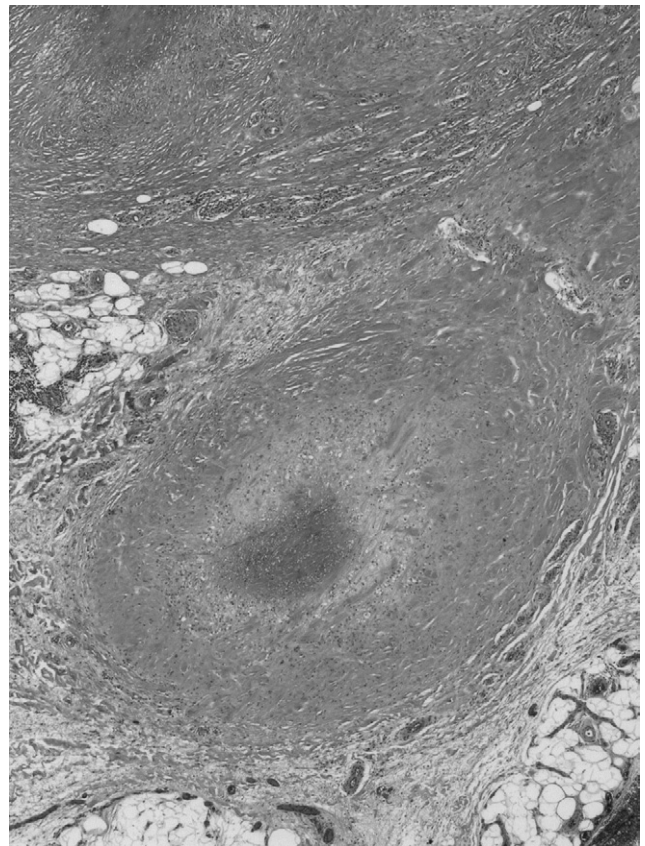


Figure 3 Rheumatoid nodule: histologic appearance. (Hematoxylin-eosin stain; original magnification $\times 25$).

heart,¹⁸ pharynx,¹⁹ vocal cords,²⁰ trachea,²¹ choroid plexus,²² liver,²³ pancreas,²⁴ buccal mucosa,²⁵ nose, ears, kidney,²⁶ breast,²⁷ nervous system, abdominal wall, and muscles.¹ It has been suggested that the development of nodules in the internal organs occur simultaneous to the appearance of cutaneous RNs.²⁸

Histopathology

The histopathologic progression of RNs occurs in 3 stages: an acute inflammatory stage, a granulomatous stage, and finally a necrotic stage. Sited primarily in the subcutaneous tissue, they may involve the deep and even superficial dermis (Fig. 3). Macroscopically, they consist of fibrous white masses in which there are creamy yellow irregular areas of necrobiosis. Old lesions may have clefts and cystic spaces in these regions.

The features of the first stage are similar to that of an evolving scar. The lesion consists in an area resembling granulation tissue with clusters of newly proliferated capillaries surrounded by undifferentiated mononuclear cells and fibroblasts.²⁹

The second stage is heralded by the development of necrosis and palisading of elongated mononuclear cells, mostly HLA-DR⁺ macrophages, at the periphery of the initial focus of granulation tissue.

The third stage begins, as the granulation-like tissue develops into a large central focus of necrotic collagen and reticu-

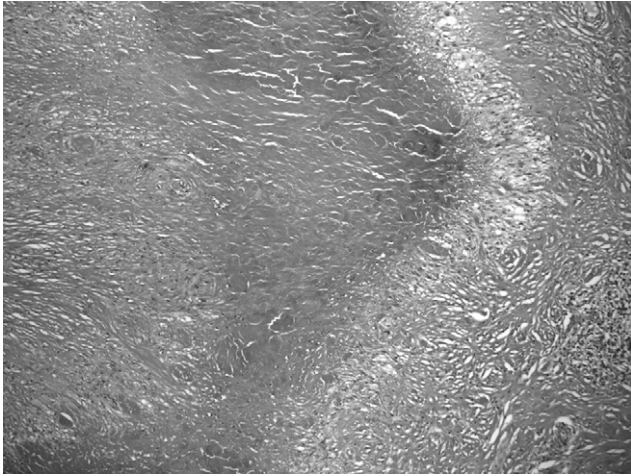


Figure 4 Rheumatoid nodules have 3 definite histologic zones: central eosinophilic area, palisade of macrophages, and an outer layer of granulation tissue. (Hematoxylin-eosin stain; original magnification $\times 50$).

lin fibers, admixed with fibrinoid material, fat globules, fragments of cellular organelles, lymphocytes, and deposited immunoglobulins. Mature nodules have a classic 3-layer structure (Fig. 4). The inner central necrotic zone appears as an intensely eosinophilic amorphous, granular or fibillary material containing collagen fibrils, fibrin, proteins, and other cellular debris. This central area is surrounded by elongated histiocytes in a palisaded arrangement (Fig. 5). Multinucleated giant cells also may be present. These macrophages are thought to come from the vessels of the outermost granulation tissue layer, migrate toward the central zone, and have high turnover.³⁰⁻³² The third zone, around the palisading macrophages, is an outer layer of vascular connective tissue, admixed with T lymphocytes and plasma cells.⁴ Mast cell and eosinophils may be present. Uncommonly, an acute vasculitis may be seen in the surrounding vessels and sometimes a necrotic blood vessel associated with nuclear fragments or sparse neutrophils may be seen in the center of necrobiotic areas. Rarely, immunoglobulins and complement have been demonstrated in altered vessels. Occasionally, superficial nodules may perforate the epidermis.³³ Old lesions show extensive fibrosis in which clefts and cystic degeneration of the necrobiotic foci persist.^{34,35}

Pathogenesis

The exact etiology of RN is unknown. It has been hypothesized that a series of events beginning with local trauma is responsible for formation of RNs.⁴ A recent study of cytokine composition suggests that the nodule is probably due to a Th-1-mediated inflammatory mechanism.³⁶

Repeated trauma to pressure points of the body induces local vascular damage, with subsequent neoangiogenesis and granulation tissue formation. Endothelial injury results in local accumulation of IgM RF immune complexes on the small vessels walls. The deposited RF directly, or by the complement pathway, induces activation and mobilization of lo-

cal monocytes and macrophages. These cells secrete interleukin-1, prostaglandin E₂ and angiogenic factors such as tumor necrosis- α and transforming growth factor- β . The fibrin that subsequently accumulates within the lesion is a procoagulant response to the angiogenesis. Cytotoxins, proteases, collagenases, and other chemotactic factors, such as granulocyte/macrophage colony-stimulating factor and fibronectin, which are secreted by lesional monocytes and macrophages, are responsible for necrosis of the connective tissue matrix and formation of palisading granuloma.^{4,31,37}

Histologic features of focal vasculitis, with associated immunoglobulin and fibrin deposition and complement activation, can be found in one-third of all RNs, throughout all stages of the development of the nodules. This has led some authors to suggest that RNs most probably result from a vasculitic process. However, even in early lesions such changes had not been observed in other studies.³⁷⁻³⁹

Associations

RNs are not exclusive of RA and histologically identical nodules can sometimes occur in patients having systemic lupus erythematosus,⁴⁰⁻⁴² ankylosing spondylitis, rheumatoid nodulosis (see below), granuloma annulare, and chronic active hepatitis.^{1,6} Increased levels of anticardiolipin and antiphospholipid antibodies have been reported in RA patients with RNs.⁴³ RNs have been observed as an isolated feature in otherwise healthy children and adults (see the section "Pseudorheumatoid nodules").^{3,44}

Diagnosis

Diagnosis of RNs is easily made in the clinical context of the disease. A complete history and physical examination, focusing on cutaneous and rheumatologic aspects, and occasionally laboratory testing are useful to diagnose RNs. Symmetric inflammatory polyarthritis, seropositivity for RF, and other associated symptoms, such as vasculitis, are highly suggestive

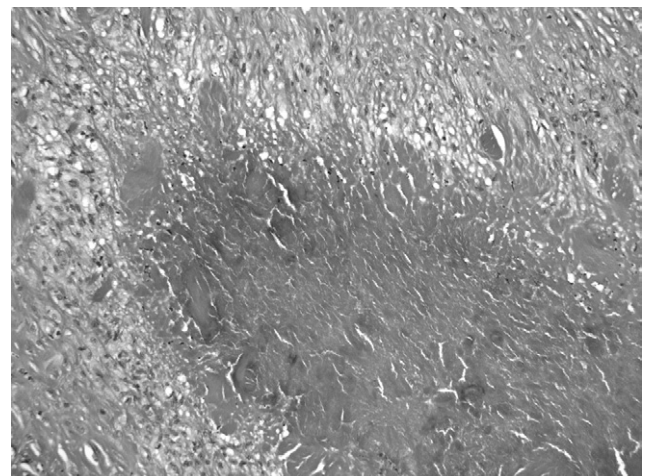


Figure 5 A palisade of elongate histiocytes surrounds a eosinophilic necrotic zone with cellular debris. (Hematoxylin-eosin stain; original magnification $\times 100$).

of RA. RNs raise a diagnostic problem mostly from the histological point of view since they correspond to a pattern of palisading necrobiotic granuloma, which may lead to many diagnostic errors. Many RNs occur in areas difficult to biopsy, such as over extensor tendons. Clinical and blood control of asymptomatic patients with RNs is advisable as the condition may evolve to RA.³

Differential Diagnosis

Nodular-type lesions seen in other conditions can mimic RNs. The clinical differential diagnosis of RNs includes gouty tophi, subcutaneous granuloma annulare, tumoral calcinosis, fibromas, xanthomas, subcutaneous sarcoidosis, lupus panniculitis, nodular or keloidal scleroderma, metastatic tumors, histoplasmosis, amyloidosis, ganglion cysts, foreign body granulomas, basal cell carcinoma, epidermoid cysts, and synovial cysts.¹ Chronic tophaceous gouty arthritis occasionally may be misdiagnosed as RA with nodules.⁴⁵ Conversely, RNs with xanthomatous appearance have been mistaken as gouty tophi and even tendinous xanthomas.⁴⁶ Lesions identical to RNs have been described in children with rheumatoid fever, although these rheumatic nodules last only briefly and eventually regress. As they mature may become histologically indistinguishable from early RNs, although they are composed of smaller granulomas with less well demarcated zones and palisading.⁴⁷

The histological differential diagnosis of RNs mainly includes necrobiotic granulomas, mainly necrobiosis lipoidica and granuloma annulare (especially if subcutaneous) are often misdiagnosed as RNs (Table 1).^{48,49} Necrobiotic granulomas can be divided into 2 subgroups based on the staining of the central area of necrobiosis. The first group is the blue granulomas. They have a basophilic center caused by either mucin deposition or to the presence of neutrophils and nuclear dust. If increased interstitial mucin is responsible for the blue color, the lesion is most likely granuloma annulare. If the basophilic central zone is caused by the presence of neu-

trophils or nuclear dust, the differential diagnosis includes Wegener's granulomatosis and rheumatoid vasculitis.

Red granulomas have a eosinophilic necrobiotic central area. If the collagen is hyalinized, the differential diagnosis includes necrobiosis lipoidica and xanthogranuloma necrobiotic. If degranulated eosinophils are responsible for the color, the lesions of Churg-Strauss syndrome and eosinophilic cellulitis (Well's syndrome) should be considered. If the red color is caused by fibrin deposition, then a rheumatoid nodule should be considered.⁵⁰ Comparable patterns are found in mixed connective tissue disease, juvenile RA, and hypogammaglobulinemia as well, although they had relatively less central necrosis and cell palisading than RNs.¹

Subcutaneous granuloma annulare often is misdiagnosed as RNs owing to comparable histologic findings.⁴⁸ Deep or subcutaneous granuloma annulare is an uncommon clinicopathologic variant of granuloma annulare that appears more frequently in children and young adults. The lesions consists of subcutaneous nodules, with no inflammatory appearance at the skin surface, that most commonly are located on the head, hands, buttocks, and the anterior aspect of the lower legs. Usually, subcutaneous granuloma annulare is an authentic and exclusive panniculitic process with no dermal participation, although in 25% of the cases lesions of subcutaneous granuloma annulare coexist with classic findings of granuloma annulare in the dermis. The histopathologic changes found in subcutaneous or deep granuloma annulare consist of areas of necrobiosis with peripheral palisading granulomas involving the septa of the subcutis. Usually the area of necrobiosis in subcutaneous granuloma annulare is larger than in the dermal counterpart. The central necrobiotic zone appears as a basophilic area of collagen degeneration along with abundant mucin deposits and nuclear dust from neutrophils, whereas the rheumatoid nodule is characterized by areas of eosinophilic degeneration accompanied by abundant fibrin deposition. The presence of nuclear dust or nuclear fragmentation within the fibrin foci and the absence of multinucleated giant cells in the peripheral palisade of his-

Table 1 Histologic Differential Diagnosis of Rheumatoid Nodule, Granuloma Annulare, and Necrobiosis Lipoidica

	Rheumatoid Nodule	Granuloma Annulare	Necrobiosis Lipoidica
Location	Usually subcutis	Upper and midreticular dermis	Entire dermis, with extension to subcutis
Pattern	Massive areas of sharply defined necrobiosis (eosinophilic necrobiotic granuloma)	Discrete foci of necrobiosis (basophilic necrobiotic granuloma)	Ill-defined areas of necrobiosis (eosinophilic necrobiotic granuloma)
Collagen degeneration	Complete	Complete	Indistinct, elongate areas of degenerate collagen
Fibrosis	Common	Uncommon	Common
Histiocytes	Well-defined palisades of histiocytes	Well-defined palisades of histiocytes	Histiocytes intermingled diffusely
Inflammatory components	Tuberculoid and sarcoid reaction common	Tuberculoid and sarcoid reaction uncommon	Tuberculoid and sarcoid reaction common
Vascular component	Capillary hyperplasia peripherally	Perivascular mononuclear cell infiltrate	Capillary wall thickening
Mucin	Variable	Common	Common

Modified from Hewitt and Cole.⁸⁵

tiocytes favor the rheumatoid nodule diagnosis. Eosinophils are more common in subcutaneous granuloma annulare than in the superficial counterpart.⁵¹

Prognosis

RNs can enlarge or regress, recur, or persist indefinitely. Although RNs are mostly benign, complications can occur. Infection, ulceration, and even gangrene can follow the rupture of skin overlying subcutaneous nodules.⁶ These lesions may require surgical excision. Occasionally, internal nodules in the synovium track up to the skin, creating a fistula. This condition is known as fistulous rheumatism and requires extensive synovectomy.⁵² Acute synovial rupture in RA patients may present with a cutaneous hemorrhagic (ecchymotic) crescent sign, due to synovial fluid enzymatic damage that causes capillary permeability.⁵³

Nodules also may contain significant amounts of lipids and cholesterol that are released into adjacent bursae and lead to milky bursal effusions, known as rheumatoid chyloid bursitis.⁵⁴ Cutaneous mucinous nodules have been described in severe RA patients with active disease. These nodules, which develop over inflamed RA joints, had mucinous granulation tissue, including neutrophilic infiltrates and mesenchymal cell proliferation, at histologic assessment.⁵⁵

RNs may often signal more severe systemic extra-articular manifestations, which subsequently lead to a clinically poorer outcome. Patients are less likely to reach remission and are prone to the development of vasculitis. This worse prognosis, however, was not noted by other authors, whose data showed no difference in mortality between RA patients with nodules and those without. RNs also do not appear to indicate a worse functional or radiographic prognosis.⁵⁶

Management

RNs typically present asymptotically as a cosmetic complaint and treatment is not necessary. In fact, nodules should not be drained, injected, or excised, because of a high risk of infection or recurrence with such interventions (Fig. 6).⁵⁷ RNs usually improve or resolve with conventional treatment



Figure 6 Fistulized and infected rheumatoid nodule after infiltration with corticosteroids.



Figure 7 Multiple painful rheumatoid nodules on the hands developed rapidly 3 years after starting methotrexate therapy for chronic rheumatoid arthritis (accelerated rheumatoid nodulosis).

for RA, although they may persist or even worsen in some instances (see below, accelerated rheumatoid nodulosis).

Indications for treatment include areas exposed to repetitive trauma and nodules on weight-bearing prominences that might cause progressive erosions and severe pain, neuropathy, limitation of motion, or deformity, and damage to underlying structures.⁵⁸ Some nodules ulcerate and lead to deep infections requiring medical and surgical treatment.¹²

There are very few treatment options for RNs. Large nodules can be surgically excised, especially if they are ulcerated or painful, but they often recur within scar tissue in zones subjected to repetitive trauma. After surgical removal, subsequent skin grafting often is required.⁶ Injecting corticosteroids directly into the lesion sometimes reduces its size.⁵⁹ Although this procedure is most effective for deep lesions in the olecranon bursa, nodules on the buttocks and feet tend to ulcerate and are likely to become infected. Once they are infected, surgical excision or drainage is required. Oral corticosteroids and hydroxychloroquine can also be used,^{6,58} but their effects on RNs vary, as most patients with RA already receive these medications.

Accelerated Rheumatoid Nodulosis (ARN)

ARN is a recognized complication of methotrexate (MTX) therapy in patients with RA.⁶⁰ This entity was first described in 1986 by Kremer and Lee during a study of long-term MTX therapy for RA in which 3 patients had increasing numbers of nodules during therapy, even despite good clinical response of polyarthritis.⁶¹ Since then, others have observed the same phenomenon of new, often painful, small nodules that prefer the hands, feet and ears of chronic RA patients who are undergoing treatment with MTX (Fig. 7).⁶²⁻⁶⁴ Ahmed and co-workers termed this picture MTX-induced ARN.⁷ A double-blind study that compared MTX and azathioprine in patients with refractory RA showed an 8% incidence of MTX-induced

ARN (with arthritic improvement) and none with azathioprine.⁶⁵

MTX-induced ARN favors male patients and can occur without the presence of pretreatment RNs. New RNs affect mainly the hands, in areas such as the metacarpophalangeal and proximal interphalangeal joints: 88% of MTX-induced accelerated RNs were on the hands, whereas only 34% of nonaccelerated RNs involve the hands. The duration of MTX therapy before MTX-induced ARN is widely variable, with a mean of 35.1 ± 31.1 months.

Most nodules are histologically identical to classical RNs. HLA-DRB1*0401 allele and RF seropositivity have been associated with MTX-induced ARN.^{7,66} Seronegativity, however, is not a prerequisite to develop MTX-induced ARN. Genetically predisposed patients with concomitant use of hydroxychloroquine treatment appear to be protected against the development of MTX-induced ARN.⁷ It has been suggested that development or progression of nodulosis is caused by adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes.⁶⁷

MTX-induced ARN is associated with minimal discomfort or morbidity in more than 80% of cases, which allows continuation of MTX for resolution of arthritis. The lesions often regress after MTX is stopped and recur after a rechallenge. Addition of hydroxychloroquine,⁶⁸ D-penicillamine,⁶⁹ colchicine,⁷⁰ or sulfasalazine⁷¹ to MTX therapy has been shown to decrease the incidence of ARN or even result in regression of subcutaneous and visceral MTX-induced nodules.

Of note, nodule development during MTX therapy also has been documented in a case of psoriatic arthritis⁷² and in other patient with systemic lupus erythematosus.⁷³ Two seropositive, polyarthritic-onset juvenile rheumatoid arthritis (JRA) patients also developed ARN after 3 to 4 months of MTX treatment. The nodules were similar in size and distribution to those found in adults and regressed on MTX withdrawal or with addition of hydroxychloroquine. MTX-induced ARN occurs in approximately 1.5% of all JRA patients and is seen most in seropositive females diagnosed of LRA later than 10 years of age, who as a group tend to have disease clinically similar to adult RA.⁷⁴ One more case of MTX-induced ARN has been observed in a patient with systemic-onset JRA, with scalp and trunk nodules 6 months after the start of treatment.⁷⁵

Other drugs have been implicated in ARN. ARN has been reported only once in association with azathioprine⁷⁶; additional cases of ARN recently have been described in relationship with antitumor necrosis factor alpha biologic therapy, and leflunomide. In 1 case, new nodules appeared over the elbows and metacarpophalangeal joints (as well as pulmonary lesions) after etanercept treatment in a seropositive RA patient with severe articular disease and HLA-DRB1 positivity.⁷⁷ Cunnane and coworkers reported 3 patients whose arthritic complaints subsided with etanercept but who had increasing numbers of painful finger and elbow RNs, internal nodules, and nail fold infarcts after 2 to 3 months of therapy. These patients had significant refractory arthritic disease and were all seropositive. Pathogenesis is unclear; vasculitis and medication-induced cell death and increased chemotaxis

have been implicated.³⁹ Rapid development of RNs of both hands has also been reported in relationship with infliximab therapy for RA.⁷⁸

Similar cases of cutaneous and pulmonary ARN have been observed in RA patients successfully treated with leflunomide. This drug inhibits dehydroorotate dehydrogenase, a key enzyme of the pyrimidine synthesis in activated lymphocytes. Monocytopenia during leflunomide therapy is proposed to be involved in pathogenesis of this rare complication of leflunomide therapy. Discontinuation of leflunomide therapy achieved clinical and radiological improvement of nodules.^{67,79}

Rheumatoid Nodulosis

RNs commonly occur in patients with severe, seropositive RA. However, in some instances skin nodules are the predominant sign, with minor or absent joint symptoms. There are 2 well-defined clinical settings in which RNs appear without RA: rheumatoid nodulosis and benign rheumatoid nodules, also named pseudorheumatoid nodules. If these clinical pictures are benign variants of RA or individualized entities remains controversial.

The first description of rheumatoid nodulosis dates from 1949. Baywaters reported the association of subcutaneous nodules and cystic bone lesions in the setting of palindromic rheumatism as a variant of RA.⁸⁰ Ginsberg and coworkers later coined the term rheumatoid nodulosis for an intermittent arthritis associated with multiple RNs usually involving the fingers, as well as hand and foot intraosseous cystic changes.⁸¹ Since then there have been many reported cases of rheumatoid nodulosis, with findings of RN histologic characteristics, minimal joint activity, cystic bone lesions, and RF positivity.⁸²⁻⁸⁵

Couret and coworkers recognized the similarities in the above cases and performed a focused review to develop the following diagnostic criteria for rheumatoid nodulosis: (1) multiple subcutaneous RNs identified by biopsy; (2) recurrent joint symptoms with minimal clinical or radiologic involvement; (3) benign clinical course; and (4) no or mild systemic manifestations of RA. RF seropositivity and radiologic evidence of subchondral cysts of small bones are frequently seen as well, but the authors noted that their absence should not rule out rheumatoid nodulosis as a possibility.⁸⁶

Rheumatoid nodulosis patients are generally men (82%) in their thirties to fifties. Unlike traditional AR, rheumatoid nodulosis appears to have a poor association with the RA-associated HLA-DRB1 alleles and does not appear to lead to future development of erosive arthritis and systemic manifestations of classical RA.⁸⁷ However, in a series of 16 patients with rheumatoid nodulosis who were followed for a period of 1 to 12 years, 6 of them had an aggressive course and developed classic erosive polyarticular RA, whereas the others continued having episodic arthritis without erosive disease. Cholesterol crystals were found in RNs or in the affected bursae, making difficult differential diagnosis with other crystal-induced arthritis, such as tophaceous gout or xanthomatosis.⁸⁸

Rheumatoid nodulosis usually is self-limited and symptomatically controlled with nonsteroidal anti-inflammatory drugs or slow-acting anti-RA drugs.^{86,89} Complete resolution with hydroxychloroquine has been documented.⁹⁰ Surgical removal of the nodules may be considered if they limit joint motion.⁹¹

Pseudorheumatoid Nodules

Pseudorheumatoid or benign RNs have been documented in healthy children without arthritis^{92,93} and most frequently arise when the children are between the ages of 8 and 10 years. In these cases, nontender nodules of undetermined cause and self-limited course are found in places that are uncharacteristic of true RNs, such as the prepatellar areas, pretibial areas, feet, scalp, and malleoli. These nodules are histologically indistinguishable from true RNs but do not herald the subsequent development of RA, as some authors have suggested.⁹⁴⁻⁹⁶ Such nodules have been also documented, though relatively infrequently, in adults.⁹⁷ As many as one-quarter of children with these RNs have superficial lesions clinically resembling granuloma annulare.⁹⁸ Therefore, some consider the condition to be a form of deep or subcutaneous granuloma annulare.

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