

Rheumatoid Nodulosis in a Patient with Lupus Erythematosus: Case Report and Review

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Abstract: Nodules are commonly found in patients with rheumatic diseases, most often in rheumatoid arthritis, but also in other conditions such as systemic lupus erythematosus (SLE). Rheumatoid nodulosis, however, is less frequent and not an established feature of SLE. We describe a patient with SLE and rheumatoid nodulosis, reviewing the literature and suggest that this manifestation falls into the spectrum of rhus.

INTRODUCTION

Rheumatoid nodules are frequent in rheumatic diseases, especially rheumatoid arthritis (RA), and occasionally can create diagnostic confusion. Nodules may appear in other conditions as well, particularly collagen and metabolic diseases, infections, and can be caused by chemicals and somatic defects. Occasionally, it is difficult to establish their cause.

Subcutaneous nodules are characterized by their association with systemic disease, location, and histopathology and may suggest a specific underlying diagnosis [1-3]. On occasion, specific staining may reveal deposits of mucin, glyco-gen, cholesterol, and amyloid, suggesting the proper diagnosis.

The first case of rheumatoid nodules in a patient with rheumatic symptoms was by Fowler in 1884 [4]. In subsequent years, it was observed that rheumatoid nodules appeared in some children without evidence of rheumatic disease with a benign course and without development of arthritis [5, 6]. However, in some cases, they heralded the later appearance of rheumatic fever [6, 7], granuloma annulare [6, 7], and rheumatoid arthritis [8]. Rheumatoid nodules have also been reported in asymptomatic adults as well as in adults with palindromic rheumatism.

Following the introduction of the concept of rheumatoid nodulosis in 1975 by Ginsberg *et al.* [9], a host of observations on this entity were reported, and after 1981, diagnostic criteria for nodules based on the histopathology were proposed. A series of investigators including Wisniewski and Askari in 1981 [10], Dreyfus and Dauplex in 1981 [11], Kaye *et al.* in 1984 [12], and Morales-Piga *et al.* in 1986 [13] elaborated on and set forth criteria for "nodulosis" based on clinical characteristics and associations (Table 1).

Couret and colleagues [1] performed a review of 26 cases published in the literature in 1988 and suggested that the first four of these aforementioned criteria were required to diag-

nose a case of rheumatoid nodulosis. Rheumatoid nodules have been described in other diseases such as systemic lupus erythematosus (SLE) [15, 16], gout [17], ankylosing spondylitis [18], chronic active hepatitis [19], and accelerated nodulosis in a patient with SLE treated with methotrexate [20]. However, rheumatoid nodulosis as defined by the aforementioned criteria have not been described in patients with SLE.

Table 1. Clinical Criteria for Nodulosis

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| 1. Multiple subcutaneous rheumatoid nodules identified histologically |
| 2. Recurrent articular symptoms generally classified as palindromic rheumatism |
| 3. Absence of or minimal articular involvement by clinical or radiologic examination |
| 4. No systemic manifestations of rheumatoid arthritis |
| 5. Positive rheumatoid factor |
| 6. Subchondral lesions of the bones of the hands and feet |

In this report, we describe a 52-year-old patient with a history of symmetric polyarthritis beginning in 1998 who was diagnosed with SLE two years later and in 2005, developed nodules on the dorsum of the hands and palms. Excisional biopsy of one of these nodes demonstrated a rheumatoid nodule. The patient fulfilled the first four of the aforementioned criteria for nodulosis and a positive anticyclic citrullinated protein antibody. A search of databases including Medline, Bireme, Lilac, and Scielo using the association of rheumatoid nodulosis and lupus recovered reports of rheumatoid nodules in patients with lupus but no reports of rheumatoid nodulosis.

CASE PRESENTATION

The patient is a 52-year-old woman with disease onset in 1998 characterized by articular pain and swelling of the proximal interphalangeal joints (PIP) of the hands, morning stiffness of 15 minutes, throbbing headache and blurry vision, marked scalp hair loss, and photosensitivity. Initial treatment was with prednisone (15 mg per day) and nonsteroidal anti-inflammatory agents for a presumed diagnosis of rheumatoid arthritis; she never received methotrexate therapy. She remained asymptomatic for almost two years. Two

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years following the initial presentation, while still on prednisone, 5 mg per day, she presented with fever, generalized lymphadenopathy, nausea, vomiting and diarrhea, low back pain, lower extremity edema, and scalp hair loss. At this admission, she was noted to have a pericardial effusion, anemia (hemoglobin, 7.6 gm/dL; hematocrit, 23.5%), leukopenia (2300 WBC/mm^3), and lymphopenia (398 cells/mm^3) and normal platelets with normal partial prothrombin time and prothrombin time. During hospitalization, she developed a membranous, proliferative glomerulonephritis (type IV-S (A)) diagnosed on renal biopsy and worsening pericardial effusion requiring removal of 300 cc of fluid.

Additional laboratory data included antinuclear antibody (ANA), 1: 1280 speckled; anti-DS-DNA (chrythidia luciliae, indirect immunofluorescence), 1: 100; and complements C3, 47 mg/dL (normal range, 10-40 mg/dL), and C4, 8.4 mg/dL (normal range, 90-180 mg/dL). A diagnosis of SLE was made. Treatment was with bolus cyclophosphamide, 500 mg, and methylprednisolone, 1000 mg daily for three consecutive days, followed by monthly boluses of cyclophosphamide for six months and prednisone at an initial dose of 1 mg/kg per day, reducing to a dose of 10 mg per day over six months. She declined further cytotoxic therapy but did well until January 2005, when she presented with symmetric polyarthritis involving the wrists, metacarpophalangeal joints (MCPs), PIPs, elbows, knees, ankles, and toes. She also developed systemic hypertension (blood pressure, 160/120 mm/Hg), for which, captopril, 150 mg per day, and verapamil, 120 mg per day, were initiated.

The subsequent course has been characterized by persistent polyarthritis, and in mid-2005, the patient developed nodules on the palms and dorsum of the hands (Figs. 1,2). An excisional biopsy of one of the nodules in January 2006 revealed changes of a rheumatoid nodule (Fig. 2). The synovitis resolved, and the persistent rheumatoid nodules were subsequently surgically excised without recurrence to date. Hand radiographs showed articular soft-tissue swelling and juxtaarticular osteopenia, but no ankylosis and erosions or other changes of rheumatoid arthritis. Laboratory evaluation at this point revealed a normal hemoglobin of 14.9 gm/dL with WBC of 4610 cells/mm^3 (61.5% polymorphonucleocytes, 24.4% lymphocytes, 9.8% monocytes), Westergren sedimentation rate of 34 mm/1 hour, C-reactive protein of 24 mg/dL (normal range, 0-6 mg/dL), normal protime and partial prothrombin time, creatinine of 0.93 mg/dL, benign urine analysis, ANA of 1: 1280 (homogeneous pattern) and anti-DNA of 1: 20, rheumatoid factor of 30.4 U (normal, to 30 U), an anti-CCP of 138.9 U (normal, <20 U), anticardiolipin IgG of 10.9 U (normal, 0-23 U GPL) and anticardiolipin IgM of 4.6 U (normal, 0-20 U MPL). Low dose oral prednisone was continued, and azathioprine therapy was initiated and continued to date.

DISCUSSION

Rheumatoid nodules are not specific for rheumatoid arthritis and can be seen in other rheumatic diseases including SLE, although they are rarely seen in this condition. Hahn *et al.* [15] described rheumatoid nodules in six patients with



Fig. (1). Hands, demonstrating rheumatoid nodules (red arrows) and slight swelling of several proximal interphalangeal joints. Nodules were also present on the flexor aspect of several digits.

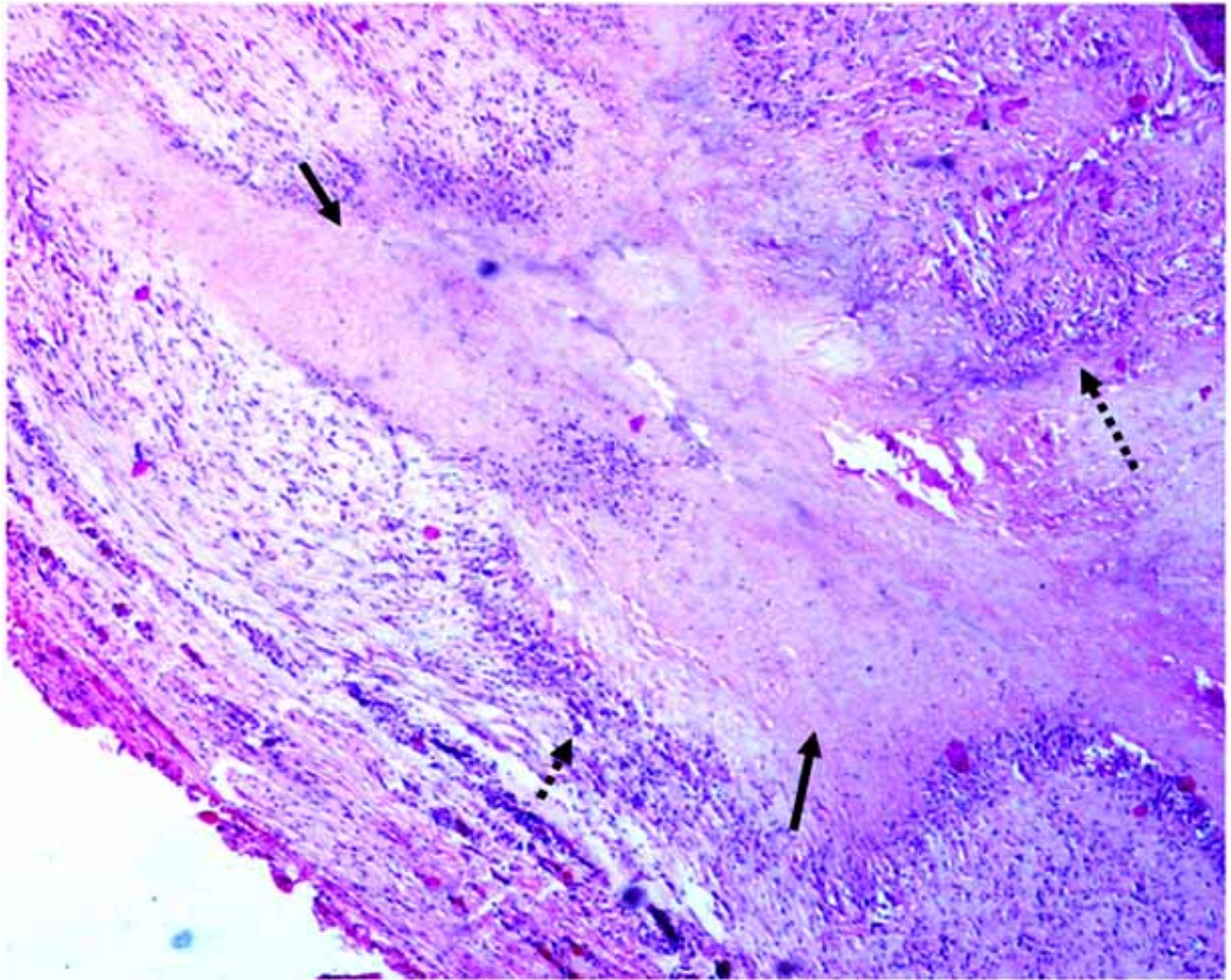


Fig. (2). Histopathology of a rheumatoid nodule demonstrating typical features of central fibrinoid necrosis (solid arrow), surrounded by fibrocytes and histiocytes and granulation and fibrosis (broken arrows; hematoxylin/eosin/hematoxylin and eosin (10x).

SLE. In five of the patients, the nodules were detected in the olecranon bursa. The diagnosis of rheumatoid nodules was confirmed on biopsy in three of these six patients, and rheumatoid factor was present in four of them. The articular disease in these patients was more rheumatoid arthritis like, suggesting a superposition of RA and SLE or a lupus related arthropathy, as described in our previous report [21]. The patient could not be diagnosed with RA according to the American College of Rheumatology classification criteria [22].

Since 1972, a number of other cases of rheumatoid nodules occurring in patients with SLE have been reported [12, 15, 16, 23-25] as well as in antiphospholipid syndrome [26] and accelerated rheumatoid nodulosis in a patient with lupus and Jaccoud's arthropathy [20]. In a majority of these cases of rheumatoid nodules occurring in patients with SLE, the nodules have appeared in the olecranon bursa, as described by Hahn *et al.* [15]. Six patients described by Dubois [16] had nodules on the forearms, two in the synovial tissue, and one within a synovial cyst, while the remaining publications describe the nodules in the palms of the hands at the level of the PIPs, as also seen in our patient, while one of the rheu-

matoid nodules was described in the vocal cords of a 28-year-old man [27]. It is uncertain how frequent rheumatoid nodules are seen in SLE, although Hahn *et al.* [15] and Schonfeld *et al.* [25] described them in five to seven percent of patients.

It is important to consider the differential diagnosis of rheumatoid nodules in evaluation of granuloma annulare, the nodules of necrobiosis lipoidica, and in xanthogranulomatous necrosis, searching for basophils, eosinophils, polymorphonucleocytes, histiocytes, multinucleated giant cells, and for the presence of cholesterol crystals, which would suggest a more specific diagnosis.

From a pathogenetic point of view, it has not been possible to elucidate the cause of rheumatoid nodules in SLE, although various theories of local trauma in the small vessels with activation of systemic macrophages as well as nodule formation as a manifestation of systemic disease evidenced by presence of rheumatoid factor, anti-CCP and anticardiolipin antibodies, may suggest more definitive conclusions about their etiology [24, 28, 29]. In our experience, the majority of patients with subcutaneous nodules have persistent articular inflammation, as occurred in our patient.

In conclusion, subcutaneous nodules have been described in various diseases. However, rheumatoid nodulosis, thus far, has only been described in RA, for which reason we think that ours represents the first case of rheumatoid nodulosis in a patient with SLE, according to previously defined criteria for nodulosis [10-12]. The significance of the anti-CCP antibody detected in this patient remains uncertain, as does its diagnostic and prognostic significance, whereby the clinical picture fits best into the concept of rhus [21].

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