

## Large elbow nodules in a patient with rheumatoid nodulosis

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### Abstract

Rheumatoid nodulosis is an uncommon pathology considered as a particular variant of rheumatoid arthritis associated with subcutaneous rheumatoid nodules, palindromic rheumatism, and mild or no systemic manifestation, usually with positive rheumatoid factor and radiological subchondral bone cysts. We describe a 58-year-old man with the diagnosis of seropositive but nondestructive, nondeforming rheumatoid arthritis, who exhibits multiple subcutaneous rheumatoid nodules associated with episodes of intermittent arthralgias and subchondral cystic lesions of the small bones of the hands and feet. Large nodules were surgically removed from the two elbows. They were histologically typical of rheumatoid nodules. All these findings were consistent with the diagnosis of rheumatoid nodulosis.

### Introduction

Rheumatoid nodulosis is a particular variant of rheumatoid arthritis (RA) associated with palindromic rheumatism, subcutaneous rheumatoid nodules, mild or no systemic manifestations, and a benign clinical course.<sup>1,2</sup> Positive rheumatoid factor (RF) and radiological subchondral bone cysts are usual, but their absence should not eliminate the diagnosis of rheumatoid nodulosis, particularly at the onset of the disease. We present a new case and review of the literature.

### Case report

A 58-year-old man with an unremarkable medical history was admitted to our department of Internal Medicine first in 1987, at the age of 36 years, with a one-year history of chronic joint disease with symmetrical inflam-

matory polyarthralgia and intermittent inflammation of the wrists, the small joints of the hands and feet, and the elbows with prolonged morning stiffness (lasting one hour). There was no family history of RA or autoimmune disease. A physical examination of the joints at that time showed synovitis of the wrists. A thorough clinical examination was normal. Laboratory tests showed moderate inflammation (erythrocyte sedimentation rate [ESR], 35 mm/h). Tests for RF were weakly positive and tests for antinuclear antibodies were negative. The radiographs of the hands and feet were normal at the time. The diagnosis of seropositive RA was made as the patient fulfilled four of the seven classification criteria of the American College of Rheumatology:<sup>3</sup> morning stiffness, symmetric arthritis, arthritis of hand joints for at least six weeks, and positive serum RF. He was treated initially with nonsteroidal anti-inflammatory drugs and intramuscular gold (1987-1996), with partial improvement. Since 1996 he had noted gradually enlarging subcutaneous nodules, first appearing around the elbows then over his hands and feet. The patient refused a biopsy of these nodules at that time. He also experienced episodes of inflammatory polyarthralgia separated by periods of spontaneous remission. Treatment with methotrexate was begun in 2008 at a dose of 10 mg once a week, and the patient improved showing a marked decrease in joint pain.

At the last admission on July 2009, he experienced a flare-up of inflammatory polyarthralgia involving the small and large joints (wrists, metacarpophalangeal [MCP] joints, elbows, shoulders, knees, ankles, and feet) with prolonged morning stiffness. On examination, there was no clinically apparent arthritis or synovial thickening in these joints. There were no deformities or destructive lesions. A skin examination showed two large nodules located under the extensor surface of both elbows, measuring 5×3 cm on the right side (Figure 1) and 2×3 cm on the left side, which were not adherent to deep surfaces and had the same color as the adjacent skin. Multiple subcutaneous nodules over the digits of the hands, plantar surfaces of the feet, and the Achilles tendons bilaterally were noted. The patient denied bleeding, pain, or purulent drainage from these sites. The rest of the physical examination was normal and there were no other extra-articular features reported.

Laboratory tests showed the following results: ESR, 49 mm/h; white blood cell count, 9500/mm<sup>3</sup>; hemoglobin, 12.4 g/dL; SGOT, 31 IU/L; SGPT, 30 IU/L. Renal function was normal. Immunological tests were positive for RF. Radiology of the hands revealed subchondral geodes of the head of the third and fifth metacarpals with juxta-articular erosions and joint space narrowing in the second and third MCP joints bilaterally. No demineralization

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was observed. Radiographs of the feet showed intraosseous cyst-like erosions involving the head of the fifth, fourth, and third metatarsals bilaterally with minimal joint space narrowing and mild erosive changes (Figure 2). Radiology of the elbows was normal. Chest radiographic findings were normal.

The episode remitted spontaneously without sequelae within three days. Surgical excision for removal of the two subcutaneous nodules overlying the elbows was performed in August 2009 at the Department of Orthopaedic Surgery. A histopathological study of one of these nodules showed features of rheumatoid nodules: there was a large central zone of fibrinoid necrosis surrounded by histiocytes in a palisade arrangement, and an infiltrate of lymphocytes comprised the peripheral zone (Figure 3). On the basis of his age, the nature of his nodules and their progression, the radiological findings, and the mild joint symptoms with the benign course of his RA, we felt this patient's clinical picture was consistent with the diagnosis of rheumatoid nodulosis.

### Discussion

We describe a middle-aged male patient who had multiple rheumatoid nodules confirmed by biopsy, but little clinical evidence of severe joint disease. The mildly elevated ESR and

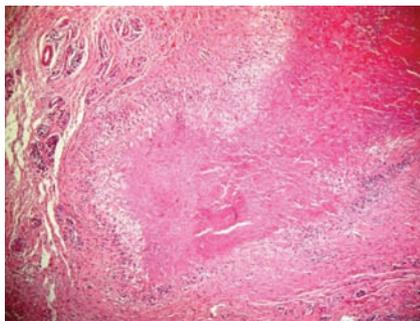


**Figure 1.** Nontender subcutaneous nodular lesion under the extensor surface of the right elbow, measuring 5×3 cm.



**Figure 2.** Radiograph of the right foot showing striking intraosseous cyst-like erosions involving the heads of the fifth, fourth, and third metatarsals, with minimal joint space narrowing and mild erosive changes.

absence of systemic manifestations, associated with subchondral cyst-like lesions of the feet and weakly positive RF, all attest to the diagnosis of the benign variant of RA called rheumatoid nodulosis. RA is a systemic inflam-



**Figure 3.** Histological findings of the rheumatoid nodule: central zone of fibrinoid necrosis surrounded by histiocytes in a palisade arrangement and an infiltrate of lymphocytes comprising the peripheral zone.

matory disease with articular and extra-articular manifestations involving almost every organ system (e.g. scleritis, interstitial lung disease, anemia, Raynaud's phenomenon).

Rheumatoid nodules are one of the most frequent extra-articular manifestations of RA, seen in approximately 20% to 25% of patients, and generally occur in patients with a severe, aggressive, and seropositive form of the disease.<sup>4,7</sup> On the other hand, patients with subcutaneous rheumatoid nodules range from those with severe seropositive RA to those in whom the nodules are the only clinical manifestation.<sup>8</sup> Our patient is one in whom the subcutaneous nodules are the predominant clinical sign accompanied by moderate joint involvement and weakly positive serum RF. There is a well-defined clinical picture, considered by some authors as a benign variant of RA or as an individualized entity called rheumatoid nodulosis by others.

The first description of rheumatoid nodulosis was reported in 1949 by Bywaters.<sup>9</sup> The author described a benign variant of RA, which was characterized by the presence of subcutaneous rheumatoid nodules and subchondral bony cysts associated with attacks of palindromic rheumatism. In 1975, Ginsberg *et al.*<sup>10</sup> defined the term rheumatoid nodulosis for subcutaneous rheumatoid nodules associated with episodes of acute intermittent arthritis, and with intraosseous cystic lesions in the small bones of the hands and feet in the absence of evident systemic involvement. In 1984, Kaye *et al.*<sup>8</sup> proposed a classification system of the clinical entities associated with rheumatoid nodules. The authors place rheumatoid nodulosis in the group IIA, involving patients with rheumatoid nodules, musculoskeletal complaints, and minimal or no synovitis. Later, in 1988, Couret and coworkers<sup>1</sup> carried out a complete revision of this pathology and established its diagnostic criteria: 1) multiple subcutaneous rheumatoid nodules identified on biopsy; 2) recurrent joint symptoms

with minor radiological lesions; 3) a benign clinical course; and 4) absence or mild systemic manifestations of RA. The presence of subchondral cystic lesions and RF seropositivity are not essential for the diagnosis, but as they are frequently seen as well, they are considered as additional data by some authors.<sup>1</sup> Our patient fulfilled all the clinical and morphological criteria for the diagnosis of rheumatoid nodulosis. In the literature, there have been many reported cases of this entity.<sup>1,5-18</sup> Table 1 shows the summarized data of some of these cases.

Rheumatoid nodulosis is a rare disease and its prevalence is difficult to establish and certainly underestimated. In contrast to the female preponderance noted in RA, the incidence of rheumatoid nodulosis is relatively common in men (82%) in their thirties to fifties.<sup>1,4,5,19</sup> Our patient was 36 years old at the onset of the disease. The joint symptoms are frequent and usually inaugural, as shown by our case. They consist of polyarthralgia lasting for a few days or polyarthritis with little or no synovitis, closely resembling palindromic rheumatism.<sup>20</sup> The serological and histological features are identical in rheumatoid nodulosis and in RA, and the percentage of seropositive patients among those with rheumatoid nodulosis is not different from the percentage of seropositivity in RA. ANA studies, on the other hand, are usually negative in rheumatoid nodulosis patients. The review of all published reports of rheumatoid nodulosis revealed that all of the 26 cases had joint symptoms, 24 of them were described as having a presentation of palindromic rheumatism, and only four were RF negative.<sup>1</sup> However, rheumatoid nodulosis is associated with a distinctive radiological pattern characterized by subchondral epiphyseal geodes that may communicate with the joint, absence of demineralization, absence of severe joint space loss, and mild or absent erosions.<sup>1,6</sup>

Given the relatively low incidence of this disorder and controversies concerning its definition, its etiopathogenesis remains unclear. Some observations suggest that rheumatoid nodulosis is a stage in the evolution or part of the spectrum of RA, as evidenced by the high prevalence of RF and the presence of nodules, but a consistently favorable course. It has also been suggested that rheumatoid nodulosis may be a separate entity of which the nodules are the only manifestation.<sup>2</sup> In fact, several special features speak for its autonomy from RA: absence or mild bone and joint destruction, even after a long evolution; absence of female preponderance; good prognosis – it does not appear to lead to future development of erosive arthritis; and systemic manifestations of classic RA<sup>21</sup> and benign outcomes have been observed in patients with long follow-up.<sup>1,19</sup> However, few cases with evolution to typical RA after many years have been documented.<sup>20,22</sup>

**Table 1. Data of some cases of rheumatoid nodulosis reported in the literature.**

References	Age/sex	Disease duration (years)	Joint symptoms	Radiologic findings	Rheumatoid factor
Bywaters, 1949 <sup>9</sup>	51/M	11	Acute migratory attacks	Subchondral cystic lesions progressed to joint destruction over 2 yr with complete loss of joint space	ND
Ginsberg <i>et al.</i> , 1975 <sup>10</sup>	39/M	10	Episodic tenderness and swelling lasting 24-48 hr	Intraosseous cyst-like radiolucencies with mild erosive changes	Positive
Brower <i>et al.</i> , 1977 <sup>12</sup>	46/M	5	Intermittent acute arthritis lasting 24-48 hr	Large cyst-like erosions, mild periarticular erosions	Positive
Wisniewski and Askari, 1981 <sup>18</sup>	58/M	25	Occasional arthralgia, morning stiffness	Multiple subcortical cysts	Positive
Thévenon <i>et al.</i> , 1983 <sup>7</sup>	28/M	4	Rapidly regressive arthralgia	Epiphyseal subchondral geodes of the metatarsophalangeal joints	Positive
Fleischer and McGrath, 1984 <sup>13</sup>	35/F	25	Mild intermittent migratory aches	Multiple small cystic lesions	Positive
Morales-Piga <i>et al.</i> , 1986 <sup>6</sup>	35/M	11	Intermittent acute arthritis lasting 4-5 d	Subchondral cystic lesions, minimal joint space narrowing	Positive
Courret <i>et al.</i> , 1988 <sup>1</sup>	34/M	4	Palindromic rheumatism	Subchondral geodes; no erosions	Positive
	42/M	10	Palindromic rheumatism	Subchondral geodes developed 6 yr after disease onset; no erosions	Positive
Despaux <i>et al.</i> , 1995 <sup>2</sup>	56/M	3		Subchondral geodes; no erosions	Negative
	35/F	5		Normal joint spaces	
Bezza <i>et al.</i> , 2002 <sup>11</sup>	41/M	13	Intermittent chronic joint disease; inflammatory polyarthralgia	Large subchondral geodes in the medial part of the first phalanx of the left great toe; small geode in the head of the left fifth metatarsal	Positive
Gomez <i>et al.</i> , 2003 <sup>5</sup>	27/F	NA	Discrete arthralgia with no signs of arthritis	Normal; no arthritis alterations	Negative
	55/M	2 yr		Normal; no arthritis alterations	Negative
Present case, 2009	58/M	22	Intermittent chronic joint disease; inflammatory polyarthralgia	Intraosseous cyst-like erosions involving the heads of the fifth, fourth, and third metatarsals bilaterally with minimal joint space narrowing and mild erosive changes	Positive

M, male; F, Female; ND, not done; NA, Not available.

In a series of 16 patients with rheumatoid nodulosis, followed for a period of 1-12 years, six of them developed classic erosive and aggressive RA whereas the others continued having episodic arthritis without erosive changes.<sup>22</sup> Our patient did not experience progression to typical RA; he had attacks of palindromic rheumatism with minimal radiological erosions in the second and third MCP joints of both hands after 22 years. Some authors suggested that repeated trauma to certain areas can be involved as possible triggering factors for the development of nodules.<sup>23</sup> The pathogenesis of the subchondral cystic lesions is also unclear. Their cause and their significance have not been well established and it is not clear whether they represent intraosseous rheumatoid nodules or are formed by synovial tissue infiltration.<sup>10,13,18</sup> Morales-Piga *et al.* have shown that intraosseous geodes exhibit histological features of rheumatoid nodules devoid of synovial tissue.<sup>6</sup>

Unlike RA, rheumatoid nodulosis appears to

have a poor association with the HLA system (RA-associated HLA DRB1 alleles), and only a few studies have investigated the role of the HLA system in rheumatoid nodulosis,<sup>21</sup> and no definitive conclusions have been made from this small number of cases. However, familial forms have been reported: Bosser *et al.*<sup>24</sup> described two cases of familial rheumatoid nodulosis in which unusual features included onset at a young age and the presence of umbilicated and ulcerated papules suggesting perforating granuloma annulare.

Rheumatoid nodulosis is usually self-limited and can be symptomatically controlled with nonsteroidal anti-inflammatory drugs, sometimes combined with analgesics.<sup>1,11,18</sup> Second-line drugs and slow-acting anti-RA drugs are used to control the articular involvement; they do not improve the nodulosis or cystic subchondral changes.<sup>22</sup> Complete resolution with hydroxychloroquine has been reported.<sup>25</sup> However, methotrexate may exacerbate the nodules despite overall disease improvement.

In fact, rheumatoid nodulosis is known as a complication of methotrexate therapy.<sup>26</sup> Specific treatment of this pathology usually is not necessary because the nodulosis is often asymptomatic. Surgical excision may be necessary in some cases if the nodules are causing a limited range of joint motion, a nerve compression, or are severely ulcerated or infected.<sup>11,27</sup>

We did not discontinue treatment with methotrexate in our patient because his response to this drug was gratifying, particularly in decreasing progressive joint destruction, and we preferred surgical removal of the nodules of the elbows, first to obtain tissue for histological diagnosis, and second to improve joint motion of the elbows.

In conclusion, there appears to be evidence that rheumatoid nodulosis exists, and its relationship with classic RA is certain but not entirely defined. A consideration of this entity may help to avoid diagnostic pitfalls and the use of aggressive therapy.

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