



**SOUMYA CHATTERJEE, MD, MS, FRCP**  
 Assistant Professor, Cleveland Clinic Lerner College of  
 Medicine of Case Western Reserve University; Staff,  
 Department of Rheumatic and Immunologic Diseases,  
 Cleveland Clinic

# The Clinical Picture

## A 51-year-old man with nodular lesions



FIGURE 1



FIGURE 2

**A** 51-YEAR-OLD DIABETIC MAN presents with a 1-year history of episodic pain, swelling, and stiffness in some of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of his fingers. During these episodes, he has significant morning stiffness. He says he has no other joint problems or back pain. A review of systems is otherwise unremarkable.

On physical examination, he has swelling and tenderness of some MCP and PIP joints in an asymmetrical distribution. The rest of the physical examination is normal, with no clinical evidence of joint deformities, and no evidence of psoriasis of the skin or nails.

Over the course of the next 2 years, nodules (FIGURES 1-4) appear over the fingers and, recently, over the Achilles tendons.

### ■ WHAT IS THE MOST LIKELY DIAGNOSIS?

- Gouty tophi
- Rheumatoid nodulosis

- Calcinosis cutis
- Tuberos xanthomas

### ■ GOUTY TOPHI: OUR INITIAL IMPRESSION

In view of the location of the nodules, the intermittent joint symptoms, and the patient's sex, our initial clinical impression was that he had gouty tophi. However, he had no history of previous attacks (including podagra). Furthermore, material aspirated from these nodules did not reveal monosodium urate crystals on polarized light microscopy.

Though our patient's initial rheumatoid factor test was negative, a test for cyclic citrullinated peptide (CCP) antibodies was positive, ie, 144 units (> 60 units is considered strongly positive). (CCP antibodies are known to be specific markers for rheumatoid arthritis, but their significance in rheumatoid nodulosis is unknown.) Acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein level)

were always normal. The serum uric acid level was 4.3 mg/dL (reference range 3.0–8.0 mg/dL). Radiographs showed focal soft tissue swellings (consistent with the nodules), but joint spaces were maintained and there were no erosions.

### ■ RHEUMATOID NODULOSIS: THE TRUE DIAGNOSIS

The patient's nodules kept growing, and new ones kept developing, causing significant impairment of hand function. Hence, some of the larger nodules were surgically removed. The resected specimens revealed a yellow nodular cut surface on sectioning. Histopathologic analysis revealed multiple necrobiotic nodules, consistent with rheumatoid nodulosis. Urate crystals were not seen on histology, although crystals can be dissolved in some tissue preparations, and gouty tophi provoke pathologically a granulomatous inflammatory reaction. However, unlike what is expected with gouty tophi, material aspirated from the nodules did not reveal monosodium urate crystals on polarized light microscopy. A repeat rheumatoid factor test 2 years after his initial presentation became positive at 57 IU/mL (normal < 20 IU/mL).

**Comment.** Rheumatoid nodules are one of the most common extra-articular manifestations of rheumatoid arthritis, seen in 20% to 25% of cases, and they are usually associated with seropositivity for rheumatoid factor and with more aggressive disease.<sup>1</sup> Rheumatoid nodulosis, on the other hand, usually runs a more benign clinical course.<sup>2</sup> It was first described in 1949,<sup>3</sup> and the diagnostic criteria were developed in 1988 by Couret et al.<sup>4</sup> Patients develop nontender subcutaneous rheumatoid nodules, usually around areas of repeated microtrauma.<sup>2</sup> Often there is a history of attacks of palindromic rheumatism, characterized by recurrent, self-limited episodes of monoarthritis or polyarthritis without an alternative explanation, as in this patient. However, systemic manifestations of rheumatoid arthritis and radiologic evidence of joint damage are often not seen. Rheumatoid factor positivity is also not a requirement. Over time, some patients progress to full-blown rheumatoid arthritis. Methotrexate use has been associated with accelerated rheumatoid nodulosis



FIGURE 3



FIGURE 4

in some rheumatoid arthritis patients.<sup>2</sup>

Rheumatoid nodulosis can be progressive and difficult to treat. Hydroxychloroquine has induced complete resolution in some cases.<sup>5</sup> Surgical removal of the nodules may be considered if they limit joint motion.<sup>6</sup> A placebo-controlled, double-blind trial of intralesional corticosteroid injection has demonstrated efficacy in reducing nodule size.<sup>7</sup>

In our patient, treatment with hydroxychloroquine, sulfasalazine, and methotrexate did not relieve the joint pain, nor did these drugs stop the nodules from growing. He was started on the tumor necrosis factor antagonist etanercept (Enbrel), which

significantly helped the joint pain, but the nodules continued to progress relentlessly. Some of the larger nodules were later injected with triamcinolone (Kenalog), which led to significant shrinkage in nodule size.

### ■ THE OTHER DIAGNOSTIC CHOICES

The other two choices are unlikely.

**Calcinosis cutis** results from the cutaneous deposition of insoluble compounds of calcium (hydroxyapatite or amorphous calcium phosphate), due to local or systemic factors, or both. This can be the result either of ectopic calcification in normal tissue in the setting of hypercalcemia or hyperphosphatemia, or of dystrophic calcification in damaged tissue. They appear as multiple, firm, whitish dermal papules, plaques, nodules, or subcutaneous nodules, which can sometimes ulcerate. They are radio-opaque. On biopsy, dermal deposits of calcium are seen, with or without a surrounding foreign-body giant-cell reaction. Calcium deposition may be confirmed on Von Kossa and alizarin red stains.

**Tuberous xanthomas** are firm, painless, red-yellow nodules that usually develop in pressure areas such as the extensor surfaces of the knees, the elbows, and the buttocks. They can be as-

sociated with familial dysbetalipoproteinemia, familial hypercholesterolemia, and even some of the secondary dyslipidemias. Histologic study shows accumulations of vacuolated lipid-laden macrophages (foamy histiocytes) and sometimes multinucleated histiocytes (Touton giant cells). The lipid droplets are dissolved during routine histologic processing, but lipid stains on frozen sections can be useful. ■

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**ADDRESS:** Soumya Chatterjee, MD, MS, FRCP, Department of Rheumatic and Immunologic Diseases, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail [chattes@ccf.org](mailto:chattes@ccf.org).