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# Multicentric reticulohistiocytosis: A mimic of gout and rheumatoid arthritis

## ■ ABSTRACT

Multicentric reticulohistiocytosis is a rare cutaneous-articular disease that may mimic more common disorders such as rheumatoid arthritis or tophaceous gout. In one fourth of patients, it is a paraneoplastic process. This brief overview is aimed at physicians who care for patients with polyarthritis, to alert them to distinctive features that differentiate multicentric reticulohistiocytosis from the common arthritides.

## ■ KEY POINTS

Multicentric reticulohistiocytosis often involves the distal interphalangeal joints, whereas rheumatoid arthritis does not.

Patients with gout may have tophi in the elbows, ears, Achilles tendon area, and first metatarsophalangeal joint; in contrast, the nodules of multicentric reticulohistiocytosis are typically found in the periungual, truncal, oral, or mucosal areas.

Radiographs of the hands of patients with multicentric reticulohistiocytosis usually show bilateral, symmetric, well-circumscribed erosions that rapidly spread from the marginal areas to the articular surface.

Patients who present with multicentric reticulohistiocytosis should undergo a focused evaluation for an underlying malignancy based on age, sex, and results of their history and physical examination.

**A** 56-YEAR-OLD woman was seen for evaluation of joint pain.<sup>1</sup> The pain was symmetric, involved the small joints of her hands and shoulders, and was associated with stiffness and diminished range of motion. She had noted a “pimple-like” rash on her chin and cheeks that occurred prior to the onset of her joint symptoms. It later spread to involve her chest, back, arms, legs, and hands.

Physical examination revealed tenderness and slight swelling of the small joints of her hands, including the distal interphalangeal joints, and painful, decreased range of motion of the shoulders. Nodules were present on the dorsum of her hands and around the fingernails. Radiographs of the hand revealed bony erosions (**FIGURE 1**), and a skin biopsy demonstrated giant cells with an eosinophilic, ground-glass-like cytoplasm. A diagnosis of multicentric reticulohistiocytosis was made.

The patient was initially treated with naproxen and hydroxychloroquine, which improved her rash but not her joint symptoms. Four months later, methotrexate 12.5 mg/week was added to the regimen. After approximately 1 month she noted modest improvement in her arthritis, and the methotrexate was increased to 22.5 mg/week over the next 4 months. The patient is currently doing well with minimal arthralgias and no rash, and continues to take hydroxychloroquine 200 mg/day and methotrexate 12.5 mg/week.





**FIGURE 1.** Multicentric reticulohistiocytosis. Radiograph of the patient from the case report demonstrates destructive changes in the proximal and distal interphalangeal joints and metacarpophalangeal joints (arrows) with erosions and joint space narrowing. Note lack of periarticular osteopenia.

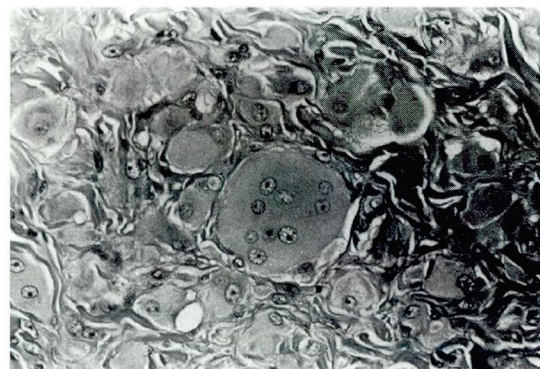
SOURCE: COURTESY OF CLEVELAND CLINIC DEPARTMENT OF MUSCULOSKELETAL RADIOLOGY.

## ■ WHAT IS MULTICENTRIC RETICULOHISTIOCYTOSIS?

Multicentric reticulohistiocytosis is a rare multisystem disorder of unknown etiology, characterized primarily by involvement of the skin and joints. Clinical manifestations include papulonodular cutaneous eruptions and a destructive polyarthritis. The term “multicentric reticulohistiocytosis” was coined by Goltz and Laymon in 1954; the disease is also known as lipoid dermatoarthritis, reticulohistiocytic granuloma, giant cell histiocytosis, and normocholesterolemic xanthomatosis. The most comprehensive reviews of this disease were published in 1969 by Barrow and Holubar<sup>2</sup> and in 1977 by Chevrant-Breton.<sup>3</sup>

## ■ EPIDEMIOLOGY

In all, fewer than 200 cases of multicentric reticulohistiocytosis have been reported; however, because it is similar to rheumatoid arthritis in some features, it may be underreported. Distribution is worldwide. There is no evidence of familial predisposition. The disease has been reported in patients as young as 6 and as old as 71; the mean age is 43.<sup>2</sup> The female-to-male ratio is 3 to 1.



**FIGURE 2.** Multicentric reticulohistiocytosis. Biopsy of an eyelid nodule shows infiltrate of histiocytes and multinucleated giant cells in densely fibrotic stroma. (Hematoxylin-eosin; original magnification, × 100.)

SOURCE: EAGLE RC JR, PENNE RA, HNELESKI IS JR. EYELID INVOLVEMENT IN MULTICENTRIC RETICULOHISTIOCYTOSIS. *OPHTHALMOLOGY* 1995; 102: 426–430.

## ■ PATHOGENESIS AND HISTOPATHOLOGIC FEATURES

In the past, multicentric reticulohistiocytosis was thought to be a disorder of lipid storage. However, serum or cellular lipid abnormalities have not been consistently identified, and most authorities now feel it is an autoimmune disorder. Moreover, it has been seen in association with other autoimmune diseases such as polymyositis, Sjögren syndrome, hypothyroidism, primary biliary cirrhosis, and vitiligo.<sup>2,4</sup>

Biopsy of the skin lesions reveals nodular, well-circumscribed, unencapsulated granulomatous infiltrates with multinucleated giant cells and histiocytes. The giant cells contain multiple vesicular, round-to-oval nuclei with prominent nucleoli, and range in size from 50 to 100  $\mu\text{m}$ . The cytoplasm of both the giant cells and histiocytes has an eosinophilic, ground-glass quality, or less often, may appear foamy and vacuolated (**FIGURE 2**).<sup>5</sup> The cytoplasm contains a periodic acid-Schiff–positive, diastase-resistant material that is composed of glycolipid or glycoprotein, neutral fats, and phospholipids.<sup>2,4,5</sup> Immunohistochemical studies confirm that the cells are of monocyte or macrophage origin.<sup>6</sup>

**25% of cases are associated with various cancers or melanoma**





**FIGURE 3.** Multicentric reticulohistiocytosis. Hands show multiple dermal nodules and shortened fingers with the characteristic telescoping deformity sometimes compared to an accordion or opera glass (*le main en lorgnette*). The deformity is due to destruction of both the distal and proximal interphalangeal joints.<sup>4</sup> Note the short, stubby fingers and the overlying wrinkled skin, which can be stretched back to their normal length. These deformities can also be seen in patients with rheumatoid or psoriatic arthritis. The overall pattern of joint involvement in multicentric reticulohistiocytosis is similar to what is seen in rheumatoid arthritis. However, distal interphalangeal joint involvement, which is classic for multicentric reticulohistiocytosis, is not a normal feature of rheumatoid arthritis. Any peripheral or axial joint may become involved.

SOURCE: EAGLE RC JR, PENNE RA, HNELESKI IS JR. EYELID INVOLVEMENT IN MULTICENTRIC RETICULOHISTIOCYTOSIS. *OPHTHALMOLOGY* 1995; 102: 426-430.

### CLINICAL FEATURES

Multicentric reticulohistiocytosis is usually insidious in onset. In 50% to 65% of cases, a symmetric polyarthritis is the first manifestation, followed months to years later (average 3 years) by a papulonodular cutaneous eruption. Skin manifestations occur first in about 20% of cases, and arthritis and nodules develop simultaneously in another 20%.<sup>2</sup>

Although the joint disease may wax and wane initially, it can progress rapidly and result in a destructive, deforming arthritis ("arthritis mutilans") in about 45% of cases (FIGURE 3).<sup>2</sup> It typically runs its course for 6 to 8 years and then stabilizes, and secondary osteoarthritis develops.

The cutaneous nodules of multicentric reticulohistiocytosis have a cephalocaudal dis-

**TABLE 1**

### Location of characteristic skin nodules in multicentric reticulohistiocytosis

LOCATION	CASES AFFECTED (%)
Face	94%
Hands	91%
Ears or periauricular area	75%
Nail folds	40%
Mucosa*	50%
Eyelids (xanthelasma)	33%

\*Lips > buccal, nasal mucosa

tribution and can be found on any part of the body. The most common sites are the face, hands, and ears, particularly postauricular region of the scalp (TABLE 1, FIGURE 4).<sup>2</sup> Mucosal nodules occur in about half of cases.<sup>2</sup> Xanthelasma occurs particularly in patients with hypercholesterolemia. Anecdotal reports have documented lesions in the bone, bone marrow, muscles, tendons, larynx, pharynx, thyroid gland, salivary glands, heart, lungs, kidney, liver, gastrointestinal tract, eyes, and genitalia.

### LABORATORY AND RADIOGRAPHIC FEATURES

There are no specific laboratory tests that establish the diagnosis. Approximately 50% of patients have an elevated erythrocyte sedimentation rate and are anemic. Synovial fluid analysis usually reveals mild inflammation with a predominance of mononuclear cells. The synovial fluid white blood cell count is typically less than  $30.0 \times 10^9/L$  and may be less than  $4.0 \times 10^9/L$ .<sup>4</sup> Synovial histology reveals the presence of histiocytes and giant cells, similar to that noted in skin and mucosal nodules.

The radiographic findings may help in making the diagnosis early, when cutaneous lesions may be lacking. Besides the characteristic distal interphalangeal joint destruction, multicentric reticulohistiocytosis usually



results in bilateral, symmetric, well-circumscribed erosions, which rapidly spread from marginal areas to the articular surface. The associated subchondral bone resorption may lead to joint space widening and destruction. The degree of destruction is disproportionate to the finding of little or no periarticular osteopenia. In contrast, in rheumatoid arthritis, periarticular osteopenia precedes erosions and may be pronounced (FIGURE 5).

### ■ ASSOCIATED DISEASES

Approximately 20% to 30% of patients with multicentric reticulohistiocytosis have an underlying malignant disease. In 1995, Snow and Muller<sup>7</sup> reviewed 133 cases of multicentric reticulohistiocytosis and found that 33 (25%) were associated with cancers of the blood, breast, stomach, cervix, mesothelium, lung, ovary, colon, skin (melanoma), or pancreas.

### ■ DIFFERENTIAL DIAGNOSIS

Although the diagnosis of multicentric reticulohistiocytosis is usually straightforward when the clinical, radiographic, and histopathologic findings are combined, some aspects of the differential diagnosis may lead to confusion. Several diseases resemble multicentric reticulohistiocytosis in some features, but with important differences.

**Rheumatoid arthritis** usually does not involve the distal interphalangeal joints. Distal interphalangeal joint abnormalities in an elderly patient with rheumatoid arthritis are usually due to concurrent osteoarthritis.

**Psoriatic arthritis** also produces lesions on the skin and nails, but these are silvery, scaly papules and plaques, not nodules. In addition, 75% of patients with psoriatic arthritis have asymmetrical joint involvement and periosteal formation of new bone (FIGURE 6), whereas the joint involvement in multicentric reticulohistiocytosis is symmetrical and includes bone destruction, not periostitis.

**Gout.** Gouty tophi are differentiated from the nodules of multicentric reticulohistiocytosis by their location in the elbow, ears, Achilles tendon area, and first metatarsophalangeal joint region. Gouty tophi are not



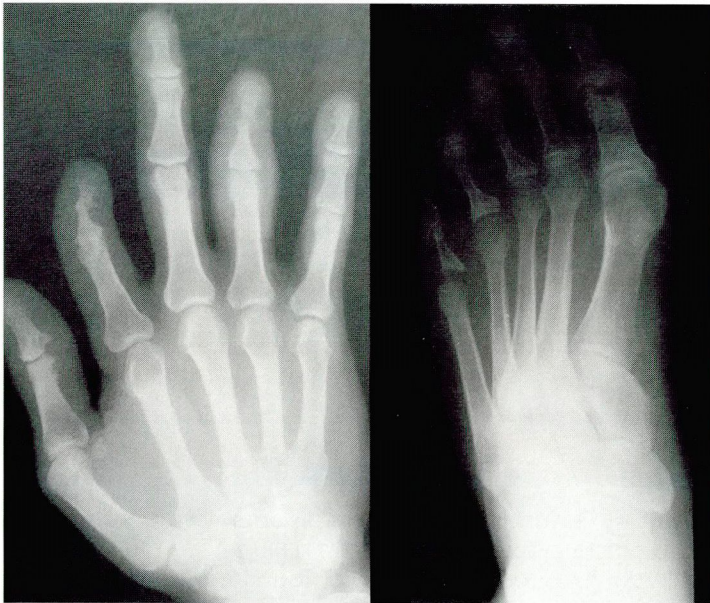
**FIGURE 4.** Periungual nodules in a patient with multicentric reticulohistiocytosis. A cutaneous hallmark of multicentric reticulohistiocytosis are nail-fold nodules, arranged in a "coral bead" pattern. In patients with extensive facial, nasal, and paranasal nodular disease, disfigured leonine facies may result. This can also be seen in patients with leprosy or Sezary syndrome. The nodules range in size from a few millimeters to several centimeters and are a light copper to dark reddish-brown color. They are usually firm and nontender. Pruritus is reported in one third of patients.

SOURCE: COURTESY OF CLEVELAND CLINIC FOUNDATION DEPARTMENT OF DERMATOLOGY.



**FIGURE 5.** Rheumatoid arthritis. Hand radiograph of a patient with rheumatoid arthritis, showing prominent periarticular osteopenia. There is also erosive disease with joint space narrowing and subluxation of the metacarpophalangeal joints as well as proximal interphalangeal joint narrowing and erosions and joint space narrowing involving the wrist. Note the symmetrical findings.





**FIGURE 6.** Psoriatic arthritis. Hand and foot radiographs of a patient with psoriatic arthritis. There is soft tissue swelling with a "sausage-like" fourth digit. Also, the second and fourth distal interphalangeal joints demonstrate a "pencil-in-cup"-like deformity characteristic of this disease. There are similar erosive destructive lesions in the foot, primarily in the first and fifth interphalangeal joints.

found in periungual, truncal, oral, or mucosal areas typical of multicentric reticulohistiocytosis. Furthermore, the articular erosions in gout are asymmetric, produce the overhanging ledge sign, and often spare the joint space (FIGURE 7).

**Erosive osteoarthritis** is differentiated from multicentric reticulohistiocytosis by its central erosions with associated osteophytes and bony sclerosis (FIGURE 8).

**Leprosy**, like multicentric reticulohistiocytosis, causes shortening of the fingers, leonine facies, and (usually) acro-osteolysis. However, unlike patients with multicentric reticulohistiocytosis, patients with leprosy have associated neurosensory findings, and tight, not wrinkled, skin overlying the stubby fingers.

## TREATMENT

The efficacy of treatment is difficult to assess, as the rarity of multicentric reticulohistiocytosis precludes controlled trials. Spontaneous

remissions occasionally occur. Twenty to 30 years ago when patients with multicentric reticulohistiocytosis were treated with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) alone, 45% developed arthritis mutilans. Recent reports suggest that aspirin, NSAIDs, D-penicillamine, azathioprine, hydroxychloroquine, and cyclosporine are generally ineffective. However, corticosteroids combined with chlorambucil or cyclophosphamide,<sup>8</sup> or methotrexate<sup>1,9-11</sup> have been shown to diminish joint and skin manifestations.

## CONCLUSION

Multicentric reticulohistiocytosis is rare, potentially destructive, disabling, and disfiguring. Although it may be confused with other types of inflammatory arthritis, one can usually confirm the diagnosis on the basis of the characteristic cutaneous, radiographic, and histologic features. Because multicentric reticulohistiocytosis can be a paraneoplastic phenomenon, evaluations must take a possible underlying malignancy into consideration.

The rarity of multicentric reticulohistiocytosis precludes precise recommendations about what evaluation to perform to search for an occult malignant disease. However, we believe it is reasonable to perform a complete history and physical examination, chest radiography, mammography (for women), complete blood count, and a chemistry profile that includes hepatic enzymes. If a malignant disease is found, treatment should focus on that disorder. For other patients, recent reports have suggested that early and aggressive treatment with steroids and cytotoxic agents may reduce disease progression.

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**FIGURE 7.** Gouty arthritis. Foot radiograph of a patient with gouty arthritis that displays the characteristic punched-out erosion of the first metatarsal with an overhanging ledge (arrow) and normal joint space.

SOURCE: COURTESY OF THE CLEVELAND CLINIC DEPARTMENT OF MUSCULOSKELETAL RADIOLOGY.



**FIGURE 8.** Erosive osteoarthritis. Hand radiograph of a patient with erosive osteoarthritis involving the distal and proximal interphalangeal joints with normal metacarpophalangeal joints and a somewhat "seagull" appearance to the second and third distal interphalangeal joints.

SOURCE: COURTESY OF THE CLEVELAND CLINIC DEPARTMENT OF MUSCULOSKELETAL RADIOLOGY.

**Perform  
a focused  
evaluation for  
an underlying  
malignancy**

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