

Multicentric Reticulohistiocytosis With Arthralgia and Red-Orange Papulonodules

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PRACTICE POINTS

- Multicentric reticulohistiocytosis (MRH) is an important entity to recognize given its association with underlying malignancy and irreversible destructive arthritis.
- Diagnosis of MRH warrants extensive review of systems, age-appropriate cancer screening, and relevant systemic workup.
- Early pharmacologic intervention should be initiated with nonsteroidal anti-inflammatory agents or immunosuppressant agents.

elevated total cholesterol (244 mg/dL [reference range, <200 mg/dL]), low-density lipoproteins (130 mg/dL [reference range, 10–30 mg/dL]), aspartate aminotransferase (140 U/L [reference range, 10–30 U/L]), alanine aminotransferase (110 U/L [reference range, 10–40 U/L]), and total bilirubin (1.5 mg/dL [reference range, 0.3–1.2 mg/dL]). White blood cell count and C-reactive protein levels were within reference range. An antinuclear antibody titer of 1:80 with a homogenous pattern was found, and aldolase levels were elevated. Laboratory investigations for rheumatoid factor, Lyme disease, tuberculosis, hepatitis, and human immunodeficiency virus were negative. A chest radiograph was normal.

To the Editor:

A 50-year-old woman presented with an asymptomatic eruption on the dorsal aspect of the hands, abdomen, and face of 6 months' duration. The eruption was associated with generalized arthralgia and fatigue. Within several weeks of onset of the cutaneous eruption, the patient developed swelling in the hands as well as worsening arthralgia. She was treated for presumed *Lyme borreliosis* but reported no improvement in the symptoms. She was then referred to dermatology for further management.

Physical examination revealed red-orange, edematous, monomorphic papulonodules scattered on the nasolabial folds, upper lip, and along the dorsal aspect of the hands and fingers (Figure 1). A brown rippled plaque was present on the left lower abdomen. The oral mucosa and nails were unremarkable. Laboratory studies showed



FIGURE 1. Red-orange, edematous, monomorphic papulonodules scattered along the dorsal aspect of the hand and fingers.

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A punch biopsy from the right dorsal hand revealed a dermal proliferation of mononucleated and multinucleated epithelioid histiocytes with ample amounts of eosinophilic ground-glass cytoplasm (Figure 2). Immunohistochemistry revealed epithelioid histiocytes reactive for CD68, CD163, and factor XIIIa, and negative for S-100 and CD1a.

The patient was diagnosed with multicentric reticulohistiocytosis (MRH) and was initially treated with prednisone. Treatment was later augmented with etanercept and methotrexate with improvement in both the skin and joint symptoms.

Multicentric reticulohistiocytosis is a rare, non-Langerhans cell histiocytosis with both cutaneous and systemic features. Although case reports date back to the late 1800s, the term *multicentric reticulohistiocytosis* was first used in 1954.¹ Multicentric reticulohistiocytosis is extremely uncommon and precludes thorough investigation of its etiology and management. The condition typically presents in the fifth to sixth decades of life and occurs more frequently in women with a female to male ratio estimated at 3 to 1.^{2,3} Pediatric cases have been reported but are exceedingly rare.⁴

Multicentric reticulohistiocytosis typically presents with a severe erosive arthropathy known as arthritis mutilans. Patients display a symmetric polyarthritis that commonly involves the elbows, wrists, and proximal and distal aspects of the interphalangeal joints. Onset and progression can be rapid, and the erosive nature leads to deformities in up to 45% of patients.^{2,5,6} Cutaneous findings arise an average of 3 years after the development of arthritis, though one-fifth of patients will initially present with cutaneous findings followed by the development of arthritis at any time.^{3,6} Clinical features include flesh-colored to reddish brown or yellow papulonodules that range in size from several millimeters to 2 cm. The

lesions most commonly occur on the face (eg, ears, nose, paranasal cheeks), scalp, dorsal and lateral aspects of the hands and fingers, and overlying articular regions of the extremities. Characteristic periungual lesions classically are referred to as coral beads.^{4,6} Patients commonly report pruritus that may precede the development of the papules and nodules. Other cutaneous manifestations include xanthelasma, nail changes, and a photodistributed erythematous maculopapular eruption that may mimic dermatomyositis.⁶

Cutaneous findings of MRH can mimic rheumatoid nodules, gout, Gottron papules of dermatomyositis, lipoid proteinosis, sarcoidosis, lepromatous leprosy, granuloma annulare, xanthoma, xanthogranuloma, and fibroxanthoma.^{6,7} Histopathologic features may distinguish MRH from such entities. Findings include fairly well-circumscribed aggregates of large multinucleated giant cells with characteristic eosinophilic ground-glass cytoplasm. Histiocytes stain positively for CD68, HAM56, CD11b, and CD14, and variably for factor XIIIa. CD68, which is expressed by monocytes/macrophages, has been universally reported to be the most reliable marker of MRH. Negative staining for S-100 and CD1a supports a non-Langerhans origin for the involved histiocytes. If arthritic symptoms predominate, MRH must be distinguished from rheumatoid and psoriatic arthritis.^{6,7}

Mucosal involvement occurs in approximately 50% of patients and includes the presence of nodules in the oral, nasal, and pharyngeal mucosae, as well as eye structures.^{2,3} Histiocytic infiltration has been documented in the heart, lungs, thyroid, liver, stomach, kidneys, muscle, bone marrow, and urogenital tract. Histiocytes also can invade the cartilage of the ears and nose causing disfigurement and characteristic leonine facies. Pathologic fractures may occur with bone involvement.⁵

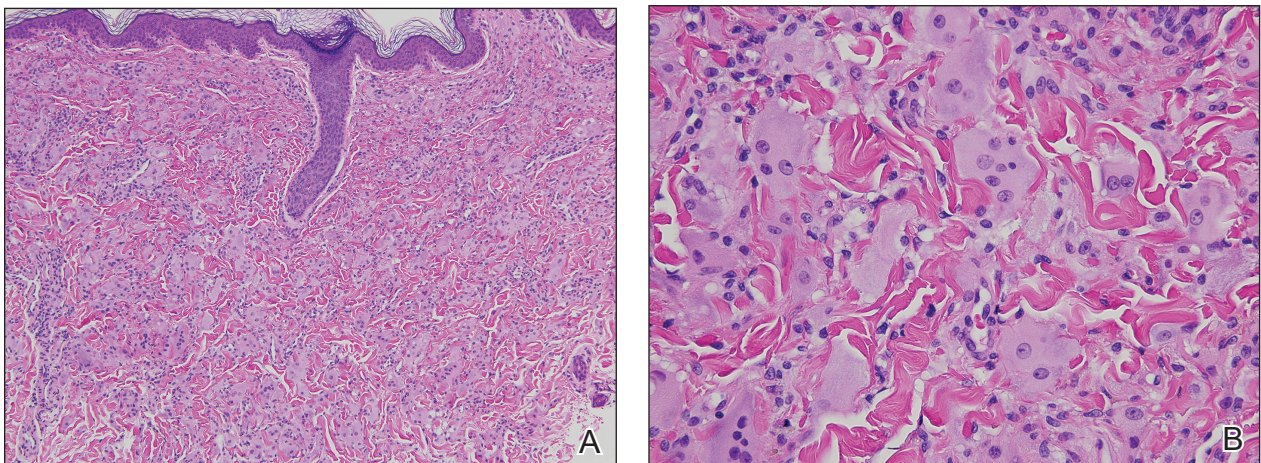


FIGURE 2. A, Punch biopsy revealed a proliferation of mononucleated and multinucleated epithelioid cells within the dermis (H&E, original magnification $\times 10$). B, Ample amounts of eosinophilic ground-glass cytoplasm as well as some multinucleated cells with multiple haphazardly oriented nuclei also were seen (H&E, original magnification $\times 40$).

Systemic features associated with MRH include hyperlipidemia, diabetes mellitus, thyroid disease, hypergammaglobulinemia, and various autoimmune diseases. Patients less frequently report fever and weight loss.^{2,5,6,8} Additionally, a positive tuberculin test occurs in 12% to 50% of patients.⁶ Various autoimmune diseases occur in 6% to 17% of cases including systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, dermatomyositis, Sjögren syndrome, and primary biliary cirrhosis.^{2,5,6,8} The most clinically salient feature of MRH is its association with malignant conditions, which occur in up to 31% of patients. A variety of cancers have been reported in association with MRH, including breast, cervical, ovarian, stomach, penile, lymphoma, mesothelioma, and melanoma.⁷

The etiology of MRH is unclear. Although onset may precede the development of a malignant condition and regress with treatment, it cannot be considered a true paraneoplastic disorder, as it has no association with a specific cancer and does not typically parallel the disease course.^{6,9} Reports of increased levels of inflammatory mediators released from macrophages and endothelial cells, specifically IL-12, IL-1 β , IL-6, and tumor necrosis factor α (TNF- α), have been thought to drive the destruction of bone and cartilage.⁶ In particular, TNF- α acts to indirectly induce destruction by stimulating proteolytic activity in macrophages, similar to the pathogenesis of joint damage in rheumatoid arthritis.⁸ Osteoclastic activity may play a role in the pathogenesis of MRH, as multinucleated giant cells in MRH can mature into osteoclasts by receptor activated nuclear factor- κ B ligand signaling. In addition, patients treated with bisphosphonates have had decreased lacunar resorption.^{2,8}

Initial management of MRH should include screening for hyperlipidemia, hypergammaglobulinemia, hyperglycemia, thyroid dysfunction, and autoimmune diseases, as well as age-appropriate cancer screening. Imaging studies should evaluate for the presence of erosive arthritis. There are no well-defined treatment algorithms for MRH due to the rarity of the disease, and recommendations largely rely on case reports. Although spontaneous remission typically occurs within 5 to 10 years, the risk for joint destruction argues for early pharmacologic intervention. Current management includes the use of nonsteroidal anti-inflammatory drugs and various immunosuppressants including oral glucocorticoids, cyclophosphamide, chlorambucil, methotrexate, or azathioprine.² A combination of methotrexate with cyclophosphamide or

glucocorticoids also has shown efficacy.¹⁰ Anti-TNF- α agents, such as etanercept, adalimumab, and infliximab, have been used with some success.² Tumor necrosis factor α inhibitors used in combination with oral glucocorticoids and methotrexate may have an increased benefit.^{2,9,11} Evidence suggesting that TNF- α plays a role in the destruction of bone and cartilage led to the successful use of infliximab in combination with oral glucocorticoids and methotrexate, which prevented possible development of antibodies to infliximab and increased its efficacy.¹² Bisphosphonate use in combination with glucocorticoids and methotrexate may prevent joint destruction without the serious adverse events associated with anti-TNF- α agents.^{2,9,13,14}

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