Multicentric Reticulohistiocytosis: Contrasting Presentations in 2 Hispanic Patients

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Practice Points

- Multicentric reticulohistiocytosis must be considered in Hispanic patients and may be underreported in this patient population.
- Pruritus can be severe and debilitating. It might be a sole feature of this condition without skin lesions.
- Early recognition is key in the hopes of halting destructive arthritis.

Multicentric reticulohistiocytosis (MR) is a rare debilitating disease that involves the skin and joints. It most commonly affects white individuals but has been reported in other ethnic groups including black individuals, Native Americans, and Asians. The Hispanic population is largely underrepresented in the epidemiology of MR. We describe 2 Hispanic patients with contrasting presentations of MR. Prompt recognition of MR is essential to expedite treatment and prevent potentially disabling sequelae of undiagnosed disease; however, diagnosis can be challenging due to the wide range of clinical presentations of MR as well as variable laboratory findings, especially in patients with skin of color. Our case reports underscore this phenomenon and demonstrate the importance of considering MR in all ethnic groups, including Hispanic patients.

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Case Reports

Patient 1—A 61-year-old Puerto Rican man presented for evaluation of persistent pruritic papules and nodules associated with joint pain of 3 months' duration. Symptoms began with hand weakness and stiffness followed by development of bilateral leg weakness accompanied by diffuse, painful, itchy red lesions that interfered with the patient's sleep. The patient also reported a poor appetite and a recent 46-lb weight loss. Treatment with hydrocortisone cream 1% and oxycodone therapy had minimal impact. On physical examination, indurated erythematous papules and nodules were noted on the forehead, ears (Figure 1A), nasal bridge, elbows, hands, nail folds (Figure 1B), knees, and dorsal aspect of first toes. The hands were diffusely erythematous over both palmar and dorsal surfaces with notable swelling of all phalangeal joints. Erythematous papules coalescing into plaques were observed on the neck, shoulders, upper chest, and back.

Laboratory results indicated anemia and an elevated erythrocyte sedimentation rate. Positive serologies included antinuclear antibodies, rheumatoid factor, anti–SS-A (Sjögren syndrome antigen A), and anti-DNA antibodies. Serum protein electrophoresis was positive for human gamma globulin. All other laboratory results were within reference range, including a negative purified protein derivative (PPD)(tuberculin) skin test. Radiographic musculoskeletal testing showed mild degenerative changes including scattered spurring of the distal

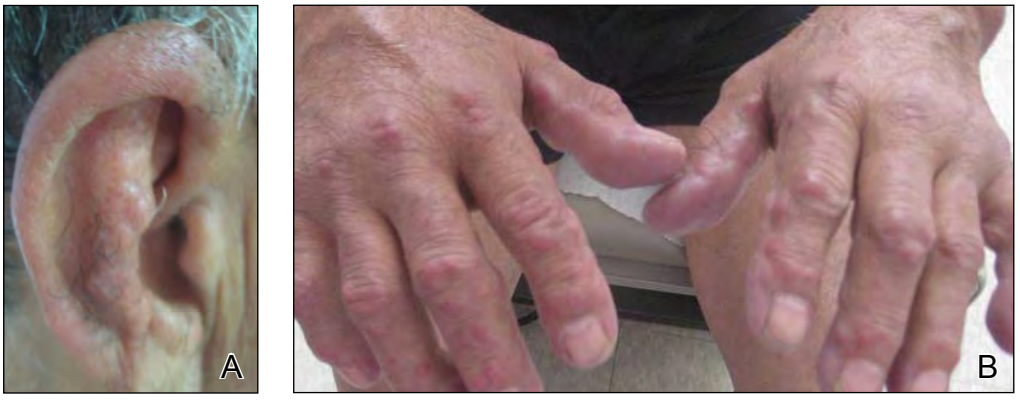

Figure 1. Indurated erythematous papules and nodules over the right ear (A), hands, and nail folds (B). The hands were diffusely erythematous with notable swelling of all phalangeal joints.

interphalangeal (DIP) joints and bilateral spurring of the first metacarpophalangeal joints as well as moderate to large bilateral superpatellar effusions with mild bilateral periarticular osteophytes. Punch biopsies of a plaque from the right shoulder and an elbow nodule demonstrated dermal collections of mono- and multinucleated histiocytes with abundant, eosinophilic, ground-glass cytoplasm. A diagnosis of reticulohistiocytoma was made and, given the constellation of findings, was consistent with multicentric reticulohistiocytosis (MR). Malignancy workup included a colonoscopy, which was negative, and computed tomography of the chest, abdomen, and pelvis, which was inconclusive. Treatment with methotrexate resulted in minimal improvement. Alleviation of symptoms was achieved with oral prednisone.

Patient 2—A 45-year-old woman who was originally from the Dominican Republic presented for evaluation of persistent pruritic papules of 3 months' duration. Symptoms began with generalized severe pruritus that was most pronounced over the arms and legs with an absence of cutaneous findings. One month later, multiple small, flesh-colored and red, itchy lesions erupted on the arms and progressed to the ears and legs. Symptoms were refractory to treatment with topical corticosteroids. Within 3 months, intense swelling and arthritis developed, restricting daily activities. The patient's medical history indicated a positive PPD skin test. A review of systems was negative. Physical examination revealed linear and grouped, 1- to 2-mm, soft, erythematous and flesh-colored papules on the ears (Figure 2A) and upper arm (Figure 2B). Erythematous linear papules coalescing into plaques were observed on the face and anterior aspect of the chest. Diffuse swelling and tenderness over the phalangeal joints as well as a 1-cm indurated erythematous papule over the dorsal aspect of the left index finger were noted (Figure 2C).

Laboratory results indicated anemia; all other results were normal. Radiographic musculoskeletal testing showed mild bilateral degenerative changes at the interphalangeal and metacarpophalangeal joints, including tiny erosions at the DIP joint of the fourth digit on the right hand, as well as bilateral knee joint effusions. Punch biopsy of a lesion on the right arm revealed collections of mono- and multinucleated histiocytes with eosinophilic cytoplasm that had a ground-glass appearance within the dermis (Figure 3). A diagnosis of MR was made. Malignancy workup including mammography, colonoscopy, and computed tomography of the abdomen and pelvis was negative. The patient was referred to the rheumatology and oncology departments and was started on oral prednisone with minimal improvement. Cladribine chemotherapy yielded mild improvement on the hands.

Comment

Multicentric reticulohistiocytosis is a rare systemic disease belonging to class II (non–Langerhans cell) histiocytoses. It is characterized by a cutaneous papulonodular eruption and progressive polyarthritis, though systemic findings are common. Disease onset is insidious, usually affecting women around the fourth decade of life, and occurs primarily in white patients, representing 80% of cases.[1] Sporadic cases also have been reported in black individuals, Native Americans, and Asians.[1,2] Strikingly, a PubMed search of articles indexed for MEDLINE using the terms *multicentric reticulohistiocytosis*, *Hispanic*, *race*, and *epidemiology* only revealed 1 case report of an MR in a Hispanic patient.[3] Therefore, it seems the Hispanic population is considerably underrepresented in the epidemiology of MR, which underscores the importance of our findings.

The course of symptoms in MR waxes and wanes, and the disease becomes clinically inactive after a

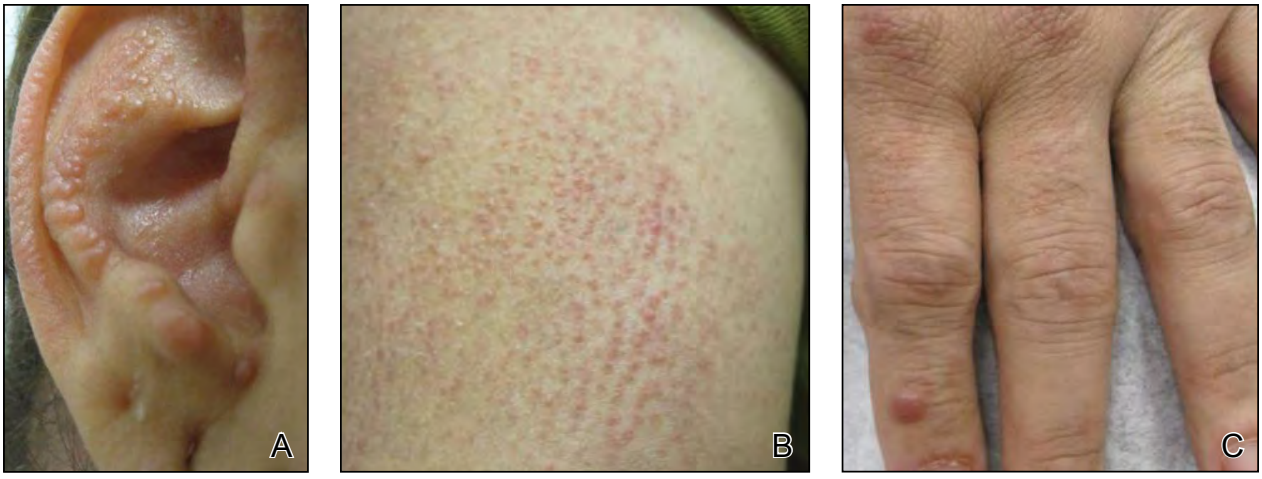

Figure 2. Linear and grouped, 1- to 2-mm, soft, erythematous and flesh-colored papules over the helix of the right ear (A) and upper arm (B). A 1-cm indurated erythematous papule also was present on the dorsal aspect of the left index finger (C).

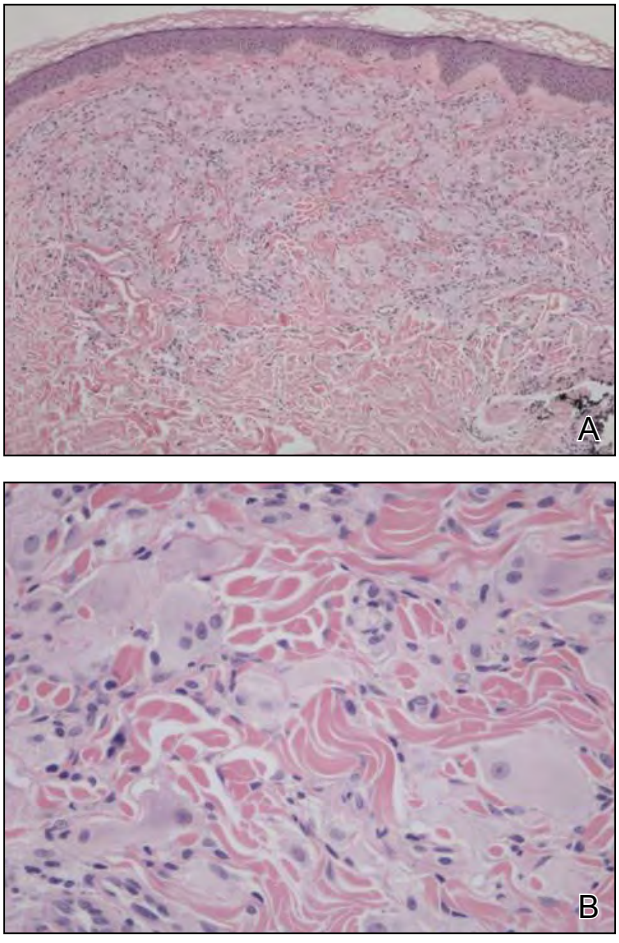

Figure 3. Punch biopsy of a lesion on the right arm revealed increased cellular infiltration on low-power magnification (A) with collections of mono- and multinucleated histiocytes with eosinophilic cytoplasm that had a ground-glass appearance within the dermis on high-power magnification (B)(H&E; original magnifications ×10 and ×40, respectively).

period of approximately 8 years.[4] Arthritis is the primary presenting feature in two-thirds of patients, followed by cutaneous manifestations developing months to years later, with an average delay of 3 years.[1] Skin involvement has been reported as a presenting sign in 18% to 20% of cases[1,4] and concurrent presentation with arthritis was reported in 21% of cases.[1] The interphalangeal joints, particularly the DIP joints of the hands, are most commonly affected (75%). Destruction of the DIP joint is the major distinguishing feature of MR.[1] Other commonly involved joints include the knees, hips, wrists, and spine.[1,4] Joint involvement often is symmetrical, well circumscribed, rapidly progressive, and destructive, resulting in arthritis mutilans in nearly 50% of patients.[1] Arthritis generally begins at the joint margins and advances to the entire joint surface,[4] leading to widening of the joint space, loss of cartilage, and resorption of subchondral bone.[5] Because arthritis typically antedates cutaneous manifestations in the majority of MR patients, radiographic findings are important in making an early diagnosis and differentiating MR from other forms of erosive arthritis.

Cutaneous manifestations typically include multiple pruritic papules and nodules that range from flesh colored to dark red-brown and vary in size from a few millimeters to several centimeters in diameter.[1,2,5] Of note, generalized pruritus may precede these skin findings.[4] Lesions may be scattered and isolated, or they may be grouped into confluent masses with a cobblestone appearance. Cephalocaudal distribution also has been described, with papules and nodules most commonly presenting on the face, ears, and hands, but also affecting the elbows, shoulders, trunk, and lower extremities.[1,5] On the hands, papules and

nodules frequently are arranged and clustered around the nail folds, which commonly is referred to as the coral bead sign.[1,2,4,5] Lesions may be associated with disorganized nail growth, including longitudinal ridging, brittleness, and hyperpigmentation. Mucosal involvement generally is seen in more than 50% of patients.[1]

Systemic concerns are common and include fever, malaise, weakness, and weight loss. Common laboratory findings include an elevated erythrocyte sedimentation rate and anemia. Patients rarely will have a positive rheumatoid factor, antinuclear antibodies, and hypergammaglobulinemia.[1,2,4,5] Multicentric reticulohistiocytosis also has been associated with hyperlipidemia, xanthelasma, and a positive PPD skin test in up to 50% of cases, though association with or presence of acid-fast bacilli have yet to be demonstrated through histology or culture.[2,5] Strikingly, concomitant carcinoma has been reported in up to one-quarter of MR patients, particularly of the muscles, breasts, or gastrointestinal tract.[1,4-6] Therefore, it is crucial to search for underlying malignancies in all MR patients. Diagnosis of MR requires clinicopathologic correlation with biopsies of nodules in the skin or synovium. Characteristic skin lesions typically present as reticulohistiocytomas, which also can occur as solitary lesions not associated with MR.

Although MR is considered self-limiting, it does have a tendency to become clinically quiescent after approximately 8 years.[1] The risk for developing disabling destructive arthritis and disfiguring dermatitis substantiates the need for aggressive treatment, which unfortunately is lacking.[5] Analgesics or nonsteroidal anti-inflammatory drugs may be useful for symptomatic relief in patients with mild or inactive disease, but these treatments are not disease-modifying interventions. Immunosuppressive and cytotoxic agents have been more successful, specifically when introduced early in the course of the disease. Corticosteroids alone or in combination with methotrexate may be used as the initial treatment in moderate to severe cases as well as cyclophosphamide or chlorambucil in more refractory cases.[4,5] Methotrexate appears to target arthritis symptoms, while cyclophosphamide and chlorambucil have been reported to be more effective in treating cutaneous lesions. The use of cyclosporine, alendronate, and tumor necrosis factor α inhibitors also has been reported with promising results.[4]

Conclusion

Multicentric reticulohistiocytosis is a rare, debilitating, and sometimes unpredictable systemic disease of unknown etiology that primarily involves the joints and skin. In the current case series, we present 2 contrasting and unusual presentations of MR in Hispanic patients. Our case reports are a unique reminder to dermatologists that MR should be considered when clinically appropriate to prevent potentially disabling and even life-threatening sequelae of undiagnosed disease.

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