Multicentric Reticulohistiocytosis

A Unique Case With Pulmonary Fibrosis

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Background: Multicentric reticulohistiocytosis (MRH) is a rare disease of uncertain etiology that most commonly presents as a papulonodular cutaneous eruption accompanied by erosive polyarthritis. Although MRH is considered a systemic disorder in that it targets skin and joints, involvement of thoracic and visceral organs is uncommon.

Observations: A woman presented with diffuse cutaneous nodules, and skin biopsy findings revealed classic features of MRH. However, she also manifested severe pulmonary symptoms. A lung biopsy specimen showed prominent histiocytic infiltrates exhibiting the same characteristic morphologic features as those seen in her skin. Furthermore, the lung biopsy findings were significant for a pattern of usual interstitial pneumonia accompanied by notable lymphoid aggregates, a pattern of interstitial lung disease typical of systemic autoimmune and inflammatory conditions.

Conclusions: These findings are notable because a histiocytic pulmonary infiltrate suggestive of direct pulmonary involvement by MRH is a rare event. In addition, presentation of MRH in the setting of usual interstitial pneumonia is unique. These observations document a new clinical and histopathologic presentation of MRH that is significant for expanding the idea of MRH as a systemic disease while supporting the notion that MRH is promoted by an inflammatory milieu.


Multicentric reticulohistiocytosis (MRH) is a disease of unknown etiology characterized by diffuse skin lesions and destructive polyarthritis. It was first described in 1937 in a 35-year-old man with a 6-month history of fevers, joint pain, and cutaneous nodules. The histiocytic nature of the disease was elucidated in 1944 by intralesional olive oil injection followed by biopsy results demonstrating phagocytosis. The term multicentric reticulohistiocytosis was coined in 1954, highlighting the systemic, multicentric nature of the disease and its origin from cells of the reticuloendothelial system.

Multicentric reticulohistiocytosis is rare, with approximately 200 cases reported in the literature to date. The disease manifests most commonly in middle-aged women, with a female predominance of approximately 2.1 to 1.3 and an average age at onset of 40 to 50 years. A few cases have been reported in children and pregnant women. Multicentric reticulohistiocytosis has been associated with tuberculosis or a positive tuberculin skin test result (12%-50% of cases), hyperlipidemia (30%-58% of cases), and malignancy. The association with malignancy is relatively common and has been reported in 15% to 31% of cases of MRH. Malignancy may be preceded by or be present concomitantly with the cutaneous manifestations of MRH, and regression of MRH has been reported subsequent to tumor treatment. No single malignant process is implicated, and reported cases include melanoma, mesothelioma, lymphoma, and carcinomas of the penis, stomach, ovary, endometrium, breast, and cervix.

The clinical differential diagnosis of MRH may be extremely broad. If erosive arthritis predominates, then rheumatoid arthritis, psoriatic arthritis, Reiter syndrome, and gout are major diagnostic considerations. If cutaneous lesions predominate, the differential diagnosis may include xanthomatosi, juvenile xanthogranuloma, generalized eruptive histiocytosis, cutaneous Rosai-Dorfman disease, lepromatous leprosy, neurofibromatosis, and sarcoidosis, among others. When present, acral or facial nodules in MRH may help to narrow this differential diagnosis.
Histopathologic findings reveal a proliferation of large, multinucleated histiocytic cells characterized by a 2-toned or a “ground-glass” cytoplasm that is finely granular and eosinophilic. Lymphocytes, plasma cells, mast cells, and eosinophils may be variably present in early lesions, but they decrease in number with time as lesions become increasingly fibrotic. Results of immunohistochemical studies vary; however, in most cases, findings are positive for CD68, CD45, CD4, HLA-DR, lysozyme, and α1-antitrypsin, whereas CD1a, S-100, CD20, and factor XIIIa generally do not stain.

The histopathologic differential diagnosis includes solitary reticulohistiocytoma and diffuse cutaneous histiocytosis. Clinical pathologic correlation is necessary to distinguish between these entities. Immunohistochemical analysis may be helpful in differentiating MRH from other histiocytoses. For example, Langerhans cell histiocytosis displays a characteristic immunohistochemical profile positive for S-100 and CD1a, whereas both of these immunohistochemical stains yield negative findings in MRH.

**REPORT OF A CASE**

A 47-year-old African American woman was referred to our institution with several months of fever and joint pain, morning stiffness, and cutaneous nodules. Family history was notable for a sister with sarcoidosis and a mother with rheumatoid arthritis. Physical examination revealed multiple nontender cutaneous nodules ranging from 1 to 5 mm, primarily localized to the base of the nails of both hands but also noted around the perioral region, chin, chest, right thigh, and left upper arm (Figure 1). In some areas, the lesions had coalesced to form plaques. In addition, she had diffuse bilateral swelling of the proximal interphalangeal, metacarpophalangeal, and wrist joints without apparent synovitis to suggest rheumatoid arthritis.

Results of laboratory analyses were significant for an antinuclear antibody level of 1:2560 (corresponding to high-titer positivity), a rheumatoid factor level of 109 IU (reference level, <20 IU), and positive findings for anti-Ro and anti-La antibodies. Negative findings included negative anti–double-stranded DNA, anti-Smith and anti-RNP antibodies, and levels of C3 and C4 within their reference ranges. An anti–crystalloid cardioplegia titer was within the reference range on 2 separate occasions.

Radiographic imaging of her hands showed reactive periostitis with proliferative and erosive changes. Imaging of the chest showed bilateral, predominantly lower lobe reticulation and honeycombing, which are characteristic features of usual interstitial pneumonia (UIP) (Figure 2). However, unusual radiographic findings included the presence of small bilateral pulmonary nodules and bilateral hilar and mediastinal lymphadenopathy.

Given her constellation of findings (UIP, erosive arthritis, and serologic findings), she was initially given a diagnosis of undifferentiated connective tissue disease. She was treated with high-dose corticosteroids and leflunomide, with little effect. Trials of methotrexate and azathioprine had to be discontinued owing to intolerance.

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Figure 1. The patient presented with innumerable 1- to 5-mm cutaneous nodules that were prominent around the nail beds (A) and the perioral region (B).

Figure 2. A computed tomographic scan of the chest was remarkable for bilateral, predominantly lower lobe reticulation and honeycombing. A indicates anterior; P, posterior.
A biopsy of the cutaneous nodules was performed, and the specimen revealed a proliferation of large histiocytes and multinucleated giant cells with ground-glass cytoplasm (Figure 3). Immunohistochemical staining for CD68 highlighted the histiocytes, whereas staining for S-100 yielded negative results. Together, the clinical and histopathologic findings supported a diagnosis of MRH. A malignancy workup was recommended at this point; however, it was not completed at our institution.

To further characterize the patient’s pulmonary disease, a wedge biopsy specimen of the lung was obtained. Biopsy results showed prominent histiocytic aggregates consisting of large cells and occasional multinucleated giant cells with a finely granular cytoplasm (Figure 4). The histopathologic features of these aggregates were the same as had been previously observed in biopsy findings of her cutaneous nodules. The lung biopsy specimen also showed a diffuse, variated, and severe pattern of fibrosing interstitial pneumonia with areas of sparing, fibroblast foci, and honeycombing. Lymphoid aggregates were scattered throughout. As will be discussed in the “Comment” section, this pattern of UIP with prominent lymphoid aggregates is often seen in UIP developing in patients with systemic autoimmune and inflammatory disease.

She was treated with a 3- to 4-month course of hydroxychloroquine, with improvement in her joint symptoms but no improvement in her cutaneous lesions. A plan was formulated for treatment with adalimumab; however, the patient did not initiate therapy and was eventually lost to follow-up.

**COMMENT**

We herein present a case of MRH in a patient with interstitial lung disease in the form of UIP. This case is unique in its pulmonary findings. To date, very few studies have shown pulmonary symptoms in patients with MRH. An early suggestion was made that there might be an association with tuberculosis; however, additional case reports have not supported this association. Several reports have observed nonspecific pulmonary pathologic findings, including hilar adenopathy, pulmonary infiltrates, and pleural effusions.

To our knowledge, only 4 reports have shown pulmonary involvement by MRH based on results of tissue examination, and ours is the first to describe UIP coincident with MRH. One case was that of a 56-year-old man with multiple nodules in the lungs bilaterally that biopsy findings suggested were consistent with MRH. The second case was that of a 78-year-old man with nonspecific bilateral parenchymal disease and focal nodules. A transbronchial lung biopsy specimen was notable for a mixed inflammatory infiltrate containing numerous foamy histiocytes. The third case involved a pleural biopsy of a 50-year-old woman with bilateral basilar alveolar infiltrates, which revealed histiocytic cells and scattered multinucleated giant cells containing material positive for periodic acid–Schiff and consistent with MRH. Finally, postmortem examination of a 75-year-old man revealed patchy pleural thickening, and microscopic examination of pleural tissue showed foamy histiocytic cells consistent with MRH.

Biopsy material from our patient showed numerous histiocytic aggregates within pulmonary tissue. The cytologic features of these histiocytes were distinct from the more traditional, scattered, desquamative, interstitial, pneumonia-like alveolar macrophages and were strikingly similar to those observed in cutaneous histiocytic nodules. Because there is no stain specific to MRH, diagnosis must be made with hematoxylin-eosin examination of histopathologic specimens and clinical information. Together, findings described are most consistent with direct pulmonary involvement by MRH, making ours the fifth case reported to date.

In addition, MRH changes in the lung occurred in a background of UIP, which has not been reported previously. Usual interstitial pneumonia is a specific form of fibrosing interstitial lung disease characterized by patchy areas of new and old fibrosis intermixed with normal areas of lung tissue. Usual interstitial pneumonia is the histopathologic correlate of the clinical disease entity idiopathic pulmonary...
fibrosis, but the disease can be seen in other clinical scenarios, such as collagen vascular diseases, asbestosis, and as a result of various medication effects.

When a UIP pattern is observed to have increased cellularity or parenchymal lymphoid aggregates, the possibility of pulmonary disease developing secondary to an underlying connective tissue or inflammatory disorder must be raised.28 The presence of lymphoid aggregates in our biopsy specimen suggests that the observed UIP was more likely related to a systemic inflammatory process rather than idiopathic pulmonary fibrosis.

Notably, the patient we describe had initially been diagnosed as having undifferentiated connective tissue disease and later was proved to have MRH. Undifferentiated connective tissue disease, also known as undifferentiated systemic rheumatic disease, is a diagnosis rendered when a patient presents with systemic inflammatory symptoms that fall short of meeting the criteria for diagnosis of any single previously established disorder.29 Our patient had serologic and radiographic findings suggestive of an inflammatory disorder but did not fulfill the criteria for rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, or sarcoidosis, all of which were considered in her differential diagnosis. In retrospect, the patient’s serologic, radiologic, and pulmonary histopathologic findings are likely all related to her underlying MRH.

The link between MRH and systemic autoimmune or connective tissue disorders is complex and poorly understood. Concomitant inflammatory disorders have been reported in 15% of cases of MRH13 and include diabetes mellitus, hypothyroidism, Sjögren syndrome, primary biliary cirrhosis, systemic sclerosis, systemic vasculitis, dermatomyositis, celiac disease, and systemic lupus erythematosus.11

The causal relationships between systemic inflammatory findings and MRH are unclear, and our current understanding of the etiology of MRH is limited. An unidentified stimulus might drive macrophage/histiocyte proliferation and secretion of various inflammatory cytokines; tumor necrosis factor, interleukin (IL) 1β, IL-6, and IL-12 have been implicated in MRH.11,14

Given the diversity of diseases associated with MRH, it seems likely that numerous different triggers of histiocytic activity may exist. Mycobacterial infection has been proposed as a potential trigger based on the early finding that a high percentage of patients with MRH had positive tuberculin skin test results.30 Equally plausible,
given the significant association with various malignant neoplasms, is that substances secreted by tumors may induce macrophage activity directly or indirectly. As for systemic inflammatory diseases, we propose that at least the following 3 possibilities exist: (1) the inflammatory disease may be the cause of MRH, providing a trigger for macrophage proliferation; (2) MRH, in response to an unknown trigger, may produce the proinflammatory agents driving the inflammatory disease; and (3) MRH and the inflammatory process are responding to the same trigger and represent parts of a complex disease spectrum rather than distinct clinicopathologic entities.

In conclusion, we present a unique case of MRH with associated UIP. Our observations add to the limited body of knowledge regarding pulmonary findings in MRH, showcase a unique presentation of MRH in the setting of UIP, and provide an additional piece of evidence regarding the interplay between MRH and systemic inflammatory processes.

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REFERENCES