BRIEF ARTICLES

A Rare Case of Multicentric Reticulohistiocytosis

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ABSTRACT

Multicentric reticulohistiocytosis (MRH) is a rare, histiocytic disorder that primarily affects the skin and joints. This disease can have systemic involvement of various organ systems and has been associated with underlying malignancy. Middle-aged, Caucasian females are the most commonly affected demographic group in this disease. We present a case of a 56-year-old African American male with debilitating joint pain and a papulonodular rash on his face, chest, arms, and hands. Biopsy of skin lesions confirmed the diagnosis of multicentric reticulohistiocytosis. Histological findings revealed dermal infiltrate composed of glassy histiocytes and giant cells with eosinophilic cytoplasm. The patient was started on 15 mg of methotrexate weekly, 1 mg of folic acid daily, and 60 mg of prednisone daily with mild improvement of skin lesions at one month follow-up. He expired from other comorbidities before long term treatment could be achieved. The potential for disfiguring skin lesions and debilitating arthropathy emphasizes the importance of early recognition and treatment of MRH. Corticosteroids and methotrexate are recommended for patients with moderate to severe disease and have been shown to be successful in some cases. More studies are needed on patients with MRH to further elucidate the etiology and pathogenesis of this disease.

INTRODUCTION

Multicentric Reticulohistiocytosis (MRH) is a rare, systemic inflammatory disease characterized by papulonodular skin lesions and severe destructive arthritis. Though MRH primarily involves the skin and joints, it has been reported to involve nearly every organ system.[1] To date, there have only been approximately 300 reported cases of this disease.[2] The average onset of MRH is in the fourth decade, but there have been reports of cases in children and the elderly.[3-6] The female to male ratio is 3:1, and there is no familial tendency.[7,8] Eighty-five percent of cases have been in Caucasians, but there have been reports in Hispanic, African American, Native American, and Asian individuals.[9]

Patients with MRH often present with a symmetrical polyarthritis involving the joints of the fingers, elbows, shoulders, and knees.[10] The arthritis may persist for several years before skin nodules erupt, making this disease difficult to differentiate from rheumatoid arthritis.[10] The papulonodular lesions in MRH appear reddish-brown and can vary in size, involving the upper trunk,

acral and extensor surfaces of extremities, and nail folds.[11] Lesions may be scattered and isolated or grouped to give a cobblestone appearance.[9] When eruptions occur in the periungual region, a pathognomonic “coral bead” appearance is seen.[12] Constitutional symptoms such as fever, malaise, weakness, and weight loss may also be present.[11]

An underlying internal malignancy is associated with about 25% of cases.[13] Various malignancies including endometrial carcinoma, adenocarcinoma of the gastrointestinal tract, Burkitt lymphoma, liver carcinoma, acute myeloid leukemia, ovarian carcinoma, melanoma, and mesothelioma have been reported.[14-20] This high rate of association has led to debate of MRH being a paraneoplastic syndrome. However, there is no consistent type of neoplasm associated with MRH, and the two diseases do not always run a parallel course.[21] Nevertheless, ruling out malignancy in a patient with MRH is crucial.

Diagnosis of MRH is made with a skin biopsy that demonstrates numerous histiocytes with multinucleated giant cells and ground-glass appearing eosinophilic cytoplasm.[2] The histiocytes contain periodic acid-Schiff (PAS) positive material.[2] Early and accurate diagnosis of MRH is important because untreated cases can progress to arthritis mutilans.[21] Despite this condition being aggressive and debilitating, the etiology of MRH remains poorly understood. Further investigation is needed to better understand the phenomenon and treatment of this disease.

CASE REPORT

A 56-year-old African American male presented with a 9 month history of symmetrical joint pain and a new onset rash on his face, arms, chest, and hands. His past medical history is significant for hypertension, hyperlipidemia, atrial fibrillation, and degenerative osteoarthritis of the knees. He complained of debilitating joint tenderness of his hands, shoulders, and knees which had significantly affected his mobility. He also reported subjective weight loss and generalized weakness. On physical exam, the patient had multiple erythematous papulonodular lesions distributed on his cheeks, ears, chest, arms, fingers and periungual regions (Figure 1A). The rash on his chest presented in a photodistributed pattern, and the lesions on both arms were grouped to give a cobblestone appearance (Figure 1B, C). He had the characteristic coral bead appearance of nodules surrounding the periungual regions (Figure 1D, E). The patient also displayed limited range of motion and was unable to lift his arms over his head, make a complete fist, or ambulate freely. X-ray imaging of his shoulders, hands, and knees are shown (Figure 2A, B, C).

Biopsy of his skin lesions revealed a diagnosis of multicentric reticulohistiocytosis. Histology showed mononuclear histiocytes and multinucleated giant cells with eosinophilic cytoplasm resembling a ground glass appearance (Figure 3A,B). The cells stained CD68(+) and PAS(+) (Figure 3C). Labs revealed the patient was slightly anemic with an elevated ESR and CRP. He tested ANA(+) with a titer of 1:640 and anti-SSA(+). Labs were negative for Rheumatoid Factor, anti-CCP, anti-SSB, anti-dsDNA, anti-SM/RNP, HCV, HBV, HIV, and TB. The patient was started on 15 mg of methotrexate weekly, 1 mg of folic acid daily, and 60 mg of prednisone daily, the latter of which was gradually tapered down to 10 mg daily. At one month

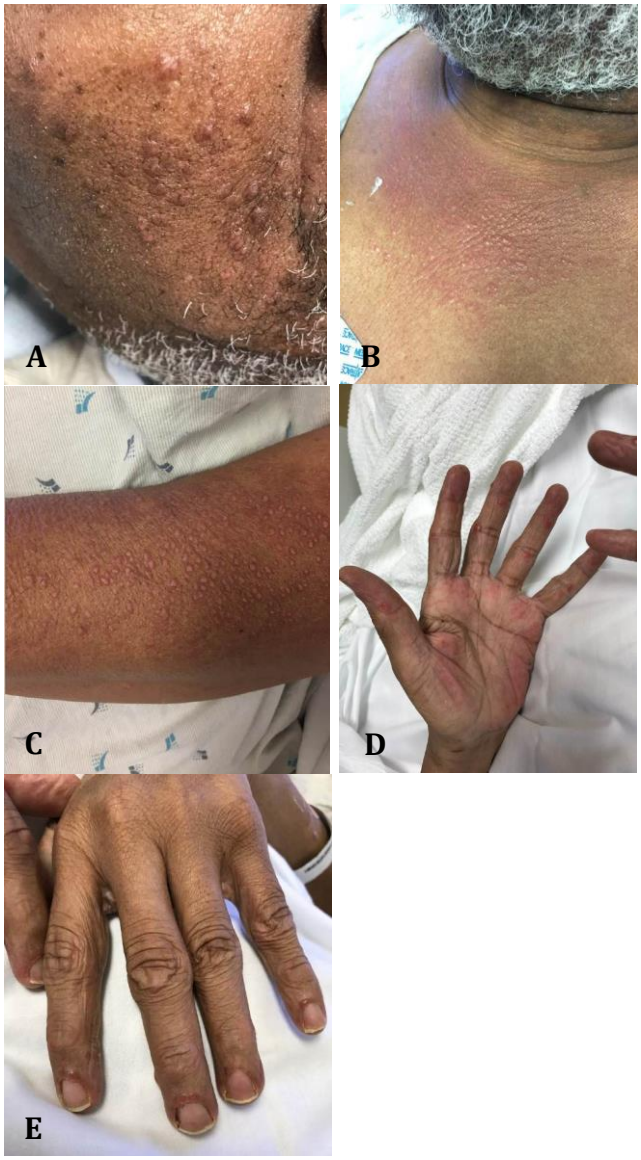
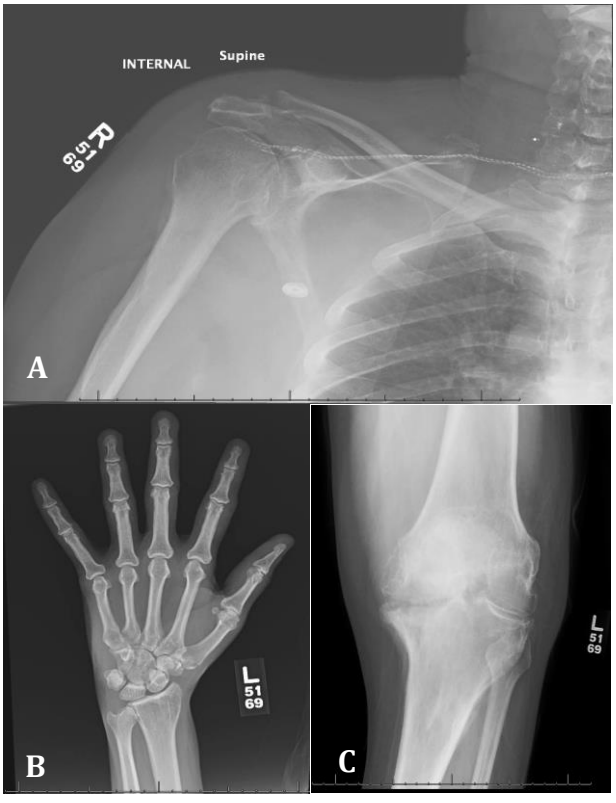


Figure 1: Multiple erythematous papules and nodules. (A) Papulonodular lesions scattered on the cheeks. (B) The rash presenting in a photodistributed pattern on the chest. (C) Papules on the arm are grouped to give a cobblestone appearance. (D) Erythematous papules and nodules are found on the fingers. (E) A pathognomonic "coral bead" appearance is seen surrounding the periungual regions.

follow up, he experienced mild improvement of his rash, with little to no improvement of his joint pain.

Unfortunately, the patient expired a few months later from sepsis secondary to hospital acquired pneumonia after a several week hospitalization. The autopsy report revealed glassy histiocytes characteristic of MRH found in the synovia of the knee and sternoclavicular joint. Similar cells were also found infiltrating the epicardium. The lungs showed extensive involvement by a fibrosing and inflammatory process with patterns of organizing pneumonia and diffuse alveolar damage. There were numerous clusters of macrophages which may have been associated with the patient's underlying MRH. The autopsy report did not reveal an underlying neoplasm.

Figure 2: X-ray imaging of the shoulder, hand, and knee. (A) Osteoarthrosis and erosive changes of the acromioclavicular joint. (B) Erosive changes in the MCP and PIP joints. (C) Severe osteoarthrosis with erosive changes in the medial compartment of the knee.



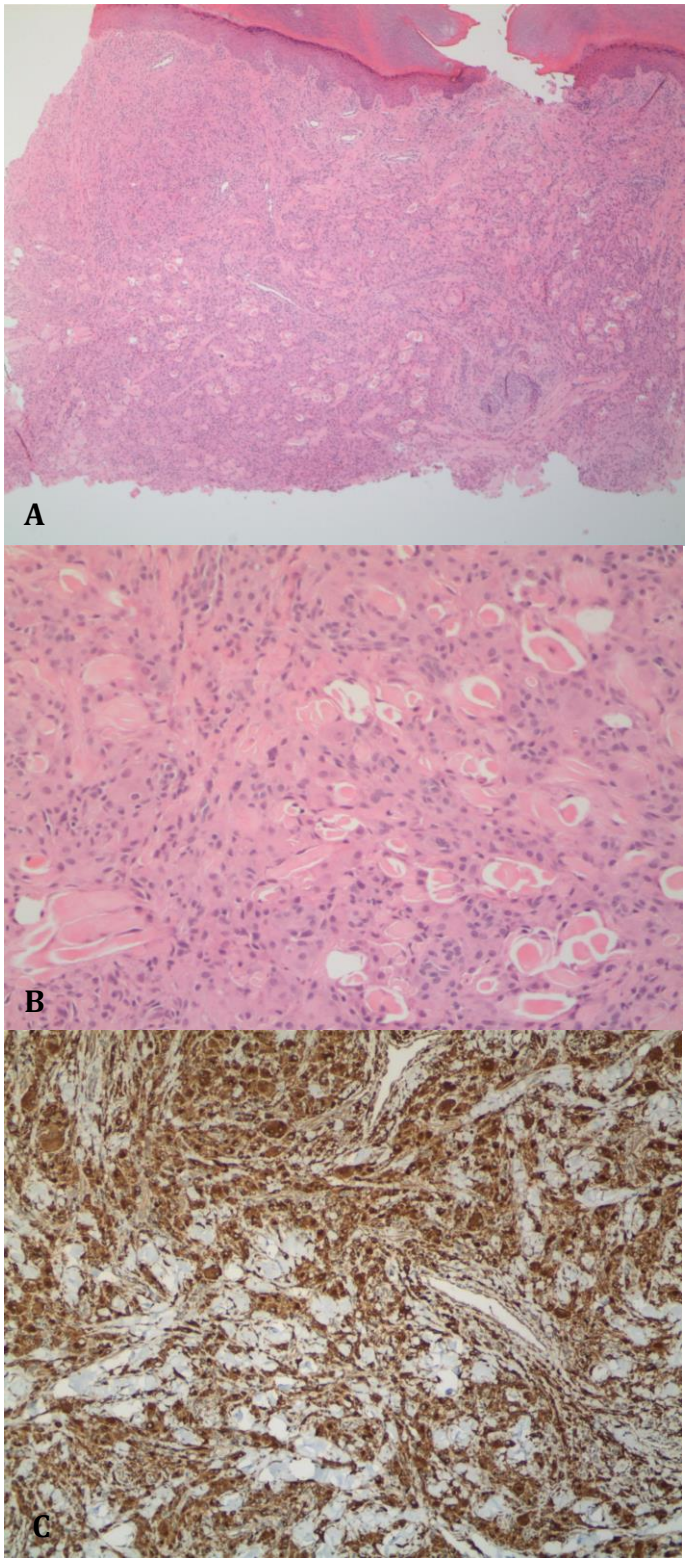


Figure 3: Histopathology of the skin shows dermal infiltration of mononuclear histiocytes and multinucleated giant cells with "ground-glass" cytoplasm. (A) H&E X40 (B) H&E X200 (C) IHC for CD68 X100

DISCUSSION

Multicentric reticulohistiocytosis is a histiocytic disorder of unknown etiology that primarily affects the skin and joints. Owing to its rarity, the diagnosis of MRH can be challenging. Patients may present with symmetrical polyarthritis for several months to years before skin changes appear.[10] The skin changes in MRH involve reddish-brown papulonodular lesions commonly found on the face and hands. Patients may present with lesions that are several millimeters to 2 cm wide, ranging in number from a few to a hundred.[22] If eruptions occur around the nail folds, a pathognomonic "coral bead" appearance is appreciated, though this only occurs in 50% of cases.[11] On rare occasions, skin changes may overlap with features seen in dermatomyositis.[2] For example, one case reported a photodistributed rash on the chest and neck with violaceous papules on the extensor surfaces of the hands, mimicking poikiloderma and Gottron's papules seen in dermatomyositis.[23] With the variability in presentation, it is not uncommon for patients to be misdiagnosed with more prevalent diseases such as rheumatoid arthritis or dermatomyositis.[24-26] Increased awareness among clinicians plays an important role in treating patients with this disease.

Although there are no specific laboratory tests for diagnosing MRH, the workup should include labs to evaluate the presence of any autoimmune, infectious, or neoplastic conditions. Mild anemia and elevated erythrocyte sedimentation rate are seen in about one half of patients.[1] One third of patients may present with hyperlipidemia or a positive PPD.[21] Rheumatoid factor (RF) and cyclic citrullinated protein (CCP) are usually negative, but there have been reports of these labs testing positive along with other autoimmune markers.[8] Imaging

studies may play an important role in differentiating MRH from other causes of arthritis. X-rays will show erosive lesions that appear discrete and well-defined but can progress to involve the entire articular surface of involved joints.[8] Unlike other forms of inflammatory arthritis, osteopenia and periosteal bone formation are absent.[9]

Definitive diagnosis of MRH is made with a skin biopsy. Histopathology will demonstrate histiocytes with multinucleated giant cells and eosinophilic cytoplasm resembling a ground-glass appearance.[2] Immunohistochemical staining is positive for CD68.[9]

Due to its rarity, a standardized treatment for MRH does not exist. A rheumatology consult should be considered for any patient diagnosed with this condition. In patients with mild symptomatic disease, nonsteroidal anti-inflammatory agents may be helpful.[27] Both systemic and intralesional steroids have been used with reported improvement in both skin and joint symptoms.[11] Various disease-modifying antirheumatic drugs have also been tried with success, often used in combination with steroids.[8] In a review by Tariq et al, methotrexate and prednisone were the most commonly used drugs to treat MRH.[2] Use of biologics such as etanercept, adalimumab, and infliximab for treatment has also shown positive results, though malignancy should be excluded before starting these drugs.[11] Without randomized control trials, it is difficult to know for sure whether improvement in symptoms is due to therapy or spontaneous remission of the disease.[1] Diagnostic test and treatment studies should be done to improve our understanding and management of MRH.

Conflict of Interest Disclosures: None.

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References:

1. Rapini RP. Multicentric reticulohistiocytosis. *Clinics in Dermatology*. 1993;11(1):107-111. doi:10.1016/0738-081x(93)90105-l.
2. Tariq S, Hugenberg ST, Hirano-Ali SA, Tariq H. Multicentric reticulohistiocytosis (MRH): case report with review of literature between 1991 and 2014 with in depth analysis of various treatment regimens and outcomes. *SpringerPlus*. 2016;5:180. doi:10.1186/s40064-016-1874-5.
3. Lesher JL, Allen BS. Multicentric reticulohistiocytosis. J Am Acad Dermatol 1984;11:713-23.
4. Jha VK, Kumar R, Kunwar A, et al. Efficacy of Vinblastine and Prednisone in Multicentric Reticulohistiocytosis With Onset in Infancy. *Pediatrics*. 2016;137(6). doi:10.1542/peds.2015-2118.
5. Olson J, Mann JA, White K, Cartwright VW, Bauer J, Nolt D. Multicentric Reticulohistiocytosis: A Case Report of an Atypical Presentation in a 2-Year-Old. *Pediatric Dermatology*. 2015;32(3). doi:10.1111/pde.12531.
6. Hotta M, Minamimoto R, Suzuki D, Takahashi A. Multicentric Reticulohistiocytosis Mimicking Malignancy on 18F-FDG PET/CT. *Clinical Nuclear Medicine*. 2017;42(7):567-568. doi:10.1097/rlu.0000000000001661.

7. Barrow MV, Holubar K (1969) Multicentric reticulohistiocytosis. A review of 33 patients. Medicine 48(4):287–305
8. Islam AD, Naguwa SM, Cheema GS, Hunter JC, Gershwin ME. Multicentric Reticulohistiocytosis: a Rare Yet Challenging Disease. Clinical Reviews in Allergy & Immunology. 2013;45(2):281-289. doi:10.1007/s12016-013-8362-2.
9. Tajirian AL, Malik MK, Robinson-Bostom L, Lally EV. Multicentric reticulohistiocytosis. Clinics in Dermatology. 2006;24(6):486-492. doi:10.1016/j.clindermatol.2006.07.010.
10. Webb-Detiege T, Sasken H, Kaur P. Infiltration of Histiocytes and Multinucleated Giant Cells in the Myocardium of a Patient With Multicentric Reticulohistiocytosis. *JCR: Journal of Clinical Rheumatology*. 2009;15(1):25-26. doi:10.1097/rhu.0b013e31817d1197.
11. Macía-Villa CC, Zea-Mendoza A. Multicentric reticulohistiocytosis: case report with response to infliximab and review of treatment options. *Clinical Rheumatology*. 2014;35(2):527-534. doi:10.1007/s10067-014-2611-5.
12. Catterall MD. Multicentric reticulohistiocytosis a review of eight cases. *Clinical and Experimental Dermatology*. 1980;5(3):267-279. doi:10.1111/j.1365-2230.1980.tb01705.x.
13. Snow JL, Muller AS. Malignancy-associated multicentric reticulohistiocytosis: a clinical, histological and immunophenotypic study. Br J Dermatol 1995; 133: 71–76.
14. Malik MK, Regan L, Robinson-Bostom L, Pan TD, McDonald CJ (2005) Proliferating multicentric reticulohistiocytosis associated with papillary serous carcinoma of the endometrium. J Am Acad Dermatol 53(6):1075–9
15. Kishikawa T, Miyashita T, Fujiwara E, Shimomura O, Yasuhi I, Niino D et al (2007) Multicentric reticulohistiocytosis associated with ovarian cancer. Mod Rheumatol/Japan Rheum Assoc 17(5):422–5
16. Han L, Huang Q, Liao KH, Chen LJ, Kong WY, Fu WW et al (2012) Multicentric reticulohistiocytosis associated with liver carcinoma: report of a case. Case Rep Dermatol 4(2):163–9
17. Hinchman KF, Wu JJ, Soden CE Jr, Waldman J, Dyson SW (2008) Multicentric reticulohistiocytosis associated with Burkitt lymphoma and adenocarcinoma. Cutis; Cutan Med Pract 82(2):113–4
18. Tirumalae R, Rout P, Jayaseelan E, Shet A, Devi S, Kumar KR (2011) Paraneoplastic multicentric reticulohistiocytosis: a clinicopathologic challenge. Indian J Dermatol Venereol Leprology 77(3):318–20
19. Kenik JG, Fok F, Huerter CJ, et al. Multicentric reticulohistiocytosis in a patient with malignant melanoma: A response to cyclophosphamide and a unique cutaneous feature. Arthritis Rheum 1990;33:1047-51.
20. Honeyboume D, Kellett JK. A mesothelioma presenting with multicentric reticulohistiocytosis. Postgrad Med J 1985;61:57-9.
21. Trotta F, Castellino G, Lo MA (2004) Multicentric reticulohistiocytosis. Best Pract Res Clin Rheumatol 18(5):759–72
22. Baek IW, Yoo SH, Yang H, Park J, Kim KJ, Cho CS. A case of multicentric

reticulohistiocytosis. Mod Rheumatol 27: 165-168, 2017.
23. Muñoz-Santos C, Sàbat M, Sáez A, Gratacós J, Luelmo J. Multicentric reticulohistiocytosis-mimicking dermatomyositis. Case report and review of the literature. Dermatology. 2007;214(3):268–271. doi: 10.1159/000099594.
24. Saba R, Kwatra SG, Upadhyay B, Mirrakhimov AE, Khan FN. Multicentric Reticulohistiocytosis Presenting with Papulonodular Skin Lesions and Arthritis Mutilans. *Case Reports in Rheumatology*. 2013;2013:201563. doi:10.1155/2013/201563.
25. Song SH, Kim HJ, Kang DH, Lim SY. A Case of Multicentric Reticulohistiocytosis Misdiagnosed as Rheumatoid Arthritis. *Kosin Medical Journal*. 2012;27(2):181. doi:10.7180/kmj.2012.27.2.181.
26. Fett N, Liu RH. Multicentric Reticulohistiocytosis with Dermatomyositis-Like Features: A More Common Disease Presentation than Previously Thought. *Dermatology*. 2011;222(2):102-108. doi:10.1159/000323254.
27. Webb-Detiege T, Sasken H, Kaur P. Infiltration of Histiocytes and Multinucleated Giant Cells in the Myocardium of a Patient With Multicentric Reticulohistiocytosis. *JCR: Journal of Clinical Rheumatology*. 2009;15(1):25-26. doi:10.1097/rhu.0b013e31817d1197.