Multicentric reticulohistiocytosis masquerading as cutaneous connective tissue disease

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Abstract

Multicentric reticulohistiocytosis (MRH) is a rare type of non-Langerhans cell histiocytosis characterized by coral-toned papules with predilection for dorsal surfaces in addition to severe arthropathy. It sometimes proves difficult to differentiate these joint and skin findings clinically from certain rheumatologic diseases, primarily dermatomyositis. Herein, we present an 82-year-old woman who presented with the clinical findings described above and was subsequently diagnosed with MRH after biopsy and review of relevant clinical history. Because about 25% of patients diagnosed with MRH have an underlying occult malignancy, our patient underwent a complete malignancy workup that was negative. She was treated with systemic corticosteroids and methotrexate, which resulted in an improvement of the arthritis and constitutional symptoms. This case demonstrates that in patients with both rheumatologic and dermatologic symptoms, particularly on acral surfaces, MRH must be a diagnostic consideration. Identifying this disease early in its course can prevent negative consequences for the patients, specifically arthritis mutilans and upper airway involvement.

Keywords: multicentric reticulohistiocytosis, non-Langerhans cell histiocytosis, paraneoplastic syndrome, arthritis mutilans

Introduction

Multicentric reticulohistiocytosis (MRH) is a rare, non-Langerhans cell histiocytosis that produces characteristic coral-toned papules and destructive arthritis. Multicentric reticulohistiocytosis can mimic other rheumatologic and dermatologic conditions, such as dermatomyositis [1], and has been described as paraneoplastic in some cases. Histopathologic evaluation demonstrating characteristic "ground glass" dermal histiocytes is a key step in the diagnosis of MRH. Age-appropriate malignancy screening and family history should be elicited, given the potential association of MRH with an underlying cancer. Herein, we report an 82-year-old woman with arthritis and cutaneous findings concerning for dermatomyositis that, upon histopathologic examination, was diagnosed as MRH.

Case Synopsis

An 82-year-old woman with glaucoma, insulin-dependent diabetes, hypertension, and hyperlipidemia presented to the dermatology clinic for evaluation of skin findings predominantly on her hands. She was referred from the rheumatology department who observed the development of new papules on the bilateral hands after their initial consultation for inflammatory arthritis. The patient explained that she developed pain in her left shoulder and left side of the neck a few days after receiving the high dose quadrivalent influenza vaccine (Fluzone). She then observed a pink to red colored "rash" on the dorsal aspect of her fingers and upper back. Furthermore, she described nodules below the nail beds with associated swelling of the bilateral fingers. The patient also endorsed progressive and generalized weakness, a twelve-pound unintentional weight loss over a four-month period, paresthesias and swelling of bilateral hands,

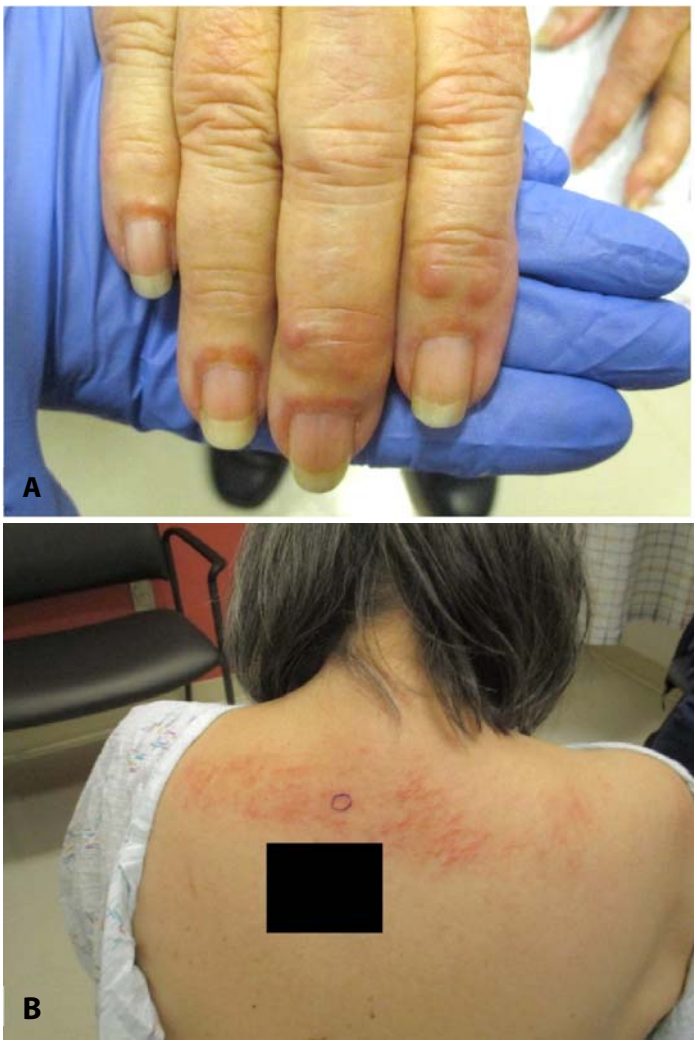

Figure 1. ***A)*** *Pink to erythematous papules extending from the metacarpophalangeal (MCP) joints to the dorsum of the fingers, most prominent over the distal interphalangeal (DIP) joint of the index, middle, ring, and fifth fingers. Erythema of nail folds and dilation of nail fold capillaries was also present.* ***B)*** *Pink to erythematous papules coalescing into a patch on the upper thoracic trunk, with a slightly flagellate appearance.*

dryness of the mouth and eyes, and intermittent diarrhea. Review of systems was otherwise negative for history of psoriasis, uveitis, oral ulceration, photosensitivity, hair loss, pleuritic chest pain, cough, shortness of breath, abdominal pain, constipation, dysphagia, heartburn, seizures, or Raynaud phenomenon.

Surgical history was pertinent for total hysterectomy without bilateral salpingo-oophorectomy 30 years prior to her presentation. She had never undergone colonoscopy and was not up to date on mammography for breast cancer screening. She denied tobacco, alcohol, or illicit drug use. She did cite a family history of breast cancer noted in her mother, sister, and maternal aunt.

Physical examination revealed diffuse non-pitting edema of bilateral hands, more prominent in metacarpophalangeal (MCP) joints in the left hand and left wrist, with associated tenderness to palpation. There were multiple pink-to-erythematous papules extending from the MCP joints to the dorsum of the fingers, most pronounced over the distal interphalangeal (DIP) joint of the index, middle, ring, and fifth fingers. Erythema of nail folds and dilation of nail fold capillaries were present (**Figure 1A)**. She also demonstrated pink-to-erythematous papules coalescing into a flagellate appearing plaque on the upper thoracic trunk (**Figure 1B)**, and a few erythematous papules localized to the glabella. Of note, there was no evidence of heliotrope sign and no nasal root swelling. Additionally, she retained full strength in flexor and extensor muscle groups of the upper and lower extremities bilaterally. Although grip strength was intact, the patient did report moderate to severe joint pain in her hands. The constellation of constitutional symptoms, oligoarthritis with concomitant edema, a somewhat flagellate erythematous plaque on the upper back, and pink papules overlying the joints of the hands lead to a differential diagnosis that included dermatomyositis (DM).

One 6.0mm punch biopsy was obtained from the mid-upper back and one tangential shave biopsy was obtained from the right thumb DIP region; these specimens were sent for hematoxylin and eosin (H&E) processing. Histologic analysis for both specimens demonstrated a dermal infiltrate of large histiocytes (**Figure 2A)** with abundant ground-glass cytoplasm and a background of lymphocytes (**Figure 2B**, **C)**, consistent with a diagnosis of multicentric reticulohistiocytosis (MRH).

A thorough workup including radiography of the bilateral hands and lumbar spine, complete blood count, comprehensive metabolic panel, C-reactive protein, erythrocyte sedimentation rate, anti-nuclear antibody, anti-extractable nuclear antibodies, anti-double stranded DNA, Sjogren antibody (anti-SS-A,

anti-SS-B), creatinine kinase (CK), electrophoresis serum protein, hepatitis C reflex, hepatitis B surface antigen, urinalysis, and urine protein/creatinine ratio were performed with no abnormalities. The negative antibody profile, normal CK level, and pathognomonic histologic findings helped to rule out DM and establish a diagnosis of MRH.

The patient was initially prescribed prednisone 20mg by mouth daily for two weeks. This was followed by a taper to prednisone 15mg by mouth daily for the remaining two weeks. Methotrexate was slowly added to the patient's treatment regimen during this time to reach a dose of 25mg by mouth weekly. Owing to significant gastrointestinal side effects, this dose was decreased to 20mg by mouth weekly and tolerated well.

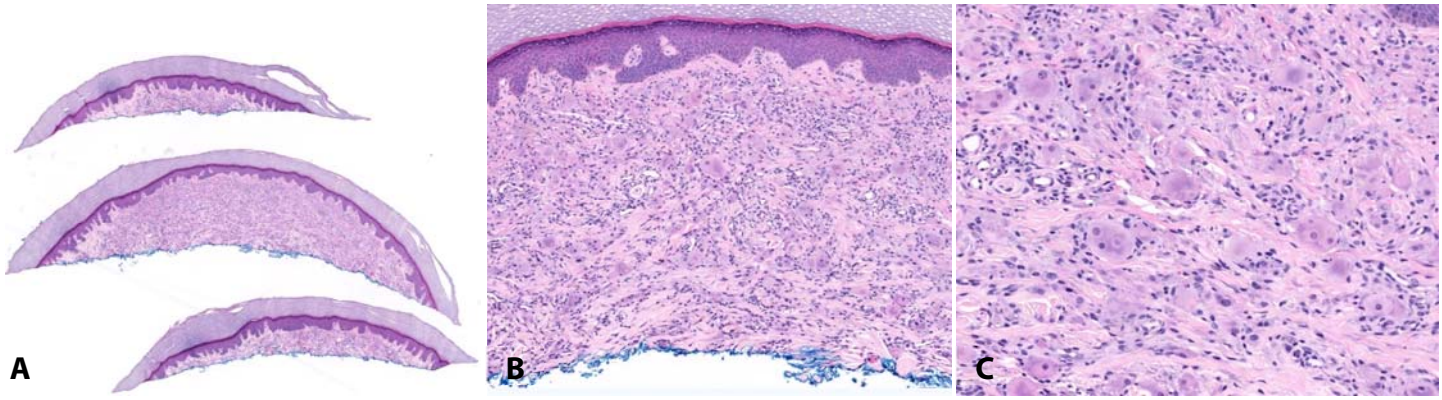

Figure 2. *Shave biopsy performed demonstrates a dome shaped papule on an acral surface with H&E staining.* ***A)****, 10×. The entirely dermal infiltrate is composed of large histiocytes with abundant ground-glass cytoplasm with a background of lymphocytes consistent with a diagnosis of multicentric reticulohistiocytosis,* ***B)*** *80×;* ***C)*** *100×.*

Upon her re-evaluation one month later, the patient noticed a 40% overall improvement in her arthralgias and constitutional symptoms while on dual therapy with prednisone and methotrexate. She had appropriately followed up with her primary care physician and undergone a full metastatic cancer workup. This included a chest radiography, mammogram, computed tomography of chest, abdomen, pelvis, and ultrasound of neck, and thyroid. All diagnostics were negative with the exception of the thyroid ultrasound, which demonstrated heterogeneous multinodular thyroid. She underwent fine needle aspiration of the left superior thyroid, left-mid thyroid, left inferior thyroid, and left inferior isthmus, all of which were negative for malignancy.

Case Discussion

Multicentric reticulohistiocytosis is an uncommon disease characterized by upper extremity papulonodular cutaneous lesions that appear after the onset of arthritis. Although the typical demographic of MRH includes Caucasian females, our patient's age of 82 years is notable, as most patients present in the fourth decade [2]. Weakness and weight loss have been reported, as well as sicca to a lesser extent [3]. Although there have been fewer than 10 cases reported of MRH mimicking dermatomyositis, a descriptive analysis of 234 MRH reports found that 27 had dermatomyositis-like features. These include erythema localized to the V of the neck, shawl sign, Gottron papules, and periungual erythema [4]. Our patient's periungual papules, known as "coral beading," are considered pathognomonic for MRH and have been noted in 28% of reported cases [3]. Involvement of the DIP joint is noteworthy as it can help differentiate MRH from rheumatoid arthritis [5]. Histopathologic analysis of skin and synovial biopsies is essential in definitively diagnosing MRH. Typical histological findings demonstrate a dermal aggregation of histiocytes, surrounding lymphocytes, and occasionally plasma cells and eosinophils. The histiocytes contain a predominantly eosinophilic, granular cytoplasm, which creates the prototypical

"ground glass" appearance. Immunohistochemical staining is a paramount feature of histologic diagnostics, as this helps differentiate Langerhans cell histiocytoses (LCH) from non-Langerhans cell histiocytoses. Classically, the ground glass histiocytes seen in MRH will stain positive for CD68, CD163, and HAM56 but are negative for S100, CD1a, and langerin (CD207), [6,7].

In patients with MRH, an underlying malignancy has been found in 25-30% of patients [8]. For example, primary cancers of the lung, breast, skin, thymus, gynecologic organs, and gastrointestinal systems have been reported, as well as leukemia [9]. In rare circumstances, monoclonal gammopathies and cryoglobulinemia may also be observed [6]. Given that our patient was not up-to-date on age-related cancer screenings and had a positive family history of breast cancer, the diagnosis of MRH warranted a complete malignancy workup. It is also recommended to tailor cancer screening based on patient symptomatology [10].

In addition to evaluating for a potential underlying malignancy, dermatologists should assess their patient with MRH for possible joint involvement. The arthritis seen in MRH is described as symmetric and erosive, and typically affects the joints of the fingers, hands, knees, and wrists. Progression to arthritis mutilans occurs in about 45% of patients with MRH [6]. It is also important to note the involvement of the oral, pharyngeal or nasal mucosa, which can occur in up to 50% of patients [6]. These findings were lacking in the case presented above.

The treatment of MRH is aimed at improving patients' dermatologic and rheumatologic symptoms, with a particular focus on preventing arthritis mutilans. The rarity of MRH has resulted in several different treatment modalities described in case reports and case series. A review of 52 cases of MRH between 1991 and 2014 by Tariq et al. found that although prednisone was used in 32 instances, it was the sole treatment only twice. In the two instances in which prednisone was used alone, it was found to result in partial resolution of patients' arthritis. Of note, one patient did experience complete resolution of cutaneous symptoms on prednisone alone. In the 18 instances in which methotrexate was used after or concomitantly with prednisone, 10 patients experienced complete resolution of joint and skin symptoms [3]. The addition of a disease-modifying anti-rheumatic drug, such as methotrexate is worth considering in patients who experience a partial resolution of symptoms on prednisone alone. Other treatments highlighted in single case reports include cyclophosphamide, azathioprine, leflunomide, cyclosporine, hydroxychloroquine, and isoniazid [3,11]. Left untreated, MRH progresses along a classic rheumatologic course characterized by a symmetric and erosive polyarthritis that eventually subsides. The result is typically permanent post-inflammatory joint hypertrophy and loss of function [12].

Conclusion

Multicentric reticulohistiocytosis is a rare disease that can mimic other rheumatologic and dermatologic conditions. Thus, clinicopathologic correlation is vital in making the correct diagnosis and expediting treatment. Early treatment of this disease can also prevent the progression to arthritis mutilans. Although there is no standard treatment for MRH, our patient achieved clinical improvement with combination therapy of prednisone and methotrexate. Malignancy screening in patients with this disease must be considered, as some categorize MRH as a paraneoplastic condition. Although reports of MRH are relatively scarce, it must be considered in patients presenting with symmetric arthritis and typical "coral beading" cutaneous lesions.

Potential conflicts of interest

The authors declare no conflicts of interest.

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