Reddish-brown, papulonodular skin lesions in the periungual region

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Abstract

Multicentric reticulohistiocytosis is a rare, non-Langerhans cell histiocytosis that most commonly presents in women in their fourth or fifth decades of life. Cutaneous involvement, characterized by reddish-brown papules in a "string of pearls" or "coral bead" linear formation, and joint involvement are the two most common manifestations at presentation. Histopathology demonstrates dermal proliferation of epithelioid histiocytic-appearing cells with ground glass cytoplasm. We report a 51-year-old woman who presented with ruddy, periungual papules and bilateral joint pain in the hands, consistent with multicentric reticulohistiocytosis. We describe the clinical and histopathologic presentation, therapeutic options, and differential diagnosis of this rare condition.

Keywords: coral bead, histiocytosis, multicentric reticulohistiocytosis, string of pearls

Introduction

Multicentric reticulohistiocytosis (MRH) is a rare non-Langerhans cell histiocytosis. The pathophysiology of MRH is unknown, but it may be due to an autoimmune, inflammatory, or malignant process [1,2]. Associations with other autoimmune conditions and malignancies have been reported [1]. Multicentric reticulohistiocytosis most commonly presents in women in their fourth or fifth decades of life [1]. Cutaneous and articular involvement are the two most common manifestations seen at presentation [1].

Case Synopsis

A 51-year-old woman presented with a nine-month history of a red, itchy rash located on her hands, arms, and upper anterior thighs. She also complained of bilateral joint pain in the hands. Review of systems was otherwise negative. Medications included valsartan-hydrochlorothiazide, metoprolol succinate, escitalopram, levothyroxine sodium, and omeprazole.

Physical examination revealed reddish-brown, dome-shaped, firm papules in the periungual region, dorsum of the hands (**Figure 1**), arms, upper thighs, and upper forehead. The periungual papules, especially along the left second digit, were grouped together in a linear formation just proximal to the nail fold. Shave biopsy of the left dorsal hand was performed and revealed dermal proliferation of epithelioid histiocytic-appearing cells with ground

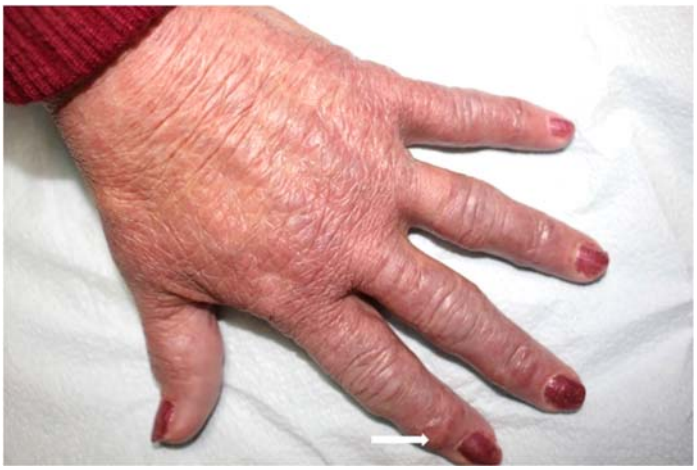

Figure 1: *Papulonodular skin lesion in the periungual region (arrow).*

glass cytoplasm (**Figure 2**). Positive immunohistochemical staining was obtained for CD68. Negative results were obtained for Melan A and pankeratin.

Radiographs of the hand demonstrated periarticular erosions with mild-to-moderate joint space narrowing primarily involving the proximal interphalangeal and distal interphalangeal joints, with relative sparing of the metacarpophalangeal and intercarpal joints. Serum laboratory studies demonstrated hypergamma-proteinemia (IgG 2.2g/dL, normal 0.6-1.5g/dL), but were otherwise within normal limits. Autoimmune workup showed positive Smith antibody and positive SS-A antibody, with rheumatoid factor and antinuclear antibody testing both negative. Cancer screenings, including colonoscopy, mammogram, and pap smear, were up to date and all negative. The combination of the physical examination and histopathology findings were consistent with a diagnosis of MRH.

This patient was initiated on methotrexate 15mg, doxepin 20mg daily, and a prednisone taper starting at 0.75mg/kg of prednisone. With worsening skin disease, she was switched to etanercept 50mg weekly. With potentially modest improvement, etanercept was maintained and methotrexate was added. Despite combination therapy, the disease continued to worsen and etanercept was switched to infliximab. Infliximab was stopped secondary to an infusion reaction and adalimumab was started but caused worsening of the skin disease. The patient began to have rising liver function tests (ALT 61U/L; AST 65U/L) so methotrexate was switched to leflunomide. However, this was quickly stopped secondary to nausea and emesis from the medication. Throughout this process, the patient received numerous courses of corticosteroids given poor disease control. Alendronate 10mg daily also had been added given long-term corticosteroid use. The patient's disease was finally controlled with cyclophosphamide 50mg twice daily.

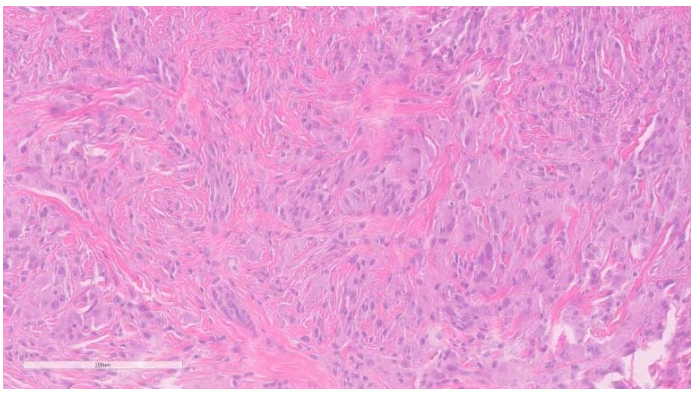

Figure 2: *Multicentric reticulohistiocytosis. Epithelioid histiocytic-appearing cells with ground glass cytoplasm. H&E, 20×.*

Case Discussion

Cutaneous and articular involvement are the two most common manifestations seen at presentation [1]. Cutaneous findings reveal papulonodular skin lesions localized to the periungual areas and dorsal hands. The classic finding of "coral bead" or "string of pearls" appearance of the periungual papulonodular skin lesions are pathognomonic for MRH. Histopathology demonstrates dermal proliferation of epithelioid histiocytic-appearing cells with ground glass cytoplasm [1]. The histiocytic cells document positivity for CD68, CD45, and vimentin, and are negative for S100, CD1a, CD34, factor X111a, and pankeratin [3].

There is no definitive laboratory test for MRH [2]. The diagnosis of MRH should prompt age- and gender-appropriate cancer screening as up to 30% percent of MRH patients are associated with malignancy at presentation [1,2].

Common articular findings include arthralgia, joint effusions, and synovitis. Constitutional symptoms, such as fatigue and unintentional weight loss, may be present. If left untreated, patients can develop a permanent disfiguring and debilitating arthritis.

Given the rarity of this condition, there are no established treatment paradigms and available therapeutic evidence is limited to case reports and series. Therapeutic options include corticosteroids, bisphosphonates, Disease-Modifying Antirheumatic Drugs (DMARDs), anti-tumor necrosis factor (TNF) biologics, and chemotherapeutic agents [2]. Corticosteroids are often utilized as a first-line therapy and initial doses less than 30mg/day have been suggested [2]. Bisphosphonates are an adjunct treatment option that can be initiated along with corticosteroid use or in combination with other therapeutic options to help limit bone destruction.

Numerous DMARDs have been utilized either alone or in combination with other therapeutic options and methotrexate may be the most efficacious initial option [2]. Anti-TNF biologics are increasingly being utilized to treat MRH and patients may demonstrate a positive therapeutic response to TNF inhibitor regimens even after failing prior treatment with a different TNF inhibitor [4]. Our patient demonstrates the need to consider multiple medication trials when treating MRH, with certain medication choices limited by therapeutic effectiveness or adverse effects. Our medication regimens often consisted of a TNF inhibitor and/or DMARD, bisphosphonates, and corticosteroids. If the patient experienced a symptomatic flare or adverse effect, then case report evidence was utilized to choose a replacement therapy within the same class [5].

The differential diagnosis of multicentric reticulohistiocytosis includes granuloma annulare, sarcoidosis, rheumatoid nodules, and erythema elevatum diutinum. Localized granuloma annulare manifests as smooth, annular plaques commonly distributed to the dorsal hands or feet. Arthritis is not directly associated with granuloma annulare. The cutaneous manifestations of sarcoidosis are variable and may demonstrate maculopapular, plaque, and subcutaneous morphologies; however, a string of periungal papules and histiocytes with ground glass cytoplasm are not seen in sarcoidosis. Rheumatoid nodules most commonly present as firm, subcutaneous nodules on the extensor surfaces of joints and our patient's diffuse reddish-brown papules on the arms would be very uncommon for rheumatoid nodules. Erythema elevatum diutinum is a rare leukocytic vasculitis characterized by progressive, red-brown round papules, plaques, or nodules distributed over extensor surfaces and not more diffusely on the hands, arms, chest, and thighs as in our patient.

Conclusion

The clinical and histopathology images and patient history demonstrate characteristic findings of multicentric reticulohistiocytosis, thereby raising awareness for this rare condition. This patient's lesions were controlled with cyclophosphamide 50mg twice daily following failure of methotrexate and multiple TNF inhibitors.

Potential conflicts of interest

The authors declare no conflicts of interest.

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