Case Reports in Dermatology

Case Rep Dermatol 2023;15:10–16
DOI: 10.1159/000528254
Received: September 4, 2022
Accepted: November 9, 2022
Published online: January 09, 2023



**Case Report**

# A Novel Case of Multicentric Reticulohistiocytosis Associated with Renal Cell Carcinoma Successfully Treated with Infliximab and Methotrexate

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**Keywords**
Multicentric reticulohistiocytosis · Arthritis · Paraneoplastic syndrome · Renal cell carcinoma · Treatment · Infliximab

**Abstract**
Multicentric reticulohistiocytosis (MRH) is categorized as a rare non-Langerhans cell histiocytosis most commonly seen in women in the fourth to fifth decade of life. This systemic inflammatory condition affects multiple organ systems and can result in severe joint destruction which can progress to arthritis mutilans. To date, various underlying malignancies have been discovered in patients with MRH including breast, gastric, thymic, hepatic, and melanoma. There has been 1 case of underlying renal cell carcinoma reported in a patient diagnosed with MRH. Additionally, there is no consistently recognized treatment for MRH described in the literature. The rarity of the disease contributes to the difficulty in defining a standardized treatment. We present the case of a patient with extensive joint and skin involvement who was successfully treated with infliximab and methotrexate, experienced clinical improvement, and was later diagnosed with clear cell renal cell carcinoma. The synergistic effects of infliximab and methotrexate, in combination with the low side-effect profile, appear to be promising in the setting of MRH and in our patient resulted in the resolution of symptoms and cutaneous manifestations. We suggest this regimen as an effective combination therapy. We emphasize thorough and continuous screening for underlying malignancy associated with MRH, despite clinical improvement or negative malignancy work-up upon initial diagnosis.



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DOI: 10.1159/000528254



## Introduction

Multicentric reticulohistiocytosis (MRH), also known as "giant cell reticulohistiocytosis," is a rare non-Langerhans cell histiocytic inflammatory syndrome characterized primarily by skin and joint involvement, though other organs can be affected [1, 2]. MRH presents between 40 and 50 years of age [3]. Females are affected more frequently than males with a ratio 3:1 with a little over 300 reported cases in current literature [1, 2].

MRH is associated with a symmetric irreversible destructive polyarthropathy primarily affecting the distal interphalangeal (DIP) joints. Polyarthralgia is often the first disease manifestation and is associated with soft tissue swelling, stiffness, and tenderness [2]. Erosive changes often are disproportionately severe radiographically in comparison to the clinical exam, and progress to arthritis mutilans in 30–50% of cases [4]. Cutaneous lesions are often papulonodular and found on acral and extensor surfaces, dorsum of the fingers, and nail folds. The characteristic periungual "coral bead" lesions vary in size and color ranging from pink, red, or brown papules and nodules that can coalesce to form plaques [1–4].

For definitive diagnosis, skin biopsy with histological analysis revealing dermal infiltration by multinucleated giant cells with ground glass eosinophilic cytoplasm is needed [5]. Immunohistochemistry reveals giant cells in MRH that are typically, but not always, periodic acid-Schiff positive, CD68 positive, and S-100 negative [3, 6–8]. In-depth screening for associated disease upon diagnosis of MRH is required as MRH is strongly associated with internal malignancies and autoimmune disease [3, 6].

The cause of MRH is unknown, but it is thought that tumor necrosis factor-alpha (TNF-α), interleukins (IL) IL-1β, IL-6, and IL-12 may be associated with its pathogenesis [7]. These cytokines are potential targets of therapy, though there is currently no standard first-line treatment regimen. The most frequently used treatments include systemic glucocorticoids, disease-modifying antirheumatic drugs such as methotrexate and cyclophosphamide, and anti-TNF biologics [1, 9, 10].

## Case Report

A 37-year-old man was referred to our office with a 1-year history of persistent papules on both hands and a diagnosis of undefined arthritis affecting the hands, hips, and knees with diffuse arthralgias that worsens with activity and improves with rest. Review of systems was positive for pruritus, a skin eruption on the dorsum of his fingers, swollen painful joints, and denial of constitutional symptoms. Physical exam revealed multiple fleshes to pink colored papules with a central puncta-like quality, both discreet and coalesced, on the extensor surface of the digits of the right and left hand with distorted 4th and 5th DIP joints (Fig. 1). The remainder of the skin exam was unremarkable, without any other lesions like those found on the fingers.

Review of plain films of the hands (Fig. 2) revealed erosive changes with soft tissue swelling to several DIP and proximal interphalangeal joints bilaterally. Biopsy revealed a dermal infiltrate of histiocytoid cells with few multinucleated cells resembling Touton-type giant cells. The cytoplasm of the cells had an eosinophilic "ground glass" appearance, consistent with changes of reticulohistiocytosis (Fig. 3). The biopsy was initially interpreted as a xanthogranuloma, but upon discussion of the clinical and radiographic features with the dermatopathologist, the formal diagnosis of MRH was made.

Routine laboratory tests for evaluation of any underlying conditions were unrevealing at initial presentation. Computed tomography (CT) imaging of the chest and abdomen revealed no abnormalities with the exception of a 2 mm noncalcified indeterminate nodule in the periphery of the right lung.

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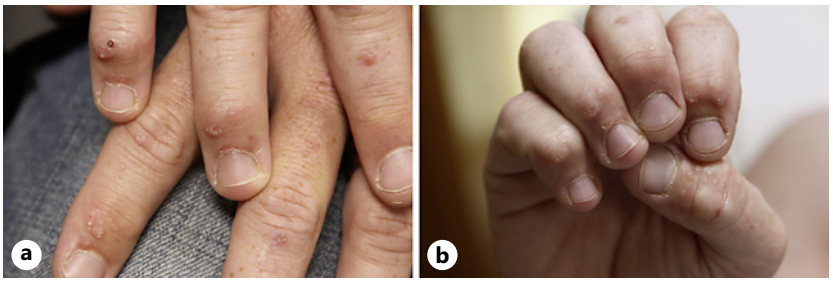

**Fig. 1. a**, **b** Flesh to pink colored papules and nodules with scale on the dorsum of the fingers with involvement of the nail folds.

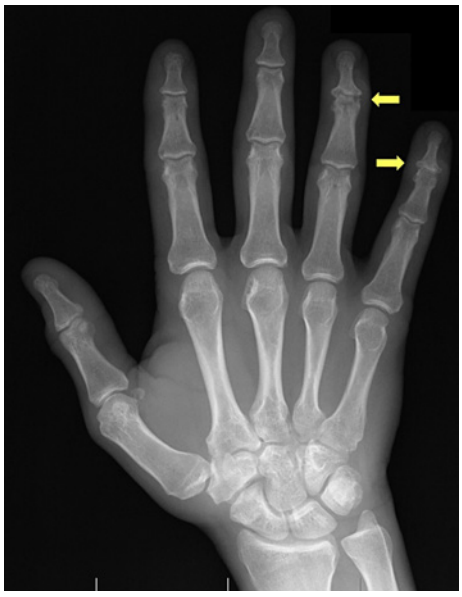

**Fig. 2.** Plain film of right hand with erosive changes in the fourth and fifth DIP joints.

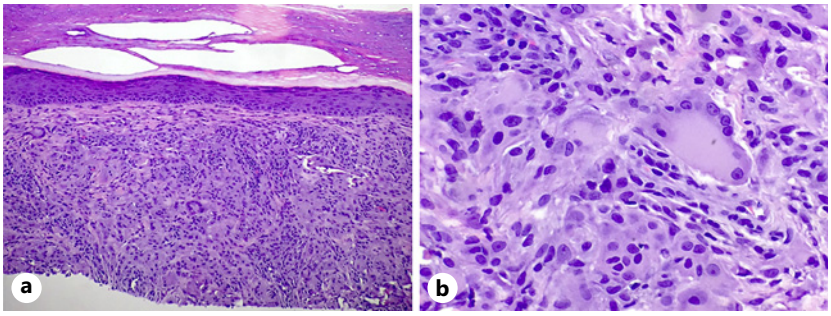

**Fig. 3. a**, **b** H&E stained section of biopsy demonstrating histiocytes and Touton-type multinucleated giant cells with abundant eosinophilic cytoplasm and a "ground glass" appearance. ×100 and ×400 magnification.

Complete blood count, complete metabolic panel, serum protein electrophoresis, QuantiFERON gold, and monoclonal protein study of the urine were within normal limits. Other testing revealed a positive rheumatoid factor, direct immunofluorescence revealed a positive antinuclear antibody for IgG and negative lupus band test, elevated SS-A

autoantibodies IgG 1.4 (0.0–0.9), C-reactive protein <0.5, normal erythrocyte sedimentation rate of 2, C3 73 mg/dL (82–185 mg/dL), and C4 13 mg/dL (15–53 mg/dL).

Treatment with 100 mg IV of infliximab every 8 weeks, 15 mg of methotrexate weekly, and 1 mg of folate daily was initiated. Early in the course of treatment, the patient developed pneumonia requiring brief cessation. Therapy restarted after recovery and continued without complication. The patient has been on nearly continuous treatment with infliximab and methotrexate for 4 years with significant improvement in his quality of life, reduction of his joint pain, and full resolution of all skin lesions.

In follow-up after several years of treatment, the patient was found to have an elevated lactate dehydrogenase level. Imaging revealed a 2.8 cm nodule on the right kidney, suspicious for malignancy not previously present. The patient underwent renal biopsy which revealed grade II clear cell renal cell carcinoma. Subsequently, a partial right nephrectomy with clear margins was performed in August 2020 for stage 1 renal cell carcinoma. Following recovery from surgery, the patient was restarted on methotrexate and infliximab. During a follow-up visit in December 2021, the patient's digital skin lesions remain completely resolved with minimal to nil arthritic symptoms. He is working full time and enjoys time with family. The current plan is to maintain treatment with methotrexate and infliximab and perform periodic computed tomography scans to monitor for possible recurrence of renal cell carcinoma. The CARE checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see www.karger.com/doi//10.1159/000528254).

## Discussion

MRH is considered a cutaneous paraneoplastic syndrome [11]. In about 33% of MRH patients, there is an association with a range of solid and hematologic malignancies [3]. In some cases, the diagnosis of MRH precedes that of cancer [12], whereas other cases describe simultaneous onset/diagnosis of MRH and associated malignancy [13, 14]. Malignancies reported in association with MRH include lung squamous cell carcinoma [12, 14], breast carcinoma [13, 15–17], pancreatic adenocarcinoma, intraperitoneal mucinous adenocarcinoma [14], melanoma [14, 18], thymic carcinoma [19], endometrial carcinoma [20], and urologic carcinoma [21]. Some cases report complete resolution of MRH only after successful treatment of breast carcinoma [13] or endometrial carcinoma [20]. The association between MRH and renal cell carcinoma was first documented in a 2003 Dutch case report, in which a 59-year-old man was diagnosed simultaneously with MRH and renal cell carcinoma with regression of MRH nodules only after nephrectomy [22]. Our case is unique in that our patient was first diagnosed with MRH, experienced clinical improvement with medical management, and years later was diagnosed with clear cell renal cell carcinoma. This highlights the importance of continued surveillance for development of occult malignancy as a paraneoplastic syndrome associated with MRH, despite clinical improvement. Lastly, MRH and autoimmune diseases like Sjogren's syndrome [3, 23], dermatomyositis [3, 24–27], and systemic sclerosis [28] can coexist.

The rarity of MRH makes it difficult to conduct controlled studies focused on identifying effective treatments. To date, only anecdotal and empirical reports are in the literature, and no consistently effective treatments are currently recognized. Medications which are reportedly helpful include corticosteroids, nonsteroidal anti-inflammatory medications, isoniazid, cyclosporine, cyclophosphamide, chlorambucil, methotrexate [4]. Antitubercular agents have been suggested in patients with MRH associated with a co-existing TB infection [2, 29].

Therapeutic attempts with TNF inhibitors have been prompted in response to recent studies that identified cytokine expression in MRH [4]. Several studies have reported that the combined use of anti-TNF drugs, particularly etanercept [30, 31] and infliximab, and

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methotrexate are beneficial in the treatment of MRH [2, 4, 5, 10]. In refractory cases, tocilizumab has been suggested as a viable choice [32]. The relative safety and tolerability of TNF antagonists lend reassurance in initiating selection earlier on rather than in refractory disease as it may induce remission and reduce the need for higher steroid doses [33].

We present a novel case of malignancy-associated MRH in a patient successfully treated with infliximab and methotrexate who later developed renal cell carcinoma. Methotrexate was used with infliximab in order to prevent development of inactivating antibodies against infliximab, as well as possible synergy with infliximab in treatment of MRH. We suggest this regimen for MRH and emphasize thorough investigation for occult malignancy at time of diagnosis and throughout follow-up. Early recognition and treatment are critical to preventing progression and permanent joint destruction.

## Conclusion

This case illustrates the importance of:

- Early recognition and biopsy of lesions suspicious for MRH.
- Prompt investigation for internal malignancy or other underlying conditions at time of diagnosis and continuously throughout follow-up, despite clinical improvement.
- Early initiation of therapy with anti-TNF and methotrexate.
- Resolution of symptoms early in the disease course is important to quality of life and prevention of progression of joint destruction.

Based on our experience with this patient, we feel that long-term concurrent therapy with infliximab and methotrexate is a promising therapeutic approach in patients with MRH. The relatively rapid and sustainable response, clearing of the skin, improvement of arthritis, and low side-effect profile suggest this regimen can easily be started early in the disease process. Biopsy of the characteristic skin lesions once MRH is suspected is critical for early diagnosis of the condition, and facilitates early initiation of combination therapy preventing progression and debilitation. A thorough and consistent investigation for potential underlying malignancy is critical to reduce morbidity and mortality for patients with MRH, even in the setting of initial negative workup. It is crucial that clinicians not be fooled by clinical improvement of MRH and continuously monitor for internal malignancies.

## Acknowledgments

We are indebted to Neil Coleman MD for providing images of the histology.

## Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

No funding for design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Author Contributions

Suraj Patel was the primary author of this manuscript. Dr. Mandy Alhajj provided guidance on organization and logical flow of the report. Dr. Conrad Brimhall provided edits during the revision process.

## Data Availability Statement

Suraj Patel, Mandy Alhajj, and Conrad Brimhall had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All data generated or analyzed during this study are included in this article.

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