

From Polyarthrititis to Aggressive Nodulosis: An Unusual Evolution of Rheumatoid Arthritis

By Kavya Mulgund; and Tripti Papneja, MD, FRCPC

Case Presentation

A 61-year-old female with hypertension presented initially in 2011 with several weeks of joint pain, morning stiffness and fatigue. Examination demonstrated swelling of multiple metacarpophalangeal (MCP) joints with no extra-articular features. Laboratory testing revealed hemoglobin 88 g/L, ferritin 8 µg/L, ESR 71 mm/hr, CRP 34.8 mg/L, rheumatoid factor 299 IU/mL, and ANA 1:640 speckled. Anti-CCP was negative. She was diagnosed with seropositive rheumatoid arthritis (RA) and was started on methotrexate and hydroxychloroquine with good response. Her RA entered remission by 2013, and she elected to discontinue disease-modifying anti-rheumatic drug (DMARD) therapy. Between 2013-2024, she was treated for osteoporosis, transitioning from bisphosphonate therapy to denosumab injections. She continued on valsartan and amlodipine for her hypertension. She developed Raynaud's phenomenon in February 2023.

She was in Pakistan from April to May 2024 and started to feel very unwell with fever, marked fatigue and joint pain/swelling. She couldn't move her right elbow. She was started on prednisone 60 mg daily, to be tapered by 5 mg every 2 days. In June 2024, she developed nodules on her hands (Figure 1) and reported anorexia with 20 lbs. weight loss, intermittent low-grade fever, cough and xerostomia. Examination detected 6 swollen joints, predominantly affecting MCP and proximal interphalangeal (PIP) joints, and multiple, discrete, tender nodules over the dorsal and palmar aspect of both hands.

Bloodwork showed the following: hemoglobin 114 g/L, WBC $4.1 \times 10^9/L$, platelets $219 \times 10^9/L$, ESR 40 mm/hr, CRP 1.3 mg/L, persistent ANA $\geq 1:640$ speckled, positive SSA/SSB (>8.0 , normal is <1.0), mildly positive RNP (2.0, normal is <1.0), low complement levels (C3 0.80 g/L, C4 0.14 g/L), and negative anti-dsDNA, hepatitis B/C, HIV and Quantiferon gold TB testing. A working diagnosis of RA flare was made, and prednisone and leflunomide were initiated.

A punch biopsy of a hand nodule (August 2024) showed dermal proliferation of histiocytes and multinucleated giant cells containing eosinophilic "ground-glass" cytoplasm with sclerotic stroma, confirming the diagnosis of multicentric reticulohistiocytosis (MRH). Biopsy of a lesion on her back was consistent with granuloma annulare.

Given the diagnosis of MRH, malignancy screening was completed. Colonoscopy, mammography and CT scan of the head were normal. CT of the abdomen/pelvis revealed hepatic and renal cysts. CT of the chest showed cystic interstitial lung disease with multiple thin-walled cysts, most consistent with lymphoid interstitial pneumonia. Her pulmonary function test demonstrated restrictive defects. She had an endobronchial ultrasound on

November 6th for sampling of mediastinal lymph nodes, results of which are pending. ENT is following her for a 3.7 x 3.0 cm right paratracheal mass, presumed to be due to an enlarged thyroid.

Discussion

Multicentric reticulohistiocytosis (MRH) is a rare, multi-system, class IIb non-Langerhans cell histiocytosis characterized by granulomatous proliferation of the mononuclear phagocyte system. It is marked by destructive polyarthrititis and papulonodular skin lesions. Polyarthrititis is often the first and most prominent feature, progressing to destructive arthritis and disability. We present a case of MRH and review current literature on its clinical features, diagnostic approach, and management.



Figure 1. Papulonodular cutaneous lesions on the hands of our patient.

Epidemiology

MRH is a rare disease with slightly more than 300 cases reported worldwide. The true incidence and prevalence of this disease is unknown. It predominantly affects Caucasian females in their fifth and sixth decade of life, with a female-to-male ratio of 3:1.

MRH is often associated with autoimmune conditions and internal malignancies. A Mayo Clinic review (1980–2017) of 24 cases reported autoimmune disease in 29%, malignancy in 25%, and five-year survival of 85% (95% CI: 74–100%).² MRH frequently coexists with autoimmune diseases, including Sjogren's disease, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, celiac disease, and primary biliary cirrhosis.

While MRH cases have been associated with nearly all types of cancer both solid and hematologic, the most common malignancies observed are carcinomas of the lung, stomach, breast, cervix, colon, and ovary. Whether multicentric reticulohistiocytosis is a true paraneoplastic disorder is controversial, because no consistent type of cancer has been associated with MRH. In addition, as multicentric reticulohistiocytosis is very rare, the association with cancer may be coincidental. Moreover, a correlation between the removal of cancer and the disappearance or improvement of multicentric reticulohistiocytosis has not been established.

Clinical Features

In half of the patients, the first sign of the disease is arthritis. In one quarter, papules and nodules are the first sign. The remainder develop skin and joint manifestations at the same time. The most frequent joint manifestations include symmetric and erosive inflammatory arthritis affecting the hands in a distal predominance, but MRH can also involve the elbows, shoulders, hips, knees and feet, and when left untreated can lead to a progressively de-

forming and destructive arthropathy including contractures and arthritis mutilans.

Cutaneous lesions usually appear within three years of arthritis onset, as acral yellowish to reddish-brown papulonodules. These lesions most commonly occur on the upper half of the body, especially the face, ears, mucosal surfaces (lips, tongue, gums, nostrils, throat, eyelids), hands, and forearms. They range in size from 1-2 mm to several centimetres in diameter and arise in isolation or in clusters or crops with a cobblestone appearance. Mucosal lesions are present in approximately 50% of cases. The skin lesions may cause destruction of cartilage around the ears and nose. Lesions are usually asymptomatic, but one third of patients complain of pruritus. Periungual papulonodular skin lesions are pathognomonic and often coalesce creating the classic "coral bead" or "string of pearls" appearance. Nodules developed a decade later in our patient from the time of initial joint symptoms.

Common systemic symptoms include fever, malaise, and weight loss, often with elevated ESR, anemia, and hypercholesterolemia.¹ Systemic involvement may include pleural or pericardial effusions, cardiac failure, mesenteric lymphadenopathy, and urogenital lesions.³

Around one third show autoimmune serologies (anti-Ro, anti-CCP, ANA). Histopathology reveals lymphohistiocytic infiltrates with multinucleated giant cells containing eosinophilic ground-glass cytoplasm.² Pathogenesis involves monocyte/macrophage activation and osteoclastic activity.

When a case of MRH is suspected, the diagnostic tests in Table 1 should be considered.

Therapeutic Approaches

Treatment aims to control inflammation and prevent joint destruction. Since MRH is a rare disease, there are no standardized treatment guidelines. Therapies include corticosteroids, DMARDs such as methotrexate, azathioprine, cyclosporine, cyclophosphamide, chlorambucil, topical tacrolimus, and rituximab.⁴⁻⁶ Tariq et al. reported methotrexate controlled arthritis in 28% and skin lesions in 38%, while cyclophosphamide achieved complete remission in 20% and partial improvement in 40–45%.⁷ Anti-TNF agents, anakinra, bisphosphonates, Janus Kinase (JAK) inhibitors (upadacitinib), and tocilizumab are additional options.⁸

In many patients, multicentric reticulocytosis can go into remission after an average course of 8 years; however, by this time considerable joint destruction may have occurred. Arthritis mutilans may develop in 50% of cases. Patients are left with crippling, deformed joints and a disfigured facial appearance.

Early diagnosis and prompt DMARD therapy are crucial, as MRH often follows an aggressive, erosive course leading to joint destruction if left untreated.

Table 1. **Common Diagnostic Tests in MRH**

Category	Tests	Typical Findings/Remarks
Bloodwork	Complete blood count (CBC)	Mild normocytic anemia; leukocytosis occasionally present
	Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)	Typically elevated in active disease
	Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), cases antinuclear antibody (ANA)	Usually negative; low-titer RF or ANA may occur in overlap
	Lipid profile	May show hyperlipidemia in a subset of patients
	Liver and renal function tests	To rule out comorbid diseases, or other organ involvement
	Immunoglobulins (IgG, IgA, IgM, IgE), serum and urine protein electrophoresis	Polyclonal hypergammaglobulinemia can be seen. To rule out monoclonal proteins
	Hepatitis B/C, HIV, tuberculosis (Quantiferon)	Expected to be negative; needed before immunosuppressants
Imaging	Radiographs of involved joints such as hands/wrists	Marginal erosions with relative preservation of joint space
	CT chest/abdomen/pelvis, mammography	Age-appropriate malignancy screening. Include colonoscopy as well
Pathology	Biopsy of skin or synovial nodule	Dermal and subcutaneous infiltration by multinucleated giant cells and histiocytes with ground-glass eosinophilic cytoplasm

Back to the Case

Despite treatment escalation with prednisone, hydroxychloroquine, leflunomide and methotrexate added in September 2024, she experienced persistent fatigue, arthritis, and progressive nodulosis. In August 2025, adalimumab was initiated. At the time of writing, she has completed eight weeks of adalimumab with no significant improvement in rheumatologic or dermatological symptoms. A change in therapy to tocilizumab is being considered.

Conclusion

MRH is a rare but severe systemic disease with distinctive skin and joint features. Its association with malignancy and autoimmune conditions necessitates thorough evaluation. Early recognition and initiation of immunosuppressive or biologic therapy improve outcomes.

Glossary:

- ANA: Anti-nuclear antibody
- Anti-CCP: Anti-cyclic citrullinated peptide
- Anti-dsDNA: Anti-double-stranded DNA
- Anti-Ro: Anti-Ro antibodies, also known as anti-SSA/Ro antibodies
- CRP: C-reactive protein
- ENT: Ear nose and throat specialist
- ESR: Erythrocyte sedimentation rate
- HIV: Human immunodeficiency virus
- RNP: Ribonucleoprotein
- SSA/SSB: Sjögren's Syndrome A antibodies/ Sjögren's Syndrome B antibodies
- TB: Tuberculosis
- WBC: White blood cell

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Kavya Mulgund
 BHSc student,
 Queen's University
 Kingston, Ontario.

Tripti Papneja, MD, FRCPC
 Clinician-Teacher,
 University of Toronto
 William Osler Hospital
 Brampton, Ontario