Efficacy of Vinblastine and Prednisone in Multicentric Reticulohistiocytosis With Onset in Infancy

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Dr Jha made provisional pathological diagnosis of multicentric reticulohistiocytosis, and conceptualized and designed the study; Dr Mahendra Kumar compiled data, drafted the initial manuscript, and approved the final manuscript to be submitted; Dr Mohan Kumar finalized the pathological diagnosis, and reviewed and approved the manuscript submission; Dr Ravindra Kumar obtained detailed clinical history of the patient along with treatment history and response; Dr Singh compiled clinical data and treatment response; Mr Kunwar provided opinion regarding joint deformities and helped to make the final diagnosis of multicentric reticulohistiocytosis; and Dr Prasad finalized clinical and treatment history, provided follow-up details and response to treatment, and reviewed and approved the manuscript for submission.

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Multicentric reticulohistiocytosis (MRH) is an unusual systemic inflammatory disorder of unknown etiology, affecting skin, mucosa, and joints; however, in some cases visceral organs also may be involved. Clinically, patients present with cutaneous papulonodular lesions and progressive symmetric and erosive arthritis.1 Review of literature showed ~13 cases of childhood MRH, including the present study, defining its rarity in childhood.1,2 To the best of our knowledge, the present case is the youngest in the literature with onset of disease in infancy. MRH is often misdiagnosed due to its rarity and overlapping clinical and histologic features. Characteristic histologic findings include infiltration of histiocytes and multinucleated giant cells with a homogeneous eosinophilic ground glass cytoplasm.1–4 Early diagnosis and immediate treatment are important to prevent irreversible joint deformity. There is no definite treatment protocol for MRH, and various drugs have been attempted with inconsistent results.1,3 We tried vinblastine and prednisone in this case with good response, which has not been attempted before.

CLINICAL HISTORY

A 3.5-year-old girl presented with red-colored skin lesions with elevated margins on the left lower neck along with pain and swelling of multiple fingers since 3 months of age. Skin lesions started as a small swelling measuring 1.5 × 1.5 cm at the left lower side of neck at 3 months of age, which gradually increased in size...
and later developed a discharging sinus that healed over the next 3 months, leaving behind a red-colored scaly scab with nodular margin. Skin lesions gradually increased in size, involving the lower neck and shoulder area with itching (Fig 1A). At 2 years of age, the child also developed a similar lesion at the lateral side of the left upper arm and at the base of nose. In addition to skin manifestations, the patient also developed pain and swelling of the right index finger at the age of 7 months, which progressed to involve the right middle finger and left index finger during the course of the next month. Fingers became sausage shaped with multiple small nodules (Fig 1 B and C), which displayed recurrent ulceration and healing leading to a small yellowish scar during a period of 3 to 4 days. Mainly metacarpophalangeal joints and proximal interphalangeal (PIP) joints were involved with joint laxity and increased range of movement. Later, at the age of 14 months, she also developed painful swelling over bilateral first metatarso-phalangeal joints of feet. There was no associated malignancy, autoimmune disorder, hypercholesterolemia, or significant family history.

Physical examination revealed moderate pallor, generalized lymphadenopathy, hepatomegaly of size 5.5 cm, and mild splenomegaly (1 cm below left costal margin). Blood investigation revealed anemia (hemoglobin 7.7g/dL), leukocytosis (total leukocyte count 23,600/cmm) with normal distribution of cells, and raised erythrocyte sedimentation rate (70 mm in first hour). Peripheral blood smear demonstrated moderate anisopoikilocytosis with presence of microcytic hypochromic cells; however, there were no blasts or atypical cells. Her renal function, liver function tests, and lipid profile were within normal range. Mantoux test, rheumatoid factor, C-reactive protein, and collagen profile were negative. Radiographs of both hands showed lytic lesions with sclerotic margin in the left second and fifth phalanges, and right second and third phalanges (Fig 1D). The patient was very ill with progressive multiple skin lesions, swelling of fingers and toes with severe arthralgia, and bacterial infection, for which the patient was admitted to the hospital.

Fine needle aspiration cytology from bony lesions revealed numerous histiocytes with vesicular nuclei and many multinucleated giant cells with abundant homogeneous eosinophilic cytoplasm. There was no associated cytologic feature of Langerhans cell histiocytosis (LCH); however, in view of clinical and radiologic findings, the possibility of LCH was suggested.

**Histopathological Findings**

Skin biopsy showed dense infiltrates of mononuclear cells and many multinucleated giant cells in the dermis extending into subcutaneous fat (Fig 2A). Mononuclear cells and giant cells had round to oval vesicular nuclei with moderate to abundant fine granular eosinophilic “ground glass” cytoplasm (Fig 2B). Overlying epidermis was focally ulcerated. Xanthogranulomatous changes, Touton giant cells, necrosis, and Langerhans cells were not seen. Ziehl Neelsen stain and periodic acid-Schiff stain did not reveal any organism. Mononuclear cells and giant cells were strongly positive for CD68 (Fig 2C) and negative for CD1a, S100, CD20, CK (Pan CK), and CD34 (Fig 2C and D).

In view of the possibility of LCH on cytology, the patient was started on vinblastine (6 mg/m² once a week for 6 weeks) and prednisolone (40 mg/m² daily for 6 weeks). This combination of drugs is safe in the pediatric population, and the patient exhibited significant clinical improvement, so we continued the same drugs even after confirmation of MRH on histopathology. Clinical improvement was evident after 4 to 6 weeks of therapy. Skin lesions showed relatively early response as compared with bony lesions. The patient developed systemic fungal (Candida) infection after 2 months and responded well to antifungal therapy. After 6 weeks, we continued...
vinblastine (6 mg/m² every 3 weeks) and prednisone (40 mg/m² daily for 5 days at every 3 weeks) with target of total duration of 6 months of therapy. Recent follow-up of the patient showed resolving skin lesions with healing of ulcerated margin (Fig 3A) and reduced joint swelling (Fig 3B); however, radiology of the hands revealed persistence of bony lesions (Fig 3C). No fresh cutaneous lesion appeared. Splenomegaly, hepatomegaly, and lymphadenopathy subsided. Erythrocyte sedimentation rate became normal and hemoglobin improved (9.6 g/dL). Liver function tests, renal function test (RFT), and other biochemical and hematologic profiles became normal. The patient did not develop hematologic or any other toxicity.

DISCUSSION

MRH is a rare multisystem histiocytic disorder, typically characterized by chronic, destructive, disfiguring polyarthritis and cutaneous nodules. Exact pathogenesis is unknown; however, a few theories suggest inflammatory and others suggest proliferative disorder.1–3 It usually affects individuals in the fourth decade of life and is very rare in children.2–4 To the best of our knowledge, ∼13 pediatric cases have been reported (Table 1), our case being the youngest of all with the earliest presentation at the age of 3 months.1, 5, 6 MRH predominately affects female individuals, both in the adult and pediatric populations. In adults, the male-to-female ratio is 1:2 to 3 and in the pediatric population, 12 of 13 reported cases are girls.1, 2, 6–17 Irrespective of age groups, this disease is more prevalent in white ethnicity.2, 5

MRH manifests with 2 major clinical features, the first being polyarthritis and the second being skin lesions. In adults, symmetric polyarthritis is the initial symptom in two-thirds of patients and skin manifestations appear after an average period of 3 years of arthritis. Cutaneous lesions as an initial manifestation are present in 20% of patients and simultaneous skin and joint lesions present in the remainder. A similar pattern of clinical presentation is also noticed in pediatric MRH.2, 3

Skin lesions are usually in the form of reddish brown papules and nodules varying in size from a few millimeters to several centimeters, which are usually asymptomatic. Skin ulceration is unusual in MRH; however, our patient had recurrent ulceration and healing of skin lesions. Both adult and pediatric MRH have similar kinds of cutaneous manifestations with respect to type and distribution of lesions.

Cervical spondylitis may be a manifestation in approximately
<table>
<thead>
<tr>
<th>SN</th>
<th>Reference</th>
<th>Age/Gender</th>
<th>Initial Lesions and Presentation</th>
<th>Cutaneous Lesion</th>
<th>Bony Lesions and Joint Lesions</th>
<th>Associated Diseases</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Melton and Irby (1972)7</td>
<td>16 y/F</td>
<td>Arthritis</td>
<td>Periungual reddish brown papules</td>
<td>Metacarpophalangeal joints, wrists, elbows, shoulders, knee, and ankles</td>
<td>None</td>
<td>None; Self-limiting</td>
</tr>
<tr>
<td>2.</td>
<td>Stogman et al (1975)8</td>
<td>10 y/F</td>
<td>—</td>
<td>Nodular lesions mainly periungual involving second to fourth fingers of both hands</td>
<td>Erosive arthritis involving DIP and PIP joints, bilateral knee swelling and effusion</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>3.</td>
<td>Migone et al (1979)9</td>
<td>7 y/F</td>
<td>Arthritis, fever, rash</td>
<td>Rash on extensor aspect of forearm and hands</td>
<td>Acute inflammation of PIP and DIP joints</td>
<td>None</td>
<td>Aspirin</td>
</tr>
<tr>
<td>4.</td>
<td>Scutellari et al (1986)10</td>
<td>18 y/F</td>
<td>Arthritis</td>
<td>Multiple nodules on hands, ear, forehead, scalp, and nasal rim</td>
<td>Erosive arthritis of the PIP and DIP joints</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5.</td>
<td>Omdal et al (1988)11</td>
<td>9 y/F</td>
<td>Skin lesion with itching at finger tips</td>
<td>Multiple papules and nodules on finger tips and front of thigh</td>
<td>Arthritis of DIP, PIP, wrist, knee, elbow, and ankles</td>
<td>None</td>
<td>Self-limiting</td>
</tr>
<tr>
<td>6.</td>
<td>Raphael et al (1989)12</td>
<td>14 y/F</td>
<td>Arthritis and cutaneous nodules</td>
<td>Multiple periungual verrucous nodules and deeper nodules along tendon sheath</td>
<td>Elbows, wrists, knees, and DIP with joint effusion, no erosion seen</td>
<td>None</td>
<td>Aspirin</td>
</tr>
<tr>
<td>7.</td>
<td>Kuramoto et al (1989)13</td>
<td>16 y/M</td>
<td>Age 6: multiple cutaneous nodules on face and trunk that resolved spontaneously</td>
<td>Age 6: fleshy papules at age 6</td>
<td>None</td>
<td>At age 16 developed lymphoma</td>
<td>Prednisolone and cyclosporine with no response; later, chemotherapy for lymphoma</td>
</tr>
<tr>
<td>8.</td>
<td>Friedman and Kalisher (1998)15</td>
<td>6 y/F</td>
<td>Multiple palmar nodules and swelling of hands, knees, and right ankle</td>
<td>Multiple reddish brown papules</td>
<td>Synovitis of left wrists, both knees, and joints of hands</td>
<td>None</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>10.</td>
<td>Havill et al (1999)17</td>
<td>12 y/F</td>
<td>Age 7.5: painful swelling of the bilateral knee, ankles, wrists, and fingers</td>
<td>Age 8: multiple papular lesions on lip, buccal mucosa, and proximal nail folds</td>
<td>Erosion of the left fourth and fifth, right second and third DIP, effusion of both knees and joints of hands</td>
<td>None</td>
<td>Responded to naproxen</td>
</tr>
<tr>
<td>11.</td>
<td>Matte et al (2003)9</td>
<td>3 y/F</td>
<td>Papular skin lesions and arthralgia</td>
<td>Pink flat-topped papular skin lesions on the finger nail margins of hands, scalp, and around the nares</td>
<td>Arthralgias of wrists and knees, osteopenia, multiple joint effusions, and synovial thickening</td>
<td>None</td>
<td>Naproxen, methotrexate, prednisone, etanercept, infliximab</td>
</tr>
<tr>
<td>12.</td>
<td>Olson et al (2015)18</td>
<td>2 y/F</td>
<td>At 2 y: cutaneous papular lesions on the thighs, elbows, and knees</td>
<td>Multiple pink, papular lesions on elbow and knees, and later also developed on nose, forehead, ears, dorsal hands, fingers, and knuckles</td>
<td>Polyarthritis of the cervical spine, bilateral wrists, right index finger, bilateral knees, ankles and subtal joints, right toe bony enlargement</td>
<td>None</td>
<td>Naproxen, methotrexate, tumor necrosis factor inhibitors, infliximab to which good response was seen</td>
</tr>
<tr>
<td>13.</td>
<td>Present case</td>
<td>3 mo/F</td>
<td>Papulonodular cutaneous lesions in neck and shoulder region</td>
<td>Spreading cutaneous lesion that ulcerates, heals, and new crop of fleshy nodules appear</td>
<td>Painful swelling of multiple bilateral hand joints and bilateral metatarsophalangeal joints</td>
<td>None</td>
<td>Initially cutaneous lesions responded well to prednisone and vinblastine for 2 mo; after that patient developed recurrence of cutaneous lesions</td>
</tr>
</tbody>
</table>

**Notes:** ANA, antinuclear antibody; DIP, distal interphalangeal joint; F, girl; M, boy; SN, serial number; —, no information available in respective study.
half of adult MRH cases; however, in childhood MRH, only 1 case with cervical joint involvement has been reported. Only 2 pediatric cases of MRH had involvement of foot joints, including present case (Table 1). Many of the adult MRH cases show association with autoimmune disorders, tuberculosis, and various malignancies (breast, cervix, stomach, hematologic malignancies, melanoma, lung and colonic carcinoma). In contrast to adult MRH, childhood MRH cases usually do not show association with autoimmune disorder and malignancy; however, 1 case of lymphoma and 1 case of autoimmune disorder have been reported in pediatric MRH.

Regarding involvement of other organs, adult MRH may involve myocardium, pericardium, and pleura. There are a few case reports suggesting association of MRH with trigeminal neuropathy, central retinal vein thrombosis, and fracture of femoral neck. Systemic involvement has not been reported in childhood MRH.

There is lack of a sufficient number of MRH cases for clinical trial, so there is no standardized treatment protocol. MRH has a variable disease course. Some of the patients have self-limiting disease, and others have unpredictable relapses and remissions or progressive disease with joint deformity. Nonsteroidal anti-inflammatory drugs, corticosteroids, cyclophosphamide, azathioprine, methotrexate, chlorambucil, and leflunomide have been used with variable responses. Some recent studies have demonstrated good response with anti–tumor necrosis factor-α (etanercept, infliximab), anti–interleukin-1 (anakinra) and interleukin-6 antagonists (tocilizumab) both in adult and pediatric cases. Considering the possibility of LCH on fine needle aspiration cytology, we prescribed vinblastine and prednisolone to our patient and she responded well to this regimen with significant clinical improvement. In view of good response and safety of these drugs in childhood, we put the patient on the same drugs. The organomegaly resolved and most of the biochemical and hematologic parameters became near normal until recent follow-up. In the present case, good response with vinblastine and prednisolone signifies their role in treatment of childhood MRH. This observation may help in understanding of pathogenesis of MRH; however, studies with large sample sizes are required.

**CONCLUSIONS**

Childhood MRH is extremely rare, although it should be considered in patients presenting with erosive arthritis and mucocutaneous lesions. A high degree of clinical suspicion, meticulous clinical examination, radiologic correlation, and histopathological examination are essential to confirm the diagnosis of MRH. Treatment with vinblastine and steroid (prednisone) may be an effective and safe alternative for the treatment of childhood MRH.

**ABBREVIATIONS**

LCH: Langerhans cell histiocytosis

MRH: multicentric reticulohistiocytosis

PIP: proximal interphalangeal joints

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