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Multicentric reticulohistiocytosis with hydrarthrosis in both knee joints: disease stabilization with synovectomy, and medication with a steroid and low-dose methotrexate

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Abstract Multicentric reticulohistiocytosis is a rare systemic disease characterized by the infiltration of histiocytes and multinucleated giant cells with cutaneous nodules, and severe destructive arthritis. It is commonly the peripheral joints which are affected, and therefore symptoms in large joints have not been fully investigated. We describe the case of a 44-year-old woman with multicentric reticulohistiocytosis, who was suffering from swelling in both knee joints and cutaneous nodules, in addition to arthritis in the elbow, hip, and peripheral joints. Magnetic resonance imaging of both knee joints showed hydrarthrosis associated with a tumor-like overgrowth of synovial tissue. These symptoms were reduced following a resection of the synovial tissue and subsequent medication with prednisone and low-dose methotrexate. It should be noted that swelling in the knee joints can be one of the symptoms caused by multicentric reticulohistiocytosis, in addition to cutaneous nodules and arthritis in the peripheral joints. Resection of synovial tissue, and medication with prednisone and low-dose methotrexate were effective in the present case.

Key words Hydrarthrosis · Knee · Methotrexate · Multicentric reticulohistiocytosis · Prednisone

Introduction

Multicentric reticulohistiocytosis was first reported by Targett in 1897,[1] and the term "multicentric reticulohistiocytosis" was proposed by Goltz and Laymon in 1954.[2] Multicentric reticulohistiocytosis is a rare systemic disease, and has been reported to occur predominantly among the female population (60%–75%), usually beginning during the fourth decade of life.[3,4] Its etiology is unknown, but it leads to severe destructive arthritis, cutaneous nodules, and a significant association with malignancies. The most frequently affected joints are the phalangeal joints of the hands; the other affected joints being the shoulders, knees, wrists, hips, elbows, ankles, feet, and spine, in descending order of frequency.[3,4] Stabilization of the disease has been reported following treatment with alkylating agents[5] or methotrexate.[4,6] We describe the case of a patient with multicentric reticulohistiocytosis, whose chief complaint was swelling in both knees and cutaneous nodules. A remission of these symptoms was achieved following a resection of the synovial tissue in both knee joints and medication with prednisone and low-dose methotrexate.

Case report

A 44-year-old woman had been suffering from swelling in both knee joints and arthritis in the hip, wrist, and phalangeal joints, in a symmetric pattern, for 3 years. The synovial fluid in the knee joints was a serious problem. Injection of a steroid into the knee joints did not effectively reduce the synovial fluid. The patient had also noticed cutaneous nodules in the face, nucha, tongue, and hands (Fig. 1). These nodules varied in size (2–10 mm diameter). Xanthomas were observed on both upper eyelids. A physical examination revealed prominent hydrarthrosis in the knee joints. Before medication, laboratory data were as follows: WBC $3.59 \times 10^3/\mu l$, RBC $4.28 \times 10^6/\mu l$, hemoglobin 8.7 g/dl, platelets $348 \times 10^3/ul$, Na 138 mmol/l, K 4.0 mmol/l, Cl 102 mmol/l, Ca 9.3 mg/dl, AST 18 U/l, ALT 20 U/l, BUN 11 mg/dl, creatinine 0.5 mg/dl, C-reactive protein 0.0 mg/dl. There was also microcytic anemia (hematocrit 30.6% (34.0–45.0); mean corpuscular volume 71.5% (82.0–95.0)). The cholesterol level was within the normal range (199 mg/dl (128–220)), but the triglyceride level was slightly elevated (172 mg/dl (30–150)). Erythrocyte sedimentation rate was slightly delayed at 18 mm/h. Tests for rheumatoid factor showed negative results. Plain radiographs showed destruc-

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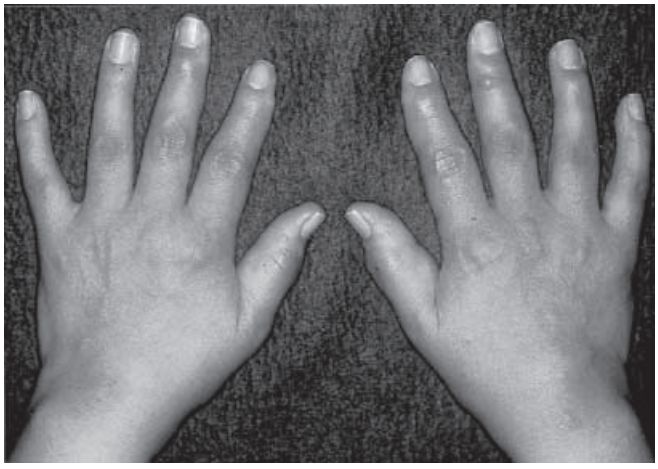

Fig. 1. Skin nodularities and swelling in both hands

Fig. 2. Plain radiographs of bilateral hands. A damaged phalangeal joint with irregular joint surfaces and subarticular osteosclerosis can be seen

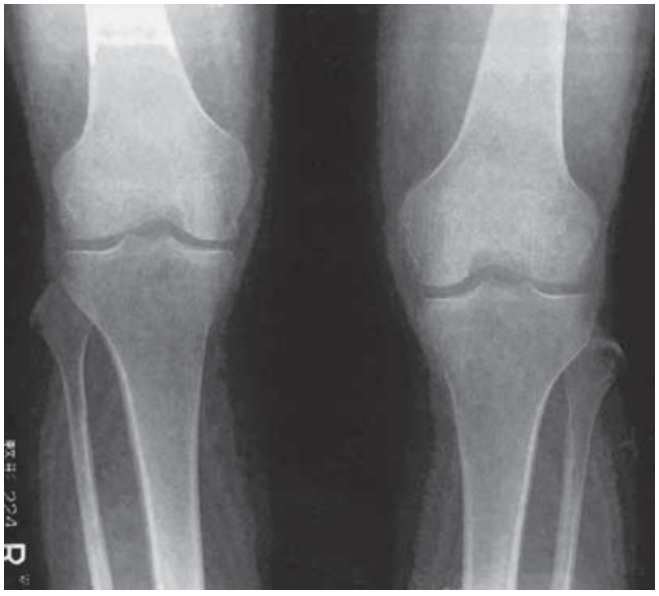

Fig. 3. Plain radiographs of bilateral knee joints. A narrowing of joint spaces and periarticular bone formation can be seen to a small extent

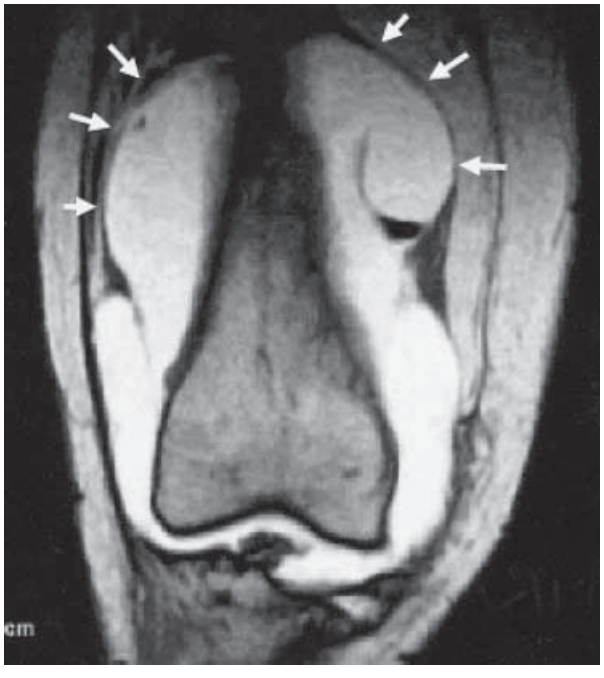

Fig. 4. Magnetic resonance image showing tumor-like hypertrophic synovial tissue (*arrows*) in the knee joints, with some fluid (T2-weighted images)

tive arthritis with marginal erosions in the phalangeal joints. The priarticular bone atrophy appeared after medication with a steroid (Fig. 2). Loss of cartilage and periarticular bone formation was slight in the knee joints (Fig. 3). Magnetic resonance imaging showed hydrarthrosis associated with a tumor-like overgrowth of synovial tissue in both knees joints (Fig. 4).

A specimen from one of the cutaneous nodules showed the infiltration of histiocytes and multinucleated giant cells whose eosinophilic cytoplasm showed the appearance of finely granulated, ground glass. The nuclei were round-to-oval and slightly pleomorphic, with prominent nucleoli (Figs. 5, 6). The tumor-like overgrown synovial tissue (a synovial nodule) of the knee joints was resected (Fig. 7), and histological findings showed villous hypertrophic synovitis with predominantly mononuclear histiocytes, some multinucleated giant cells, and other inflammatory cells (Figs. 8, 9). The other part of the synovial tissue also showed moderately inflammatory cells, which were mainly lymphocytes with some mononuclear histiocytes. These features in specimens from both the skin and the synovial tissue are consistent with multicentric reticulohistiocytosis.

Nonsteroidal anti-inflammatory drugs were not effective in reducing the cutaneous and joint lesions. However, although prednisone (20 mg/day for 2 weeks) resulted in no reduction in the cutaneous nodules, it produced a slight

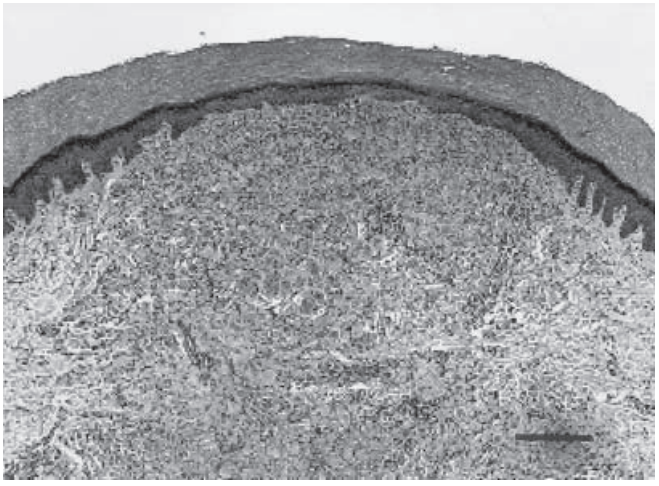

Fig. 5. Specimen from a cutaneous nodule. Aggregates of mononuclear histiocytes and multinuclear giant cells can be seen infiltrating the dermis, with thinning of the epidermis. Hematoxylin and eosin. *Bar* 90 μm

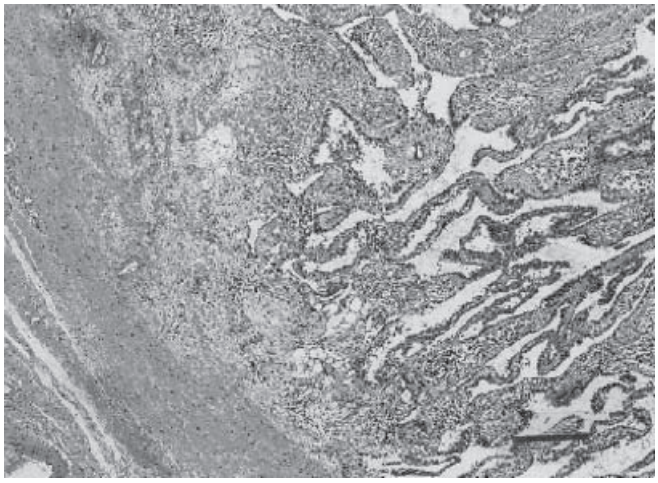

Fig. 8. A specimen from the knee joint shows hypertrophic synovial tissue. Hematoxylin and eosin. *Bar* 90 μm

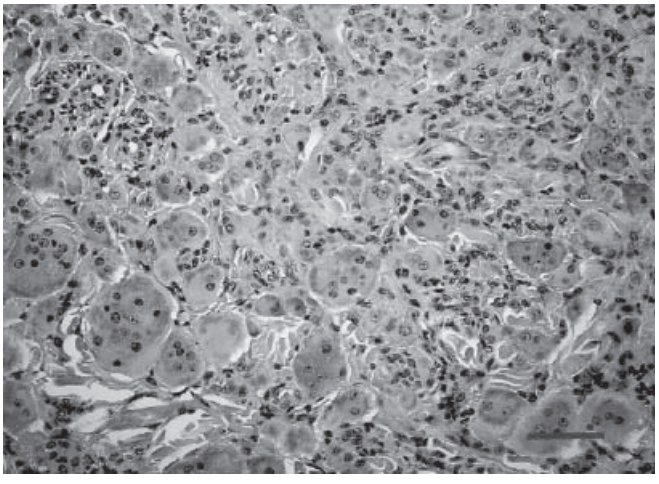

Fig. 6. Specimen from a cutaneous nodule. Mononuclear histiocyte-like cells and multinuclear giant cells have round-to-oval nuclei and eosinophilic cytoplasm with a ground-glass appearance. Hematoxylin and eosin. *Bar* 47 μm

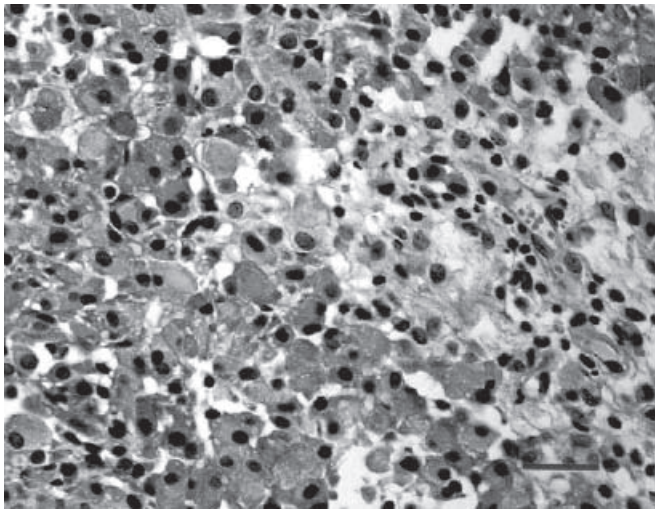

Fig. 9. A specimen from the knee joint. Aggregate of mainly mononuclear histiocytes, some multinuclear giant cells, and other inflammatory cells are seen. Hematoxylin and eosin. *Bar* 50 μm

Fig. 7. The synovial tissue is overgrown and resembles a tumor lesion

reduction in wrist pain. The prednisone was gradually tapered down to 10 mg/day. Then weekly low-dose pulse methotrexate was added to the regimen for a period of 3 months, with the dosage being increased gradually to 7.5 mg/week. The initial dose of methotrexate was 2.5 mg/week, it was then increased to 5 mg/week, and the final dosage was 7.5 mg/week, each dosage lasting for 4 weeks. During the medication, no further lesions developed, and there were no side-effects from the methotrexate. By the end of the course of medication, the cutaneous nodules, hydrarthrosis, and arthritis had completely disappeared. The patient had suffered no return of cutaneous nodules or arthritis when she was last seen at follow-up 6 months later.

Discussion

The etiology of multicentric reticulohistocytosis remains unclear despite numerous investigations and speculations. Most studies have suggested that multicentric reticulohistiocytosis is of a monocyte/macrophage origin.[7–9] On the other hand, dermal dendrocytes[10] or lymphocytes[11,12] have also been suggested. Gorman et al.[13] supported the notion of a monocyte/macrophage origin, and surmised that the production of cytokines (TNFα, IL-1, and IL-12) by activated macrophages is involved in the disease process.

Multicentric reticulohistiocytosis is characterized by polyarthritis (50%), cutaneous nodules (25%), or concurrent arthritis and cutaneous nodules (25%).[3,4] The polyarthritis is usually destructive, progressive, and symmetrical, and for this reason, arthritis in multicentric reticulohistiocytosis often simulates other forms of destructive arthritis, such as rheumatoid arthritis (especially seronegative rheumatoid arthritis), seronegative spondylitis, and crystal-induced arthritis. In the present case, the chief complaint of the patient was the swelling of both knee joints. The presence of hydrarthrosis associated with an overgrowth of synovial tissue in the knee joints as a symptom of multicentric reticulohistiocytosis has not been fully described before. It should be explained that multicentric reticulohistiocytosis is a rare lesion in itself, and although large joints are less frequently affected than phalangeal joints, it should be borne in mind that hydrarthrosis in both knee joints can be caused by multicentric reticulohistiocytosis.

The skin is a commonly affected organ. The nodules are usually asymptomatic, and located mainly on the face, hands, ears, forearms, elbows, scalp, neck, and chest.[4] The bone, tendon sheaths, muscles, eyes, larynx, pharynx, thyroid glands, salivary glands, bone marrow, heart, lung, kidney, liver, gastrointestinal tract, and genitalia have also been reported to be involved in multicentric reticulohistiocytosis, although these sites are less common.[4] In addition to cutaneous and joint lesions, general symptoms of fever, weakness, and weight loss are known to occur. Mild anemia, elevated erythrocyte sedimentation rate, concurrent hypercholesterolemia, and xanthoma are reported in about 30% of multicentric reticulohistiocytosis cases,[3,4] and these were all seen in the present case.

A wide spectrum of associated malignancies, including carcinoma, sarcoma, lymphoma and leukemia, has been reported in 15%–28% of multicentric reticulohistiocytosis cases, and a coexistent autoimmune disease has been reported to be present in 6%–17% of cases.[14] Liango and Granston[15] reviewed around 200 cases of multicentric reticulohistiocytosis in the English-language literature, but they found only 13 cases of complete or near complete remission. Complete remission of the disease has been reported in association with treatment with alkylating agents[5] or methotrexate.[4,6] Corticosteroid has been reported to be effective, but it is known that the use of corticosteroid alone will not induce complete remission. Alkylating agents (i.e., cyclophosphamide and chlorambucil) are thought to be toxic with routine use, and to have the potential to inducte malignancies.[15] Methotrexate has been used to treat this disease since 1991,[6] and a combined medication with corticosteroid and methotrexate has been reported to be effective.[15,17,18] In the present case, nonsteroidal anti-inflammatory drugs were not effective. Therefore, after resection of the overgrown synovial tissue, combined medication comprising prednisone (maximum dosage 20 mg/day) and methotrexate (maximum dosage 7.5 mg/week) was administered for 3 months, and a remission was obtained without any side-effects from these agents.

We have reported a case of multicentric reticulohistiocytosis, where the chief complaint was swelling in both knee joints caused by hydrarthrosis associated with an overgrowth of synovial tissue. In addition to resection of the synovial tissue, the cutaneous nodules and arthritis disappearing following medication with prednisone and low-dose methotrexate. However, long-term follow-up is essential in such cases owing to the high frequency of accompanying malignancies.

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