Multicentric Reticulohistiocytosis without Arthritis Successfully Treated with Systemic Corticosteroids
- A Case Report and Literature Review -
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A 46-year-old male presented with a 2-month history of multiple red papules on the cheeks and extremities without mucosal involvement or arthritis. There were only some lesions on the dorsal hands without periungual involvement. Biopsy of a skin lesion showed a dermal infiltrate consisting of mononuclear and multinucleated histiocytes with granular "ground glass"-like cytoplasm. These histiocytes were CD68-positive, and S-100 protein and CD30 negative in immunohistochemical studies. The diagnosis of multicentric reticulohistiocytosis without arthritis was made. Laboratory data were within normal limits except mild hypercholesterolemia and hypertriglyceridemia. A survey for internal malignancy showed negative results. The skin lesions responded to prednisolone 0.5 mg/kg daily. The dose was tapered gradually; the cutaneous lesions almost completely resolved after 15 weeks of treatment. Whether multicentric reticulohistiocytosis without arthritis is a subtype with better response to treatment remains to be confirmed by more clinical observation, but systemic corticosteroids may be tried first before starting other immunosuppressive or cytotoxic drugs. (Dermatol Sinica 24: 119-122, 2006)

Key words: Cutaneous, Reticulohistiocytosis, Reticulohistiocytoma, Corticosteroids
INTRODUCTION

Multicentric reticulohistiocytosis (MR) is a rare disorder of unknown etiology. It is characterized by mucocutaneous papulonodular eruptions on the face and hands, and symmetric destructive arthritis, which may finally evolve into "arthritis mutilans". Histopathologically, the skin lesions reveal an infiltrate of mononuclear or multinucleated giant CD68-positive histiocytes containing an eosinophilic, granular "ground glass" material in the cytoplasm. Fifteen to 31% of the cases have been reported to be associated with malignancy in the literature, but most of them did not run a course parallel to neoplasm. Other associations include hyperlipidemia, autoimmune diseases, pregnancy and tuberculosis. Although there is no well established treatment, immunosuppressive and cytotoxic agents have the best results.

Cases of MR without arthritis are rarely reported. We report a case manifesting only cutaneous lesions which responded to low-dose systemic corticosteroid, and review the updated information of MR.

CASE REPORT

A 46-year-old male presented with a 2-month history of slightly tender, non-itching red papules on the face and extremities. Lesions appeared firstly on the thighs, and then the upper extremities and the face. He noticed spontaneous resolution of individual lesions, but new lesions continued to appear. Physical examination showed multiple, discrete, 2-3 mm in diameter, dark red, dome-shaped papules with elastic consistency (Fig. 1A). Lesions on the face were mainly distributed over cheeks without mucosal involvement. Some lesions were present on the dorsal hands without periungual involvement. The patient denied constitutional symptoms including fever, malaise, or loss of body weight. He had no arthralgia or lymphadenopathy either. Biopsy of a skin lesion showed a nodular dermal infiltrate of mononuclear and multinucleated histiocytes with glassy cytoplasm mixed with abundant neutrophils, eosinophils, and lymphocytes (Fig. 2). These histiocytes were CD68-positive, and S-100 protein and CD30-negative in immunohistochemical studies. Thus, the diagnosis of multicentric reticulohistiocytosis was made.

Laboratory data, including complete blood cell count with differential count, blood urea nitrogen, creatinine, aminotransferase, albumin, globulin, and thyroid stimulating hormone were within normal limits except for mild hypercholesterolemia (207 mg/dl) and hypertriglyceridemia (188 mg/dl). Studies for autoimmune disease showed negative results. Tumor markers such as carcinoembryonic antigen and alpha-fetoprotein were within normal limits. Immunoelectrophoresis showed no monoclonal gammopathy. The chest radiography was unremarkable. Abdominal sonography showed two hepatic cysts, and a hyperechoic hepatic nodule 1.2 cm in diameter at segment 6-7, which was not identified in abdominal computer tomography.

Fig. 1
Multiple dark red, dome-shaped papules on the face (A) disappeared after treatment with systemic corticosteroids for 15 weeks (B).

Fig. 2
Histopathology reveals an infiltrate of mononuclear or multinucleated giant histiocytes containing an eosinophilic, granular "ground glass" material in the cytoplasm. (H & E, x 400)
Prednisolone 0.5 mg/kg daily was given initially. One week later, the skin lesions became smaller, flattened and fading in redness. In light of good response to corticosteroids, prednisolone was continued with decreasing dose. The papules mostly disappeared by 15 weeks with residual pigmentation (Fig. 1B). There were no symptoms of arthritis during the course of treatment.

DISCUSSION

MR is a rare disease, and only about 200 cases have been described in the literature. Several reviews summarized the majority of published cases in the world literature since 1937 to 2001. MR is usually insidious in its onset and progressive. In almost 40% of the cases, joint symptoms occur first, while 30% begin with skin manifestations and 29% with both skin and joint symptoms. The cutaneous lesions are reddish-brown papules and nodules, and most commonly located on the hands, followed by the face, arms, trunk, legs, ears, mucosa and neck. Small papules around the nail folds represent a typical clinical sign called "coral beads", which is found in 27% of the cases. Buccal mucosa, nasal mucosa and tongue are the most affected mucosa. A destructive chronic diffuse symmetric arthritis is another characteristic manifestation of MR. Hands, especially distal interphalangeal joints, are most frequently involved. Arthritis of knees, wrists, shoulders, elbows, ankles, hips and feet has been reported in decreasing frequency. It may evolve into an end-stage, "arthritis mutilans", in half of the patient. MR may result in disabling "opera-glass" deformity of the interphalangeal joints. Elevated erythrocyte sedimentation rate, anemia, and hypercholesterolemia are the more common abnormal laboratory findings.

MR has been described in association with various conditions. Among them, autoimmune disorders have been reported in 15% of MR patients. Fifteen to 31% of the MR cases has been reported to be in association with malignancy including several carcinoma, hematological neoplasia or metastasis from an unknown primary tumor. According to such a high association rate, some authors have proposed MR to be a paraneoplastic syndrome, but the hypothesis remains questionable due to the wide spectrum of associated malignancies and lack of parallel course. Nevertheless, a survey for malignancy is recommended in MR patients.

The histopathology of the skin lesion is typified by an infiltrate of mononuclear or multinucleated giant histiocytes containing an eosinophilic, granular "ground glass" material in the cytoplasm. These histiocytes are positive for CD68 and CD45, while negative for CD20, S-100 protein, and factor XIIIa, findings consistent with a monocyte-macrophage origin of the tumor cells. In the synovial biopsy, an increase in interleukin-12 (IL-12) has been described, as well as IL-1β, IL-6 and tumor necrosis factor α (TNF-α) similar to that observed in rheumatoid arthritis. These macrophage-derived cytokines have a variety of proinflammatory actions that could explain the bony and cartilaginous erosions seen in MR.

Although MR may be considered as a "self-limiting" disease which fades approximately 7 years after its beginning, aggressive treatment has been suggested due to the permanent disfiguring sequelae. The best results have been achieved mainly with immunosuppressive or cytotoxic agents, such as corticosteroids, cyclophosphamide, methotrexate, azathioprine, and chlorambucil, usually in combination. On the basis of increase in the presentation of TNF-α in the synovial tissue, anti-TNF-α agents, etanercept and infliximab, also have been used in the treatment of MR and achieved remission in cutaneous and articular symptoms. Alendronate, an aminobisphosphonate, has also been shown to achieve 2-year remission. The drug is supposed to act directly on monocyte/macrophages to inhibit their infiltration into the skin or impair their induction of necrosis and apoptosis.

MR without arthritis is a more rarely reported disease. Goette et al. defined three distinct clinical patterns of this reticulohistiocytosis: (i) solitary cutaneous reticulohistiocytosis;...
(ii) multiple or diffuse cutaneous reticulohistiocytosis; and (iii) multicentric reticulohistiocytosis. Our case fits in the second category. Zelger et al.\textsuperscript{15} studied the expression of factor XIIIa in 4 cases of MR and 6 cases of solitary or multiple reticulohistiocytoma, and found that factor XIIIa was positive in reticulocytoma but negative in MR. They suggested these two conditions represent two distinct entities. The findings need to be further confirmed by additional studies.

The present case could either be in the category of 30\% of MR that develop cutaneous manifestation as initial presentation, or, have MR without arthritis (or so-called multiple cutaneous reticulohistiocytosis). His cutaneous lesions responded very well to low-dose prednisolone alone. Giam et al.\textsuperscript{16} reported a case of MR without arthritis; the response to methotrexate was poor. Dawe et al.\textsuperscript{17} reported a case of diffuse cutaneous reticulohistiocytosis successfully treated with 8-methoxypsoralen-ultraviolet A photochemotherapy (PUVA) without recurrence one year after stopping the treatment. Whether MR without arthritis is a subtype with better response to treatment remains to be confirmed by more clinical observation, but systemic corticosteroids may be tried first before starting other immunosuppressive or cytotoxic drugs.

REFERENCES