Mod Rheumatol (2007) 17:422–425
DOI 10.1007/s10165-007-0600-0

CASE REPORT

**Takayuki Kishikawa · Taichiro Miyashita
Emiko Fujiwara · Osamu Shimomura · Ichiro Yasuhi
Daisuke Niino · Masahiro Ito · Misato Amenomori
Hideaki Osumimoto · Mitsuhiko Osumi · Katsumi Eguchi
Kiyoshi Migita**

Multicentric reticulohistiocytosis associated with ovarian cancer

Received: February 7, 2007 / Accepted: May 8, 2007

Abstract Multicentric reticulohistiocytosis (MR) is an uncommon disease characterized by joint and cutaneous manifestations. The diagnosis must be confirmed by histological evidence of typical histiocytes and multinucleated giant cells. Many conditions, including malignancy, have been described in association with MR. We herein report a female case of MR in whom partial improvement was obtained by steroid and low-dose methotrexate treatments. However, ovarian cancer was found and therefore a surgical resection and chemotherapy were performed. These treatments resulted in the complete resolution of the skin and joint symptoms. These findings support the close linkage between MR and malignancy and the efficacy of cytotoxic drugs for the treatment of MR.

Key words Cytotoxic drugs · Multicentric reticulohistiocytosis · Ovarian cancer · Paraneoplastic syndrome

Introduction

Multicentric reticulohistiocytosis (MR) is a rare systemic disorder of unknown cause, characterized by the presence of cutaneous papules and nodules and destructive polyarthritis.[1] The characteristic histopathological findings of nodules in the skin are the infiltration of foreign body-type mononuclear histiocytes with multinucleated giant cells.[2] Although the etiology of MR is unknown, uncontrolled macrophage activation is evident with the release of monokines and cytokines.[3] Approximately one third of patients with MR have been reported to have an associated internal malignancy.[4] We herein describe a patient with MR and overlapping ovarian cancer. In our case, the complete resolution of MR was achieved by treatments for ovarian cancer, including a surgical resection and chemotherapy.

T. Kishikawa · T. Miyashita · M. Amenomori · H. Osumimoto · M. Osumi
Department of General Internal Medicine, NHO National Nagasaki Medical Center, Nagasaki, Japan

E. Fujiwara · O. Shimomura · I. Yasuhi
Department of Obstetrics and Gynecology, NHO National Nagasaki Medical Center, Nagasaki, Japan

D. Niino · M. Ito
Department of Pathology, NHO National Nagasaki Medical Center, Nagasaki, Japan

K. Migita (✉)
Clinical Research Center, NHO National Nagasaki Medical Center, 2-1001-1 Kubara, Omura, Nagasaki 856-8562, Japan
Tel. +81-957-52-3121; Fax +81-957-53-6675
e-mail: migita@nmc.hosp.go.jp

K. Eguchi
First Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

Case report

A 64-year-old Japanese woman was admitted to our hospital in October 2003 for papules and nodules on her hands, in addition to polyarthralgia. She noticed arthralgia of the right shoulder in February 2003. Six months later, she developed multiple skin nodules on the dorsal aspect of her fingers, in addition to swelling of the proximal interphalangeal (PIP) joints and distal interphalangeal (DIP) joints. Physical examination revealed fresh-colored erythroid papules on the fingers, mainly on the DIP joints (Fig. 1). A musculoskeletal examination revealed pain and swelling of the shoulders, elbows, and knees, in addition to the DIP, PIP, and metacarpophalangeal (MP) joints. Laboratory studies disclosed elevated levels of C-reactive protein (CRP; 0.63 mg/dl, normal range: 0–0.30 mg/dl) and matrix metalloproteinase-3 (MMP-3; 91 ng/ml, normal range: 17.3–59.7 ng/ml). Tests for antinuclear antibody, rheumatoid factor, and anti-DNA antibody were all negative. A biopsy of the papules on her fingers revealed the existence of nodular and granulomatous lesions composed of many multinucleated giant cells containing eosinophilic cytoplasm (Fig. 2). Immunohistochemical analysis showed the positive staining for CD68 (Fig. 3A) and negative staining for S-100 (Fig. 3B) in the multinucleated giant cells seen in the biopsied skin nodules. From these findings, a diagnosis of

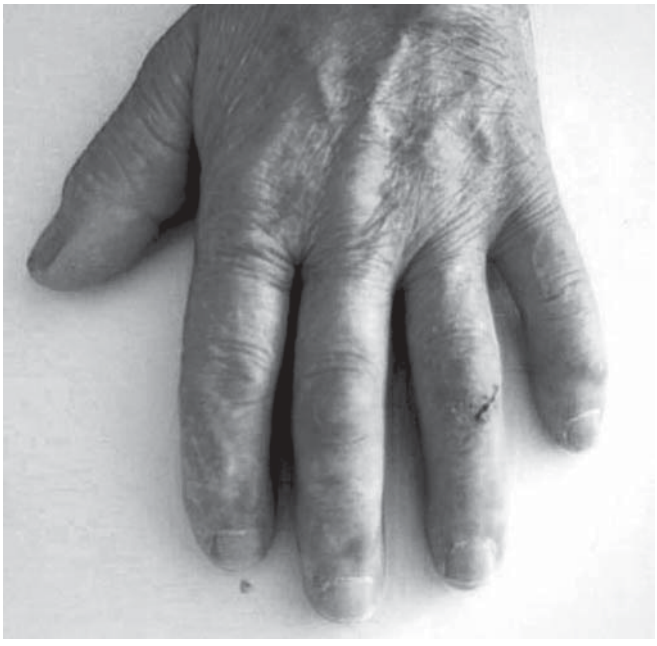

Fig. 1. Multiple fresh-colored erythroid papules and nodules on the dorsal aspect of the fingers

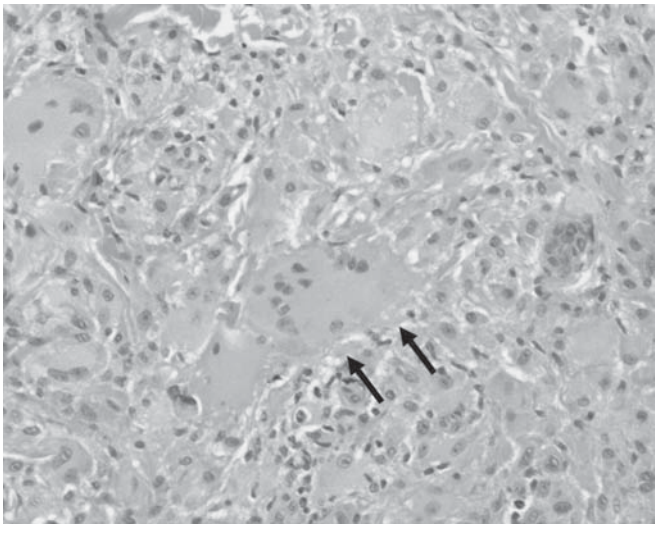

Fig. 2. Histology of the biopsied skin specimen shows a diffuse proliferation of histiocytes with eosinophilic cytoplasm and scattered multinucleated giant cells (*arrows*) (hematoxylin–eosin stain, ×400)

multicentric reticulohistiocytosis was made. Treatment with prednisolone (10 mg/day) and low-dose methotrexate (MTX; 6 mg weekly) were started. The patient's arthralgia and swelling of the joints gradually improved; however, the papules and nodules on the fingers remained. During the first admission, we performed various examinations, and evidence of malignancy was obtained.

Two months after discharge, she noticed abdominal distention. Computed tomography (CT) of her abdomen showed a mass with cystic lesions in the Douglas pouch, which had originated in the right ovary (Fig. 4). A diagnosis of adenocarcinoma originating from the ovary was sus-

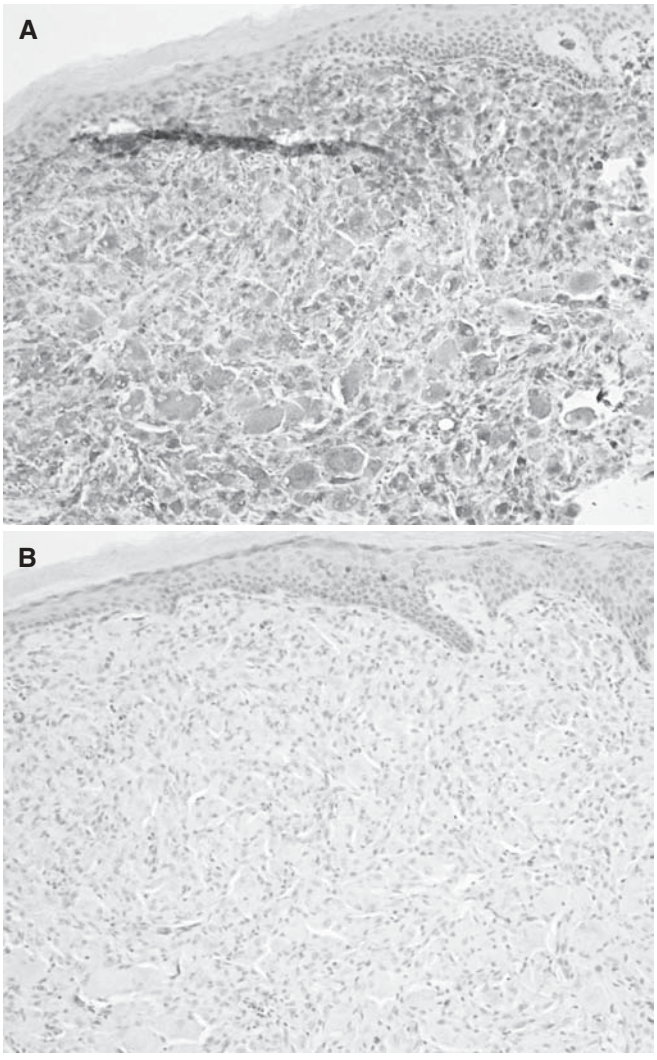

Fig. 3A,B. Tissue samples obtained from a skin nodule ware studied by immunohistochemical staining. **A** CD68 cell staining within the histiocytes and multinucleated giant cells. **B** S-100 cell staining was not demonstrated in the same tissue (×100)

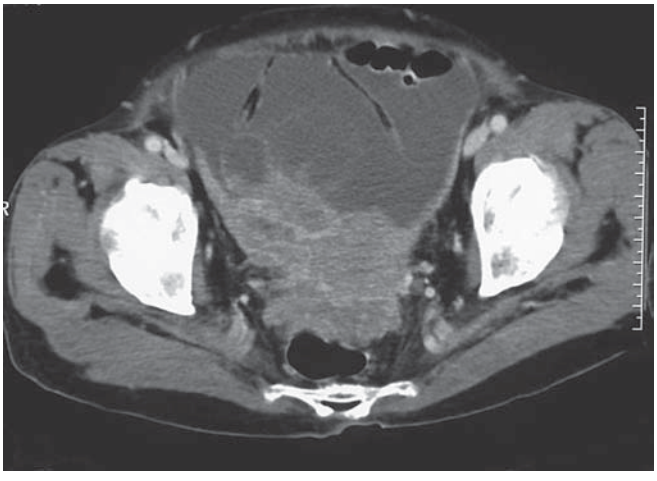

Fig. 4. Abdominal computed tomography shows a giant mass with cystic lesions in the Douglas pouch

pected based on the cytological findings of aspirated ascites. In July 2004, a total hysterectomy was performed. The histology of the right ovary showed a sheet-like proliferation and a nestic growth of severely atypical cells with prominent nuclei pleomorphism. Multinucleated giant cells were also present (Fig. 5). In addition, massive CD68 positive histiocytic infiltration was also found around the malignant cells (Fig. 6). Poorly differentiated serous carcinoma of the ovary was diagnosed. In addition to surgical treatment, cytotoxic chemotherapy with paclitaxel (80 mg/day) and carboplatin (600 mg/day) was initiated. Following these treatments, the arthralgia as well as the papules and nodules on the hands disappeared completely, and therefore the administration of steroid and MTX could be withdrawn.

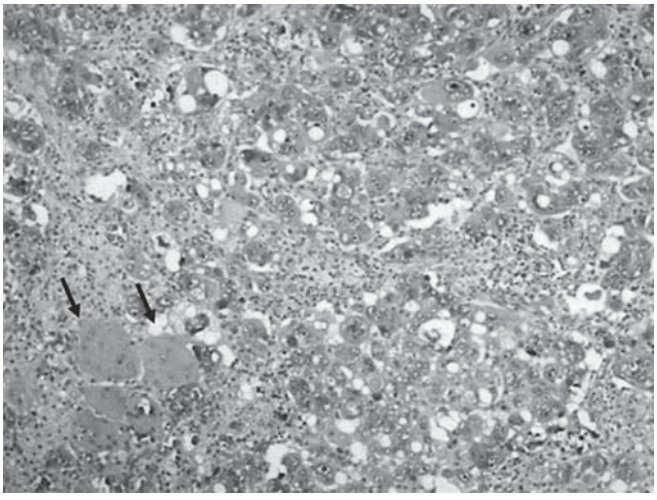

Fig. 5. The resected ovarian tissues showing histiocytes and multinucleated giant cells infiltration (*arrows*), in close proximity to poorly differentiated adenocarcinoma cells (H&E, ×100)

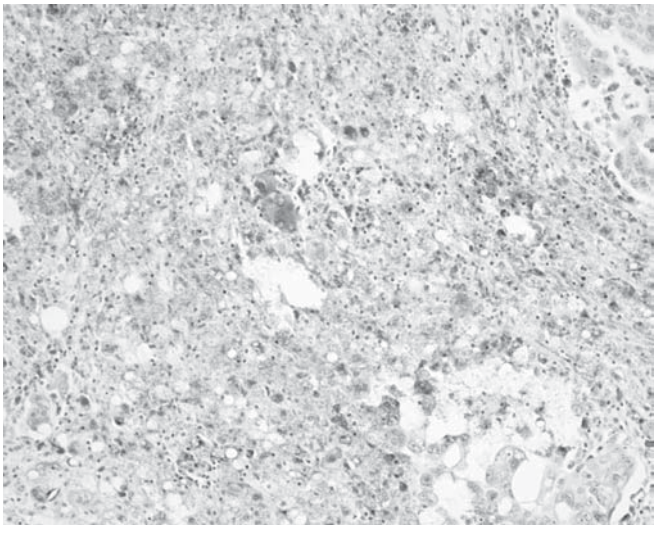

Fig. 6. Tissue samples obtained the resected ovarian tumor were studied by immunohistochemical staining. CD68 staining was observed in some infiltrated histiocytes around the malignant cells (×100)

Discussion

Multicentric reticulohistiocytosis is a rare systemic disorder of unknown etiology, characterized by tissue infiltration by histiocytes and multinucleated giant cells.[1] In all histiocytes, an uncontrolled macrophage activation is evident with a release of cytokines.[3] Many conditions have been described in association with MR, and the clinician should be aware that many cases are associated with malignancy.[4] Multicentric reticulohistiocytosis has been reported in association with a variety of malignancies, including carcinoma of the breast, colon, cervix, stomach, and ovary, as well as leukemia and lymphoma.[5–7]

Our patient developed ovarian cancer after the onset of arthritis and skin nodules. However, these conditions occurred almost simultaneously, and the start of the MTX treatment may not necessarily have played a role in the occurrence of the ovarian tumor in our case. We first prescribed MTX to our patient, and a partial response and control of the disease progression were obtained. However, a complete resolution of MR was confirmed after the surgical resection of ovarian cancer and subsequent chemotherapy.

The efficacy of different drug therapies for MR is difficult to assess due to disease fluctuations and the rarity of this disorder. However, a previous report showed a response of both the cutaneous and articular manifestations to cytotoxic drugs, including alkylating agents.[8] Liang and Granston reviewed the treatment success in newly diagnosed MR and found 13 cases of complete or nearly complete remissions.[9] Cyclophosphamide was effective in 8 cases, MTX in 4 cases, and chlorambucil in 3 cases. They proposed MTX or MTX plus cyclophosphamide as a new treatment regimen for persistent or resistant MR cases.[9] Either treating or removing the primary malignancy has, in several cases, resulted in a complete amelioration of MR.[10] Similarly, previous reports including our case suggest that cytotoxic chemotherapy may have an ability to induce a resolution of MR. In addition, the improvement of malignancy-associated MR coincident with chemotherapy, as well as the reappearance of MR before a malignancy recurrence, has been previously reported.[11] Two Japanese MR cases have been reported to occur in association with laryngeal cancer and breast cancer.[12,13] In these cases, MR occurred around the time of the development of cancer or recurrence of a previously diagnosed and treated cancer (Table 1). These findings raise the possibility that MR is a paraneoplastic disorder.

Table 1. Reported Japanese cases with multicentric reticulohistiocytosis associated with malignancy

Case	Age (years), sex	Associated malignancy (onset)	Treatment	Outcome	First author[Ref.]
1	76, M	Laryngeal cancer (concomitant)	Radiation, chemotherapy, methotrexate	Good response	Kishimoto[12]
2	64, F	Breast cancer (10 years prior to MR)	Chemotherapy	Partial response	Ohda[13]

Interestingly, the histological features of MR have been reported in close histological proximity to malignant cells in the associated internal malignancy.[14] In addition, in our case the characteristics of the cutaneous lesion were found to be in close histological similarity to those of the ovarian tumor with regard to the infiltrated histiocytes and multinucleated giant cells. Although we do not have any direct evidence, it is possible that tumor-related factors are linked to the development of our patient's MR.

The etiology of MR is unknown. However, the clinical findings of the present case suggest that some features of MR appear to be indicative of a reactive disorder in which some as yet unknown tumor-related stimuli lead to histiocytic activation and proliferation. Further studies are needed to explore the reactive linkage between MR and malignancy.

References

1. Trotta F, Castellino G, Lo Monaco A. Multicentric reticulohistiocytosis. Best Pract Res Clin Rheumatol 2004;18:759–72.
2. Gorman JD, Danning C, Schumacher HR, Klippel JH, Davis JC Jr. Multicentric reticulohistiocytosis: case report with immunohistochemical analysis and literature review. Arthritis Rheum 2000;43:930–8.
3. Campbell DA, Edwards NL. Multicentric reticulohistiocytosis: systemic macrophage disorder. Baillieres Clin Rheumatol 1991;5: 301–19.
4. Barrow MV, Holubar K. Multicentric reticulohistiocytosis. A review of 33 patients. Medicine 1969;48:287–305.
5. Kenik JG, Fok F, Huerter CJ, Hurley JA, Stanosheck JF. Multicentric reticulohistiocytosis in a patient with malignant melanoma: a response to cyclophosphamide and a unique cutaneous feature. Arthritis Rheum 1990;33:1047–51.
6. Gibson G, Cassidy M, O'Connell P, Murphy GM. Multicentric reticulohistiocytosis associated with recurrence of malignant melanoma. J Am Acad Dermatol 1995;32:134–6.
7. Janssen BA, Kencian J, Brooks PM. Close temporal and anatomic relationship between multicentric reticulohistiocytosis and carcinoma of the breast. J Rheumatol 1992;19:322–4.
8. Ginsburg WW, O'Duffy JD, Morris JL, Huston KA. Multicentric reticulohistiocytosis: response to alkylating agents in six patients. Ann Intern Med 1989;111:384–8.
9. Liang GC, Granston AS. Complete remission of multicentric reticulohistiocytosis with combination therapy of steroid, cyclophosphamide, and low-dose pulse methotrexate. Case report, review of the literature, and proposal for treatment. Arthritis Rheum 1996;39:171–4.
10. Valencia IC, Colsky A, Berman B. Multicentric reticulohistiocytosis associated with recurrent breast carcinoma. J Am Acad Dermatol 1998;39(5 Pt 2):864–6.
11. Nunnink JC, Krusinski PA, Yates JW. Multicentric reticulohistiocytosis and cancer: a case report and review of the literature. Med Pediatr Oncol 1985;13:273–9.
12. Kishimoto K. A case of multicentric reticulohistiocytosis whose cutaneous lesions rapidly improved after treatment of pharyngeal carcinoma (in Japanese). Rinsho Hifuka 2005;59:986–9.
13. Ohda C. A case of multicentric reticulohistiocytosis preceding the aggravation of breast cancer (in Japanese). Rinsho Hifuka 2004;58:732–4.
14. Malik MK, Regan L, Robinson-Bostom L, Pan TD, McDonald CJ. Proliferating multicentric reticulohistiocytosis associated with papillary serous carcinoma of the endometrium. J Am Acad Dermatol 2005;53:1075–9.