

## Case Report

# Erythema, papules, and arthralgia associated with liver cancer: report of a rare case of multicentric reticulohistiocytosis

Liang Hu, Jun-Hua Mei, Jin Xia, Quan-Shui Hao, Li-Ping Cheng, Yao-Hua Wu

Hubei Huanggang Central Hospital, Huanggang 438000, Hubei Province, China

Received December 24, 2014; Accepted February 23, 2015; Epub March 1, 2015; Published March 15, 2015

**Abstract:** We report a rare case of multicentric reticulohistiocytosis (MRH) associated with liver carcinoma. A 36-year-old man who had been diagnosed as having liver carcinoma for 2 years presented with a 2-month history of multiple papulonodules on the face, ears, neck, and upper chest, accompanied by progressive polyarthralgia of the hands, wrists, elbows and knee joints without fever or chills. Skin histology revealed well defined dermal infiltrate consisting of multinucleated giant cells and macrophages having abundant eosinophilic finely granular cytoplasm with ground glass appearance. Further immunohistochemical studies characterized the lesions as positive for CD68, CD45 and Vimentin. A diagnosis of MRH that was associated with liver cancer was made. Treatment with prednisolone for 2 months resulted in a significant improvement of the skin and joint symptoms, but was discontinued due to his significant enlargement and extensive metastases of the liver carcinoma.

**Keywords:** Multicentric reticulohistiocytosis, liver cancer, malignancy

## Introduction

Multicentric reticulohistiocytosis (MRH) is a rare multisystem syndrome featured by polyarthritides, skin papules and nodules with typical dermal infiltration of histiocytes and multinucleated giant cells. The skin, tendon sheath, synovium, bone, liver, salivary gland, kidney, lymph node, heart and lung could be involved in MRH, and that an association with hyperlipidemia (30-58%), a positive skin tuberculin test (12-50%), systemic vasculitis and autoimmune disease has been described [1].

Importantly, MRH is also clinically associated with a variety of underlying internal malignancies. Such an association has been documented in up to 28% of all reported cases in the literature, typically being bronchial, breast, stomach, and cervical carcinomas [2]. Here, we report a case of MRH which occurred 2 years after definite diagnosis of liver carcinoma, highlighting the association of MRH with malignant disease.

## Case report

A 36-year-old male presented with multiple papulonodules on the face, ears, neck, and

upper chest for 2 months. The patient denied any history of photosensitivity, but complained progressive polyarthralgia of the hands, wrists, elbows and knee joints without accompanying fever or chills. The skin lesions were erythematous, glistening, dome-shaped, asymptomatic and non-tender, varying from 1 mm to 5 mm in diameter, with a tendency to grouping (**Figure 1**). The surrounding skin and oral mucosa were normal. X-ray of the pained joints was unremarkable. The patient had a 15-year history of hepatitis B. He also had a 2-year history of hepatocellular carcinoma and had undergone transcatheter arterial chemoembolization (TACE) chemotherapy for 11 times, during which the serum level of alpha fetal protein (AFP) was always above 50,000 ng/ml. Pulmonary metastases were also detected in his last examination 3 months ago (current staging T4N1M1).

As cutaneous paraneoplastic syndromes, cutaneous bacterial infections, deep cutaneous fungal infections, and cutaneous metastases should be excluded in cancer patients receiving chemotherapy, a skin biopsy was taken from a nodule post aurem in this patient. The pathological examination revealed well defined dermal infiltrate consisting of multinucleated giant



**Figure 1.** The skin lesions post aurem, which were erythematous, glistening, dome-shaped and non-tender, varying from 1 mm to 5 mm in diameter, with a tendency to grouping.

cells and macrophages having abundant eosinophilic finely granular cytoplasm with ground glass appearance (**Figure 2A**). Further immunostains characterized the lesions as positive for CD68, CD45, Vimentin (**Figure 2B-D**) and negative for S-100, CD1a, AFP. These features are consistent with MRH associated with liver carcinoma. Treatment with a 2-month course of prednisolone 24 mg per day had excellent response, his erythematous rash and grouped papules partially resolved and joint pain gradually improved. However, due to the presence of active hepatitis B (HBV DNA copies  $0.22 \times 10^9$ /ml blood), enlargement and extensive metastases of the tumor (**Figure 3**), the patient was forced to discontinue this medication according to oncologist's advice and was lost for follow-up.

### Discussion

MRH is very rare; fewer than 300 cases have been reported worldwide. It has few other names as lipoid dermatoarthritis, giant cell histiocytoma, reticulohistiocytic granuloma. MRH is a multisystem, granulomatous, non-Langerhans cell histiocytosis in which skin, mucosa,

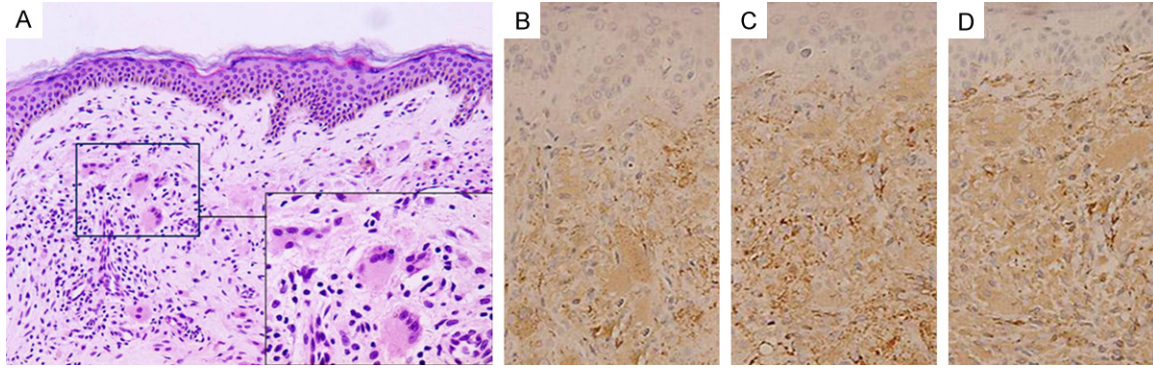
joints and any internal organs can be involved, characterized most frequently by disfiguring cutaneous papulonodules and destructive polyarthritis [1, 2]. Initial clinical manifestations include polyarthritis in 40-50% of cases, skin rash in 25-30%, and in the remainder of cases articular and cutaneous features present simultaneously [2]. The typical cutaneous manifestations consist of non-pruritic, flesh colored to reddish brown yellow papules and nodules that may be developed anywhere in the body with a predilection for face, hands and around joints [1, 2]. The contribution of Köbner's phenomenon to the development of skin lesions sometimes could be observed in MRH [3].

The diagnosis of MRH mainly depends on histopathology of the cutaneous nodules and/or synovial membrane by the presence of CD68-positive histiocytes and multinucleated giant cells with an eosinophilic ground-glass cytoplasm [2, 4]. Differential diagnosis of the cutaneous lesions includes dermatomyositis, lepromatous leprosy, sarcoidosis, xanthomatosis, histiocytosis X, juvenile and adult xanthogranuloma, generalized eruptive histiocytoma, familial histiocytic dermatoarthritis and neurofibromatosis [1]. The presence of prominent skin manifestations with erosive arthritis usually differentiates MRH from other diseases.

The onset of MRH is usually insidious and mostly of uncertain etiology. Elevated serum levels of Th1 profile cytokines support the concept that MRH is a macrophage/monocyte reactive process where pro-inflammatory cytokines may be released and account for the systemic symptoms [5]. So, abnormal histiocytic reactions to an undetermined stimulus, possibly an associated mycobacterial infection, autoimmune or neoplastic process have been proposed as an underlying mechanism.

MRH is associated with multiple medical conditions, including hyperlipidemia, tuberculosis, pregnancy, autoimmune disorders, and internal malignancy [1, 6]. It is of utmost clinical importance that about 15-30% of the cases are associated with a variety of underlying malignancies [1, 4]. The malignancies were most commonly hematological, breast or gastrointestinal tract carcinomas [2]. However, the two diseases do not generally progress in parallel. For most cases, the onset of malignancy and MRH occurred within approximately 3 years, and

## Multicentric reticulohistiocytosis and liver cancer



**Figure 2.** A. The histology of a nodule from post aurem revealed multinucleated giant cells and macrophages in the dermis having eosinophilic cytoplasm with ground glass appearance (H&E staining, original magnification  $\times 40$ , right down panel  $\times 200$ ); B. Immunohistochemical staining of CD68 (DAB, original magnification  $\times 200$ ); C. Immunohistochemical staining of CD45 (DAB, original magnification  $\times 200$ ); D. Immunohistochemical staining of vimentin (DAB, original magnification  $\times 200$ ).



**Figure 3.** Significant enlargement and extensive metastases of the liver carcinoma in the patient by CT scanning.

MRH may precede the onset of cancers [7]. The cutaneous signs of MRH in our patient occurred 2 years after diagnosis of his liver cancer, while in another patient, which is the only MRH case reported to be associated with liver cancer, they almost happened simultaneously [8]. Treatment of carcinoma can significantly improve the skin and joint symptoms, for instance, the cutaneous lesions disappear spontaneously within several weeks of surgical excision of primary carcinoma [9]. Thus, the hypothesis that MRH reflects a true paraneoplastic syndrome is supported by the frequency of associated neoplasm, the remission of the lesions after tumor treatment and the onset of MRH just prior to the relapse of the neoplasm [9, 10]. Therefore,

it appears prudent to carefully evaluate and monitor patients with MRH, to identify an underlying malignancy.

MRH is sometimes self-limited, and remission of the disease has been reported with different immunosuppressants and biologicals. However, patients associated with malignancy often carry a poor prognosis [2].

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Yao-Hua Wu, Hubei Huanggang Central Hospital, Huanggang 438000, Hubei Province, China. E-mail: 391246380@qq.com

### References

- [1] Tajirian AL, Malik MK, Robinson-Bostom L, Lally EV. Multicentric reticulohistiocytosis. *Clin Dermatol* 2006; 24: 486-492.
- [2] Luz FB, Gaspar AP, Kalil-Gaspar N, Ramos-e-Silva M. Multicentric reticulohistiocytosis. *J Eur Acad Dermatol Venereol* 2001; 15: 524-531.
- [3] Aldridge RD, Main RA, Daly BM. The Köbner's response in multicentric reticulohistiocytosis. *Cutis* 1984; 34: 78-80.
- [4] Barrow MV, Holubar K. Multicentric reticulohistiocytosis. A review of 33 patients. *Medicine* 1969; 48: 287-305.
- [5] Bennàssar A, Mas A, Guilabert A, Julià M, Mascaró-Galy JM, Herrero C. Multicentric reticulohistiocytosis with elevated cytokine serum levels. *J Dermatol* 2011; 38: 905-910.
- [6] Gold KD, Sharp JT, Estrada RG, Duffy J, Person DA. Relationship between multicentric reticulo-

## Multicentric reticulohistiocytosis and liver cancer

- histiocytosis and tuberculosis. *JAMA* 1977; 237: 2213-2214.
- [7] Valencia IC, Colsky A, Berman B. Multicentric reticulohistiocytosis associated with recurrent breast carcinoma. *J Am Acad Dermatol* 1998; 39: 864-866.
- [8] Han L, Huang Q, Liao KH, Chen LJ, Kong WY, Fu WW, Xu JH. Multicentric reticulohistiocytosis associated with liver carcinoma: report of a case. *Case Rep Dermatol* 2012; 4: 163-169.
- [9] El-Haddad B, Hammoud D, Shaver T, Shahouri S. Malignancy-associated multicentric reticulohistiocytosis. *Rheumatol Int* 2011; 31: 1235-1238.
- [10] 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: 1075-1079.