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Original Article

Reticulohistiocytosis: a case series in Hong Kong

網狀組織細胞增多症：香港的個案系列

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Background: Reticulohistiocytosis is a rare histiocytic proliferative disorder one form of which, multicentric reticulohistiocytosis, may mimic rheumatoid arthritis. ***Objective:*** To report on a case series of reticulohistiocytosis in Hong Kong and focus on the clinical presentation and course of disease. ***Materials and method:*** Case records with the biopsy results of reticulohistiocytoma in the period of 2005 to 2011 were retrieved from the database of the Social Hygiene Service, Department of Health, Hong Kong. ***Results:*** Three cases of reticulohistiocytoma were found, one each of solitary histiocytoma, multiple cutaneous reticulohistiocytosis and multicentric reticulohistiocytosis. One of the patients had polyarthritis and none of them had associated connective tissue disease nor malignancy. ***Conclusion:*** Reticulohistiocytosis may present as solitary or multiple lesions. It may be associated with severe arthritis and mimic rheumatoid arthritis. However, it may or may not be associated with connective tissue disease or malignancy.

背景：網狀組織細胞增多症是一種罕有的組織細胞增生症，多中心性網狀組織細胞增多症其表徵近似類風濕性關節炎。**目的：**報告香港網狀組織細胞增多症一系列病例並聚焦於臨床表現及疾病進程。**取材及方法：**檢索由二千零五年至二千零壹拾壹年香港衛生署轄下社會衛生科的病歷檔案並抽取有病理學確診的網狀組織細胞增多症資料。**結果：**三人確診而其中一人爲獨立性網狀組織細胞增多症，一人爲多發性網狀組織細胞增多症，一人爲多中心性網狀組織細胞增多症，一人有多樣關節炎而沒有人有結締組織病或癌病。**結論：**網狀組織細胞增多症可表現爲獨立或多個病變，既可顯生關節炎及相類似類風濕關節炎，亦可有或可無地併發爲結締組織病或癌病。

Keywords: Multicentric reticulohistiocytosis, rheumatoid arthritis

關鍵詞：多中心性網狀組織細胞瘤病，類風性濕關節炎

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Introduction

Reticulohistiocytosis is a rare histiocytic proliferative disorder of unknown origin. There are three main types which include solitary cutaneous reticulohistiocytosis, multiple cutaneous reticulohistiocytosis and multicentric reticulohistiocytosis. Multicentric reticulohistiocytosis may present as multiple periarticular skin papules and symmetrical polyarthopathy and may be confused with rheumatoid arthritis. It is important to rule out

any association with tuberculosis, malignancy and autoimmune disease.

Materials and method

Case records with a diagnosis of reticulohistiocytoma proven by biopsy from 2005 to 2011 were retrieved from the database of the Social Hygiene Service, Department of Health, Hong Kong. Three patients with reticulohistiocytoma were identified, one each from Sai Ying Pun Dermatology Clinic, Yung Fung Shee Dermatology Clinic and Tuen Mun Dermatology Clinic. The demographic data, clinical presentation, course of the disease of these patients were compared in the study (Table 1 and Table 2).

Results

Demographic features

Two males and one female Chinese patients were found to have reticulohistiocytoma in this case series. The age ranged from eight years to 56 years old. Their family histories were unremarkable. Patients 1 and 2 were smokers and patient 3 was a non-smoker.

Table 1. Demographic data, clinical presentation, course of the disease of patients 1, 2 and 3

Patient	Year of diagnosis	Past medical illness	Age/Gender	Type of skin lesions	Site of skin lesion	Symptom	Internal organ involvement/ Autoimmune disease/ Vasculitis/ Malignancy/ Tuberculosis
1	2011	Road traffic accident 2003 with left foot reconstructive surgery	56/Male	Multiple itchy erythematous papules	Extensor elbow, forearm, hand, trunk, thigh, knee, feet	Itchy papules for 6 months	Arthropathy
2	2002	Gout NIDDM Childhood asthma	29/Male	Multiple 1-2 mm diameter skin-coloured/ erythematous papules	Dorsum of hand, feet nape of neck, extensor aspect of elbow, leg	Asymptomatic papules for 6 months	Negative
3	2008	Good past health	8/Female	Single erythematous nodule	Left abdomen	Itchy papule for 1 month	Negative

NIDDM=non-insulin dependent diabetes mellitus

Table 2. Associated features, treatment and clinical course of the patients

Patient	Lipid profile	Arthritis/Arthopathy	Treatment	Outcome
1	Normal	Back, knee, shoulder pain; Synovial biopsy positive for reticulohistiocytosis	Steroid + Methotrexate	Skin lesions persist
2	Normal	Negative	0.0125% Fluocinolone acetonide cream; Loratadine	Lesions mostly subsided 2 years after onset of lesions, then wax and wane for 1 year, then no new lesions for few years
3	Normal	Negative	No specific treatment	No new lesion

Clinical features

Patient 1 (Figures 1 & 2) developed multiple itchy small erythematous papules, 1 to 2 mm in diameter, over the trunk and limbs (the elbows, forearms, hands, trunk, thighs, knees and feet) and arthritis (back, knee and shoulder pain) for six months. Patient 2 (Figures 3 and 4) developed multiple asymptomatic small skin coloured/ erythematous papules, 1 to 2 mm in diameter, over the dorsa of the hands, feet, nape of neck, elbows, legs for six months with no arthritis. Patient 3 (Figure 5) developed a single itchy erythematous nodule over the left abdomen for one month with no arthritis. The liver or spleen was not palpable in all patients. One non-specific cervical lymph node was found in patient 1 and biopsy showed no evidence of lymphoma.

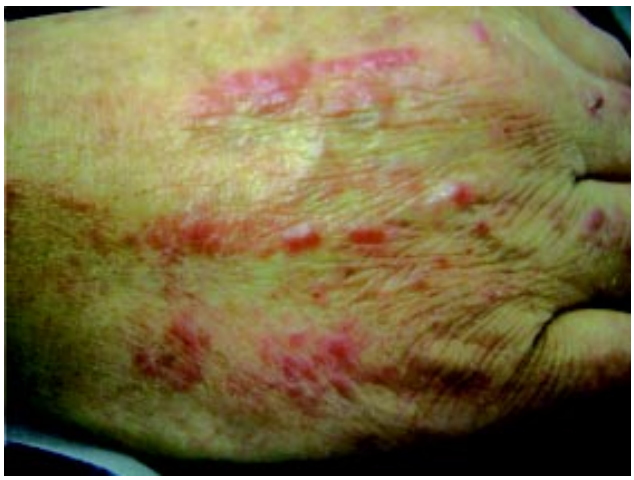

Figure 1. Multiple erythematous papules over the dorsum of the hand (Patient 1).

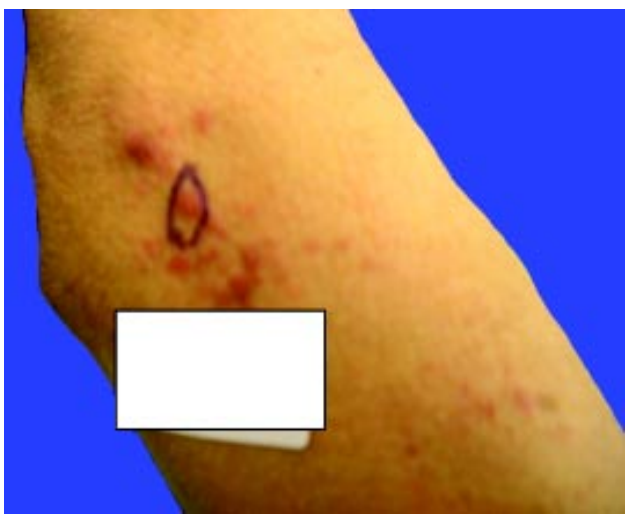

Figure 2. Multiple erythematous papules over the right elbow (Patient 1).

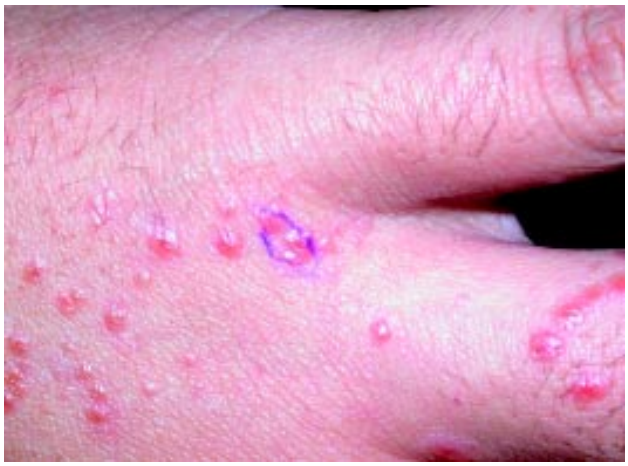

Figure 3. Multiple erythematous papules over the hand (Patient 2).

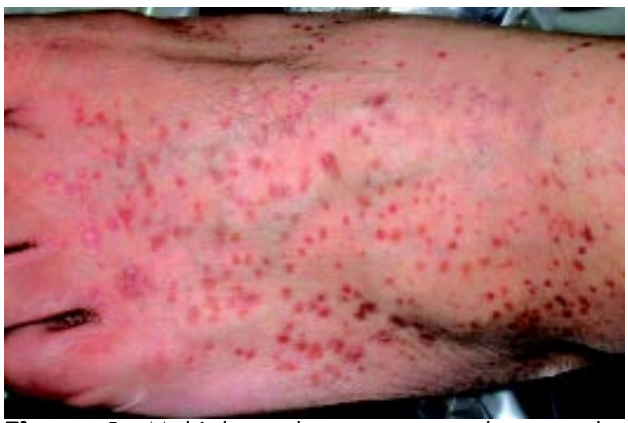

Figure 4. Multiple erythematous papules over the dorsum of the left foot (Patient 2).

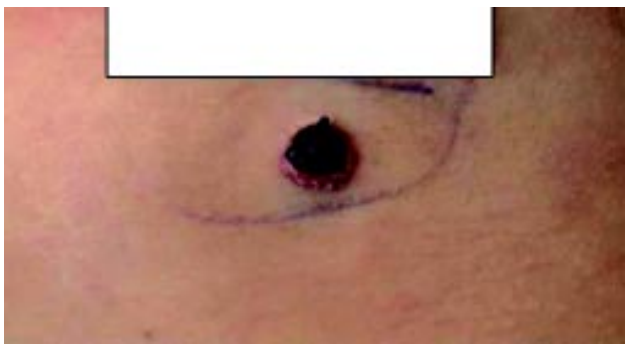

Figure 5. Single erythematous nodule over the abdomen (Patient 3).

Histology

Patient 1, 2 and 3 showed features compatible with reticulohistiocytoma.

Patient 1:
Biopsy showed a circumscribed infiltrate of mononuclear and multinucleated histiocytes with eosinophilic, finely granulated ground glass cytoplasm. Immunohistochemically, the histiocytes were positive for CD68 and negative for S100. Birbeck granule was absent (Figures 6-8).

Patient 2:
Biopsy showed papules which consist of circumscribed collection of mononuclear and occasional multinucleated pink histiocytic cells in the upper dermis and about the basal epidermis. The histiocytic cells are negative for S100.

Patient 3:
Biopsy showed the lesion was composed of very large cells with moderately atypical round, folded or lobulated nuclei, with abundant lightly eosinophilic cytoplasm. CD68/PGM1 is positive and staining for another histiocytic marker CD163 is focal.

Investigation, association and systemic involvement:
Complete blood picture, liver function tests, renal function tests were normal for all of the patients. Autoimmmune disease screening and lipid profiles were also unremarkable. Moreover, there was no evidence of tuberculosis, internal organ involvement or malignancy found in these patients. Destructive arthopathy which developed a few months after onset of skin rash was found in patient 1.

Management and outcome

Oral steroid and methotrexate was given to patient 1 for arthopathy with improvement of arthritis but the skin lesions persisted. Patient 2 was treated with topical steroid and oral antihistamine and

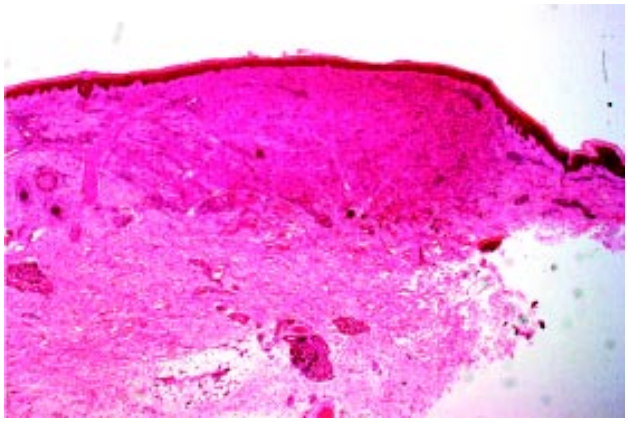

Figure 6. 2x objective. Low power view shows a well-circumscribed, nodular infiltrate of histiocytic cells (Patient 1).

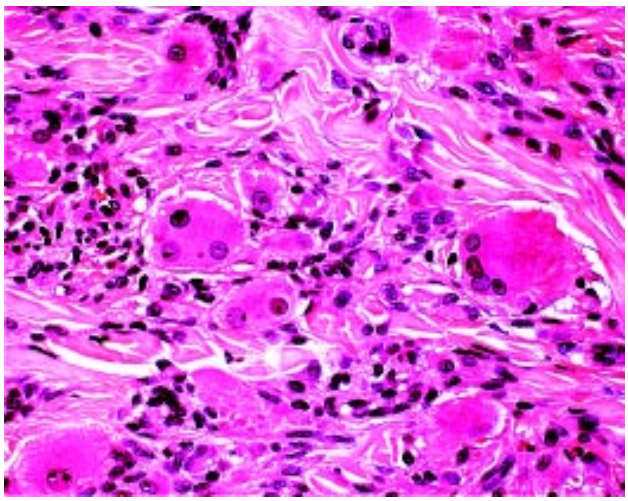

Figure 7. 40x objective. High power view shows the mononuclear and multinucleated histiocytes to have eosinophilc, ground-glass cytoplasm (Patient 1).

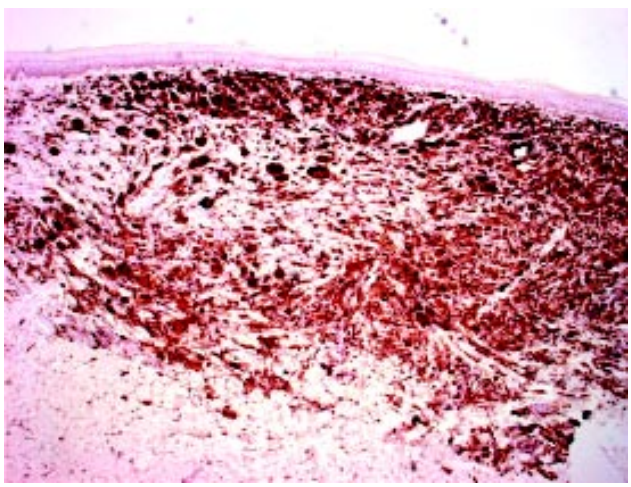

Figure 8. The histiocytic cells are diffusely CD68 positive (Patient 1).

lesions mostly subsided after two years of treatment. However, the disease recurred and ran a waxing/waning course for 1 year before finally becoming inactive. No new lesions were found afterward. Patient 3 underwent excisional biopsy and no new lesion developed afterwards.

Discussion

Reticulohistiocytosis is a class II, non-Langerhans cell histiocytosis. It can be classified into 3 forms: solitary cutaneous reticulohistiocytosis, multiple cutaneous reticulohistiocytosis and multicentric reticulohistiocytosis. Solitary cutaneous reticulohistiocytosis presents as a single asymptomatic papule without systemic involvement in young adults.[1,2] There is no sex predilection. Any site, especially the scalp, may be involved. Multiple cutaneous reticulohistiocytosis is characterized by multiple papules without systemic involvement. There is no disease association. Multicentric reticulohistiocytosis may develop destructive arthopathy or systemic involvement. Less than 500 cases have been reported in the world literature to date. Most of these patients are Caucasians. Age groups affected range from adolescents to the elderly and most patients are 40 to 50 years old.[1,3] It is insidious yet progressive in its onset. The aetiology is unknown and an abnormal response to various stimuli is postulated. Uncontrolled macrophage activation is found resulting in the release of monokines and cytokines that cause proinflammatory reaction, indirect induction of bone resorption, and histiocyte differentiation into osteoclast-like multinucleated giant cell.[4] Hence, bony and cartilaginous erosions may be found.[5]

Clinical presentation of multicentric reticulohistiocytosis includes skin, mucous membrane and joint manifestations.[6] Symmetrical papular to nodular mucocutaneous lesions and arthopathy may be seen. Pruritus is a prominent symptom. Skin lesions are mostly symmetrical and acral in distribution affecting mostly the face and hands. Multiple discrete, firm, pink, pinkish-brown, reddish-yellow, reddish-grey or purple papules and nodules with a size of few millemetres to few centimetres over the joints may simulate periarticular rheumatoid-like nodules.[1,4] Lesions may coalesce into plaques and may mimic leonine facies.[4] 'Coral beads' which consist of tiny papules along proximal nail fold is pathognomonic.[7] Atypical skin findings include atypical 'dermatomyositis-like' presentation (macular photodistributed erythema, periungal telangiectasia, photosensitivity), hypochromic plaques on the face and arms, telangiectasia over nodules, telangiectasia and bleeding gums in pregnancy, deep nodules larger than 1 cm, erythroderma, Koebner phenomenon, neurofibroma-like nodules, palpebral xanthelasma-like lesions, xanthomas and ulcers.[1,4,8] Mucous membrane involvement occurs mostly on the buccal mucosa, nasal mucosa and tongue.[1,4] Sixty per cent of the patients have a diffuse, symmetrical, progressive, destructive arthopathy involving especially the distal interphalangeal joints which may be confused with rheumatoid arthritis or psoriatic arthopathy.[7,9] More than 10% of the patients suffer from a symmetrical erosive arthritis affecting multiple joints for six to eight years before progressing to arthritis mutilans.[4] Any joint can be involved; wrist, hand, finger and knee joints are commonly affected. Systemic symptoms include fever, malaise, weakness, weight loss, anorexia but systemic infiltration is uncommon.[2] Rarely, histiocytic involvement of the heart (pericarditis, heart failure), lung (bronchus, pleural effusion) and other internal organs have been reported.[4]

Reticulohistiocytoma has nodular infiltrate of histiocytic cells. Infiltration by mononucleated histiocytes as well as multinucleated giant cells with haphazardly arranged nuclei and eosinophilic, finely granulated ground glass cytoplasm dissociating collagen fibres are found.[1] Other inflammatory cells are present in lesser extent and electron microscopy show no Birbeck granules.[1] Immunohistochemical stain is negative for S100 and CD1a but positive for CD68.

Multicentric reticulohistiocytosis may be associated with a variety of conditions including hyperlipidaemia, tuberculosis (~6%), autoimmune disease (~15%) and malignancy (~30%).[1,7,10] The associated autoimmune diseases included lupus erythematosus, dermatomyositis, Sjögren's syndrome, systemic sclerosis, primary biliary cirrhosis, diabetes mellitus, hypothyroidism, coeliac disease and systemic vasculitis.[10] Malignancies commonly associated with this condition include carcinoma of the breast, gastrointestinal tumours such as carcinoma of the stomach, colon and pancreas.[2,10] Melanoma, leukaemia, lymphoma, sarcoma, metastases and carcinoma of ovary, cervix and lung are also possible and with no predominance of any particular type of cancer.[4,5,10] The condition may precede the diagnosis of malignancy.[4] It may occur within two years of detection of a malignancy or occur at the time of metastasis or recurrence. Treatment of the malignancy may cause the cutaneous lesions and joint symptoms to improve but there is no correlation between the evolution of the neoplasia and multicentric reticulohistiocytosis.[1]

There are no specific investigations for multicentric reticulohistiocytosis. Mild anaemia, moderate increased erythrocyte sedimentation rate may be found.[1,2] Autoimmune markers are usually negative. X-ray of the joints showing an erosive arthopathy is an important tool in diagnosis. Screening for tuberculosis, autoimmune disease and malignancy before treatment is essential.

Solitary cutaneous reticulohistiocytosis may be treated by excision. Multiple cutaneous reticulohistiocytosis may be treated with topical steroid for symptom control. No effective treatment has been found for multicentric reticulohistiocytosis.[7] Systemic steroid (1 mg/kg) has a palliative effect but does not induce remission. Methotrexate (7.5-25 mg/wk for arthopathy), cyclophosphamide (200 mg/day for cutaneous lesion), chlorambucil (0.1 mg/kg/day), etanercept (25 mg SC 2x/wk), infliximab, bisphosphonates (improve both arthritis and skin lesions), alendronate, zolidronic acid have been reported to have some therapeutic effect.[2-4] Substantial benefits have been reported with the combination of methotrexate plus cyclophosphamide or systemic steroid.[4,5] In a patient with associated tuberculosis, psoralen and ultraviolet A therapy, topical nitrogen mustard and rifampicin with ethambutol improved the skin lesions.[2] It is suggested that systemic steroid plus cyclophosphamide or chlorambucil should be used for skin involvement while systemic steroid plus methotrexate should be considered for joint involvement.[1]

Multicentric reticulohistiocytosis runs a relapsing and remitting course. It typically regresses, with or without treatment, after an average of eight years.[3,10] However, it often leaves patients with permanent joint damage and cutaneous scarring.[10] Early and aggressive treatment to prevent destructive arthropathy and disfiguring cutaneous lesion on the face is essential.

Conclusion

Reticulohistiocytosis is a rare histiocytic proliferative disorder of unknown origin. It may present with solitary or multiple firm, discrete skin-coloured/erythematous papules. Multicentric reticulohistiocytosis may be confused with rheumatoid arthritis and may be associated with internal malignancy, tuberculosis, and autoimmune disease. These must be ruled out before aggressive treatment to prevent destructive arthopathy is given.

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