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Original Article

Cutaneous sarcoidosis: a case series from a regional hospital in Hong Kong

香港某一區域醫院皮膚類肉瘤病的病例系列

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Sarcoidosis is a non-caseating granulomatous systemic disorder of unknown aetiology. It is seldom reported in Asians and local data is lacking. We report a retrospective cohort of patients with cutaneous sarcoidosis in a tertiary referral hospital from January 2002 to December 2011. We aim to describe the epidemiological pattern and cutaneous involvement in a predominantly-Chinese population. Sarcoidosis was diagnosed in 10 patients and all had pulmonary involvement. Cutaneous sarcoidosis was diagnosed in five patients: four were Chinese, one was Caucasian. Cutaneous manifestations included plaques, nodules and non-scarring alopecia. There was a case with acute presentation as Löfgren's syndrome. Other extra-cutaneous involvement included eye, muscle and joint. Histopathological examination revealed non-caseating epithelioid granulomas with variable infiltrates in the dermis without the presence of infection or foreign body. The mainstay of treatment was topical or systemic corticosteroids to which most patients had a good response. No mortality was noted. In general, cutaneous sarcoidosis is rare in Chinese and a thorough evaluation for systemic involvement is necessary.

類肉瘤病是一種非乾酪性肉芽腫，其病因不明的全身性疾病。這是很少在亞洲人中報導，亦缺乏本地數據。我們報告一個從二零零二年一月至二零一一年十二月在一間第三轉診推薦醫院類肉瘤病患者的回顧性隊列研究。我們的目標是描述這病在一個以中國人爲主要人口的流行病學模式和皮膚的牽連。十個患者被診斷爲類肉瘤病。他們所有都有肺部牽連。五例被確診爲皮膚類肉瘤病：四個是中國人，一個是高加索人。皮膚表現包括斑塊、 結節和無疤痕的脱髮。有一宗個案爲洛夫格倫綜合症的急性表現。其他皮膚以外的牽連，包括眼睛，肌肉和關節。病理組織學檢查發現在眞皮層內有非乾酪性上皮樣肉芽腫及可變的滲入，而沒有感染或異物。主要的治療方法是外用或內服皮質類固醇，大部份患者都有良好的反應。並無死亡個案。在一般情況下，皮膚類肉瘤病在中國人中是罕見的，深入的系統性評估是必要的。

Keywords: Cutaneous sarcoidosis, non-caseating granuloma, sarcoidal granuloma, sarcoidosis

關鍵詞：皮膚類肉瘤病，非乾酪性肉芽腫，類肉瘤肉芽腫，類肉瘤病

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Introduction

Sarcoidosis is a multi-system non-infective granulomatous disorder of unknown aetiology. Following the lungs, the skin is the second commonly involved organ. It is characterised by the infiltration of non-caseating epithelioid granulomas in various organs, leading to a variable disease manifestation. It has a bimodal peak of onset, with a female predominance in the later peak. It is most commonly reported in Swedish Caucasians and Black Americans and is apparently rare in Asians and currently, local data is lacking.

Materials and method

A 10-year retrospective analysis of patients with a clinic-pathological diagnosis of sarcoidosis at the Prince of Wales Hospital from 2002 to 2011 was conducted. Histological records of skin and tissue biopsies were retrieved from the pathology database through the Laboratory Information System. Case notes of those with biopsy confirming non-caseating, epithelioid or sarcoidal granulomas with negative infective stains were retrieved and reviewed. All the histologically-confirmed cases of sarcoidosis had compatible clinical histories and radiological findings and were evaluated and managed by respective respiratory, dermatology and rheumatology physicians. Demographic data, clinical features, histological and radiological findings, disease course and treatment were analysed.

Results

Ten patients were diagnosed to have sarcoidosis over 10 years in Prince of Wales Hospital from 2002 to 2011. At presentation, their age ranged from 29 to 60 years (mean age: 44 years), with a male to female ratio 1:1.5. The majority were Chinese (80%), with one Caucasian (10%) and one Indian (10%). Pulmonary involvement was most common and was found in 100% of patients, in which the majority had stage I disease. Skin was the second most commonly involved organ (50%), followed by eye (uveitis), bone (osteitis, arthritis) and muscle (granulomatous myositis). The mainstay of treatment was systemic corticosteroids and one patient required methotrexate for declining lung function (Table 1).

Cutaneous sarcoidosis was found in five patients, with three males and two females (ratio 1.5:1). The age of onset ranged from 29 to 60 years, with a mean age of 41 years. The majority were Chinese (80%), with one Caucasian (20%). The length of duration of skin lesions prior to diagnosis ranged from three months to five years (Table 2). Sarcoid-specific cutaneous manifestations were most commonly plaques (80%) which were found in four patients, followed by non-scarring alopecia (20%) and subcutaneous nodules (20%, patient 2

Table 1. Baseline demographics and clinical features of patients with sarcoidosis

Clinical characteristics	No. of patients (n=9)	Percentage
Sex		
Male	4	40%
Female	6	60%
Ethnicity		
Chinese	8	80%
Caucasian	1	10%
Indian	1	10%
Cutaneous sarcoidosis	5	50%
Extracutaneous involvement		
None	0	0%
Pulmonary	10 (stage I: 7, II or above: 3)	100%
Eye	3	30%
Bone and joint	2	20%
Muscle	1	10%
Treatment modality		
Conservative	2	20%
Topical and intralesional steroid	2	20%
Prednisolone	5	50%
Methotrexate	1	10%

had co-existing plaques). Other sarcoid non-specific manifestations included acquired ichthyosis (20%) and panniculitis (20%).

All patients with cutaneous sarcoidosis were found to have extra-cutaneous systemic involvement (Table 3). Pulmonary involvement occurred in 100% of patients. This was followed by eye involvement (40%) and bone involvement (40%). One patient presented acutely as Löfgren's syndrome (patient 5) with persistent fever, arthritis, uveitis, parotid swelling, erythema nodosum, hilar lymphadenopathy. In fact, all Chinese patients with cutaneous sarcoidosis had involvement of at least two extra-cutaneous organs. None of them had associated hypercalcaemia or hypercalciuria.

Histologically, classical non-caseating "naked" epithelioid granulomas in dermis were found in 40% of patients, while the rest (40%) who had epithelioid granulomas had a variable degree of lympho- or lympho-plasmacytic infiltration (Figures 1b, 2b, 2c, 3c). Foreign body was found under polarised microscopy in one patient (Table 3). Cutaneous infection was excluded in all cases with negative Gram-stain, Periodic acid-Schiff, Grocott, Ziehl Nielson, Wade-Fite and Warthin-Starry stains. Polymerase chain reaction for mycobacterial DNA was negative in skin biopsy specimens in two patients.

The majority of patients (60%) received systemic corticosteroids (prednisolone 0.4-0.6mg/kg daily over 3-6 months) due to multi-system or generalised cutaneous involvement (Table 3). Patient 2 and 5 received a therapeutic trial of antituberculous chemotherapy without response before being commenced on corticosteroid. Both cutaneous and extra-cutaneous organ involvement were deemed in remission in all Chinese patients. There were no complications of note. Patient 4, a Caucasian gentleman with infiltrative lung disease, was given a prolonged course of systemic corticosteroid over two years

Table 2. Clinical characteristics of patients with cutaneous sarcoidosis

Clinical characteristics	No of patients (n=5)	Percentage
Sex		
Male	3	60%
Female	2	40%
Age		
Range	29-60 years old	Not applicable
Mean	41 years old	
Duration of lesions		
Range	3 months to 5 years	Not applicable
Mean	31.8 months	
Extra-cutaneous involvement	5	100%
Cutaneous lesions		
Acute	1 (erythema nodosum)	20%
Chronic	4 (plaques)	80%
Location		
Limbs	4	80%
Head and neck	2	20%
Histology		
Naked granuloma	2	40%
Granuloma with variable infiltrates	2	40%
Panniculitis	1	20%

Table 3. Clinical and pathologic features and treatment outcomes of patients with cutaneous sarcoidosis

Patient	Age/ sex/ race	Cutaneous lesions	Duration	Pulmonary involvement	Other extra-cutaneous involvement	Histology	Treatment	Response
1	29/M/Chi	Plaques on arms, non-scarring alopecia	3 years	Stage I	Lymph-adenopathy	Epithelioid granuloma	Intralesional steroid	Partial response initally. Complete remission after being given prednisolone
2	60/F/Chi	Plaques and nodules on chin, arms, legs, buttock	3 years	Stage I	Uveitis, osteitis, carpel tunnel syndrome	Epithelioid granuloma with intense infiltration of lymphocytes	Prednisolone	Complete
3	42/M/Chi	Plaques on forehead and scalp	2 years	Stage I	Uveitis	Naked granuloma	No	Partial
4	34/M/Cau	Annular plaques on legs	5 years	Stage III	No	Naked granuloma with foreign body present	Prednisolone	Complete
5	40/F/Chi	Erythema nodosum	3 months	Stage II	Löfgren's syndrome (uveitis, arthritis, parotid swelling)	Septal panniculits	Prednisolone	Complete

Chi: Chinese; Cau: Caucasian.

for control of lung disease. His cutaneous disease went into remission completely within a few weeks of steroid commencement. However, he developed adrenal insufficiency due to prolonged steroid use.

Discussion

Cutaneous sarcoidosis occurs in about 30% of cases of sarcoidosis, often occurring as the initial presentation of the disease.[1] The manifestations are vast and it is often considered to be a great mimicker. We report 10 cases of sarcoidosis and the clinical and pathological features of five patients with cutaneous sarcoidosis. We found an earlier age of onset (41 years) in patients with cutaneous sarcoidosis, with a slight male predominance with plaques being the most common form (80%). We noted a very high rate of extra-cutaneous involvement, most commonly pulmonary (100%), followed by eye and bone (both 40%). Histologically, the lesions varied from typical sarcoidal naked granulomas (40%) to granulomas with moderate to intense infiltrates (40%).

The incidence of sarcoidosis is highest among Northern European countries with 5-40 new cases/million annually.[2,3] It is considered to be a rare disease in Asia, but the annual incidence has been rising, especially in Japan (1-2 new cases/ million) and in India. There are more studies on sarcoidosis in predominantly-Chinese population in Taiwan (331 cases over the past 5 decades), China and Singapore (incidence 0.56/100000/ year).[4-8] In Hong Kong, with 13 cases in 1981-1998, sarcoidosis is rarely reported.[9-11] In our study, the projected annual incidence based on the population of New Territories East Cluster was 0.77 new case/million, although it might be under-estimated as cases managed in the dermatology clinics of Department of Health or private sector were not taken into account.

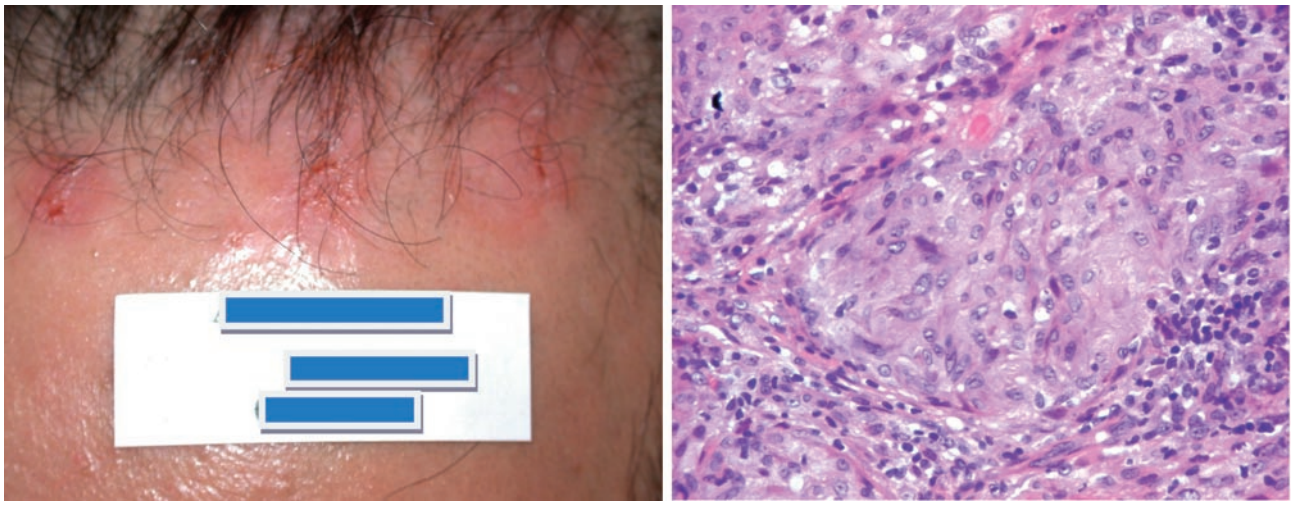


Figure 1. A patient with erythematous plaques on forehead and scalp (patient 3). Histology showing a classical sarcoidal "naked granuloma" (H&E x 200).

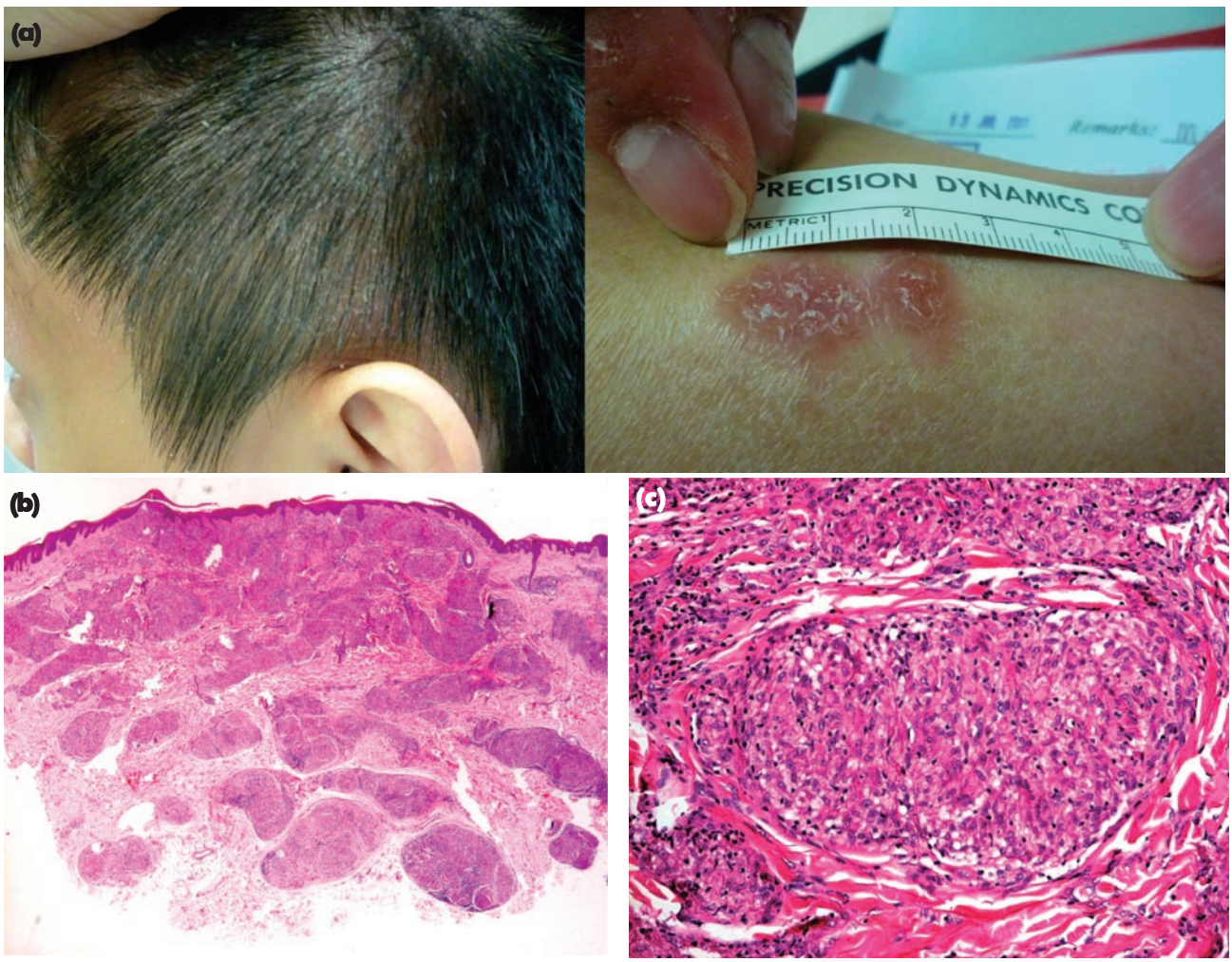
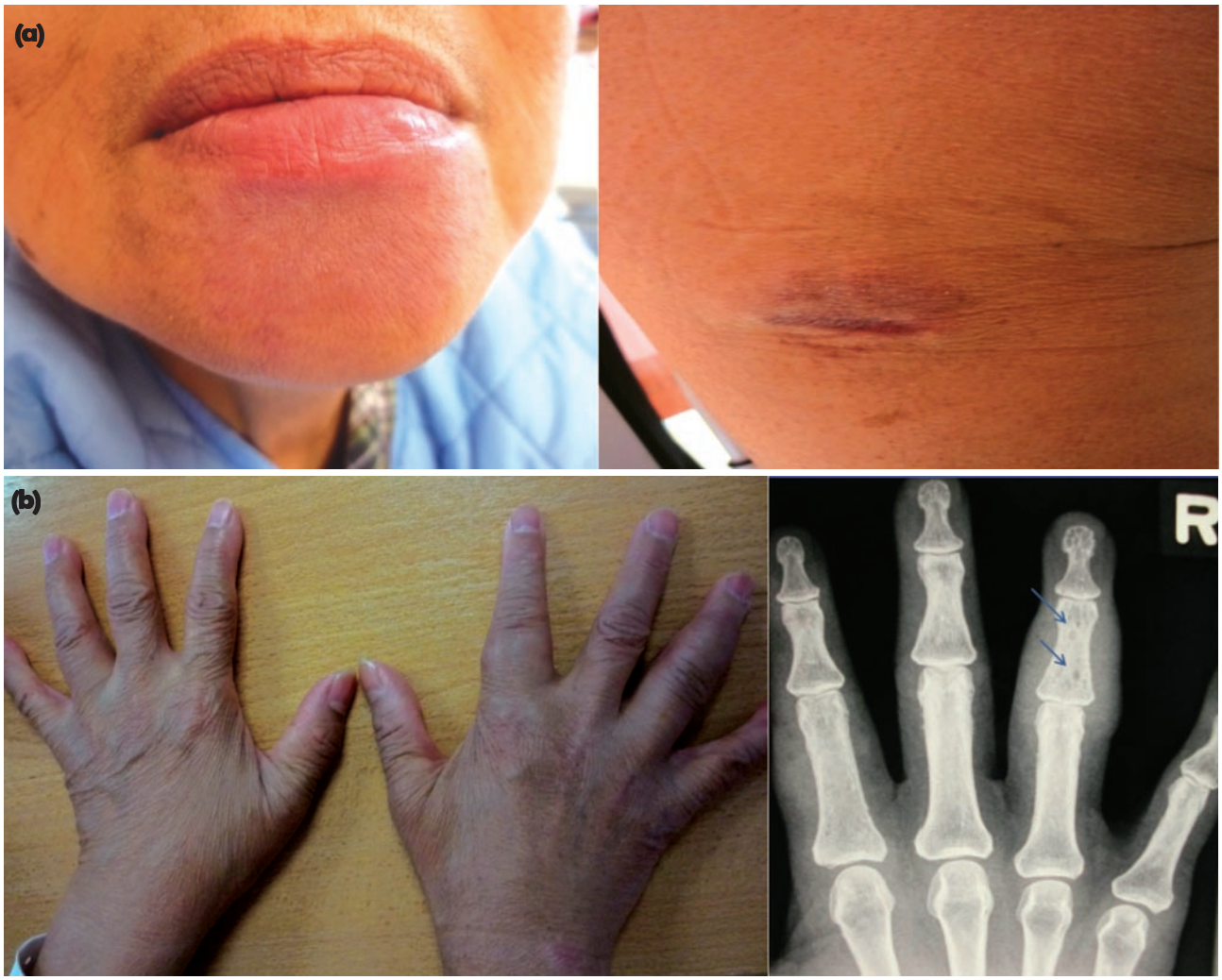


Figure 2. (a) A young patient with non-scarring aloepcia and erythematous papulo-squamous plaques on arm (patient 1). (b) Biopsy on arm showing multiple well defined epithelioid granuloma in the superficial and deep dermis (H&E x 20). (c) Epithelioid granulomas with moderate lymphocytic infiltrates (H&E x 100).



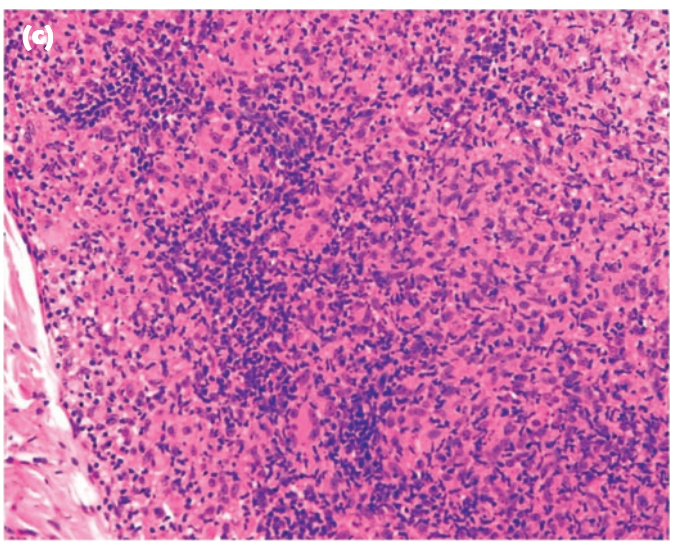


Figure 3. (a) An middle-age lady (patient 2) with generalised plaques on the face, limbs and buttock. (b) Osteitis of proximal phalanges in the same patient. (c) Biopsy on buttock showed epithelioid granulomas with intense lymphocytic infiltrates but no perineural invasion (H&E x 100).

Cutaneous sarcoidosis includes sarcoid-specific lesions, defined histologically by non-caseating granuloma, and non-specific lesions with non-diagnostic inflammatory reaction pattern. Common sarcoid-specific lesions include maculo-papules, papules, plaques, subcutaneous nodules.[1,3] Lupus pernio, ulcerative and scar sarcoid are reported mostly in pigmented skin types, especially African-Americans.[12,13] Ichthyosiform, annular, mucosal, angiolupoid or hypopigmented variants are rarely reported.[1,12] In Chinese, plaques, papules and subcutaneous nodules on limbs are the most commonly reported lesions.[4-7,9,10] A recent Taiwanese series involving 37 patients reported a high percentage of angiolupoid facial plaques.[5] Our finding in the study concurred with previous reports in Chinese, with most patients having mildly papulo-squamous chronic plaques on the limbs. Scar sarcoid or lupus pernio lesions were not found. It was also consistent with the current belief that the presence of plaques and polymorphous lesions were associated with more systemic sarcoidosis,[1,12] as reflected by 100% extra-cutaneous involvement in our series. The presence of erythema nodosum, a non-specific reaction pattern, is common and thought to be associated with transient disease.[1,12] We had a patient with Löfgren's syndrome with erythema nodosum and acute sarcoidosis which resolved rapidly on a short tapering course of prednisolone.

Extra-cutaneous sarcoidosis commonly involves the lungs (up to 90%), eyes (25-80%, prevalent in Japanese), lymph nodes and heart (25-30%).[1,3,13,14] We found an exceptionally high proportion (100%) of patients having lung involvement with mainly asymptomatic radiological hilar lymphadenopathy, similar to other series reported in Chinese.[4-7,9,10] This was followed by uveitis and bone involvement. All of which were associated with the finding of plaque sarcoid.

Sarcoidosis is a diagnosis of exclusion based on compatible clinical and radiological features and classic histopathological findings in at least one organ.[3,14,15] The role of biopsy is crucial, except for Löfgren's syndrome in which it can be omitted.[1,3,14,15] Histologically, sarcoidosis is characterised by superficial and deep dermal non-caseating epithelioid ganulomas with a minimal lymphocytic infiltrate (naked) and exclusion of infective causes.[1,3] Some of the multinucleated giant cells may contain non-specific inclusion bodies (Shauman or asteroid bodies).[1,3,12] However, recent pathology series revealed that up to 30% of cases were atypical granulomas with moderate to intense lymphocytic infiltrates.[5,6,16] A significant proportion contained foreign body (16%), focal fibrinoid necrosis (23%) or peri-adnexal granuloma (32%) and the presence of which did not exclude the diagnosis of sarcoidosis.[5,17] Likewise, co-existing infection with mycobacterium species had been reported with sarcoidosis.[11,12] In our series, we also found 40% of granulomas with moderate to intense infiltrates, and those patients seemed to have more systemic involvement.

The initial differential diagnoses for our patients include subacute cutaneous lupus and lupus tumidus, infective granuloma due to tuberculoid leprosy, mycobacterial, atypical mycobacterial or deep fungal infection, and interstitial granulomatous dermatitis. In our locality where tuberculosis is still prevalent, exhaustive workup was performed. They include tissue specimen for acid-fast stain, culture and polymerase chain reaction for *M. tuberculosis* and systemic workup including chest X-ray, Mantoux test and interferon assays with careful interpretation to exclude latent tuberculosis. Two patients even had a therapeutic trial of antituberculous medication before consideration of systemic steroid. In patients who come from areas of leprosy, like part of South East Asia and China, screening for leprosy is vital.

Other positive findings such as hypercalcaemia, hypercalciuria, elevated angiotensin-converting-enzyme level, polyclonal gammopathy may be helpful but not confirmatory in diagnosis.[3,12] Most experts agreed that initial assessment should include baseline urinalysis, chest radiograph, lung

function test with carbon monoxide diffusion capacity, electrocardiogram, echocardiogram and routine ophthalmological review to document the extent of involvement.[1,3,12,14] There are no established guidelines as to how to monitor patients with cutaneous sarcoidosis with systemic involvement. Regular evaluation of symptoms by a team-approach with experts in dermatology, ophthalmology and respiratory medicine is generally recommended for subsequent follow-up.[18]

There are so far no concrete guidelines or evidence-based recommendations for treatment of cutaneous sarcoidosis. Most data were extrapolated from pulmonary sarcoidosis, or from small case series or anecdotal reports.[1,3,18,19] The prognosis of sarcoidosis depends on organ involvement and around two-thirds of cases will remit within ten years. Cutaneous sarcoidosis without significant cosmetic or functional impairment could be left for observation. Potent fluorinated topical steroid or intralesional steroid could be used for isolated symptomatic lesions. When lesions are extensive, disfiguring, refractory to topical therapy, systemic corticosteroid at moderate dose (0.5 mg/kg tapered over 4-6 months), hydroxychloroquine, or minocycline had been shown to be effective.[1,3,19] Other agents shown to be successful in refractory or ulcerating cases include methotrexate, thalidomide, infliximab and adalimumab.[1,19] Systemic corticosteroid is the first-line therapy for sarcoidosis with major organ involvement or hypercalcaemia.[1,3] In our series, cutaneous sarcoidosis responded best to prednisolone and partially to intralesional steroid with no complications of note.

The study is limited by its single-centre retrospective design, small sample size, selection bias (recruitment of severe cases with multi-system involvement in a tertiary referral centre) and under-estimation of true incidence. A multi-centre prospective study would be desirable to show more significant findings and address the above issues.

In conclusion, we reported the first local series of cutaneous sarcoidosis from a tertiary referral hospital. Plaque sarcoid was the most common form in Hong Kong Chinese. Systemic involvement, especially pulmonary and ocular involvement frequently occurred. Clinical response to short course systemic corticosteroids was notable and Chinese patients seemed to fare well during the course of disease. Due to the scarcity of disease, its polymorphous manifestations and high local prevalence of tuberculosis, it is difficult to ascertain a definite diagnosis of sarcoidosis at first presentation and the diagnosis could be delayed, or even missed. Heightened clinical suspicion amongst dermatologists and physicians would be necessary.

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