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Cutaneous tuberculosis in Hong Kong: an update

香港的皮膚性結核病最新情況

Objective. To provide an update on cutaneous tuberculosis in Hong Kong.
Design. Retrospective study.
Setting. Social Hygiene Service (Dermatology Division), the largest dermatological referral centre in Hong Kong.
Patients. Patients presented with cutaneous tuberculosis between 1993 and 2002 inclusive. Case notes, histology reports, and microbiological reports were reviewed with particular reference to the epidemiology, duration of illness, history of contact with tuberculosis, culture results, and response to treatment.
Results. There were 147 patients with cutaneous tuberculosis; among these a few had true cutaneous tuberculosis (n=16) and the remainder were tuberculids (n=131). In all they accounted for 0.04% of new dermatology cases diagnosed. Cases of cutaneous tuberculosis were distributed as follows: lupus vulgaris (n=6, 4%), tuberculosis verrucosa cutis (n=6, 4%), tuberculosis of the skin unclassified (n=2, 1%), and orificial tuberculosis (n=2, 1%). Culture and polymerase chain reaction was positive in less than half of the latter cases. All responded well to anti-tuberculosis therapy. Erythema induratum was the most common form (n=127, 86%), but papulonecrotic tuberculids (n=4, 3%) were uncommon. Erythema induratum affected the lower limb in all patients, with a female predominance, and responded to isoniazid monotherapy, multidrug anti-tuberculosis therapy, or doxycycline.
Conclusion. Lupus vulgaris and tuberculosis verrucosa cutis remain the commonest forms of true cutaneous tuberculosis, and erythema induratum is the most common tuberculid. Culture and polymerase chain reaction are positive in a small proportion of patients.

目的：了解香港的皮膚性結核病的最新情況。
設計：回顧研究。
安排：全香港最大的皮膚病科轉介中心：社會衛生科（皮膚病分組）。
患者：1993至2002年間出現皮膚性結核病的病人；範圍包括病人的診治紀錄、顯微解剖學報告和微生物學報告，並特別留意疾病的流行情況、持續時間、感染結核病菌的過程、細菌培植的結果和對治療的反應。
結果：147名病人患上皮膚結核病。少數（16人）是真的皮膚性結核病，其餘則為結核疹（131人），兩者共佔皮膚科新診0.04%。各種皮膚性結核病分佈如下：尋常狼瘡（6人，佔4%）、疣狀皮膚結核（6人，佔4%）、未能分類的皮膚結核（2人，佔1%）和孔結核（2人，佔1%）。少於半數的病人於細菌培植檢查和聚合酶連鎖反應呈陽性。所有病例對結核治療都反應良好。結核疹方面，最常見的是硬結性紅斑（127人，佔86%），但丘疹壞死性結核疹並不常見（4人，佔3%）。硬結性紅斑全在病人下肢發生，大部分為女性。異煙肼、混合藥物療法和多西環素都有治療作用。
結論：尋常狼瘡和疣狀皮膚結核仍然是常見的真正皮膚性結核病，而硬結性紅斑則是最常見的結核疹。少數病人在細菌培植檢查和聚合酶連鎖反應呈陽性。

Key words:
Erythema induratum;
Isoniazid;
Lupus;
Tetracycline;
Tuberculosis, cutaneous

關鍵詞：
硬結性紅斑；
異煙肼；
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Introduction

Cutaneous tuberculosis (CTB) is caused by *Mycobacterium tuberculosis* and is classified into true CTB or tuberculids. In true CTB, there is a well-defined tuberculous origin. In tuberculids, the pathogenesis is believed to be a hypersensitivity reaction to haematogenous spread of *M tuberculosis*, whilst the actual relationship to tuberculosis (TB) is less clear.

Table 1. Clinical forms or subtypes of cutaneous tuberculosis

True cutaneous tuberculosis	Tuberculids
Lupus vulgaris (LV)	Erythema induratum (EI)
Tuberculosis verrucosa cutis (TVC)	Papulonecrotic tuberculid (PNT)
Scrofuloderma (SFD)	Lichen scrofulosorum (LS)
Orificial tuberculosis (OTB)	
Miliary tuberculosis affecting skin	

The various clinical forms of true CTB (Table 1) can be attributed to: *M tuberculosis* inoculation from an exogenous source (tuberculosis verrucosa cutis [TVC], some cases of lupus vulgaris [LV]), or endogenous *M tuberculosis* (scrofuloderma [SFD], orificial tuberculosis [OTB]), as well as haematogenous spread (giving rise to miliary TB affecting skin and some cases of LV). The tuberculids constitute erythema induratum [EI], papulonecrotic tuberculid [PNT], lichen scrofulosorum [LS].

Lupus vulgaris has a multifactorial pathogenesis (inoculation, haematogenous) and presents as reddish-brown plaques typically on the head and neck. This can be associated with TB of the lung, bone, lymph node, and joint. Lesions of TVC are due to direct inoculation and present as a warty plaque often on the lower limbs and buttocks. Scrofuloderma results from direct extension of an underlying tuberculous focus in patients with poor immunity (eg lung, lymph node) and may present as ulcers, sinuses, or nodules. Orificial TB is due to auto-inoculation of *M tuberculosis* from internal organs (eg lung, gastro-intestinal tract, genito-urinary tract). It usually presents as an ulcer in the perianal, oral, or vulval areas. Miliary TB affects young children and immunosuppressed patients manifesting as crops of papules or nodules, from a focus of infection in the lungs or meninges.

In EI, subcutaneous nodules with or without ulceration are most often found on the lower limbs. Females are affected more often than males and usually there is no evidence of a tuberculous focus. In PNT, there are symmetrical crops of papular lesions with central necrosis and ulceration and depressed scars. It most commonly affects the limbs of young adults. It has a more definite association with TB. Lichen scrofulosorum is a rare tuberculid and presents with lichenoid papules, which may involute with scarring and usually occurs in young adults and children.

Cutaneous TB was once relatively common in Hong Kong.[1] Two studies of CTB in 1968 and 1995 have shown that this disease has become much less common locally despite the persistently high incidence of pulmonary tuberculosis (PTB).[1,2] As 10 years have passed since the last local study, this survey aim to provide an update on the current situation in Hong Kong.

Methods

A retrospective study of cases of CTB presenting to the Social Hygiene Service between 1993 and 2002 inclusive was performed. Almost all dermatology cases in the public sector in Hong Kong are managed under the Social Hygiene Service. Case records, histological reports, and culture results of confirmed cases were retrieved and reviewed. Inclusion criteria were as follows:

1. Histological diagnosis of a subtype of CTB (LV, TVC, SFD) or tuberculid (EI, PNT, LS).
2. A positive culture for *M tuberculosis*, though the clinical features did not fit into a subtype of CTB.

We also included cases with negative tissue culture but with clinical features and histological findings compatible with CTB, which showed clinical response to appropriate anti-TB treatment. Variables studied included the epidemiology (age, sex, occupation, ethnic origin, medical history) of the patient, duration of illness, history or contact with TB, histological and culture results, chest radiograph appearance, presence/absence of extra-cutaneous tuberculosis (ECTB) or PTB, and response to treatment. Hospital in-patients and patients in the private sector were not included in the study.

Results

A total of 147 new cases of true CTB (n=16) and tuberculids (n=131) were detected between 1993 and 2002 inclusive. During this period, there were a total of 345 394 new dermatology cases seen at the Social Hygiene Service. The incidence of CTB was therefore 0.04% of new dermatology cases. The overall male-to-female ratio for true CTB was 2.6 to 1 and for tuberculids, 1 to 11.9; female preponderance in the latter group was mainly due to patients with EI (Table 2).

Lupus vulgaris (Fig 1a) and TVC (Fig 1b) were the most common types of true CTB, and EI, the most common tuberculid (Fig 2). There were no cases of SFD, LS, or miliary TB affecting the skin or TB associated with human immunodeficiency virus (HIV) infection. The Mantoux test was rarely performed as most patients had been vaccinated with bacille Calmette-Guérin (BCG) at birth. The face was affected in all cases of LV and the lower limbs were affected in all cases of TVC, PNT (Fig 3), and EI. Most patients were Chinese. Among the ethnic minorities, the disease distribution was as follows: Filipino (1 LV, 2 EI), Indian (1 LV), Thai (1 EI), Indonesian (2 EI).

There were two (12.5%) cases of true CTB with concurrent active PTB. One of them had OTB (a 72-year-old male presented with a 10-year history of perianal ulceration) in whom urinary tuberculosis (UTB) was also found.[3] His X-ray revealed diffuse mottling on the chest radiograph with multilobular opacities. Granulomas were seen on skin biopsy and both polymerase chain reaction (PCR) and culture were positive for *M tuberculosis*. Acid-fast bacilli (AFB) were seen on the early morning urine specimen. He refused gastro-intestinal tract investigation. He was treated with isoniazid (INH) 300 mg every morning

Table 2. Types of cutaneous tuberculosis (n=147)

Type*	LV	TVC	TB skin (unclassified)	OTB	EI	PNT
No. of patients	6 (4%)	6 (4%)	2 (1%)	2 (1%)	127 (86%)	4 (3%) [2 had concurrent EI]
Mean age (range) [years]	51.3 (32-65)	59.5 (26-80)	46 (30-44)	72 (72-72)	46 (13-81)	34.3 (3-67)
Male:female	2:1	4:1	2:1	1:1	1:11.6	All females
Mean duration (range)	5.6 years (0.5->10 years)	11.3 years (8 months-40 years)	10 weeks (4-16 weeks)	5.23 years (6 months->10 years)	11 months (2 days-20 years)	1 year (1-24 months)
No. of PCR AFB† positive	1	1	2	1	0	0
No. of positive culture	1	1	1	2	0	0
Cases with active TB‡	0	0	0	1 PTB, 1 PTB+UTB	6 PTB, 2 LNTB	1 PTB
History of TB	1	0	0	0	4	0
Contact with TB	0	0	0	0	4	0
Site	Face	Lower limbs	Thumb	Buttock, chin	Lower limbs	Limbs

* LV denotes lupus vulgaris, TVC tuberculosis verrucosa cutis, TB tuberculosis, OTB orificial tuberculosis, EI erythema induratum, and PNT papulonecrotic tuberculid
† PCR denotes polymerase chain reaction, and AFB acid-fast bacilli
‡ PTB denotes pulmonary tuberculosis, UTB urinary tuberculosis, and LNTB tuberculous lymphadenitis

Fig 1. (a) Lupus vulgaris—an infiltrated, reddish plaque on the face, apple-jelly nodules were seen on diascopy; (b) tuberculosis verrucosa cutis—warty plaque on the left thigh

Fig 2. Erythema induratum
Multiple subcutaneous nodules on the thighs

(om), rifampicin 600 mg om, and pyrazinamide 1.5 g om and the lesions started to resolve by 8 weeks. Another patient with active PTB was a 72-year-old woman who presented with a 6-month history of an ulcer on the chin. She had no history of TB but sputum culture was positive for *M tuberculosis*. The lesions started to heal after treatment with multidrug anti-TB therapy at 2 weeks.

In 13 patients, culture for *M tuberculosis* from the lesion was undertaken, of which five (38%) were positive.

Fig 3. Papulonecrotic tuberculid
Recurrent crops of lesions on the legs, some of which are crusted, while others are slowly resolving

Specimens from seven suspected true CTB patients were subjected to PCR; five (71%) confirmed the diagnosis of TB. Changes in the chest radiograph were seen in three patients with TVC. Old TB changes were seen in one patient, right apical thickening in another, and right upper zone haziness in the third. None of these cases had a history of PTB. These cases were referred to chest physicians for further investigation.

Two patients with lesions affecting the thumb could not be classified into a particular type of CTB and were labelled as skin TB. One was a 44-year-old man with a 4-month history of a plaque on the right thumb; the lesion yielded *M tuberculosis* by culture and PCR, and granulomatous changes were seen in the skin biopsy. He was treated with anti-TB therapy. The other patient, a 30-year-old laboratory technician developed a nodule on the thumb after a needlestick injury. Acid-fast bacilli were seen in his skin biopsy and *Mycobacterium bovis* was detected on PCR. There was no history of TB and chest X-ray was normal. He refused treatment and defaulted.

Of the 16 cases of true CTB, seven defaulted, one refused treatment, and eight were available for follow-up. There was a good response to anti-TB treatment in all subtypes of CTB. Treatment varied between 6 and 13 months. No relapses were seen after treatment. The lesions started to improve by as early as 2 weeks in one case of OTB. Two patients developed liver dysfunction and pyrexia after starting therapy (one each of LV and TVC). However, these reactions resolved after treatment was stopped and did not recur after therapy was restarted.

Twelve (9%) patients with EI were associated with TB: six were on treatment for active PTB; two had concurrent ECTB (tuberculous lymphadenitis) and four had a history of PTB. In four (3%), there was a history of contact with TB (Table 2). Investigation of patients with EI was undertaken by PCR (n=3) and culture for TB (n=34). The results of these tests were all negative. Treatment for EI were INH monotherapy, multidrug anti-TB therapy, or doxycycline as shown in Table 3. Sixteen of these patients had a relapsing course. One (25%) of the four PNT patients was associated with active PTB (Table 2). She was a 15-year-old girl with a 6-week history of dusky brown patch on the ankle followed by a papulovesicular rash on the upper and lower limbs. She was a known case of PTB on treatment. The lesions resolved after 16 weeks of treatment with INH, rifampicin, and pyrazinamide. The latter and one other PNT patient also had EI. This was a 52-year-old female who had received a bone marrow transplant for chronic lymphocytic leukaemia, who presented with a 6-month history of erythematous papules on the legs that spread to the upper limbs. Her chest radiograph was normal and she was started on INH, rifampicin, and pyrazinamide.

Discussion

The present study did not include patients in the private sector, but it is likely that the majority with dermatology complaints are managed in the public sector and seen by the Social Hygiene Service. The current study may therefore provide some indication of the epidemiology of CTB in Hong Kong. Two retrospective studies on new cases of CTB in the Social Hygiene Service in Hong Kong have been performed, using the same methods as in the current investigation.[1,2] The incidence of CTB in these studies was 0.4% and 0.066% of new skin cases, respectively. In the 1968 report,[1] TVC was the most common form of true CTB, and PNT, the most common tuberculid. However, the second study in 1995[2] found that LV and EI were the most common causes of true CTB and tuberculids, respectively. This trend may be related to better housing conditions and health services as well as BCG vaccination at birth.

Table 3. Treatment regimen for erythema induratum

Type of treatment	Isoniazid	Multidrug therapy	Doxycycline	Non-steroidal anti-inflammatory drugs
Mean duration of treatment (range) [months]	7 (2-8.5)	7 (6-9)	11 (6-24)	3.75 (2-34)

In the present series, the mean age in each subtype (Table 2) was older[1,2] and LV and TVC were the two most common forms of true CTB but both were much less common than EI. There were no cases of SFD or LS in the current study; both were also uncommonly encountered in the two previous studies.[1,2] In contrast to other studies,[4] there was a male preponderance in cases with LV. Despite the relatively long duration of the disease (mean duration, 5.6 years), no lesion was reported to undergo malignant transformation. However, the significance of this observation is uncertain, due to the small number of our cases. Apart from one patient with perianal TB associated with UTB,[3] there was no other associated extrapulmonary TB.

Lupus vulgaris was the most common form of CTB reported in studies from Africa and India.[5-7] Tuberculosis verrucosa cutis accounted for 4% of all cases in this study, in contrast to 46% reported previously,[1] and has been regarded as a form of inoculation TB. Due to the lower overall incidence of PTB than in the past and improved hygiene (eg prohibition of spitting in the streets, leading to a decrease in contamination by AFB),[8] the incidence of such inoculation disease in Hong Kong appears to have diminished.

The two patients with OTB were the only two (12.5%) cases of true CTB associated with active PTB. Urinary TB was detected in one patient. This low incidence of extracutaneous involvement in true CTB in our series is in contrast to other reports detailing 40% of LV cases associated with tuberculous lymphadenitis and 10 to 20% with involvement of the lungs and bones.[4] Orificial TB tends to affect elderly patients and is often associated with TB in other organs. It is attributed to auto-inoculation and is associated with decreased cell-mediated immunity. Our two cases were believed to be due to auto-inoculation of AFB into the skin from infected sputum or urine.

The diagnosis of CTB is based on clinical features, skin biopsy, culture, and in recent years, PCR. However, the yield from culture and PCR is often low and diagnoses may need to depend on clinical features, histological findings, and retrospective review of response to treatment (as described in this study). Tuberculosis DNA was detected in a total of 71% (5/7 PCR tests) cases of true CTB, while the yield from culture was only 38% (5/13 cultures). According to other reports, the yield from PCR has been low in paucibacillary cases (LV, TVC).[9] The low yield from PCR and culture may be due to the low number of viable bacilli within the specimen and/or to degradation of DNA material. Compared with PTB, the number of bacilli encountered in CTB is low.[10] Moreover, culture of *M tuberculosis* is time-consuming and the yield is low.[5] Polymerase chain reaction is a rapid method of diagnosis but requires expertise, as it is prone to contamination and false positives. In the two unclassified patients, CTB was diagnosed by PCR, illustrating its complementary role in diagnosis. However, tissue culture remains the gold standard for diagnosis and for monitoring the emergence of drug-resistant strains. Cutaneous TB can therefore be difficult to confirm, and on occasions, the diagnosis is only established retrospectively, after response to a therapeutic trial. Cutaneous TB is less common than PTB and therefore non-dermatologists may be less familiar with the entity, possibly resulting in underreporting.

Erythema induratum remains the most common tuberculid, responsible for the majority (86%) of cases in this study (Table 2). It mainly affected the legs and was most common in females, which is in accordance with other reports. In our series, 12 (9%) of EI patients had concurrent PTB, ECTB, or a history of prior TB. In other studies, the association with a history of TB (pulmonary or tuberculous lymphadenitis) varied between 28% and 56%.[11,12] Hitherto, there is still controversy as to whether EI is a true tuberculid. Thus, the decline in the incidence of PTB has not been accompanied by a similar decline in the incidence of EI, suggesting that other aetiological agents may be involved. Moreover, EI has been reported to respond to anti-TB therapy as well as non-steroidal anti-inflammatory drugs (NSAIDs), and doxycycline.[13] The efficacy of NSAIDs and doxycycline may be due to their anti-inflammatory properties. However, the response to anti-TB therapy supports the association with TB. In our study, there seems to be a more definite association with TB in the two cases with concurrent EI and PNT. Although the mean duration treatment with NSAIDs was shorter than with anti-TB therapy (Table 3), it is not possible to draw any pertinent conclusions as this study was retrospective and these treatments were not compared formally.

Papulonecrotic tuberculids continue to be uncommon, but the association with TB is better defined,[10] as mycobacterial DNA has been detected in PNT lesions and in patients in whom EI has occurred simultaneously.[14,15] In previous reports, PNT mostly occurred in young adults and children.[16] They were older in our series (mean age, 34.3; range, 3-67 years) and all were female, but the number of cases was too small to draw any conclusions.

In all cases of true CTB, there was a good response to anti-TB treatment. This is reassuring since there have been isolated case reports of multidrug-resistant CTB.[17,18] Unlike PTB, there are no guidelines on the treatment of multidrug-resistant CTB. Regimens used were based on clinical response, drug sensitivity of the strain, or guidelines for multidrug-resistant PTB. With the advent of HIV infection, the problem of multidrug-resistant TB has increased, highlighting the importance of continued surveillance and compliance to appropriate treatment. Although the level of drug resistance in Hong Kong is still low, a recent study reported INH resistance in 2.6% of isolates.[19]

A drawback of the present study is that hospital in-patients and private hospital patients were not studied.

Moreover, there has been an increase in the number of immunocompromised patients (due to organ transplantation and HIV infection). It is therefore entirely possible that more advanced CTB such as acute disseminated miliary TB or CTB associated with immunosuppression were missed. Yet the Hong Kong Social Hygiene Services has not encountered any associated increase in reported cases of CTB.

Conclusion

The findings of this study are similar to those of the 1995 study.[2] Overall, true CTB is uncommon. Lupus vulgaris and TVC are the two common forms of true CTB. The latter patients are older than previously reported, and only a small percentage are associated with TB elsewhere. Erythema induratum remains the commonest tuberculid and the papulonecrotic variety is uncommon. As CTB is an uncommon condition associated with a low index of suspicion, cases may well be misdiagnosed or missed—leading to underreporting.

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