Review Article

Cutaneous tuberculosis: clinical features, diagnosis and management

皮膚結核病：臨床表現、診斷及治療

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The clinicopathological manifestations of cutaneous tuberculosis are protean. Compared to pulmonary tuberculosis, cutaneous tuberculosis is uncommon and more difficult to diagnose. The use of polymerase chain reaction (PCR) has enhanced detection of cutaneous tuberculosis. The clinicopathological features, diagnosis, and treatment of cutaneous tuberculosis are reviewed. Exclusion of concurrent tuberculosis at other sites is important.

皮膚結核病的臨床及病理表現十分多樣化。與肺結核病比較，皮膚結核病不常見，亦較難診斷。用多聚醣鍵反應有助發現皮膚結核病。本文綜述皮膚病的臨床表現、診斷及治療。排除身體其它部位的結核十分重要。

Keywords: Cell-mediated immunity, cutaneous tuberculosis, tuberculids

關鍵詞：細胞中介免疫，皮膚結核病，結核疹

Introduction

Tuberculosis is caused by Mycobacterium tuberculosis and Mycobacterium bovis. An attenuated strain of Mycobacterium bovis, Bacille Calmette Guerin (BCG) may occasionally be responsible. The most common manifestation is lung infection, while cutaneous tuberculosis is relatively uncommon and accounts for 1% of extrapulmonary tuberculosis. The skin may be infected via haematogenous spread, direct inoculation or auto-inoculation.

Pathogenesis

The presentation of cutaneous tuberculosis depends on the pathogenicity of the mycobacteria, route of infection, and level of cell-mediated immunity (CMI) of the host. Following infection, the mycobacteria are phagocytosed by macrophages, which circulate to lymph nodes and then by haematogenous spread to other parts of the body. Macrophages act as antigen presenting
cells and interact with T lymphocytes. Memory T lymphocytes are generated during initial sensitisation within three to ten weeks and circulate in the blood and internal organs.

As CMI may deteriorate as a result of illness, immunosuppression, ageing, HIV infection and malnutrition, there is a long-term risk of reactivation. This risk is greatest two to three years after primary infection.²

**Pathology**

In early lesions, there is non-specific inflammation consisting of polymorphs and macrophages. Tubercles appear after three to six weeks as immunity develops.³ The tubercle consists of a collection of epithelioid cells at the centre with a variable number of Langhans giant cells surrounded by a rim of lymphocytes. As the inflammation progresses, the centre of the granuloma undergoes caseation necrosis, which is a distinctive feature of tuberculous infection.

In patients with adequate CMI, the granuloma is able to contain the infection with progressive fibrosis and finally calcification. In 10% cases, tuberculosis infection will lead to active disease.⁴

In lupus vulgaris (LV), there is effective CMI in the host. Granulomas are formed with little caseation and acid-fast bacilli (AFB) are infrequently found. There are tuberculoid granulomas in the upper dermis.

In scrofuloderma (SFD), there is moderate cell-mediated immunity in the host. The granulomas are less well formed and are located at the periphery of the lesion with more caseation necrosis at the centre. In addition, some AFBs can be found.

In tuberculosis verrucosa cutis (TVC), there are often epidermal changes such as warty hyperkeratosis or pseudoepitheliomatous hyperplasia with epithelioid and giant cells in the mid-dermis. Tubercles are less common and AFBs are occasionally seen. At the other end of the immunological spectrum, there is miliary tuberculosis with poor or absent granuloma formation and marked tissue necrosis. Numerous AFBs are present. The histological picture is similar in primary tuberculous chancre, but as CMI develops, tuberculoid granulomas are formed.

In patients with poor CMI such as in acute disseminated miliary tuberculosis, mycobacteria are present. There is massive necrosis and non-specific inflammation.

Differentiation from other types of mycobacteria can only be achieved by cultures. Sarcoidosis may be distinguished from mycobacterial infection by the paucity of lymphocytes around the granuloma; so called naked granulomas. Tertiary syphilis is characterised by plasma cell infiltration and vascular changes. In tuberculoid leprosy, the granulomas tend to be located around cutaneous nerves.

**Clinical subtypes of cutaneous tuberculosis**

A classification of cutaneous tuberculosis is shown in Table 1.³,⁵ The clinical presentation of cutaneous tuberculosis depends on whether the patient has been previously sensitised. In primary infection, there is no previous sensitisation and tuberculous chancre, acute miliary disseminated tuberculosis are the main presentations. Re-infection may result in LV, TVC, and re-activation can lead to tuberculosis cutis orificialis or SFD. Secondary infection comprises more than 95% of cutaneous tuberculosis infections.

**I. Inoculation tuberculosis**

1. Primary inoculation tuberculosis (tuberculous chancre)
   Incidence
   Primary inoculation tuberculosis (PIT) mainly affects
children in endemic areas and accounts for 1-2% of cutaneous tuberculosis.\(^2\)

Clinical features
PIT is due to direct inoculation of \(M.\) tuberculosis into the skin in a non-sensitised patient.\(^3,6\) This may result from minor abrasions, tattooing, ear-piercing, minor surgical procedures or injections. A red/brown nodule develops two to four weeks after inoculation, which erodes to form an ulcer. There is an indurated base and the edges may be undermined.

There is lymphatic spread of the bacilli to produce painless lymphadenopathy in the next three to four weeks. The combination of the chancre and regional lymphadenopathy is equivalent to the Ghon focus in pulmonary tuberculosis.

The lesions often affect the face but may involve the mucous membranes as well. This may present as ulceration or oedema if the eyelids are affected. It usually resolves after three to 12 weeks as immunity develops, leaving an atrophic scar.

PIT may occasionally evolve into LV or TVC. Alternatively, the regional lymph nodes may erode, leading to SFD. The tuberculin test is initially negative and becomes positive as CMI develops.

2. Lupus vulgaris
Incidence
Lupus vulgaris has declined since a post war peak of 775 per million in the 1950s.\(^6\) It is found in cool, moist environments and is still the most common form of cutaneous tuberculosis in Europe. There is a higher incidence in women and all age groups are affected.

Clinical features
Lupus vulgaris may develop as a result of inoculation or it may follow primary inoculation tuberculosis or BCG vaccination. Some cases of LV are due to spread of tuberculosis from elsewhere in the body (often lung or cervical lymph nodes) via the lymphatic system or direct spread. It may also follow SFD or tuberculous infection of the mucous membranes. Rarely, it may follow haematogenous dissemination. LV has been associated with tuberculous lymphadenitis in 40% cases, SFD in 30% of cases, and tuberculosis of the lungs or bones in 10 to 20% cases.\(^3,6,7\)

The lesions are usually solitary and progress steadily, affecting the head and neck in most cases. Multiple lesions may occur when the immune response has been lowered especially after measles. The earlobe, nose or cheeks are most often affected. In tropical countries, the buttocks and lower limbs are more frequently affected.\(^2\)
A brownish-red, soft plaque is formed as the initial papule enlarges or by coalescence of several smaller papules. Tubercles can be seen on diascopy as "red currant jelly" nodules on the surface of the plaque. Spontaneous involution in one area may be followed by progression in another area. Involvement of the mucous membranes is more likely to result in deformity such as destruction of the nasal bridge or laryngeal stenosis.

There are five clinical variants:

i) **Plaque** forms are flat plaques in which the surface may be smooth or scaly. There is minimal central scarring or infiltration.

ii) **Hypertrophic** forms can be associated with lymphoedema and limb deformity. The surface is nodular and soft, with a tendency to ulcerate.

iii) **Ulcerative** forms can lead to severe mutilation if the nasal or auricular cartilage is affected.

iv) **Tumour-like** forms present as a collection of soft nodules or as plaques with deep infiltration and respond poorly to treatment. Large tumours may affect the ear lobe and lymphoedema may be present.

v) **LV** may also be present in a *papular or nodular* form often as multiple lesions.

Although there may be periods of inactivity, LV runs a chronic course without treatment. There is a 10% risk of developing squamous cell carcinoma from LV and this may delayed from 10 to 15 years.

3. Tuberculosis verrucosa cutis

**Incidence**

Tuberculosis verrucosa cutis is less common in western countries. It is more common in the tropical regions and was the most common form of cutaneous tuberculosis reported in Hong Kong in 1968 (46% of cases).³ The age of onset was before ten years in over half of the cases.⁹

**Clinical features**

**TVC** is due to direct inoculation into the skin in a previously sensitised patient. This has been associated with certain professions in the past, namely, pathologists (prosector's wart), laboratory workers and medical students.

**TVC** is often found on the hands and areas prone to trauma as single lesions, although multiple lesions are occasionally seen. In tropical areas, the buttocks and lower extremities are commonly affected sites. This affects children in particular as they play on the pavement and become infected via contaminated sputum.⁹

The lesion begins as a papule or papulopustule and slowly enlarges to form a plaque. Occasionally, the plaque is psoriasiform or keloidal and deformity of the limbs may result from papillomatous or sclerotic forms. It is frequently misdiagnosed as a wart. Spontaneous healing may occur at the centre and the entire lesion may resolve after several months or years.

### II. Secondary tuberculosis

1. Scrofuloderma

**Incidence**

Scrofuloderma was common before anti-tuberculous therapy was available. It is now more common in immigrants from developing countries.⁶ In U.K, most cases in the indigenous population affect patients older than 50 years old, while in the Asian community most cases are between 10 to 50 years of age.⁷

**Clinical features**

SFD is due to reactivation of dormant tuberculosis. There is contiguous involvement of overlying skin from an underlying tuberculous focus such as tuberculous lymphadenitis or tuberculous bone disease. Tuberculin test is usually positive. A cold abscess is formed and the overlying skin is eroded.
SFD from tuberculous lymphadenitis often affects the parotid, submandibular, supraclavicular and both sides of the neck.

The lesions begin as subcutaneous nodules, which become doughy in consistency. With progressive liquefaction, a cold abscess is formed and the skin erodes to form a discharging sinus. There may be healing with scarring and recurrence of disease over several years.

2. Oroficial tuberculosis (Tuberculosis Ulcerosa Cutis et Mucosae)
Incidence
Oroficial tuberculosis a rare condition affecting approximately 0.2% of tuberculosis. It is more common in males and with advancing age.

Clinical features
This is due to auto-inoculation at mucosal orifices adjacent to organs (especially lung, gastrointestinal tract, genito-urinary tract) infected with tuberculosis. Commonly affected sites include the mouth, oropharynx, soft or hard palate, larynx, perianal area, and genitalia. The tuberculin test is weak or negative.

A small red or yellow nodule develops which then breaks down to form an ulcer. There may be a pseudo-membrane with surrounding inflammation and oedema. Severe pain may interfere with eating, micturition, or defaecation. The ulcers may enlarge and persist if not treated properly.

III. Haematogenous tuberculosis

1. Acute disseminated miliary tuberculosis
Clinical features
Acute disseminated miliary tuberculosis is a rare condition, affecting mainly infants with a decreased immune response resulting in haematogenous spread of bacilli to the rest of the body. This may follow viral infections such as measles. The patient is often ill with widespread tuberculosis (the focus of infection is often the lung or the meninges).

Skin lesions consist of discrete, pin-head sized, red-blue papules that are topped by small vesicles. These rupture and form a crust, leaving a depressed scar after resolution. The tuberculin test is negative.

2. Tuberculous abscess (tuberculous gumma)
Incidence
Tuberculous gummata are more common in immigrants from endemic areas.

Clinical features
Tuberculous gummata are due to haematogenous spread of tuberculosis from a primary source as a result of either breakdown of an old healed tubercle, or due to reduced immunity.

The lesions present as solitary or multiple subcutaneous abscesses that break down to form a discharging sinus. In immunocompetent patients, the lesions are solitary and may resolve spontaneously, but in immunocompromised cases, multiple lesions may occur and are associated with a poorer prognosis.

IV. The tuberculids

The tuberculids are believed to be hypersensitivity reactions to blood spread of tuberculosis. However, this definition has been used freely in the past and many conditions like acne agminata, rosacea-like tuberculid, lichenoid tuberculid had been included under this group. This has led to confusion and controversy regarding the relation between tuberculosis and the tuberculids.

i) The evidence against a tuberculous pathogenesis is as follows:
   • Mycobacteria frequently cannot be found in these lesions.
• The tuberculoid features, which are seen histologically in tuberculids, are also seen with other conditions such as deep fungal infection and therefore does not provide definitive evidence of a tuberculous origin.

ii) The evidence suggesting a tuberculous origin include:
• Tuberculids have become uncommon where there has been a decline in tuberculosis but not in areas where it has persisted. In areas where there has been a resurgence of tuberculosis, the tuberculids have also increased in incidence.
• Tuberculids respond to anti-tuberculous therapy.

The tuberculids have been divided into those which have good evidence in association with tuberculosis and facultative tuberculids. The former include lichen scrofulosorum and papulonecrotic tuberculid. Erythema induratum has been classified as a facultative tuberculid. Tuberculosis may be one of several aetiological factors in erythema induratum, but up to date, there have been no other agents implicated in its pathogenesis.

1. Papulonecrotic tuberculid

Incidence
Papulonecrotic tuberculid (PNT) was common in the past and remains relatively common in areas with a high incidence of tuberculosis. In one series, 91 cases were reported in South Africa over a 17-year period. In areas with low incidence of tuberculosis, it has become rare.

Clinical features
The most commonly affected sites are the buttocks, extensor aspects of the knees and elbows and lower trunk. There are recurrent crops of red papules in a symmetrical distribution, persisting over months or years. Central necrosis and a crust may develop on the top of the papules. Spontaneous resolution of the lesion or removal of the crust will leave a depressed scar. PNT has also been associated with erythema induratum. LV developed in four cases from pre-existing PNT lesions.

Histopathology
There is wedge-shaped necrosis of the upper dermis and epidermis resulting from a leucocytoclastic vasculitis. This area may be surrounded by histiocytes and blood vessel involvement may lead to endothelial damage and thrombosis.

Differential diagnosis
PNT may resemble pityriasis lichenoides et varioliformis acuta (PLEVA), although the latter is more widespread. Other conditions including leucocytoclastic vasculitis, nodular prurigo and secondary syphilis also need to be distinguished from PNT.

2. Lichen scrofulosorum

Incidence
Lichen scrofulosorum (LS) was first described by von Hebra and has been an uncommon condition, even in the past. It usually affects children and young adults and is often associated with tuberculosis of the bone, lymph nodes or pleura. It has been reported after BCG vaccination.

Clinical features
There is a lichenoid eruption often in children with tuberculosis. The lesions are perifollicular and are yellow-brown or pink papules with a scaly or hyperkeratotic top. These are seen mainly on the trunk with a lichenoid distribution and persist for months before resolving spontaneously. Discoïd plaques may be formed as the papules coalesce. The lesions resolve with anti-tuberculous therapy within weeks to months.

Histopathology
Superficial granulomata are present within or near hair follicles and sweat ducts. There is no caseation and mycobacteria are not found.

Differential diagnosis
This includes other lichenoid conditions such as...
lichen nitidus, lichen planus, lichenoid secondary syphilis and micropapular sarcoidosis.

3. Erythema induratum

Incidence

Erythema induratum (EI) was the most common form of tuberculid in Hong Kong.\textsuperscript{15} It is found mainly in females and affects all ages, although there are two peaks at adolescence and menopause. It is also more prevalent in the spring and autumn.

Clinical features

Affected patients present with erythrocyanotic changes in the lower limbs. The blood vessels react abnormally to the cold and perniosis may be present.\textsuperscript{16} There has been a debate about the tuberculous origin of EI as active tuberculosis is not always present. However, \textit{M. tuberculosis} DNA has been detected by PCR,\textsuperscript{17} which suggests that at least some cases are associated with tuberculosis. The backs of the legs are commonly affected in a symmetrical pattern. Affected patients tend to have plump heavy legs. There are indolent, ill-defined nodules, which may improve in the summer and are exacerbated by cold. These may regress or ulcerate over several months. The resultant ulcers are irregular and may have bluish borders. Spontaneous resolution with scarring occurs after several months.

Histopathology

A nodular vasculitis with areas of fat necrosis, lobular panniculitis and foreign body reaction may be seen. Tuberculoid granulomas can also be found, although there is no caseation.

BCG vaccination and tuberculosis of the skin

BCG vaccination has been associated with cutaneous tuberculosis infections including:

i) LV, SFD may develop at the injection site and the clinical features, treatment and course are similar to ordinary LV.\textsuperscript{18}

ii) Severe regional lymphadenitis is the most common complication and affects younger patients.

iii) Generalised tuberculid-like reactions have been reported on rare occasions.\textsuperscript{19}

Diagnosis

I. Absolute criteria

Culture

The only absolute criteria in confirming a diagnosis of cutaneous tuberculosis is a positive culture of \textit{M. tuberculosis} from the biopsy material on Lowenstein Jensen's media. However, culture of \textit{M. tuberculosis} requires up to four to six weeks, leading to considerable delay in diagnosis.

However, the incidence of positive cultures for cutaneous tuberculosis is low,\textsuperscript{20} and diagnosis frequently relies on relative criteria.

II. Relative criteria

In the absence of positive cultures, relative criteria are used for diagnosis as follows:\textsuperscript{3,6,20}

i) Evidence or history of active tuberculosis at other sites.

ii) Clinical history and physical appearance.

iii) The presence of acid-fast bacilli.

iv) Tuberculoid granulomas seen on histology.

v) Positive Mantoux test.

vi) Response to anti-tuberculosis therapy.

III. Polymerase chain reaction in the diagnosis of cutaneous tuberculosis

The polymerase chain reaction (PCR) can aid in the diagnosis of cutaneous tuberculosis.\textsuperscript{21} Primers targeting the IS 6110 repetitive insertion sequence of \textit{M. tuberculosis} DNA have been used.\textsuperscript{22} PCR has proved useful in the diagnosis of various forms of cutaneous tuberculosis including inoculation tuberculosis,\textsuperscript{21} LV,\textsuperscript{23} and SFD.\textsuperscript{24} However, PCR is not always positive in paucibacillary cases (LV, TVC).\textsuperscript{25}
M. tuberculosis DNA has been detected in some cases of EI, providing evidence to support the role of tuberculosis in these lesions, although it is possible that the mycobacterial DNA detected may have been from previous tuberculous infection. The association between tuberculosis and EI remains unclear. Although PCR does not distinguish between current and past infections, it does distinguish between M. tuberculosis DNA and atypical mycobacterial DNA.

Possible reasons for these discrepancies may be found at the various stages in the PCR methodology. Many studies were done on archival DNA, resulting in suboptimal DNA extraction and false negatives. In addition, suboptimal DNA extraction may be due to the resistant lipid-rich wall of mycobacteria. Conversely, false positives may be due to contamination. Therefore the diagnosis should not be based on PCR alone.

**Treatment**

**Principles of chemotherapy**
The aim is to eradicate all viable mycobacteria in the patient, which can be divided into three groups:

i) Freely dividing extracellular bacilli.

ii) Dormant bacilli within cells and caseous material.

iii) Slowly dividing bacilli within the macrophages and in inflammatory lesions.

The treatment of cutaneous tuberculosis is similar to that of pulmonary tuberculosis (Table 2). This consists of two phases:

- Phase I targets rapidly dividing bacilli and consists of an initial phase of intensive therapy with three or four drugs for two months.
- Phase II is directed at the remaining dormant bacilli (maintenance therapy) and consists of isoniazid and rifampicin for four further months.

The advantage of the initial two-month intensive treatment is that a significant proportion of bacilli will be eradicated even if the patient defaults after this period. The sensitivities may vary with the locality and need to be adjusted accordingly. The regimens recommended by the WHO are given in Table 3. In patients with HIV, treatment with isoniazid and rifampicin is continued for seven months after the initial two months of quadruple therapy.

Surgical measures may complement medical therapy. For example, localised lesions of LV or TVC may be excised while continuing on medical therapy and surgical correction of deformity may be required. It is important in the initial assessment of cutaneous tuberculosis, to look for any concurrent tuberculosis at other sites.

### Table 2. Dosage regime of the first-line anti-tuberculous drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 mg/kg/day</td>
<td>450 mg/day</td>
</tr>
<tr>
<td></td>
<td>(&lt;50 kg)</td>
<td>600 mg/day</td>
</tr>
<tr>
<td></td>
<td>(&gt;50 kg)</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg/day</td>
<td>15 mg/kg/day</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30 mg/kg/day</td>
<td>1.5 g/day</td>
</tr>
<tr>
<td></td>
<td>(&lt;50 kg)</td>
<td>2 g/day</td>
</tr>
<tr>
<td></td>
<td>(&gt;50 kg)</td>
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</tbody>
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### Table 3. WHO recommended drug regimens for treatment of tuberculosis

<table>
<thead>
<tr>
<th>Phase I (Intensive): 2 months</th>
<th>Phase II (Maintenance): 4 months</th>
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</thead>
<tbody>
<tr>
<td>Standard regimen: daily treatment</td>
<td>INH, RIF, PYR INH, RIF</td>
</tr>
<tr>
<td>Regimen suggested when drug resistance suspected:</td>
<td>INH, RIF, PYR, STP INH, RIF</td>
</tr>
<tr>
<td>Intermittent regimens: three times/week</td>
<td>INH, RIF, ETH, PYR INH, RIF, PYR</td>
</tr>
<tr>
<td>INH, RIF, STP, PYR</td>
<td>INH, RIF, PYR</td>
</tr>
</tbody>
</table>

*INH = isoniazid; RIF = rifampicin; PYR = pyrazinamide; ETH = ethambutol; STP = streptomycin*
Conclusion

Cutaneous tuberculosis can be difficult to diagnose, as cultures are often negative. Polymerase chain reaction may aid in the diagnosis although it should be interpreted in the light of the clinical and histological features. If in doubt, an empirical course of anti-tuberculous treatment may be required to confirm the diagnosis.

References