Tuberculide - A Clinical and Epidemiological Review

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ABSTRACT

Tuberculide is a rare cutaneous disorder but its recognition is important as it is a readily treatable disease. True tuberculide mainly consists of three main types, namely, papulonecrotic tuberculide, lichen scrofulosorum and erythema induratum of Bazin. While there is still much controversy about its relationship with tuberculosis, application of DNA technique has provided us with a more definite answer. In the following article, we first update the diagnostic criteria and classification of tuberculide. This is followed by a comprehensive review on the epidemiology of the tuberculides. Important clinical features of the tuberculides will be highlighted in the article. Finally, the modern development of polymerase chain reaction with its application in the study of tuberculide will be discussed.

Keywords: tuberculide, diagnostic criteria, classification, epidemiology, polymerase chain reaction

INTRODUCTION

Historical perspective

It was two hundred years ago since the first case of papulonecrotic tuberculide (PNT) was reported by Darier in 1896.[1] Later his student, Pautrier made the original observation that PNT was a skin disease associated with tuberculous infection.[2] Hebra in 1868 described a patient suffering from a perifollicular papular eruption over the trunk and he named it lichen scrofulosorum (LS).[3] Since then, there were so few reports of this condition in the literature that LS almost become an unrecognizable skin disease among the dermatologists. In 1861, Bazin reported that erythema induratum (EI), a chronic ulcerative condition involving both calves of middle aged women, as a cutaneous manifestation of tuberculosis[4] and this disease entity was referred as erythema induratum of Bazin (EIB) in the classical texts.[5]

PNT, LS and EIB belonged to tuberculides, a form of cutaneous eruption in which its aetiopathogenesis with tuberculosis still remained controversial as *Mycobacterium tuberculosis* can never be cultured in the tissues. Due to the inability to identify the causative pathogen in the lesion, eminent pathologist like Koch and other dermatologists in the nineteenth century, refuted the notion that tuberculides were true form of cutaneous tuberculosis. However, with the development of DNA amplification technique like polymerase chain reaction (PCR) and ligase chain reaction (LCR), some of these old concepts might be revised in the future.

An update on the diagnostic criteria of tuberculide

In the past, different authors had been using different criteria to diagnose tuberculide. This inevitably led to an erroneous estimation of the true incidence of the condition. In order to diagnose a true tuberculide, the skin eruption should satisfy all of the major criteria and most of the minor criteria as listed in table 1. For example, the condition lupus miliaris disseminatus faciei, alternatively known as acne agminata, had once been regarded as a form of tuberculide. The histology of this facial papular eruption showed very discrete tuberculoid granulomatous inflammation. However, we now know that acne agminata is classified under non-tuberculides. Firstly, most of the patients with this condition did not show a positive tuberculin test.

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Secondly, this facial eruption did not respond at all to systemic anti-tuberculous therapy but to oral tetracycline.

On the other hand, one should not apply these diagnostic criteria too stringently without elaboration. For instance, there are many conditions that may give rise to a tuberculous granulomatous infiltrate.[7] The tuberculin test may not always be discriminatory between active infection or previous exposure to tuberculosis, especially in areas where the prevalence of tuberculosis is high.[9] The tuberculin test may not be positive at all if the patient is immunosuppressed. Some cases of PNT may only show a partial, slow and insidious response to systemic anti-tuberculous therapy.[7] Finally, some reported cases of progression of PNT to lupus vuglaris[10] suggested that the failure to grow *M. tuberculosis* may be due to a lack of sensitivity of the tissue culture. Nonetheless, devising a clear and practical set of diagnostic criteria is the very first step to study the epidemiology, pathogenesis and natural history of tuberculide.

Classification of tuberculides

Table 2 is a recent update on the classification of tuberculides. PNT and LS are the only cutaneous conditions that are agreed by most of the dermatologists as true tuberculide. But with the recent application of PCR, as illustrated later in this article, we now know that there is a large number of cases of EI which are in fact associated with past tuberculous infection. Hence it is necessary to include some form of EI or better termed as EIB in honour of the original description by Bazin,[4] under the true tuberculide. On the other hand, however, there is a group of EI that even with the application of sophisticated technique like PCR, failed to provide sufficient proof that it is tuberculous in origin. These are termed nodular vasculitis-erythema induratum complex and classified under facultative tuberculide. Likewise, erythema nodosum (EN), a cutaneous vasculitis characterized by septal panniculitus is also classified as facultative tuberculides as only a small number of cases of EN are associated with tuberculosis. The non-tuberculides are conditions that definitely have no aetiopathogenetic relationship with tuberculous infection.

Epidemiology of tuberculides

Tuberculosis had been declining in most of the western countries but an upsurge of tuberculosis was

Table 1. Major and minor criteria for diagnosing tuberculides[6,7,8]

Major criteria	· histological evidence of tuberculous granulomatous inflammation on the skin biopsy of these lesions
	· no evidence of Mycobacterium bacilli identified in the routine culture and acid fast staining of these lesions, detailed investigations including CXR, gastric aspirate, early morning urine and guinea pig inoculation of lesions failed to locate the source of mycobacterium
	· usually strongly positive tuberculin test
	· good response to systemic anti-tuberculous therapy with almost complete resolution of the lesions without recurrence
Minor criteria	· patient is generally in good health and shows a high degree of immunity to tuberculosis
	· skin eruption is usually symmetrical
	· skin eruption is usually disseminated

Table 2. An update on the classification of tuberculides[7,11]

1. Obligate or true tuberculides	a) Papulonecrotic tuberculide
	b) Lichen scrofulosorum
	c) Erythema induratum of Bazin
2. Facultative tuberculides	a) Nodular vasculitis- erythema induratum complex
	b) Erythema nodosum
3. Non-tuberculides	a) Lupus miliaris disseminatus faciei
	b) Rosacea-like tuberculide
	c) Lichenoid tuberculide

seen in the late 1980s and early 1990s.[14] This increase in the notification of tuberculosis had been attributed to socioeconomic deprivation like increased poverty, overcrowding, refugee movements and the increased incidence of HIV infections.[14] The emergence of multiple drug resistant strains of *M. tuberculosis* had also been suggested to be a cause of the recent increase.[14] Cutaneous tuberculosis including tuberculide overall constitutes 0.15% of all the reported cases of tuberculosis and 1% of extra pulmonary tuberculosis.[6] Hence, although tuberculosis is a common disease, tuberculides and other cutaneous tuberculosis is a relatively rare disease.

Table 3 is a summary of all the major series of reported cases of tuberculides documented in the world literature. Since tuberculides are very rare diseases, there are very few well published reports on its epidemiology; most of these studies are from countries where tuberculosis are already very prevalent in the population. It is interesting to note that the incidence of PNT and EIB differed in different geographical locations and changed over time.

The incidence of PNT (n = 38) as reported by a large study by Visser and Heyl in South Africa almost doubled the incidence of EIB (n = 20) and PNT represented 61.3% while EIB represented 32% of all the reported cases of tuberculides.8 On the other hand, the prospective study of cutaneous tuberculosis by Yates and Ormerod in the United Kingdom showed a reverse of this frequency of distribution: only 10% of the tuberculides are PNT and nearly half are due to EIB.[12] This change in pattern can also be observed when one compared the data with the Hong Kong studies. Wong and colleagues reported a relative incidence of PNT of 56.8% and EIB of 43.2%.[13] However, this distribution reversed dramatically 15 years later as illustrated by the study of Chong and Lo which showed that EIB contributed 93.3% of all cases of reported tuberculides and only 4.7% were PNT.[9] In other words, EIB has replaced PNT as the commonest tuberculide in the region studied.

This change in the prevalence of PNT and EIB can be explained by the fact that true tuberculide is a disease that is greatly influenced by the economic status and affluence of the population. Places like South Africa and Hong Kong in the 1960s are characterized by poor housing, overcrowding living condition, lack of sanitation and a high influx of refugees from surrounding poor areas; all these are high risk factors for tuberculosis and likewise, we can observe a high incidence of true tuberculides like PNT. On the other hand, places like the United Kingdom and Hong Kong in the 1980s are much well developed with adequate housing, good social support and effective control programs of notifiable disease like tuberculosis. As a result, true tuberculides like PNT dropped to a very low level while facultative tuberculide form of EIB become relatively more important. The reported high incidence of EIB in some of these series as some authors suggested

Table 3. A summary of the major studies documented in the world literature in estimating the incidence and prevalence of tuberculides.[8,9,12,13]

	South Africa	United Kingdom	Hong Kong	Hong Kong
Place of study	Medunsa, South Africa	Blackburn District UK	Social Hygiene Service	Social Hygiene Service
Period of study (total years)	1981-1993 (12)	1981-1995 (15)	1962-1967 (5)	1983-1992 (10)
Population served (million)	0.75	0.27	2	4.5
Types of study	retrospective	prospective	retrospective	retrospective
Cutaneous tuberculosis/ cases	92	47	160	176
Tuberculides/ cases	62	10	37	150
PNT (%)	38 (61.3)	1 (10)	21 (56.8)	7 (4.7)
EIB (%)	20 (32.3)	5 (50)	16 (43.2)	140 (98.3)
LS (%)	3 (4.8)	0 (0)	0 (0)	3 (2.0)
EN (%)	0 (0)	3 (30)	0 (0)	0 (0)

may also be due to the fact that EI is a multifactorial disease and different dermatologists have been using different criteria in diagnosing the disease.[9]

The main demographical characteristics like age and sex of the tuberculides had remained fairly constant among the various studies. PNT, as shown by all these studies, is a disease mainly affecting the adolescent, young adult and occasionally children, with an age range of 2.5-35 (mean = 22.6). It shows a female predominance with a ratio of 2:1.[15] EIB is a disease affecting mostly middle aged women with an age range of 7-82 (mean = 34) and a very high female domination with a ratio of 4.4:1.[9] Unfortunately, there are too few well reported series on LS to make a significant epidemiological observation. The latest and largest series of report on LS is by Smith which reported 4 patients suffering from this condition.[16] The results suggested that LS affected patient with an age range of 18-66 and showed no sexual predilection.

Papulonecrotic tuberculide

PNT is a rare but true cutaneous form of tuberculosis. Some authors preferred the name "papulonecrotic tuberculosis" because it is generally agreed to be aetiologically related to tuberculosis.[17] PNT are more often seen in areas where tuberculosis infections are prevalent, such as, South Africa, India and South East Asia like Hong Kong. Cases of PNT had been reported as a result of *Mycobacterium bovis* infection[18] and post BCG vaccination.[19] It is a disease mainly affecting the adolescent and young adults, occasionally children. Jordaan reported a series of 8 children presented with PNT and showed that PNT in children, like its adult counterpart, showed a female predominance with a female to male ratio of 2:1. The median time of appearance of characteristic lesions before diagnosis is 4 weeks.[17]

PNT usually presents as asymptomatic, dusky red papules and papulopustules with a lesional size ranging from 1-5 mm. Some of these lesions may undergo necrosis and form crusted ulcers. The healed lesions may result in pigmentary changes and scarrings. PNT are classically distributed symmetrically over the extensor aspects of the skin of the upper and lower limbs. The trunk and the head and neck region are usually spared. PNT like lesions have been reported to occur in the ear lobes[17] and the shaft and glans of the penis.[10,13,20] As with the other form of tuberculides, patients with PNT are generally well and healthy, and only very occasionally showed evidence of tuberculous infection apart from the histopathology of the skin lesion. PNT had been described to progress to lupus vuglaris.[10] It had been reported to complicate a case of scrofuloderma in a health care worker.[21] PNT had also been reported to occur in the same patient suffering from EIB.[22] The diagnosis of PNT is usually based on clinical, histopathological feaures, positive tuberculin test and a good response to systemic anti-tuberculous therapy. Important clinical differential diagnoses of PNT include pityriasis lichenoides et varioliformis acuta, secondary syphilis, papular urticaria and reactive perforating collagenosis.

Lichen scrofulosorum

LS, though rare, like PNT is a definite clinical and pathological entity which showed an aetiological relationship with tuberculosis.[16] LS typically presents as asymptomatic, grouped, sometimes annular, perifollicular papules distributed over the trunk anteriorly or posteriorly. The lesion size is minute, usually of 0.5-3 mm in diameter. The color of the lesion is usually reddish brown or dark yellowish. LS are easily mistaken with lichen nitudus, keratosis spinulosa, lichenoid drug eruptions and rarely sarcoidosis. The characteristic histopathological features of LS can usually resolve the confusion. The histology usually shows superficial dermal granulomatous infiltrations surrounding hair follicles and sweat ducts. The infiltrate mainly consists of epitheloid and some Langhans giant cells. Like other tuberculides, tuberculous bacilli are not evident and tissue cultures are negative. Sarcoidosis is the main histological differential diagnosis. LS shows excellent response and complete remission with full course of systemic anti-tuberculose therapy. LS associated with tuberculous dactylitis has been reported.[23]

Erythema induratum

EI is a controversial disease entity. Its exact relationship with tuberculosis is still much debated. It is Bazin's original observation that EI is a disease associated with tuberculosis, hence the term erythema induratum of Bazin (EIB).[4] However, there are many cases of the so called EI are just cases of allergic nodular vasculitis. These cases failed to cultivate any tuberculous bacilli and also they settled even without full course of systemic anti-tuberculous therapy.

It is now believed that it is better to divide EI into two separate categories, that is, those which showed evidence of past tuberculous infection by culture or PCR as EIB; and those without such evidence as nodular vasculitis-erythema induratum complex.[11] PCR technique had shown clearly that some cases of EI was in fact associated with M. tuberculosis. Furthermore, it is important in separating the two conditions because not only the clinical management of the two conditions are different, for example, the institution of full term multiple systemic anti-tuberculous therapy in the former, but also the confusion in terminology would result in an erroneous estimation and report of the true incidence of true tuberculides.

EIB usually presents as a chronic, nodular, ulcerative eruption symmetrically distributed over the calf of the legs of middle aged, over-weight women. The histological feature is characterized by granulomatous vasculitis with lobular panniculitis. Clinical important differential diagnoses of EIB include erythema nodosum, allergic nodular vasculitis, bromoderma and iododerma. Some suggested that in cases of EIB, besides performing routine tissue culture and screenings tests like CXR, early morning urine and gastric aspirates to identify *M. tuberculosis*, PCR should be performed unless resources are not available.

Erythema nodosum (EN)

Erythema nodosum is not a true tuberculide. It represents an Arthus type tissue reaction pattern resulted from a number of causative agents. EN is a common disease but EN due to tuberculosis infection is rare and is more often seen in children.[8,9] Study by Chong and Lo suggested that only 2.33% of EN showed evidence of concomitant extracutaneous tuberculous infection.[9] Clinically, EN lesion must be differentiated from EIB and if in doubt, a full thickness skin biopsy including the adipose tissue of EN will show up the classical vasculitis with septal panniculitis.

The non-tuberculides

The conditions acne agminata, acne rosacea and lichenoid tuberculides[24] have, due to various reasons in the past, been regarded as tuberculides. They all have one thing in common that the histology of all these lesions showed tuberculoid granuloma. However, they have no relationship at all with tuberculous infection. Tissue culture almost certainly failed to grow *M. tuberculosis*. Tuberculin tests only show weakly positive or no reaction. All these conditions did not respond to systemic anti-tuberculous therapy. Some authors have suggested that lichenoid tuberculid as described by Ockuly and Montgomery may in fact be cutaneous sarcoidosis.[16,24]

Pathogenesis and immunohistochemistry of tuberculides

The exact pathogenesis of tuberculides is still largely unknown. By using monoclonal antibodies like UCHL-1 which binded specifically to T-cell receptor like CD45, immunohistochemistry had shown that T-lymphocytes and macrophages were the predominant cell types that were involved in the pathogenesis of tuberculides.[19] This suggested that delayed type IV hypersensitivity reaction is involved in the pathogenesis. However, as suggested by some authors, it is very likely that the initial process also involves a type III reaction in which the immuncompetent host produces antibodies which subsequently coats and opsonizes the invading tuberculous bacilli. These then inactivate the bacilli and travel through the blood stream to the small vessels of the skin especially the arms and the lower legs and initiate a hypersensitivity reaction.[10,15]

Treatment of tuberculides

The modern treatment of confirmed case of true tuberculide like PNT, LS and EIB are full course systemic multiple tuberculous drug therapy (MDT). The MDT should include, as a minimum, isonizaid at a daily dose of 5 mg/kg, rifampicin at a daily dose of 10 mg/kg, ethambutol at a daily dose of 20 mg/kg or pyrazinamide at a daily dose of 25 mg/kg.[12] The duration of the therapy should be 6-9 months.[12] Compliance to the regime is important and most of the cases of true tuberculides show good response with complete clearance of the lesions. For drug resistant mycobacteria, second line therapy like ethionamide, kanamycin, p-aminosalicylic acid and the quinolones should be used. For facultative tuberculide like nodular vascilitis-erythema induratum complex in which *M. tuberculous* cannot be identified, monotherapy with isoniazid 300 mg daily for 9-12 months give satisfactory results with complete remission of the lesion.[9] However, whether the response is due to the anti-tuberculous or anti-inflammatory action of the drug is unknown.[9]

Polymerase chain reaction (PCR)

One of the major advances recently in studying mycobacterium is the application of DNA amplification technique like PCR and LCR in identifying Mycobacterium bacilli in cutaneous tuberculosis including tuberculides. The advantage of PCR technique is that it can provide reliable, rapid and accurate results for the diagnosis of different form of cutaneous tuberculosis including the oligo- and pauci-bacillary form. The problem surrounding the diagnosis and the aetiopathogenesis of tuberculides is that the traditional culture technique of tuberculosis, though highly specific, has a relatively low sensitivity. The number of the bacilli in the tissue can be so small; as few as only one tuberculous bacillus, that culture is no longer an ideal method in evaluating the cause of the disease. On the other hand, PCR ,by copying part of the DNA sequence of the mycobacterium and magnifying it a billion times, can accurately detect even a few or a fragment of the bacterium after being inactivated by the immune mechanisms.

PCR has been shown to have a 75% positive predictive value (PPD) in identifying in the condition of lupus vuglaris while culture only yield a PPD of 57.1%.[25] Seckin also showed that in 11 cases of lupus vuglaris which are shown positive for Mycobacterium by PCR, only one case has been cultured positive.[26] Moreover, in his series, he identified 6 cases of PNT which were all PCR positive for *M. tuberculous* but were negative with traditional staining and culture methods.[26] Furthermore, the two cases of EIB that he revealed were culture-negative but PCR-positive for mycobacterium.[26] Similarly, Degitz had also been able to detect Mycobacterium DNA in 5 of his 7 cases of EI and 4 of his 6 patients with PNT. All his internal control of normal skin was PCR negative.[27] Finally, Victor and co-workers had also been successful in demonstrating the presence of DNA fragments specific for in 50% of his PNT cases.[28] By employing the PCR technique, Degitz concluded that despite the failure of culture to grow M. tuberculosis in most cases of tuberculides, the evidence suggested that the true tuberculides like PNT and EIB has a genuine aetiopatholoical relationship with M. tuberculosis and the so called tuberculides may better be regarded as forms of post primary tuberculosis.[27]

The problem of PCR has been its high degree of false positivity. This false positivity may be the result of a number of factors like the variability of the fixation time of the tissue, the type of tissue studied, the nuclease contents of the tissue, and tissue necrosis.[25] All these factors can greatly influence the detection rate of microbial DNA by PCR. Hence, it is extremely important to perform both internal positive and negative control when PCR method is used. In addition, all the details of the PCR methods including its primer set and techniques should be well documented and illustrated in the methodology of the study.

CONCLUSION

As modern western medicines are evidence and scientifically based, PCR has, no doubt, shown clearly that tuberculides are aetiologically and pathogenetically related to *M. tuberculosis*. Whenever resources are available, PCR should be performed in clinical suspected cases of cutaneous tuberculosis. DNA amplification technique will certainly remodel our understanding about cutaneous tuberculosis including tuberculides in the coming millennium.

Learning points:

Erythema induratum of Bazin is the most prevalent tuberculide in most of the developed countries. Early recognition of tuberculides is important so that effective, curative therapy can be offered to the patients.

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