

Cutaneous Tuberculosis – Where Children Are Placed**Ashish Kumar Jaiswal¹, Vidushi Jain²****¹TB Chest, Associate Professor, Vedantaa Institute of Medical Sciences, Saswand, Dahanu (Palghar) Maharashtra****²MD Dermatology, Associate Professor, Vedantaa Institute of Medical Sciences, Saswand, Dahanu (Palghar) Maharashtra****Received: 10-02-2023 / Revised: 19-03-2023 / Accepted: 30-04-2023****Corresponding author: Dr. Vidushi Jain****Conflict of interest: Nil****Abstract**

Cutaneous tuberculosis continues to be a significant medical problem even with the advent of highly effective antituberculous drugs. It constitutes about 1.5% of all extrapulmonary tuberculosis. The prevalence in children varies from 18 to 54% in India. There is no gender predilection and the infection occurs with increased frequency in 10-14 year age group. Intrafamilial source of TB has been observed very frequently. A concomitant TB lymphadenitis is most common while involvement of other Systemic organs like lung, bone and abdomen has also been served. Protective efficacy of BCG is debatable and not yet fully defined. Of all the clinical types, scrofuloderma (SFD) is the most commonly encountered variant followed by lupus vulgaris(LV) and tuberculosis verrucosa cutis(TBVC). Lichen scrofulosorum (LS) is generally found to be associated with systemic TB focus in about 72% of cases. The impact of HIV on childhood cutaneous TB seems to be minimal. Similar to adults, the diagnosis of cutaneous tuberculosis relies mainly on histopathology, culture on LJ medium or radiometric BACTEC 460 TB culture system and PCR. In addition Mantoux positivity and a positive therapeutic trial with anti-tubercular drugs may be a good pointer to tubercular infection. A thorough clinical evaluation and exhaustive investigations to pinpoint associated systemic focus is advocated as the latter has an impact on the duration of treatment. Cutaneous TB in children is treated as per the recommendations of therapy for extrapulmonary TB.

Keywords: Cutaneous tuberculosis, Children, India

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Introduction

Despite the availability of effective chemotherapy and implementation of strategic health programs, tuberculosis (TB) still remains a formidable infection globally and an economic burden for resource- constrained countries. In 2007, India ranked first in terms of total number of TB cases(2.0million) globally.[1] The persistent adverse social conditions, high rates of migration of infected people from areas of relatively high prevalence to low endemic areas, the co-existent human

immunodeficiency virus (HIV) epidemic and the emergence of multidrug-resistant (MDR) Mycobacterium tuberculosis have contributed to the resurgence of TB as a major public health problem.

Childhood TB represents 5–15% of all cases of TB. Similar to adults, pulmonary TB is most common, with extrapulmonary disease occurring in 20% of the children.[2] Cutaneous TB accounts for about 1.5% of extrapulmonary cases.[3]

Epidemiology

Cutaneous TB is caused by *M. tuberculosis* in a majority of cases and, rarely, by *M. bovis*. It accounts for 0.1–0.9% of the total dermatology outpatients in India.[3-5] The reported prevalence of cutaneous TB in children has varied in different studies depending on the geographical region. In older surveys from Hongkong, up to 50% of all cases of cutaneous TB were found in children, although now the overall incidence of the disease is very low in that country.[6,7] In India, the prevalence of childhood skin TB has been reported to be 18.7% of all cases of skin TB in Chandigarh, 20.4% in Varanasi, 24.41% in Chennai and higher prevalence ranging from 31.7% to 53.9% in recent case series from Delhi. [4,8-12] The difference in local prevalence of TB in certain parts of North India is suggested by a differential accumulation of cases over a period of

time. In a case series from Delhi, Vashisht et al. reported 75 children diagnosed over 18 months and Pandhi et al. Reported 68 children seen over just 15 months. [5,11] However, Kumar et al. from Chandigarh and Ramesh et al. from Delhi reported similar number of cases (75 and 63 cases) detected over longer periods of 25 years and 7 years, respectively. [4,10] Different upper limits for childhood case definition (ranging from <14 years to <19 years) in different studies might have also contributed to this statistic disparity.

Cutaneous TB affects the entire age spectrum in children. The incidence of disease in the 0–10 years age group has ranged widely from 12.8% in Delhi to 36.3% in Hongkong. [6,13] However, a majority of the cases are seen in children 10–14 years of age, as reported by Kumar et al., Pandhi et al.

Table 1: Major studies on cutaneous tuberculosis from India

	Ramesh et al.[10]	Kumar et al.[4]	Singalet al.[12]	Pandhi et al.[5]	Vashisht et al.[11]
Study location and year	Delhi, 1999	Chandigarh, 2000	Delhi, 2002	Delhi, 2004	Delhi, 2007
Study period	7 years	25 years	7 years	15 months	18 months
Sample size	63	75	160	68	103
Age group for inclusion (years)	≤15	≤16	≤14	≤14	<19
% age of total cutaneous TB cases	63/199 (31.7%)	75/402 (18.7%)	160/449 (35.6%)	68/142 (47.9%)	103/191 (53.9%)
Male:female ratio	0.91:1	0.74:1	1.1:1	0.7:1	0.98:1
Positive family history	19.0%	NM	30.0%	41.2%	32.0%
BCG vaccination (%)	57.2	50.0 ^c	66	41.2	51.4
Clinical types and main sites of involvement SFD	23 (36.5%) ^a , neck	40 (53.3%), neck	75 (46.9%), neck	30 (44.1%), neck	38 (36.9%), neck

LV TBVC	40 (63.5%) ^b , lower limbs-	30 (40.0%), face, lower limbs 3 (4.0%)	46 (28.8%), lower limbs, face 5 (3.1%)	15 (22.1%), face, lower limbs 3 (4.4%)	22 (21.3%), lower limbs 4 (3.9%)
Gumma	-	1 (1.3%)	3 (1.9%)	0	2 (1.9%)
LS	0	1 (1.3%)	27 (16.9%)	16 (23.5%)	34 (33.0%)
PNT	0	0	0	0	4 (3.9%)
Others	-	-	2 (1.3%) ^e	-	3 (2.9%) ^e
Multiple patterns	1	0	5	4	5
Systemic involvement	8 (12.7%)	16 (21.3%)	38 (23.7%)	26 (38.2%)	55 (53.4%)
Mantoux reactivity	62 (98.4%)	61 (85.9%) ^d	120 (75%)	66 (97.1%)	68 (66.0%)
Clinicohistolo gical conco dance	NM	48 (64.0%)	137 (85.6%)	54 (80.6%)	73 (70.9%)
AFB histology	3 (4.7%)	13 (17.3%)	9 (5.6%)	2 (2.9%)	17 (16.5%)
AFB positivity on cytology	NM	NM	3 (2.1%)	7 (10.3%)	19 (18.4%)
AFB culture positivity	4 (6.3%)	NM	NM	6 (8.8%)	11 (10.7%)
% age of patients completd treatment	38.1%	NM	71.8%	73.5%	84.5%

AFB: Acid-fast bacilli, BCG: Bacillus calmette guerin, LS: Lichen scrofulosorum, LV: Lupus vulgaris, NM: Not mentioned in study, PNT: Papulonecrotic tuberculid, SFD: Scrofuloderma, TBVC: Tuberculosis verrucosa cutis, ^aIncluded four patients with associated scrofulous gumma, ^bHypertrophic variant of LV was considered represented by TBVC, which was seen in 11 children, ^cBCG vaccination data available for 62 children only, of which 31 (50.0%) had been vaccinated, ^dMantoux reactivity data available in 71 children, of which 61 (85.9%) were Mantoux-positive, ^eErythema nodosum Singhal et al. [4,5,12] In most of the studies, both sexes were either equally affected or there was a marginal female preponderance, especially in cases of scrofuloderma (SFD). [4,5,10-12]

The duration between the onset of lesions and detection in the hospital has widely ranged from 2 months to up to 10 years. Kumar et al. reported that the time interval to seek medical attention was within 1 year of the disease onset in most of the cases, although a delay of more than 3 years was seen in a few cases. [4] Such children are more likely to present with widespread or disseminated disease and remain as potential reservoirs of infection.

The source of skin TB in a child is often a household contact with present or past history of TB. History of TB (most commonly pulmonary) in a parent or close household relative in Delhi was found in 12 of 63 patients (19%) by Ramesh et al., 32% by Vashisht et al. and as high as 41.2% by Pandhi et al. [5,10,11] Most of the patients in the Indian series belong to families of low

socioeconomic status with poor living conditions. Pandhi et al. reported that 69% of childhood cutaneous TB patients were residing in overcrowded dwellings. [5] Singal et al. have reported a case of widespread cutaneous TB with systemic involvement secondary to immunosuppression resulting from severe malnourishment in an Indian child. [14]

Cutaneous TB may remain localized to the skin alone, but frequently involves regional lymph nodes. Disease is considered to be disseminated if there is presence of generalized lymphadenopathy and/or involvement of other organ systems. [4] Compared to adults, children have a higher incidence of tuberculous lymphadenitis, seen in upto 29.2% of the cases. [11] Children are also more likely to have underlying systemic involvement compared to adults. Systemic involvement in children with skin TB in different case series has been reported to be present in 12.7–53.4% of the cases, with a higher incidence in cases with SFD. [4,5,10,11] Of the extracutaneous sites involved, pulmonary infection is most common, seen in up to 20% of the cases, bone infection in up to 10% and abdominal TB in 5.8% of the children. [11] Concomitant involvement of the skin, lungs and bones has also been reported in a few cases.

BCG Vaccination and Cutaneous Tuberculosis

At present, the role of BCG as a preventive measure against cutaneous TB is difficult to define. Protective efficacy of BCG vaccine in TB in various clinical trials has ranged from 0% to 80%. [15] In a meta-analysis, a high rate of 65–86% protection against tubercular meningitis and miliary disease was reported. [16] Zodpey et al. demonstrated BCG vaccination to be moderately effective in adults against skin TB, with an efficacy of 60.9%. [17] Kumar et al. reported that BCG-vaccinated children did not develop disseminated disease. [4] However, others found no significant differences between the vaccinated and the unvaccinated groups. [10,12] Protective efficacy of BCG has been reported to decrease with time interval since vaccination.

Clinical Types

There are various classification systems of cutaneous TB in vogue. However, to simplify the understanding of the different types of cutaneous TB in children, they may be classified as true TB and tuberculids. [18]

Depending on previous sensitisation, true TB may further be subdivided into primary or secondary types [Table 2].

Table 2: Clinical types of cutaneous tuberculosis

- | |
|---|
| <ol style="list-style-type: none"> 1. Cutaneous tuberculosis <ol style="list-style-type: none"> a. TB chancre b. Miliary TB c. Scrofuloderma d. Lupus vulgaris e. Tuberculosis verrucosa cutis f. Tubercular gumma (metastatic abscess) 2. Tuberculid <ol style="list-style-type: none"> a. Lichen scrofulosorum b. Papulonecrotic tuberculid c. Erythema induratum d. Erythema nodosum |
|---|

Scrofuloderma

SFD is the most common form of cutaneous

TB seen in children. [4,5,11,12] Vashisht et al. observed SFD in 36.9%, Singal et al. in 46.9% and Kumar et al. in 53.3% of the cases. [4,11,12] SFD arises due to direct extension of the infection from an underlying tuberculous focus into the skin. Lymph nodes are the most common foci, of which cervical node infection with SFD of the neck region is the most common site of involvement. [4,5,11,12] This may possibly be due to the prevalent habit of drinking unboiled or unpasteurized milk in many parts of the country, with subsequent infection of the cervical lymph nodes. [4] Other lymph nodes may also be involved, including inguinal, axillary, submandibular, supraclavicular and epitrochlear. [18] Primary infection of the bone, including spinal TB, is another source of SFD in childhood. Rarely, intestinal Koch's and hepatic TB may also lead to secondary cutaneous involvement. [5,19] Multifocal SFD is also known to occur in children. [14] SFD usually starts as

subcutaneous swellings or nodules, which rupture over a period of time to give rise to shallow ulcers with undermined edges [Figure1]. Formation of intermittently discharging sinus tracts occurs, which heal with characteristic puckered scarring. While biopsy from the periphery of the lesion may show granulomas suggestive of tubercular etiology, the histopathology is nonspecific in many cases. [4,5] Caseation necrosis, ulceration and abscess formation are commonly encountered. Vashisht et al. observed that, compared with other forms of skin TB, SFD showed granulomatous involvement of the entire dermis, with giant cells as the predominant cell infiltrate. [11] SFD lesions are more likely to show presence of acid-fast bacilli (AFB) from stained cytology smears or biopsy samples as well as positive cultures for mycobacteria compared with other types of cutaneous TB. [5,11] The tuberculin test is usually positive.



Figure 1: Scrofuloderma overlying the inguinal lymph nodes. Note: tubercular dactylitis of the right middle finger

Lupus vulgaris

Lupus vulgaris (LV) is the most common clinical type of cutaneous TB in adults, and the second most common type seen in children. [4,12] Ramesh et al. found it to be the most common form (63.5%) in their series. [10] It usually occurs in individuals

previously sensitized to tubercular infection. The typical lesion is a well-demarcated skin-colored to erythematous plaque that shows evidence of healing and scarring in one area and activity in another [Figure 2]. While Kumar et al. reported the face to be the most common site, overall,

LV is mostly seen in the lower half of the body, involving legs, knees, thighs, buttocks and feet. [4,5,10-12] This has been attributed to the prevalent local habit of children playing without clothing and defecating in the open. [10] Involvement of the upper limbs and trunk is also known to occur, and multifocal cases have also been reported. [4,10] While LV localized to the genitalia is rare in children, it often results in mutilation and severe disfigurement, especially of the vulva. [10] Contractures involving the knee, elbow and wrist and destruction of ear and nose [Figure 3] are other rare disabling sequelae of LV in children. [5,10] Many morphological variants have been described: classic plaque or keratotic type, hypertrophic, ulcerative, atrophic and planar. Of these, the keratotic type is the most common whereas ulcerative and atrophic forms are the least

common in children. [5,10,11] Other unusual presentations, e.g. lesions in sporotrichosis pattern, occurrence at the site of BCG vaccination and in the vicinity of SFD have been rarely reported. [4,11,18] Although regional lymphadenopathy is commonly encountered in LV, systemic involvement is seen less. often when compared with SFD. Histopathology of LV lesions reveals typical epithelioid granulomas in the upper dermis, with lymphocytes and Langhans giant cells in up to 80% of the cases, with the remainder showing nonspecific changes. [4,5,11] The hypertrophic form additionally shows the presence of epidermal hyperkeratosis, papillomatosis and acanthosis. Necrosis is usually not seen and fibrosis is evident in areas of healing and scarring. [11] AFB are scanty and difficult to detect by staining methods or mycobacterial culture. [18]



Figure 2: Erythematous, scaly plaque of lupus vulgaris with intervening atrophy and advancing margin on the left buttock

Tuberculosis Verrucosa Cutis

This form of the disease, also known as warty TB, occurs due to exogenous inoculation of tubercle bacilli in a previously sensitized individual with good immunity. Clinically, it presents as verrucous papules and plaques, with the surface showing fissures or clefts that may extrude pus and, often, perilesional erythema. It may be difficult to differentiate it from hypertrophic LV as well as verruca vulgaris or common warts. While

tuberculosis verrucosa cutis (TBVC) was once seen in 65.5% of the childhood cases from Hongkong, it is an uncommon form of the disease in Indian children. [6] Although Arya et al. have reported TBVC in 15% of their patients (3/20), most of the other series from India have reported it to contribute to <4.5% of all cases of pediatric skin TB. [4,5,11,20] Exposed body parts, in particular the lower limbs, are the most common site for warty TB in children, possibly due to inoculation by unnoticed trauma. In contrast to SFD and LV,

lymphadenopathy is not seen. Histology shows hypertrophic changes like pseudoepitheliomatous hyperplasia, the presence of acute infiltrate in the upper

dermis and characteristic tuberculoid granulomas in the mid dermis. [11] AFB are rarely demonstrated.



Figure 3: Mutilating lesion of lupus vulgaris over the nose in a young girl

Tuberculargumma

Tubercular gumma or metastatic abscess results from disseminated infection by the hematogenous route. Clinically, it presents as dermal or subcutaneous nodules that soften to form fluctuant nontender abscesses and later break down to form sinuses or undermined ulcers. It is commonly seen in malnourished or immune suppressed children. [17] This form has been infrequently reported in Indian children. [4,10-12,21] Presence of tubercles with widespread caseation necrosis and copious amounts of AFB is seen on histopathology.

Other Types of “True Cutaneous Tuberculosis”

Primary inoculation TB or tubercular chancre occurs uncommonly due to exogenous infection in previously unsensitized children or as noduloulcerative lesions secondary to BCG inoculation in infants. [22,23] Acute miliary TB caused by hematogenous dissemination of the organism with widespread internal involvement is also rarely seen in children, following exanthems or in disorders that predispose to

poor immune status, like anhidrotic ectodermal dysplasia. [24,25] Orificial TB manifesting as perianal tubercular ulcers has been reported in a 13-year-old boy from Tunisia. [26]

Tuberculids

A tuberculid is a cutaneous immunological reaction to the presence of occult TB in a patient with moderate to high immunity. The main features of tuberculid are the absence of organism in smears and negative mycobacterial culture, positive tuberculin test and rapid resolution of the lesions with antitubercular therapy. However, based on the detection of *M. tuberculosis* DNA by polymerase chain reaction (PCR), only lichen scrofulosorum (LS) may be considered to be true tuberculid, as PCR positivity has been observed in other tuberculids, i.e. papulonecrotic tuberculid and erythema induratum. [27]

Lichen Scrofulosorum

LS is an infrequently reported but fairly common tuberculid occurring in patients with a systemic focus of TB and good immunity to the tubercle bacilli. It presents as grouped or clustered follicular papules, most commonly present on the trunk

[Figure 4]. Earlier studies have reported a low prevalence of LS in children. Kumar et al. and Ramesh et al. did not report seeing any patients in their childhood series. [4,10] The low reporting of LS cases in earlier studies may be due to subtle and asymptomatic lesions getting missed by the patient as well as the physician and misdiagnosis as some other follicular disorder such as keratosis pilaris, lichen spinulosus, pityriasis rubra pilaris or lichen nitidus. [11] However, recent studies by Pandhi et al. and Vashisht et al. reported it to be the second most common pattern of cutaneous TB in children, occurring in 23.5% and 33% of the cases, respectively. [5,11] A high index of suspicion might have been responsible for the higher reporting in these studies. In the largest published series of LS by Singal et al., 84% of the 39 patients were children <15 years of age. [28] The reason for this may be a decrease in delayed hypersensitivity response with increasing age.

A systemic focus of TB is detected in a majority of LS cases, the most common being involvement of lymph nodes (cervical, mediastinal or hilar). [11] Singal et al. reported an associated focus of TB elsewhere in the body in 72% of the cases; 33% had tubercular lymphadenopathy while 28%, 8% and 15% had pulmonary TB, intracranial TB and other forms of cutaneous TB, respectively. [28] Fifteen percent had tubercular foci at multiple sites. Other foci detected in other studies include bones, joints and intestine or peritoneum. [11] Thus, a thorough systemic evaluation should be performed in all patients with confirmed or suspected LS. Apart from the trunk, LS may involve the axilla, groin, thighs, buttocks and arm. LS confined to the vulva, associated with cervical and inguinal tubercular lymphadenitis, has been reported in an 11-year-old girl. [29] Phlyctenular keratoconjunctivitis as a manifestation of immunological response to suspected TB antigen has also been reported with LS in a child with SFD/LV.

[30]

Histology from lesions shows superficial perifollicular epithelioid granulomas without any caseation. [11,28] AFB are not detected, mycobacterial cultures are negative from lesional biopsies and PCR is also negative. [28] Prompt and excellent response to antitubercular therapy is seen within 4–6 weeks, with complete clearance in 12 weeks, irrespective of the presence of tubercular focus elsewhere. [28]

Papulonecrotic Tuberculids

These lesions are characterized by symmetrically distributed firm and dusky red necrotizing papules present predominantly over the extremities that heal with varioliform scarring. Jordaan et al. reported eight children with papulonecrotic tuberculids (PNT), of which seven had associated pulmonary TB and three had phlyctenular conjunctivitis. [31] It has also been reported in children with active tubercular lymphadenitis and disseminated LV. [32,33] However, PNT has been infrequently reported in Indian children, with only four cases in the series by Vashisht et al. [11] Histology shows wedge-shaped necrosis with nonspecific perivascular infiltrates or tubercular granulomas surrounding the necrosis. [11] Leukocytoclastic vasculitis, a histological feature characteristically present in PNT lesions in adults, has been unequivocally reported in children. While Vashisht et al. and Ramdial and colleagues found vasculitis as a prominent feature in their cases, Jordaan et al. did not observe it any of their children with PNT. [11,31,34] Although AFB are not demonstrable in papulonecrotic skin lesions, *M. tuberculosis* DNA is frequently detected by PCR. [35] Jordaan et al. have suggested that in cases where *M. tuberculosis* DNA can be confirmed by PCR, the term “papulonecrotic tuberculosis” should be preferred over papulonecrotic tuberculid.” [31]



Figure 4: Erythematous, scaly and grouped lesions of lichen scrofulosorum over the back

Erythema induratum of Bazin (EIB)

This is another tuberculid characterized by subcutaneous nodules over the posterior legs, which break down into deep ulcers followed by crusting and finally heal with atrophic scarring. It is very uncommon in children, with only few cases reported till date and no childhood case from India. [36-38] Association with pulmonary TB is frequent and nodular episcleritis has been reported in a 6-year-old girl. [37,38] Biopsy shows lobular panniculitis with vasculitis and Mantoux test is strongly positive. *M. tuberculosis* DNA is detected by PCR in more than 50% of the cases. [39]

Erythema Nodosum

It is characterized by painful subcutaneous nodules mainly on the shins, and septal panniculitis without vasculitis on histology, may also be associated with TB, especially in India. However, children are rarely affected. Vashisht et al. reported only three cases out of 103 and Singal et al. reported only two cases out of 160 children with cutaneous TB. [11,12]

HIV and Cutaneous TB

Pulmonary TB and certain extrapulmonary forms of TB are more common and extensive in HIV-infected patients. Cutaneous TB, including tubercular ulcers, PNT and disseminated miliary forms may

be more severe in HIV-positives. [40] In various Indian series, none of the children with cutaneous TB tested positive for HIV by enzyme-linked immunosorbent assay. [5,10-12] In a series of 231 patients from South India (adults as well as children), only two tested positive. [9] Thus, larger studies are required to assess the impact of HIV seropositivity on cutaneous TB.

Diagnosis

The diagnosis of cutaneous TB is based on the characteristic clinical morphology of the lesions as well as laboratory tests. Common clinical differential diagnoses of skin TB include cutaneous leishmaniasis, leprosy, atypical mycobacterial infections, fungal infections like chromomycosis and sporotrichosis and sarcoidosis. Many of these conditions also show granulomas on histology and thus definitive diagnosis relies on the direct demonstration of tubercle AFB on stained smears or biopsies, isolation by culture or detection by PCR and related molecular techniques.

Histopathology

The hallmark of cutaneous TB histology is the presence of characteristic tubercular granulomas with epithelioid cells, Langhans giant cells and lymphocytes. However, characteristics such as the distribution of granulomas in the dermis, nature of cellular infiltrate, presence of

necrosis and certain specific epidermal changes aid in classifying and diagnosing the variants of skin TB, which have been discussed before (vide supra). But, the difficulty of histological interpretation in TB is well recognized as many other diseases can produce a tuberculoid granuloma. A clinic histological concordance was observed in 64–85.6% of the cases of childhood cutaneous TB. [5,11,12] Classical tubercular histology is seen more often in lesions of LV compared with SFD. Histopathology is especially useful for diagnosis of tuberculids where bacilli cannot be isolated by culture or demonstrated by AFB staining.

Mantoux Test

The Mantoux or tuberculin test is a good screening test to detect the presence or absence of tubercular infection. It is performed by injecting 0.1 ml (5TU) of the purified protein derivative (PPD) on the volar surface of the forearm using a 27-gauge needle and measuring the induration after 48–72 h. Induration of 10 mm or more is considered significant, but indicates infection and not necessarily the disease. False-positive results may occur due to exposure to environmental mycobacteria as well as within 1 year of BCG vaccination. False-negative reactions may also be seen in patients with disseminated infection like military TB or in immune suppressed states like severe malnutrition in children or HIV infection. Pandhi et al. reported 66 of 68 children (97.1%) with positive Mantoux test, with induration ranging from 10 to 32 mm. [5] Kumar et al. observed that of their children with cutaneous TB, 91.8% patients with localized disease had positive Mantoux test as against only 50% of the cases with disseminated disease. [4] Severe reactions resulting in vesiculation or ulceration have also been observed in children. [5,11] Tuberculin test is more commonly positive in tuberculids, as reported in all cases of LS by Singal et al. [28]

Demonstration of AFB

Direct demonstration of the organism in tissue smear or biopsy specimens by staining for AFB is one of the most important tests for diagnosis of skin TB in children. Compared with culture by the traditional Lowenstein–Jensen (L-J) medium, direct AFB staining is inferior due to lesser sensitivity but has the advantage of early availability of results. Vashisht et al. reported AFB positivity in 36.8% of the cases of SFD and 13.6% cases of LV. [11] In the same study, cytology smears showed 18.44% AFB positivity, with most of them being SFD. [11] Pandhi et al. additionally noticed that identification of AFB was higher (10.3%) in cytology smears from lymph nodes compared with detection on histological sections of skin biopsies (2.9%). [5] Authors suggested that culturing the organisms from cytology smears may be a good alternative in the future.

Culture

As for any other infectious disease, a positive culture for *M. tuberculosis* is considered to be the gold standard for the diagnosis of cutaneous TB. An additional use of culture is for testing drug susceptibility. Using the traditional L-J medium for culture, low rates of 8.8% and 10.7% positivity were reported by Pandhi et al. and Vashisht et al., respectively. [5,11] The possible reason for overall low isolation of *Mycobacteria* could be that the bacilli are destroyed, nonviable or highly attenuated. [41] For some unexplained reasons, the culture positivity has been higher in adult cases. Owing to the tedious procedure of traditional culture systems, the focus is shifting to the use of culture methods like the radiometric BACTEC 460 TB culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) that is more rapid than the conventional culture procedures. [42] This medium uses Middlebrook 7H12 broth medium containing 14 C-labeled palmitic

acid for the radiometric detection of mycobacterial growth. In a recent study, Aggarwal et al. reported the sensitivity of the BACTEC system to be much higher (62.8%) compared to the L-J medium (25.7%), with marked reduction in the mean detection time (17.3 vs. 39.4 days). [42] The combined isolation rate on both media was 74.3% (26/35), greater than that of either used separately. Similar results have been observed by Cutler et al., although their study involved <2% cutaneous TB cases. [43] The logical extrapolation of this principle would suggest that even in cutaneous TB, the “gold standard” for mycobacterial isolation would be a combination of both solid and liquid culture media.

Quanti FERON-TB Gold in-tube (QFT-IT)

This in vitro interferon-gamma-release assay is useful in the diagnosis of tubercular infection. Although it is considered to be superior to tuberculin skin testing owing to its higher specificity, the clinical experience with this test in the pediatric population is limited. [44] In fact, in a rural and predominantly BCG-vaccinated pediatric population in India, the tubercular skin test and QFT-IT assay were found to produce comparable results in the diagnosis of tubercular infection without any obvious advantage of the latter. [45] At present, the utility of this test is not well defined in cases of childhood cutaneous tuberculosis.

PCR

DNA amplification by PCR is another rapid, sensitive method that has been used to detect cutaneous TB in several studies, most commonly targeting the IS 6110 gene specific for the *M. tuberculosis* complex. However, PCR is a labor-intensive technique and is susceptible to several technical errors. It may provide false-positive results by carry-over contamination. False-negative results may be caused by degraded target DNA, the presence of PCR-inhibiting substances in

clinical samples or insufficient extraction of target DNA. [42] Moreover, it cannot be used to test drug susceptibility. Finally, the high cost of this technique becomes prohibitive for its use, especially in a resource-poor country like India.

Antitubercular Drug Trial (Therapeutic Trial)

The concept of therapeutic challenge as a valid diagnostic method in doubtful cases of cutaneous TB (where laboratory results are equivocal) has been corroborated in adults and can be extended to the pediatric population as well. [46,47] Four-drug antitubercular (ATT) therapy (consisting of isoniazid, rifampicin, pyrazinamide and ethambutol) is initiated and the clinical response is assessed in 4–6 weeks. Ramam et al. have suggested that 5 weeks appears to be an adequate duration of a therapeutic trial in patients suspected to have cutaneous TB. [48,49] If there is no significant response by 5 weeks, it is unlikely that further treatment may be beneficial. [49] In such a case, either the diagnosis should be reviewed or possibility of MDR TB should be considered. However, patients with tuberculids and those with minimally active disease may take longer than 5 weeks to respond, and thus it may be worthwhile to prolong the therapeutic trial in such cases before considering alternative diagnoses. [49]

Systemic Screening for Tubercular Focus

In all children, clinical assessment of lymph nodes, pulmonary and gastrointestinal system, nervous system, eyes and musculoskeletal system should be performed. Fine-needle aspiration cytology should be performed from the enlarged lymphnodes, and a part of the aspirate should be used for the culture of *M. tuberculosis*. Roentgenogram of chest and computed tomography (CT) scan (if required) should be performed and the sputum should be sent for AFB and mycobacterial culture. Because children

have difficulty in producing sputum, it may be induced by saline nebulization. Children tend to swallow the sputum, and this can be retrieved as the gastric aspirate, which may be stained for AFB. Ultrasonographic assessment should be performed to screen for abdominal and pelvic TB. In select cases, imaging studies of the brain using CT scan or magnetic resonance imaging (MRI) may reveal intracranial tuberculoma. Assessment of cerebrospinal fluid is required only when tubercular meningitis is suspected. X-rays of the joints and bones suspected with tubercular osteomyelitis or arthritis and biochemical and microbiological evaluation of the joint aspirate may be performed. MRI spine is required to diagnose Pott's spine in cases with paravertebral cold abscesses.

Treatment

Cutaneous TB is treated as per the recommendations of therapy for extrapulmonary TB. Apart from the investigations to establish the diagnosis of cutaneous TB, HIV testing should be carried out in all patients with confirmed or suspected TB because their HIV status makes a difference to their antitubercular treatment. [50] As per the latest recommendations (2009) of the World Health Organization (WHO), cutaneous TB in HIV-negative individuals (adults as well as children) should be treated by directly observed treatment short course (DOTS) chemotherapy consisting of four drugs, isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given for 2 months (intensive phase), followed by isoniazid and rifampicin given for the next 4 months (continuation phase). [50] Fixed-dose combinations (FDCs) should preferably be used. The drugs may be administered daily or three times weekly. The WHO recommends that daily dosing throughout the duration of therapy (2HRZE/4HR) is optimal for all newly diagnosed patients with TB. Alternatively, daily intensive phase followed by three-times weekly continuation phase [2HRZE/4(HR)3] or

three-times weekly dosing throughout therapy [2(HRZE)3/4(HR)3] may also be used provided that every dose is directly observed. TB patients with known positive HIV status or living in an HIV-prevalent setting should receive daily doses of antitubercular drugs, at least during the intensive phase. [50] For the continuation phase, the optimal dosing frequency for such patients is also daily, although the three-times weekly dosing is an acceptable alternative.

In view of the growing evidence that the use of ethambutol is safe in young children, the WHO recommends that similar to adults, this drug should be used in all pediatric cases, irrespective of the age. [51] In a case of cutaneous TB where some systemic focus is detected, the corresponding disease categorization and recommendations should guide the choice of drugs and duration of therapy.

Adverse events caused by anti-TB drugs are much less common in children than in adults. [52] The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Because asymptomatic elevation of serum liver enzymes (less than five- times normal) is not an indication to stop treatment, they should not be monitored routinely. However, clinical signs such as liver tenderness, hepatomegaly or jaundice should prompt immediate stoppage of all potentially hepatotoxic drugs, assessment of serum liver enzyme levels and the patients should be screened for other causes of hepatitis. [52] No attempt should be made to reintroduce these drugs until liver functions have normalized. An expert should be involved in the further management of such cases. Isoniazid may cause symptomatic pyridoxine deficiency, especially in severely malnourished children and HIV-infected children on highly active antiretroviral therapy. Supplemental pyridoxine (5–10 mg/day) is recommended in malnourished children,

HIV-infected children, breastfeeding infants and pregnant adolescents. [52]

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