Review Article

Tuberculids: A Narrative Review

Abstract

Tuberculids are a group of dermatoses with tuberculoid histology and the absence of tubercle bacilli. They are considered to be hypersensitivity reactions to circulating *Mycobacterium tuberculosis (M. tb)* or its antigens in individuals with good immunity. The objective of the review is to provide a detailed literature review of all available articles on tuberculids in the past 10 years and provide an update on epidemiology, etiopathogenetic mechanisms, clinical manifestations, and treatment. A search was performed on PubMed using the keywords lichen scrofulosorum, papulonecrotic tuberculid, erythema induratum, and erythema nodosum tuberculosis for all articles, with no restrictions on age, gender, or nationalities. An update on tuberculids, including some new concepts in pathogenesis, atypical presentations, new investigative modalities, and treatments are reviewed.

Keywords: *Erythema induratum, erythema nodosum, lichen scrofulosorum, papulonecrotic tuberculid, tuberculids*

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Introduction

Tuberculids are a manifestation of cutaneous tuberculosis (TB), resulting from delayed hypersensitivity reactions to *Mycobacterium tuberculosis (M. tb)* or mycobacterial antigens in individuals with strong cell-mediated immunity. The diagnostic criteria include tuberculoid granuloma on histopathology, strongly positive Mantoux test, absence of *M. tb* in smear and culture, and resolution of skin lesions with antituberculosis therapy (ATT).

Materials and Methods

In January 2022, an extensive review of the published literature of the past 10 years using the PubMed database was conducted using the following keywords: lichen scrofulosorum, papulonecrotic tuberculid, erythema induratum, and erythema nodosum tuberculosis. Two hundred and thirty five articles were retrieved, which were then manually screened for pertinent articles regarding any update on etiopathogenesis, clinical presentations, associations, investigative modalities, and treatments. Studies were selected based on titles and abstracts and were then read in full.

Epidemiology

The prevalence of tuberculids among cutaneous TB varies from 4% to as high as 44.2% across various parts of the world.[1-4] Whereas erythema induratum of Bazin is reported as the most common tuberculid in many parts of the world,[3-5] studies from India report lichen scrofulosorum as the most common.[2,6]

Erythema induratum of Bazin has been typically known to affect young to middle-aged women. In a study of 22 patients of erythema induratum of Bazin, 90.9% were women, the mean age being 57.2 ± 12.9 years. The lesions were located in the lower extremity in all patients and in the upper extremity in 31.8%.[7]

Lichen scrofulosorum is known to be common in children. In a study of 221 patients of lichen scrofulosorum, 156 (70.5%) were children. The trunk was the most common site involved (98.6%), followed by the lower limb (25.33%), upper limb (15.83%), face (5%), and external genitalia (3.6%).[8]

Classification

The clinical classification of tuberculids is given in Table 1.

Etiology

In lichen scrofulosorum and papulonecrotic tuberculids, *M. tb* is the consistently reported causative organism, hence termed

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Table 1: Clinical classification of tuberculids	
True tuberculids	
Micropapular	Lichen scrofulosorum
Papular	Papulonecrotic tuberculid
Facultative tuberculids	
Nodular	Erythema induratum, erythema nodosum

as true tuberculids. Erythema nodosum and erythema induratum can have a variety of etiological factors, of which one is *M. tb*, hence termed as facultative tuberculids.

Rare causes of lichen scrofulosorum include *Mycobacterium szulgai*, *Mycobacterium avium-intracellulare* complex, *Mycobacterium leprae*, *Mycobacterium bovis*, or the bacillus Calmette–Guerin (BCG) vaccination and purified protein derivative used in Mantoux testing.[9-13]

Similarly, papulonecrotic tuberculids have been rarely known to occur secondary to *Mycobacterium kansasii*, *Mycobacterium avium-intracellulare* complex, BCG vaccination, and Mantoux testing.[14-17] There have been few case reports of the occurrence of papulonecrotic tuberculid in HIV-positive patients with variable CD4 counts and viral loads. This association is interesting as tuberculids characteristically occur in patients with good immunity. One plausible explanation suggested by Farrell *et al*. is that it could be related to immune dysregulation and paradoxical activation of immune responses.[18]

Erythema induratum has been reported in association with tubercular causes including *Mycobacterium chelonei* and BCG vaccination as well as non-tubercular causes including infections such as chronic hepatitis C, *Nocardia, Pseudomonas,* and *Fusarium;* diseases such as Takayasu arteritis, and Crohn's disease; and drugs such as propylthiouracil, TNF alpha inhibitors, BRAF and MEK inhibitors.[19-26] It is now recommended to use the term "Erythema induratum of Bazin" when the association with TB is proven and "nodular vasculitis" for non-tuberculous causes.

Erythema nodosum can result from a wide array of conditions including bacterial, viral, fungal, and protozoal infections, drugs, malignancies, and autoimmune diseases.

Pathogenesis

The consensus is that tuberculids are immunological reactions to degenerated dead bacilli or antigenic fractions of *Mycobacterium* rather than true infection. This process occurs in patients with good immunity, as evidenced by medium to strong tuberculin sensitivity in most patients. Evidence of Mantoux test positivity was observed in 79% to 83.2% of cases in recent studies.[5,8] Rare cases with negative tuberculin tests could be due to temporal variability in the immune status of the patient. Hematogenous dissemination of mycobacteria occurs from an active internal tuberculous infection, which is followed by a type III hypersensitivity response. The continuous formation of antigen–antibody complexes then leads to a type IV hypersensitivity reaction, resulting in granuloma formation. The reaction pattern that occurs is highly individualized and unpredictable, and why one individual develops a certain type of tuberculid, and why most of the others do not develop any, is not known.

There are reports of tuberculids occurring after the start of anti-tubercular treatment, probably due to inflammatory response that may follow the treatment of a multibacillary infection.[27]

There has been a new and interesting observation regarding a possible sexual route of tuberculid of the penis from reproductive tract TB of the partner. *Mycobacteria* could be inoculated directly onto the glans penis during sexual activity as it is the most common site to be microtraumatized during sexual contact, and inoculation is easier than into the more keratinized epithelium of the shaft.[28,29]

Tuberculids have also been linked with immune activation of Kawasaki disease in a case report of two infants in Japan, where the infants developed papulonecrotic tuberculid and lichen scrofulosorum during the convalescent phase of Kawasaki disease.[30]

Clinical Features Including Atypical Manifestations

Micropapular: Lichen scrofulosorum

Lichen scrofulosorum presents as multiple, flat-topped, follicular and perifollicular, skin-colored, lichenoid, or erythematous asymptomatic usually grouped papules [Figure 1]. Usually, generalized involvement over the trunk or proximal extremities including the buttocks is common, but localized forms involving the face, genitals, or palmoplantar area can also be seen.[31-33] The surface of the lesions may show fine scaling or horny spines. The lesions resolve in about 2 weeks, but crops may come and go over several months. Systemic symptoms such as fever, weight loss, and malaise may be present.

An underlying focus of infection can be detected in 60–70% of cases.[8] The most frequent foci are lymph nodes (cervical, hilar, axillary, or mediastinal) and lungs, but other forms such as generalized lymphadenopathy, miliary TB, tuberculomas in the central nervous system, bone TB, and more recently, phlyctenular conjunctivitis and tonsillar TB have been rarely seen.[33-36]

Other types of cutaneous TB, such as scrofuloderma, lupus vulgaris, TB gumma, and TB verrucosa cutis,[37,38] as well as other tuberculids such as papulonecrotic tuberculids, erythema induratum can present along with lichen scrofulosorum.[39,40] Notably, transformation from papulonecrotic tuberculids to lichen scrofulosorum has been seen.[41]

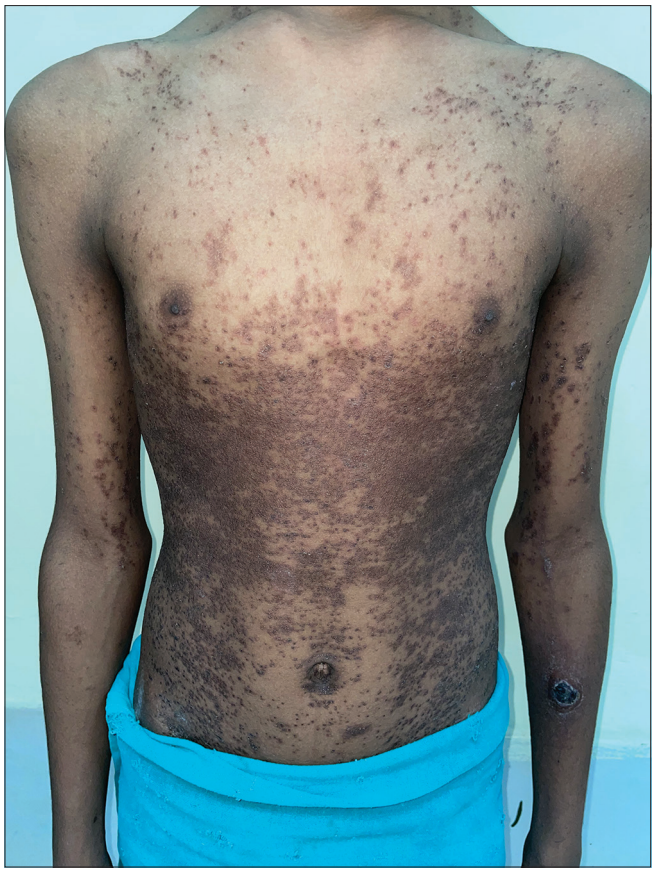

Figure 1: Closely grouped erythematous to hyperpigmented plaques with few discrete papules

Papular: Papulonecrotic tuberculid

Papulonecrotic tuberculids present as recurrent crops of symmetrically distributed firm and dusky-red papules with central ulceration, which heal with atrophic varioliform scarring. They are commonly seen over perniotic areas such as the ears, acral parts of limbs, and extensors of lower limbs but can also occur on the lower abdomen, trunk, buttocks, and scalp. Localized forms mainly involve the genitalia, especially the glans penis [Figure 2].[42]

Usually, an underlying focus of infection is found in 38–75% of cases.[43] Lymph nodes are the most common primary site, followed by the lungs, bones, and rarely genitourinary, nasopharyngeal, and renal tracts.

Among other types of cutaneous TB, it has coexisted with lupus vulgaris, scrofuloderma and tubercular gummas, and other tuberculids.[27,40,44,45]

Nodular: Erythema induratum of Bazin and Erythema nodosum

Erythema induratum of Bazin affects young to middle-aged women but may rarely be seen in children.[46] It presents as bilateral, tender, erythematous nodules or subcutaneous plaques involving the flexor aspect of thighs and legs and uncommonly on upper limbs, trunk, and buttocks.[47,48] However, unilateral presentations have also been reported.[49] They usually ulcerate centrally and heal with atrophic, hyperpigmented scarring [Figure 3]. The disease runs a chronic course with recurrent lesions.

Figure 2: Erythematous papules over glans penis

Underlying active TB is not seen commonly, but previously treated infection has been reported in as many as 11–31% of patients.[47,48]

Coexistence with other forms of cutaneous TB including scrofuloderma and tuberculids (lichen scrofulosorum, papulonecrotic tuberculid) is rare but known.[39,45,50]

Erythema nodosum presents as recurrent crops of tender, erythematous, subcutaneous nodules on the extensor aspect of extremities which subsides in 3–7 days, leaving behind hyperpigmentation [Figure 4]. Ulceration and atrophic scarring as seen in erythema induratum of Bazin are distinctly absent.

Erythema nodosum is seen worldwide and is mostly idiopathic (55%); in children, frequent association with streptococcal infections are seen.[51] TB is an important cause in areas where TB is endemic and must be excluded in all cases. In the majority of the cases, a focus of infection may not always be detected after a detailed workup. Some authors have even justified a therapeutic trial of anti-tubercular therapy in such cases with a strongly positive Mantoux test (>20 mm) and subsequent follow-up for recurrences.[52] Globally, however, the incidence of TB has decreased. In a study of 24 children with erythema nodosum from Israel, no underlying focus of TB was detected in any.[53]

Atypical Presentations of Tuberculids

Table 2 lists the atypical presentations of various types of tuberculids.

Discoid or annular lichen scrofulosorum: Lichenoid grouping results in the formation of rough discoid plaques that tend to coalesce.[54]

Psoriasiform lichen scrofulosorum: Extensive inflammatory plaques with fine, adherent scales resembling psoriasis even exhibiting Koebner's phenomenon have been reported.[55,56]

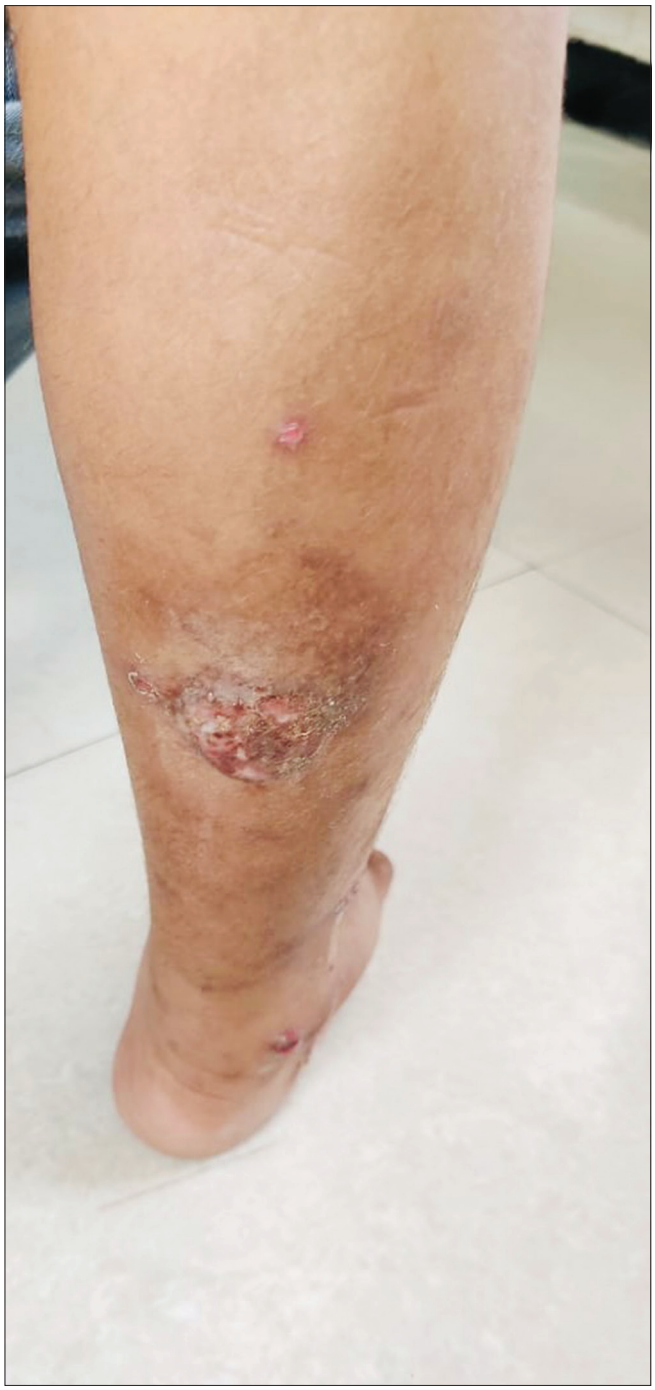

Figure 3: Ulcerated plaque over posterior right leg with atrophic scarring at places

Granuloma annulare-like lichen scrofulosorum: Arcuate, yellow-brownish plaques with beaded morphology have been seen.[57]

Lichen planus-like lichen scrofulosorum: Multiple, itchy, flat-topped papular lesions having polygonal shapes and shiny surfaces with sharply defined erythema have been reported.[58]

Micropustular lichen scrofulosorum: There is a case report of acne-like lesions of lichen scrofulosorum on the face and psoriasiform plaques studded with pustules.[59,60]

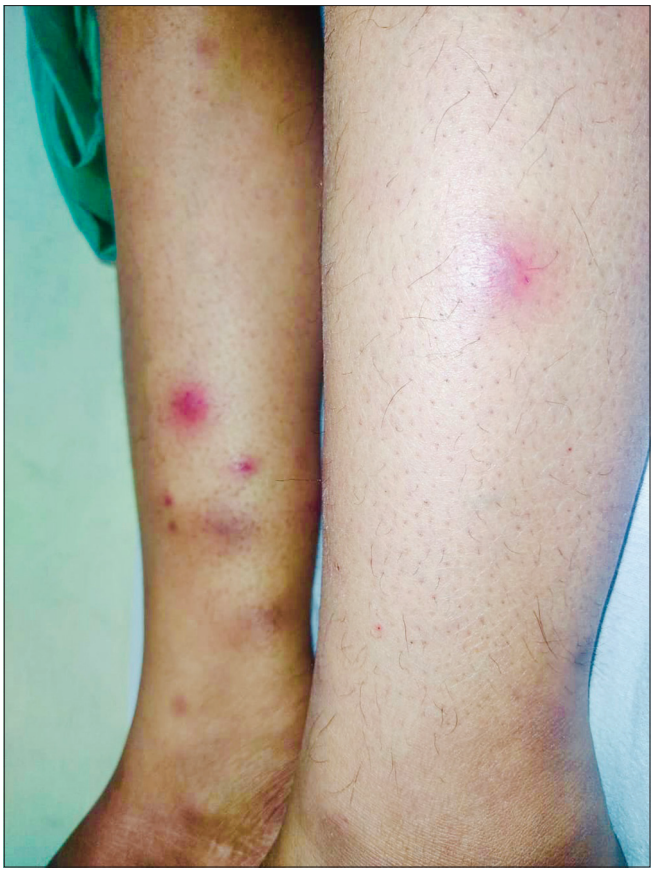

Figure 4: Erythematous, tender nodules over lower limbs

Table 2: Atypical presentations of various types of tuberculids

Lichen scrofulosorum	Discoid or annular lesions
	Psoriasiform lesions
	Granuloma annulare-like lesions
	Lichen planus-like lesions
	Micropustular lesions
Papulonecrotic tuberculid	Molluscum-like lesions
	Perforating granuloma annulare-like lesions
	Pityriasis lichenoides chronica-like lesions
	Papulonecrotic tuberculid with systemic features
Erythema induratum	Ecthyma gangrenosum-like lesions
	Disseminated lesions
Verrucous tuberculid	
Nodular granulomatous phlebitis	
Nodular tuberculid	
Tuberculous mastitis	
Koebnerization	

Molluscum-like papulonecrotic tuberculids: Papulonecrotic tuberculids can present as pink, umbilicated, and molluscum-like papules.[61]

Perforating granuloma annulare-like papulonecrotic tuberculids: Erythematous umbilicated papules centered by

a small crust and with discrete perilesional desquamation have been described.[62]

Pityriasis lichenoides chronica-like papulonecrotic tuberculids.[63]

Papulonecrotic tuberculids associated with ophthalmological complications: Uveitis and optic neuritis have been described as a part of the immune-mediated reaction in association with papulonecrotic tuberculids.[64,65]

Papulonecrotic tuberculids associated with Poncet disease: Poncet disease is a rare, paucibacillary manifestation of TB having an immune-mediated, inflammatory, non-erosive, and non-deforming asymmetric oligoarthritis. Both papulonecrotic tuberculids and Poncet disease were reported in a patient, both being temporally related and resolving with ATT.[66]

Ecthyma gangrenosum-like erythema induratum: Multiple necrotic ulcers with black eschars over both legs were seen in an immunocompromised adult.[67]

Disseminated erythema induratum: Disseminated lesions of erythema induratum have been rarely reported.[68]

Verrucous tuberculids: It presents with follicular and perifollicular verrucous papules, nodules, and plaques on the face, earlobes, and extremities. Histopathology revealed parakeratotic follicular plug invaginating into the dermis with multiple caseating epithelioid cell granulomas.[69]

Nodular granulomatous phlebitis: Considered to be the fourth type of tuberculids by some authors, it is characterized by subcutaneous nodules along the course of veins of the legs, which on biopsy show epithelioid cell granulomas and Langhans giant cells in the walls of cutaneous veins.[70,71]

Nodular tuberculid (NT): It is another entity first described by Jordaan and colleagues presenting as 1 to 2 cm red or blue non-ulcerating nodules, usually of the lower limbs, with granulomatous vasculitis at the dermal-subcutaneous junction. In this, the pathology is found at the dermal-subcutaneous junction, in contrast to the superficial dermis in papulonecrotic tuberculids and subcutaneous fat in erythema induratum.[72]

Tuberculous mastitis: It is considered to be a form of NT affecting the breast tissue. Unilateral ulcerative plaques, nodules, abscesses, and occasionally sinuses are seen in young female patients usually with a positive contact history of TB. On histology, granulomas are seen with fat necrosis.[73]

Koebnerization: It has been reported in lichen scrofulosorum, papulonecrotic tuberculids, and erythema induratum. The postulated pathogenic factors include immunologic, vascular, dermal, enzymatic, inhibitory, neural, genetic, and hormonal influence.[74-76]

Differential Diagnosis

Lichen scrofulosorum: Lichen nitidus, lichen spinulosus, keratosis pilaris, lichenoid sarcoidosis, and pityriasis rubra pilaris.

Papulonecrotic tuberculid: Pityriasis lichenoides et varioliformis acuta, secondary syphilis, necrotizing leukocytoclastic vasculitis, and perforating dermatosis.

Erythema induratum: Polyarteritis nodosa, lupus profundus, subcutaneous sarcoidosis, cutaneous lymphoma (subcutaneous panniculitis-like T-cell lymphoma).

Investigations

1. Mantoux: Tuberculin positivity is a part of the diagnostic criteria of tuberculids. A rare case of lichen scrofulosorum with a negative test attributed to malnutrition has been documented.[54]
2. Interferon-γ releasing assay (IGRA): It was introduced as a promising tool in the diagnosis of latent TB having several advantages over the tuberculin skin test including higher specificity and no influence from past BCG exposure. Its use has been evaluated in patients with erythema induratum, which may not have a tubercular cause. A retrospective study evaluating 22 patients of erythema induratum of Bazin demonstrated a positive response to IGRA in all cases (100%), and the authors suggested that if erythema induratum of Bazin is clinicopathologically suspected, IGRA should be performed due to its excellent diagnostic performance.[48,77] However, the World Health Organization discourages its use in low- and middle-income countries.
3. Dermoscopy: Dermoscopy of two pediatric cases of lichen scrofulosorum showed pale round monomorphic grouped perifollicular dots with a central brown follicular plug and marginal rim of fine white scaling [Figure 5].[78] More studies are needed to document the dermoscopic features of various types of tuberculids and whether this tool can be used in accurately differentiating tuberculids from other conditions.
4. Histopathology: Table 3 describes the histopathological features of each type which are characteristic and help in differentiating it from other conditions.
5. Polymerase chain reaction (PCR): Previously, many studies have demonstrated PCR positivity in the biopsy specimens of tuberculids. A recent study evaluated the use of nested PCR targeting the IS6110 insertion sequence of *M. tb* to improve the *M. tb* detection rate in blood samples of 14 patients of erythema nodosum or erythema induratum of Bazin. Eleven (78.6%) patients tested positive, but the difference between the outcomes of the QuantiFERON and the IS6110-nested PCR tests was not statistically significant.[85] More studies are

Table 3: Histopathological features of various types of tuberculids

Lichen scrofulosorum	Dermis shows perifollicular and perieccrine granuloma composed of epithelioid histiocytes, Langhans-type multinucleated giant cells, and lymphocytes at the periphery. In some cases, granulomas appear free in the dermis and are not related to adnexal structures.
	Superficial and deep perivascular lymphocytic inflammatory infiltrate is usually appreciable [Figure 6].
	Bacilli are not demonstrable with acid-fast bacilli stains nor can be cultured, but polymerase chain reaction (PCR) has shown positivity in some cases.[79]
Papulonecrotic tuberculid	Dermis shows a wedge-shaped infarct with central necrosis surrounded by palisading of typical tubercular granulomas.
	Inflammation is prominent in the superficial to deep dermis.
	Lymphohistiocytic vasculitis with fibrinoid necrosis and thrombotic occlusion is seen. However, leukocytoclastic vasculitis (LCV) has also been found in as high as three-quarters of cases in some studies.[80]
	Bacilli are not demonstrable, but PCR may show positivity as in lichen scrofulosorum with rates varying from 0 to 80%.[81,82]
Erythema induratum	Subcutis shows lobular or septo-lobular panniculitis with vasculitis [Figure 7].
	Large areas of caseous necrosis can be seen surrounded by poorly formed palisading and lipophilic granulomas due to the engulfment of lipid released by necrosed adipocytes.
	A diagnostic criterion has been proposed and three out of four of the following should be present: (1) lobular panniculitis, (2) fat necrosis, (3) small or large vessel vasculitis, and (4) granulomas. In a study of 101 biopsy specimens from 86 patients to establish whether or not vasculitis is a histopathologic requirement to establish the diagnosis of erythema induratum of Bazin, vasculitis was evident in 91 cases (90.09%). However, it was concluded that in some cases with all clinicopathologic features of erythema induratum of Bazin, vasculitis could not be demonstrated with serial sections throughout the specimen, and hence, it should be not considered as a sine qua non for the histopathologic diagnosis of erythema induratum of Bazin.[83]
	Acid-fast bacillus (AFB) is not demonstrable. Exceptionally, a single case report has demonstrated positivity in lesions of erythema induratum of Bazin and sites of Mantoux testing; the authors did not mention the reason for AFB positivity.[76]
Erythema nodosum	Subcutis shows septal panniculitis without vasculitis.
	Connective tissue septa of subcutis appear thickened due to edema and infiltration by inflammatory cells, mainly lymphocytes which may extend to surround the adipocytes [Figure 8].
	In contrast to lobular panniculitis, necrosis of adipocytes in the fat lobule is never seen.
	Late stages may show septal fibrosis and periseptal granulation tissue.
Tuberculid with atypical histopathological features	Recently, lichenoid granulomatous dermatitis (LGD) with a band-like lymphocytic infiltrate, typical of lichenoid dermatitis, combined with dermal histiocytes and granulomatous inflammation has been described as a tuberculid.[84]

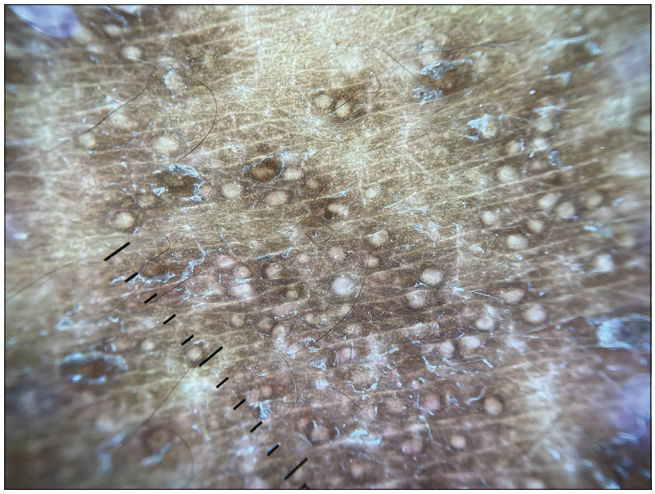

Figure 5: Dermoscopy showing a central structureless area surrounded by brown hyperpigmentation and fine white scaling at places [Dermlite DL4, non-polarized, 10×]

needed to establish the efficacy and usefulness of these PCR-based blood tests in diagnosing underlying TB in suspected tuberculid cases.

Treatment

Despite the presence of strong tuberculin positivity and characteristic clinical and histopathological features of each subtype of tuberculid, establishing a diagnosis of tuberculids beyond any doubt may not be possible in every case. In developing countries such as India, a modification of the criteria recommended for cutaneous TB[52] may be used as a guideline:

- Patients have characteristic histopathological features of true tuberculids.
- Patients have strong tuberculin positivity along with a highly suggestive clinical picture of true tuberculids even though histopathological features are equivocal.

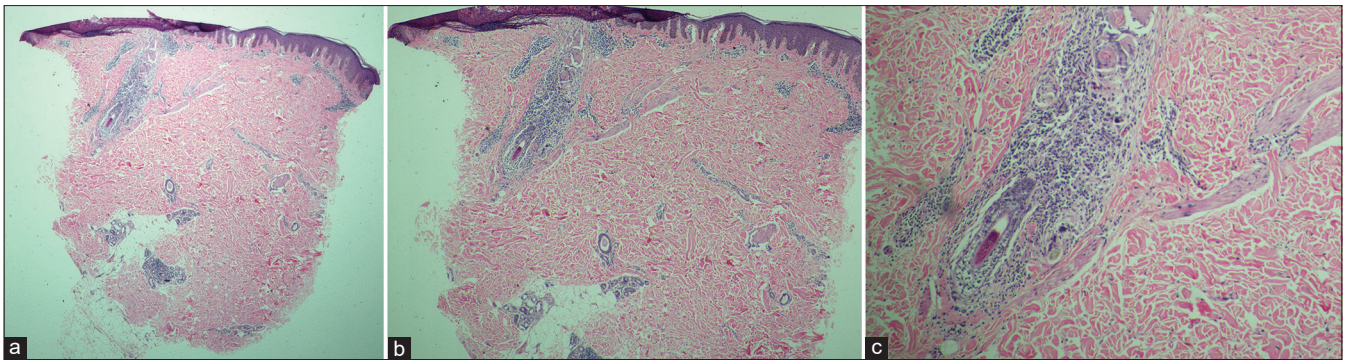

Figure 6: (a-c) Dense perifollicular infiltration of lymphohistiocytes characteristic of lichen scrofulosorum [H and E ×20, ×40, and ×100, respectively]

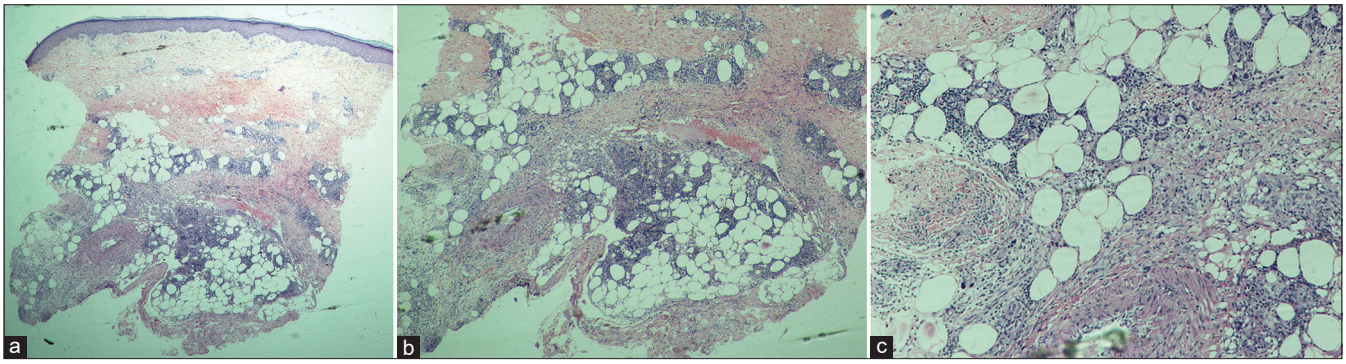

Figure 7: (a-c) Lobular panniculitis with infiltration of lymphohistiocytes and Langhans giant cells in erythema induratum [H and E ×20, ×40, and ×100, respectively]

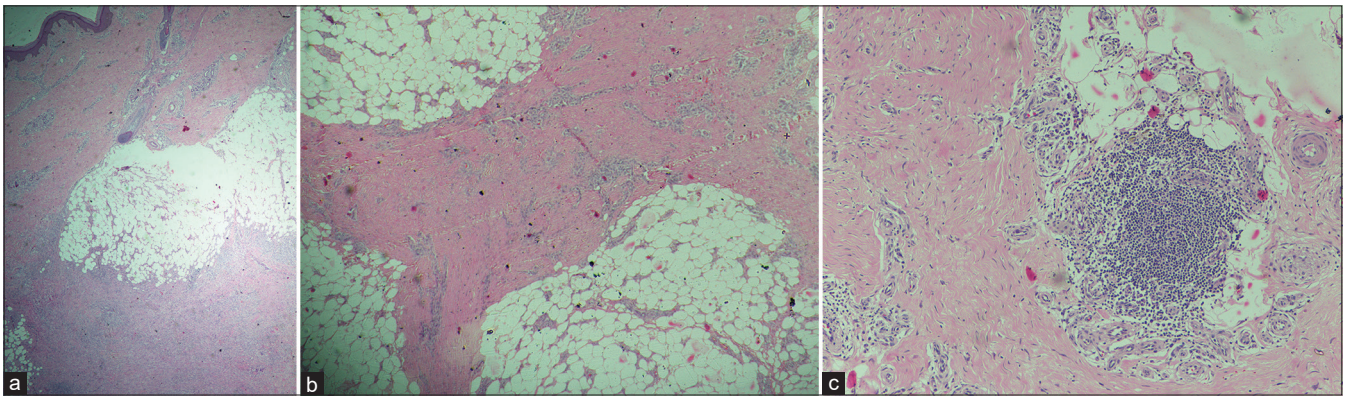

Figure 8: (a-c) Thickened septae with infiltration of lymphocytes in erythema nodosum [H and E ×20, ×40, and ×100, respectively]

- Clinically and histopathologically, lesions are suggestive of tuberculids, and there is a systemic tuberculous focus elsewhere in the body.
- Patients have strong tuberculin positivity with clinical and histopathological features of non-specific or undescribed tuberculids when other causes have been ruled out.

Treatment of tuberculids follows the same regimen recommended for true cutaneous TB consisting of an intensive phase of isoniazid, rifampicin, pyrazinamide, and ethambutol for 8 weeks, followed by a continuation phase of isoniazid, rifampicin, and ethambutol for 16 weeks according to the weight band. In an adult woman with papulonecrotic tuberculids, a triple-drug regimen with rifampicin, isoniazid, and pyrazinamide was given for 6 months. After an initial clinical remission, the patient developed recurrence of lesions after 4 months. The patient was then retreated with the four-drug regimen for 9 months, but the lesions continued to recur for 2 years. The authors attributed the failure of treatment to the low compliance of the patient but also kept the possibility of drug resistance.[86] Thus, one must ensure that the standard four anti-tubercular drug regimen is strictly followed.

Incomplete treatment has been raised as a concern in erythema induratum of Bazin. In an 11-year retrospective review of 21 cases of erythema induratum of Bazin, 76% had improvement or resolution of disease after ATT of a

median duration of 6 months (range 5–9 months).[87] Some authors propose a longer period of treatment with isoniazid, maintaining for up to two years in erythema induratum of Bazin.[88] Dapsone, potassium iodide, and doxycycline have been used as adjuvants to treat the inflammation, as well as corticosteroids or tuberculin protein in various dilutions for desensitization.[89]

There is a case report of successful treatment of erythema induratum with topical application of 3.75% isoniazid twice daily (prepared by crushing and mixing 15 isoniazid 100 mg tablets with 40 g zinc oxide ointment).[90]

Conclusion

Tuberculids, though considered a controversial entity by some, still appear to be related to tuberculous infection. Some of them have been removed from the list, e.g. LMDF (Lupus miliaris disseminatus faciei) and rarer presentations are being added. The essential pathogenesis is that this is a hypersensitivity related to tubercle bacillary antigens that continues. Unusual presentations of cutaneous tuberculosis may sometimes mimic tuberculids both clinically and histopathologically. Strong mantoux positivity, characteristic histopathological features and absence of *M. tuberculosis* in culture help in establishing diagnosis. Though acid-fast bacilli are not demonstrable by definition, PCR has been found to be positive in many cases. An underlying focus of infection may not always be found but standard antitubercular therapy should be given to all patients of tuberculids.[91]

Patient consent

Taken.

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Conflicts of interest

There are no conflicts of interest.

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