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Papulonecrotic tuberculid—clinicopathologic and molecular features of 12 Indian patients

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ABSTRACT

Background: Papulonecrotic tuberculid (PNT) is said to be a hypersensitivity reaction to *M. tuberculosis*. Some reports indicate that organisms are demonstrable by polymerase chain reaction (PCR).

Methods: We describe 12 patients with PNT over 6 years. We reviewed the histopathologic features, clinical data and follow-up. PCR for *M. tuberculosis* DNA was done in all cases.

Results: There were 7 men and 5 women. The ages ranged from 3-58 years. Upper limbs were commonly involved (8 cases). All patients had multiple papulonodular lesions, 5 showed ulceration and scarring. Mantoux test was strongly positive in all. Seven patients had systemic tuberculosis.

On microscopy, necrosis was seen in 11 cases, varying from minimal to extensive. Epithelioid granulomas were common, except for 1 case with palisading and interstitial patterns. The infiltrate showed mostly lymphocytes, while 3 cases showed eosinophils. Vasculitis was seen in 8 cases. Two cases had dermal mucin, one also with interface dermatitis. This patient had concurrent LE. Mycobacterial DNA was detectable by PCR in 3 cases. Seven patients showed improvement/resolution of lesions on treatment.

Conclusions: PNT is a rare disease. A positive PCR reiterates the question whether these are "tuberculids". PNT may be better classified as true cutaneous tuberculosis and patients screened for systemic disease.

Introduction

India has the highest burden of tuberculosis (TB) in the world and cutaneous TB accounts for about 1.5% of extrapulmonary disease [1,2]. It is seen in greater frequency with HIV infection, which is also rampant there [1,3]. Skin lesions could be either "true" cutaneous TB (lupus vulgaris, TB verrucosa cutis, scrofuloderma, orificial TB, military TB) or tuberculids [4]. The latter are believed to represent an Arthus-type hypersensitivity reaction to a focus of infection elsewhere and by definition are culture negative [4]. Tuberculids include lichen scrofulosorum (the commonest), erythema induratum of

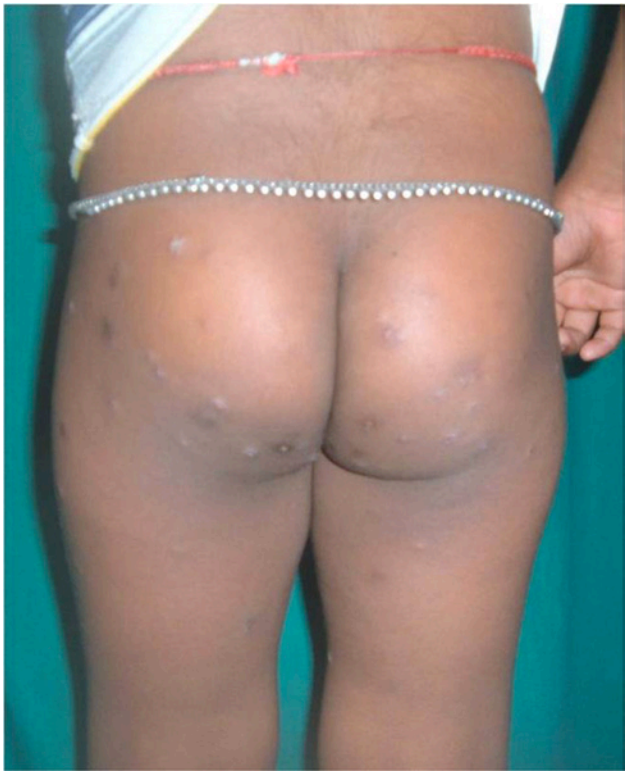

Figure 1A. Papulonodular lesions over buttocks and lower limbs in a child. [Copyright: ©2014 Tirumalae.]

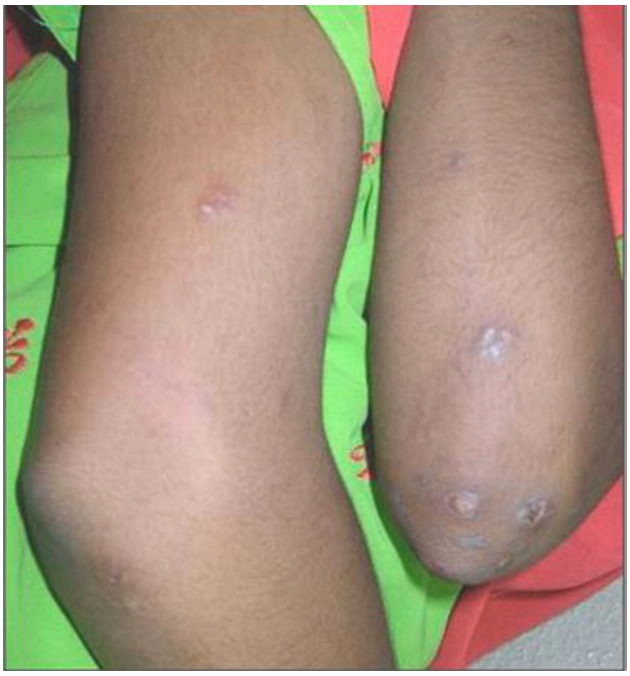

Figure 1B. Lesion on the arm showing ulceration and scarring at the periphery. [Copyright: ©2014 Tirumalae.]

Bazin and papulonecrotic tuberculid. PNT is a rare tuberculidwith very few case series in literature [5,6,7]. Indian data is limited mainly to case reports or to broader studies on cutaneous TB in general [8,9,10]. There are reports which state that mycobacteria are detected by polymerase chain reaction (PCR) in these lesions [11,12]. We seek to describe the clinicopathologic features of PNT and to study the role of PCR in identifying *M. tuberculosis* DNA in these lesions.

Material and methods

There were 12 cases diagnosed as papulonecrotic tuberculid between 2006 and 2011 based on clinical and histopathologic criteria. Two cases signed out as papulonecrotic tuberculid on histopathology were excluded. One of these was culture positive for *M. tuberculosis* and the other one did not fit the clinical picture. We reviewed hematoxylin and eosin stained sections, special stains for acid-fast bacilli (Ziehl-Nielsen) and fungi (periodic acid-Schiff, Gomori methenamine silver). The slides were assessed in particular for epidermal changes, type and location of granulomas, necrosis, nature of inflammatory cell infiltrate and presence of vasculitis and dermal mucin (confirmed by Alcian blue stain, pH 2.5).

Clinical data was retrieved from patient records. We particularly noted the age, gender, nature and distribution of lesions, associated systemic features, Mantoux test, treatment and follow-up data.

Sections were recut from the paraffin blocks and stained with H&E to ensure adequacy and representativeness of the samples for PCR. After this, 20µ sections were cut from each block and placed in sterile microcentrifuge tubes. DNA was extracted using the "DNA extraction kit" (Qiagen India Pvt Ltd)after deparaffinization with xylene. The samples were subjected to nested PCR using primers specific to heat shock protein hsp65gene (Eurofins MWG Operon, India) with appropriate positive and negative controls [13].The positive controls comprised of skin, lung and lymph nodes, two of which were also culture positive. The reaction products were visualized after agarose gel electrophoresis.

Results

There were 12 patients, 7 men and 5 women. There were 4 children and 8 adults. The age ranged from 3 to 58 years (mean age: 28.1 years); 8 cases were in the first three decades.

All patients had multiple papulonodular lesions in a somewhat symmetric distribution (Figure 1A). Ulceration and scarring were seen in 5 cases. Upper limbs were most commonly involved (8 cases) (Figure 1B), followed by the lower limbs, trunk and face (6, 5 and 3 cases respectively).

All patients showed strong Mantoux positivity. Evidence of systemic TB was found in 7 cases. Of these, 3 had TB lymphadenitis, 2 patients had osteomyelitis, and 1 patient had hepatic and pulmonary TB. One case had associated HIV infection and one had concurrent systemic lupus erythematosus (LE) with joint involvement.

The histopathologic findings are detailed in Table 1. Most cases had tuberculoid granulomas (Figure 2A), with

TABLE 1. Histopathologic findings in 12 cases of PNT

Psoriasiform acanthosis	12
Interface dermatitis	1
Type of granulomas	
Tuberculoid	10
Palisading	1
Interstitial	1
Dermal necrosis	10
Minimal	3
Extensive	7
Perifollicular location of granulomas	8
Superficial and deep infiltrates	8
Neutrophils	6
Eosinophils	3
Leucocytoclastic vasculitis	8
Extravasated RBCs	6
Dermal mucin	2
Acid-fast bacilli & fungi	0

minimal to extensive necrosis (Figures 2B & C). The necrosis was focal in 3 cases. The remainder showed extensive caseous necrosis. In 1 case, the necrosis was wedge-shaped, reminiscent of an infarct. One case showed interstitial and palisading granulomatous patterns (Figures 3A & B). Leucocytoclastic vasculitis was present in 8 cases (Figures 3C & D). Most cases had a preponderance of lymphocytes, while

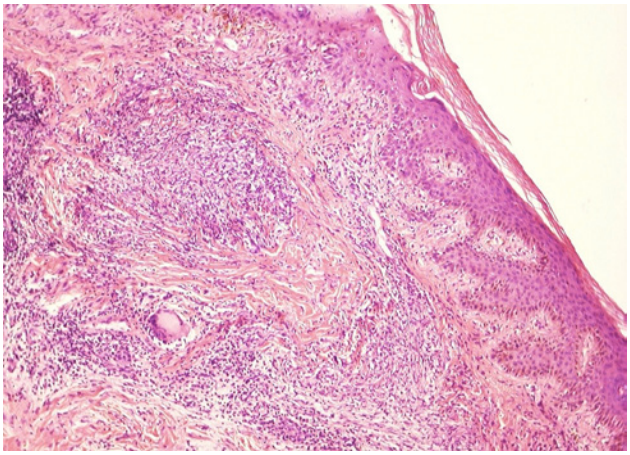

Figure 2A. Tuberculoid granulomas with lymphocytes and overlying psoriasiform acanthosis (H&E, x40). [Copyright: ©2014 Tirumalae.]

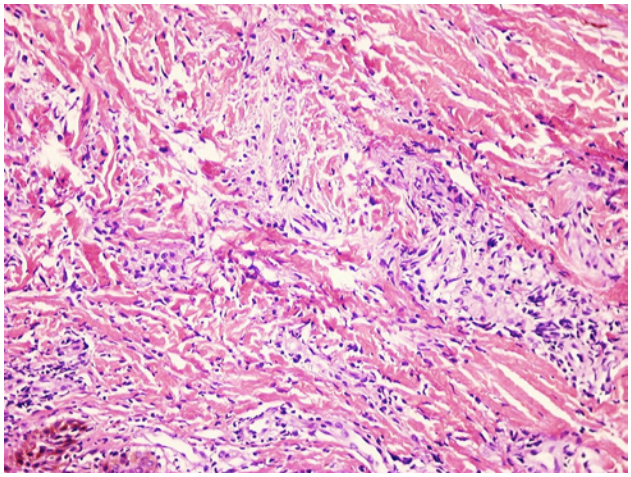

Figure 2B. Interstitial granulomatous pattern with epithelioid cells and histiocytes (H&E, x200). [Copyright: ©2014 Tirumalae.]

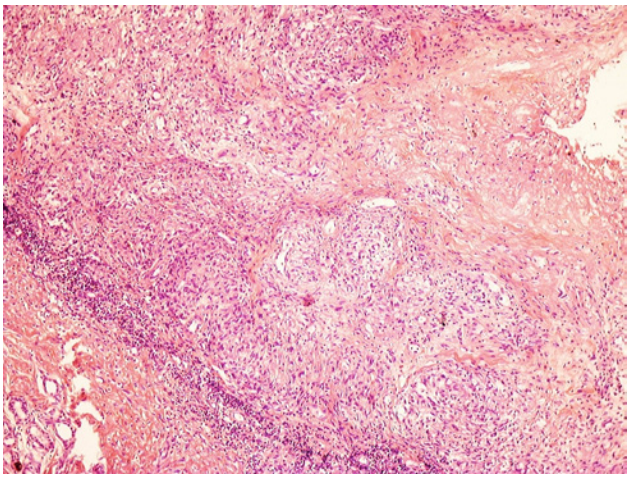

Figure 2C. Palisading granuloma with central necrosis (H&E, x200). [Copyright: ©2014 Tirumalae.]

3 of them showed an admixture of eosinophils. Abundant dermal mucin was seen in 1 case, together with extensive interface dermatitis and cellular infiltrate consistent with SLE (Figures 4A & B). This patient tested positive for antinuclear antibodies, anti-SS-A and anti-Ro. Special stains for

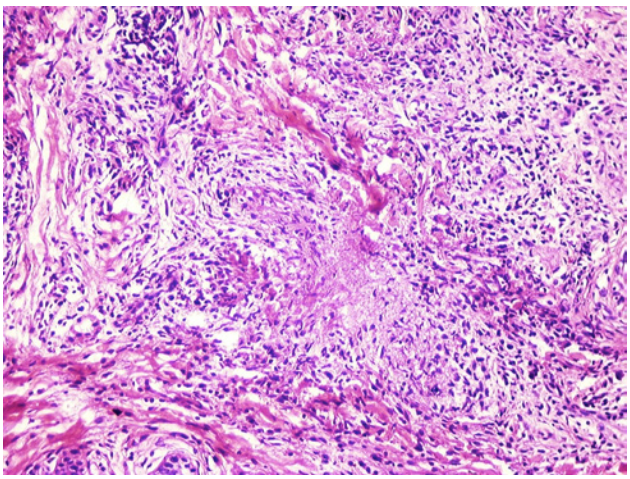

Figure 3A. Epithelioid granulomas with minimal necrosis (H&E, x200). [Copyright: ©2014 Tirumalae.]

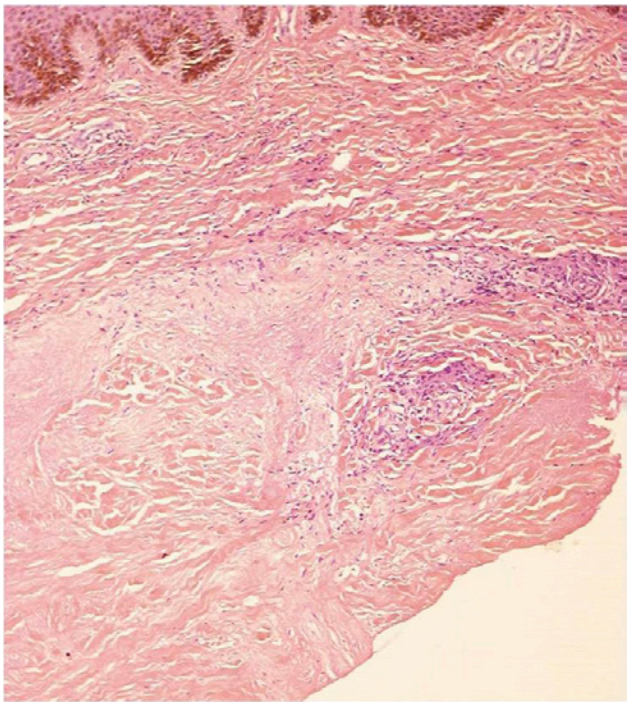

Figure 3B. Extensive dermal necrosis (H&E, x40). [Copyright: ©2014 Tirumalae.]

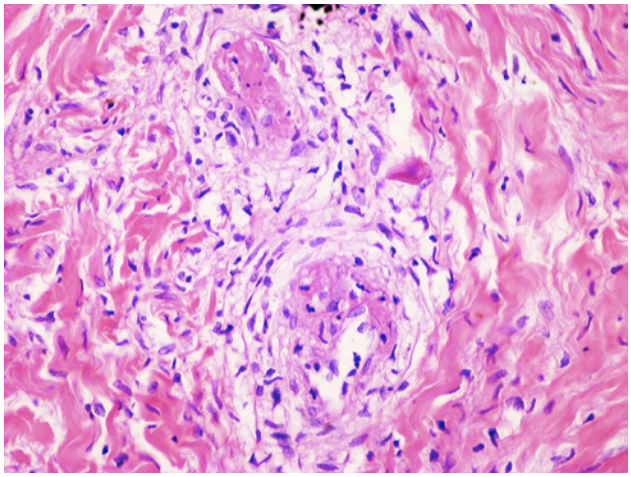

Figure 3C. Blood vessels showing fibrinoid necrosis, microthrombi and leucocytoclasis (H&E, x400). [Copyright: ©2014 Tirumalae.]

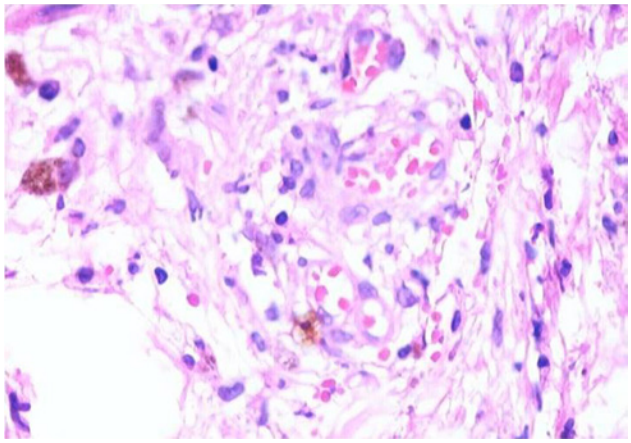

Figure 3D. Dilated blood vessels and extravasated red cells (H&E, x400). [Copyright: ©2014 Tirumalae.]

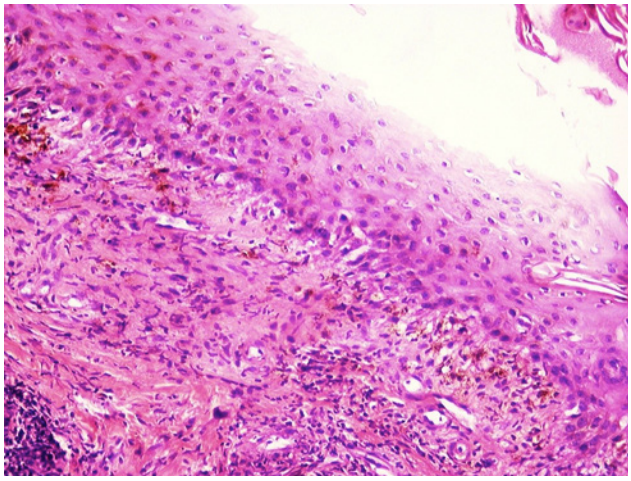

Figure 4A. Extensive interface dermatitis, melanophages and underlying granuloma (H&E, x200). [Copyright: ©2014 Tirumalae.]

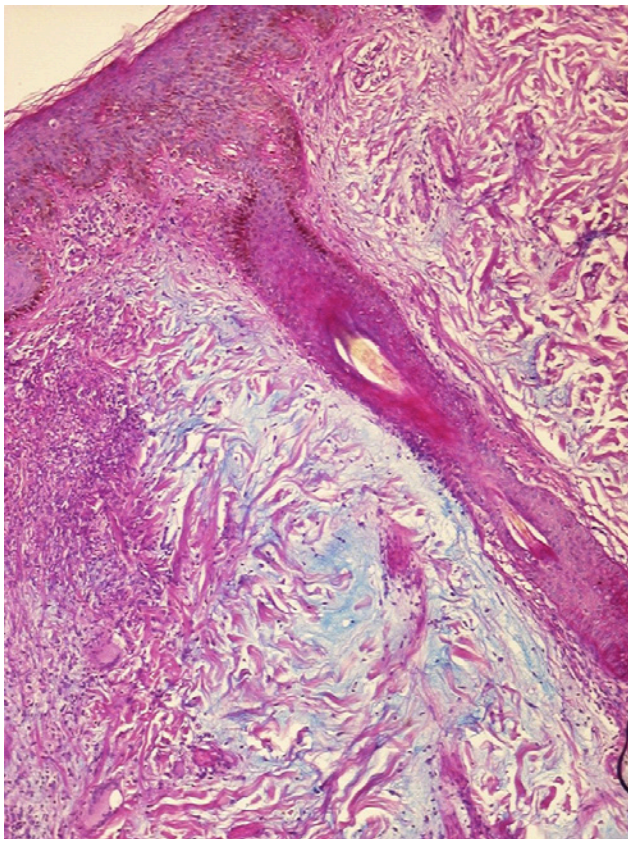

Figure 4B. Abundant Alcian blue positive dermal mucin (Alcian blue, x40). [Copyright: ©2014 Tirumalae.]

fungi and mycobacteria were negative in all cases. Culture was done in 2 cases, both being negative.

Mycobacterial DNA was detected by RT-PCR in 3/12 cases.

Treatment and follow-up

Of the 12 patients, 1 refused treatment. Eleven patients were started on first-line tuberculostatic chemotherapy as per the guidelines on RNTCP (Revised National Tuberculosis

Control Programme). This consisted of isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months (intensive phase) followed by isoniazid and rifampicin for 4 months (continuation phase). Three patients were lost for follow-up. The remaining 8 patients showed significant improvement/ resolution of lesions by 6 weeks, including the 3 PCR positive cases. Two patients developed drug-induced hepatitis. One patient developed neurotuberculosis.

Discussion

Papulonecrotic tuberculid seems to be the least common form of cutaneous TB, even in countries with a high prevalence of TB [9,10]. It is deemed to be a type III hypersensitivity reaction to the presence of a focus of infection elsewhere in the body. By definition, tuberculids do not show bacilli on special stains and are negative by culture [4]. There has been conjecture about the association of papulonecrotic tuberculid with TB, but a positive tuberculin skin test and resolution of lesions following anti-tubercular therapy are strong proofs in its favor. Similar lesions have also been documented following BCG immunization, but a temporal link is difficult to establish [14].

It is generally seen in young adults, as in the present study [5,6]. Only one patient had concurrent HIV infection. Only sporadic occurrences of papulonecrotic tuberculid with HIV have been reported [15]. In a recent study from India, there were 5 cases of papulonecrotic tuberculid out of 131 cutaneous TB and none of them were retroviral positive [3]. It is mostly seen in immunocompetent hosts.

Clinically, papulonecrotic tuberculid is characterized by papulonodular, pustular or necrotic lesions with crusting in a more or less symmetric fashion, with a predilection for extremities [4,5,6]. This was also the case in the present study with upper limbs being the commonest involved site. The lesions heal over several weeks with residual scarring. Genital involvement is rare [8]. None of our cases had mucosal/genital lesions. Association with other tuberculids, particularly erythema induratum of Bazin, have been recorded, but we did not observe this [5].

It is noteworthy that almost half of our cases showed evidence of systemic TB in the past or simultaneously, particularly the extrapulmonary forms. Papulonecrotic tuberculid may be regarded as a "sentinel" lesion, and these patients should be thoroughly investigated for systemic involvement. Previous studies report that between 38 and 75% cases have evidence of TB elsewhere, most commonly in lymph nodes [16,17]. We concur with these findings. Some cases have been associated with Takayasu's arteritis and gangrene of extremities [18]. All our patients showed strong Mantoux positivity, which is essential for diagnosis [4].

Histopathology of the lesions showed psoriasiform epidermal hyperplasia in all our cases. Most cases showed epithelioid granulomas with lymphocytes and Langhans giant cells with variable amounts of necrosis. They were mostly seen in the upper and mid-dermis with a perifollicular distribution in most instances. This is reminiscent of lichen scrofulosorum [4]. Some reports of follicular destruction by the infiltrate are found in literature but none in the present study [5]. LS does not show follicular involvement. The Grenz zone was never clear and we noted granulomas impinging on the epidermis insome cases. This feature is likely to precede transepidermal elimination of granulomas and subsequent healing.

One case showed interstitial granulomas with chiefly histiocytes while another showed a palisading granuloma with central necrosis, mimicking granuloma annulare. This has been reported in one previous study [5]. However, there was no dermal mucin or altered collagen. It is important to be aware of these variations, as granuloma annulare is also a clinical mimic, especially the perforating form. In some cases, necrosis was very focal.

Leucocytoclastic vasculitis (LCV) was found in three-quarters of our cases. This is an important finding to support the diagnosis. The pathogenesis of PNT has been explained by an Arthus-like phenomenon where mycobacterial products cause initial vascular endothelial damage [17]. In patients with a potent immune system, this later transforms into a delayed hypersensitivity-like picture with the occurrence of granulomas. Some authors opine that established lesions of papulonecrotic tuberculid do not show LCV, as the neutrophils are replaced by lymphocytes or macrophages [16]. Our findings differ. In addition, we also saw microthrombi within some vessels, endothelial swelling and extravasated red cells. The finding of LCV in a majority of our cases underscores the importance of an immune-complex mediated mechanism. The infiltrate around the necrotic areas consisted of lymphocytes, neutrophils and in some, eosinophils. If considerable numbers of eosinophils are present, other parasitic infections or arthropod bite reactions need to be excluded.

An unsual finding in the present series is the abundant dermal mucin in two cases. One of them also had extensive interface dermatitis, thickened basement membranes and clinical features consistent with associated SLE. It is known that TB is more common in patients with SLE and usually lupus vulgaris is the common form [19]. Our case represents a rare occurrence of papulonecrotic tuberculid in SLE.

Acid-fast bacilli were not seen in any of our cases. Sporadic reports of papulonecrotic tuberculid lesions showing positive mycobacterial cultures exist, but on review, these were better classified as lupus vulgaris [16].

PCR is a very sensitive tool to demonstrate organisms and the first instance of PNT yielding *M. tuberculosis* DNA was reported by Victor et al. in 11/22 cases [11]. Following this,

there have been other series reporting positive rates varying from 0 to 80% [12,20]. Twenty-five percent of our cases showed amplification by PCR, and this is the first study from India exploring this link. The rate may actually be higher, depending on the fixation and age of the blocks. Other mycobacteria have also been identified, such as *M. bovis* and atypical mycobacteria [21]. Our findings further support a strong link between PNT and TB.

To summarize, papulonecrotic tuberculid is a distinct clinicopathologic form of TB. These patients require a detailed workup to look for systemic disease and should receive a complete course of multi-drug therapy. Based on identification of mycobacteria from the lesions and bolstered by the resolution of lesions after anti-tubercular therapy, it is perhaps better to classify PNT as a morphologic form of "true" cutaneous TB rather than a "tuberculid."

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