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## Correlation between clinical and histopathological findings of five puzzling cases of cutaneous tuberculosis

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## Case Report

# Correlation between clinical and histopathological findings of five puzzling cases of cutaneous tuberculosis

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## Abstract

**Background:** Cutaneous tuberculosis refers to the clinical manifestation of extrapulmonary tuberculosis affecting the skin. Determining the type of cutaneous tuberculosis from a patient afflicted with is challenging because clinical and histopathological similarities exist between types. Moreover, confirming a diagnosis of cutaneous tuberculosis is difficult because of its similarity with other diseases. For instance, typical and atypical cutaneous tuberculosis may have similar manifestations, but each disease is managed by completely different approaches. Microbiological examination with polymerase chain reaction and bacterial culture are the gold standard methods used to confirm a diagnosis of cutaneous tuberculosis. However, results often demonstrate negative findings.

**Case Illustration:** Five cases of cutaneous tuberculosis, which include two cases of tuberculosis verrucosa cutis, two cases of scrofuloderma, and one case of lupus vulgaris were presented in this article. Four of the five cases demonstrated significant improvement after initiation of an antituberculosis drug regimen.

**Discussion:** Diagnosis of cutaneous tuberculosis in these cases was confirmed through clinical findings and histopathological and microbiological examination.

**Conclusion:** A negative result following microbiological examination does not completely exclude the diagnosis of cutaneous tuberculosis. Investigating the pathognomonic findings of cutaneous tuberculosis through histopathological examination is important to differentiate among its types correctly. Therefore, correlations between clinical and histopathological results are essential to establish a diagnosis of cutaneous tuberculosis.

**Keywords:** cutaneous tuberculosis, lupus vulgaris, scrofuloderma, tuberculosis verrucosa cutis

## Background

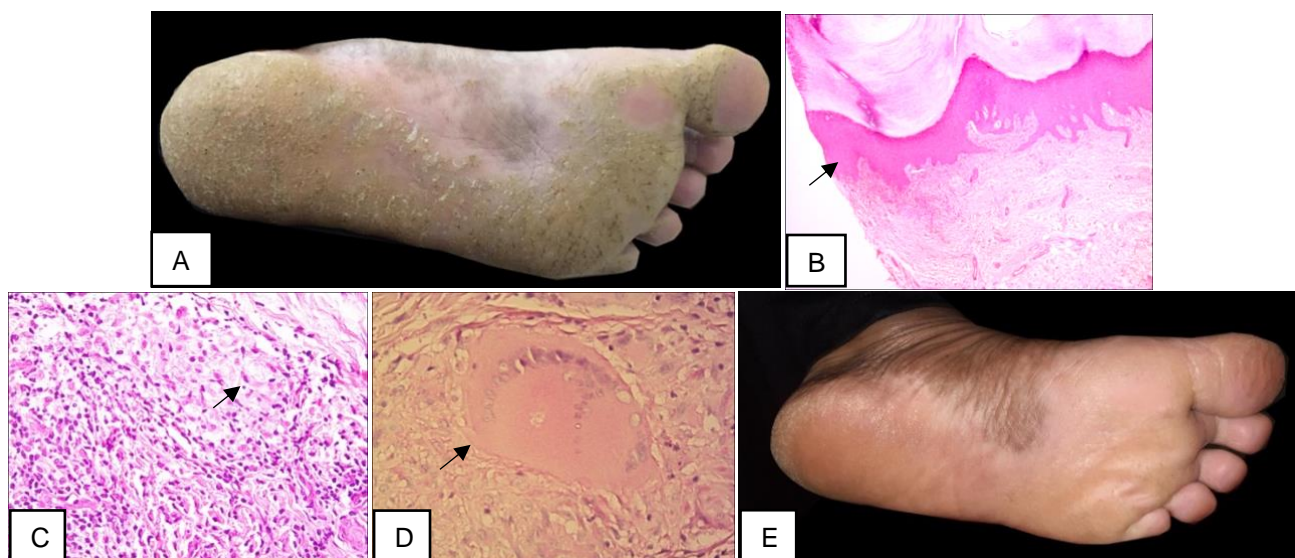
Cutaneous tuberculosis refers to the clinical manifestation of extrapulmonary tuberculosis affecting skin of a patient who has chronic infection of *Mycobacterium tuberculosis*.<sup>1</sup> Although the incidence of cutaneous tuberculosis had significantly diminished after the development of the Bacillus Calmette–Guerin vaccine and implementation of effective antituberculosis drug regimens, the prevalence of this disease recently began to increase.<sup>2,3</sup> The reported prevalence of cutaneous tuberculosis is only 1%–2% of all tuberculosis cases.<sup>4</sup> According to outpatient data

collected from 2012 to 2015 at the Department of Dermatology and Venereology, Dr. Cipto Mangunkusumo National General Hospital, Indonesia, 37 cases of cutaneous tuberculosis were identified from 2435 tuberculosis patients, thereby indicating a prevalence 1.52%.<sup>5</sup> The major predisposing factors of cutaneous tuberculosis include the growing incidence of HIV/AIDS, the continuing spread of multidrug-resistant tuberculosis, and the rising cases of drug-induced immunosuppressive patients.<sup>2,3</sup>

The clinical manifestations of cutaneous tuberculosis depend on the appearance of the skin

lesions, the mode of transmission, the extent of bacteria on the skin (multibacillary or paucibacillary), and the factors affecting the host including age, immunocompetency, and previous history of tuberculosis<sup>6</sup> Depending on the mode of transmission, the morphological variants of cutaneous tuberculosis could be further classified as primary inoculation tuberculosis and tuberculosis verrucosa cutis, which result from

inoculation from an exogenous source; scrofuloderma, tuberculosis cutis orificialis and lupus vulgaris, which result from autoinoculation or adjacent expansion through endogenous dissemination; lupus vulgaris, acute miliary cutaneous tuberculosis, and metastatic tuberculous abscess, which result from hematogenous dissemination.<sup>6,7</sup>



**Figure 1.** A. Before initiation of an antituberculosis drug regimen. B. Histopathological examination at 100x magnification revealing epidermal hyperkeratosis (arrow). C. Histopathological examination at 400x magnification revealing epithelioid granuloma (arrow). D. Histopathological examination at 400x magnification of the results of periodic acid-Schiff staining revealing giant cells (arrow). E. After 5 months of an antituberculosis drug regimen.

Because most diagnostic modalities are limited by low sensitivity and specificity, the diagnosis of cutaneous tuberculosis requires correlation among clinical and histopathological findings and bacterial examinations, including acid-fast bacilli (AFB) staining, polymerase chain reaction (PCR), and microbiological culture.<sup>6</sup> Agarwal et al.<sup>8</sup> reported that the sensitivity of histopathological examination and culture are 91.8% and 16.3%, respectively.<sup>8</sup> Khadka et al.<sup>9</sup> demonstrated PCR test sensitivity ranging from 24.5% to 100%. However, PCR results may be inconclusive because of the uneven mycobacterial spread in paucibacillary type of the disease. Thus, the accumulation of positive outcomes from each complementary diagnostic test performed is essential to diagnose cutaneous tuberculosis accurately.

Recognizing cutaneous tuberculosis is challenging, and knowledge of the precise diagnosis is required to implement the appropriate

treatment. Furthermore, the cutaneous manifestations of nontuberculous bacilli often mimic the skin lesions of cutaneous tuberculosis.<sup>10</sup> In this paper, we present five cases of cutaneous tuberculosis that include two cases of tuberculosis verrucosa cutis, two of scrofuloderma, and one of lupus vulgaris.

## Case Illustration

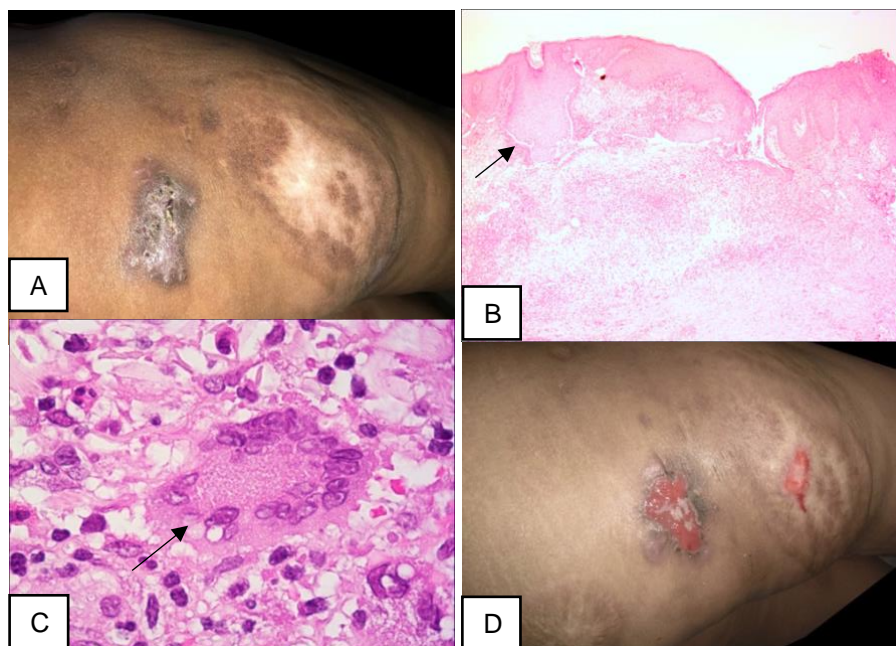
### Case 1

A 41-year-old woman presented with a 35-year history of nonhealing, malodorous, and hyperkeratotic plaques on her left foot. The lesion first developed on the sole and slowly extended to the dorsal part of her foot. Upon reaching adulthood, the lesion on the back of her foot healed; however, the lesion on her sole persisted. The patient had sought medical care several times

for this problem, but the lesions did not respond to previous treatments. Her last treatment was set of 500 mg of erythromycin QID, followed by erythromycin gel 2% BID and Benzolac-CL® (benzoyl peroxide gel 5% and clindamycin phosphate gel 1.2%) failed to improve the symptoms. Physical examination revealed multiple, circumscribed, hyperkeratotic, yellowish plaques ranging from lenticular to plaque in size (Figure 1A). The patient was initially diagnosed with pitted keratolysis and treated with erythromycin gel BID and 3% salicylic acid in vaseline album with minimal improvement. She was later reassessed as having unilateral punctate plantar keratoderma and treated with tretinoin cream 0.1% BID. However, no significant improvement was noted. Histopathological examination revealed epidermal hyperkeratosis, parakeratosis, and dermal epithelioid granuloma with giant cells. Dermal lymphocytes and histiocytes infiltration were also noted (Figure 1B–D). The chest X-ray was clear. The patient was then diagnosed with tuberculosis verrucosa cutis and treated with a standard antituberculosis drug regimen. Two weeks after treatment initiation, the patient developed drug-induced liver injury as evidenced by elevated liver transaminase enzyme levels. Pyrazinamide was then substituted with streptomycin. The patient showed good clinical improvement over the next 2 months of intensive-phase treatment and continued to the maintenance phase of treatment for a minimum of 7 months (Figure 1E).

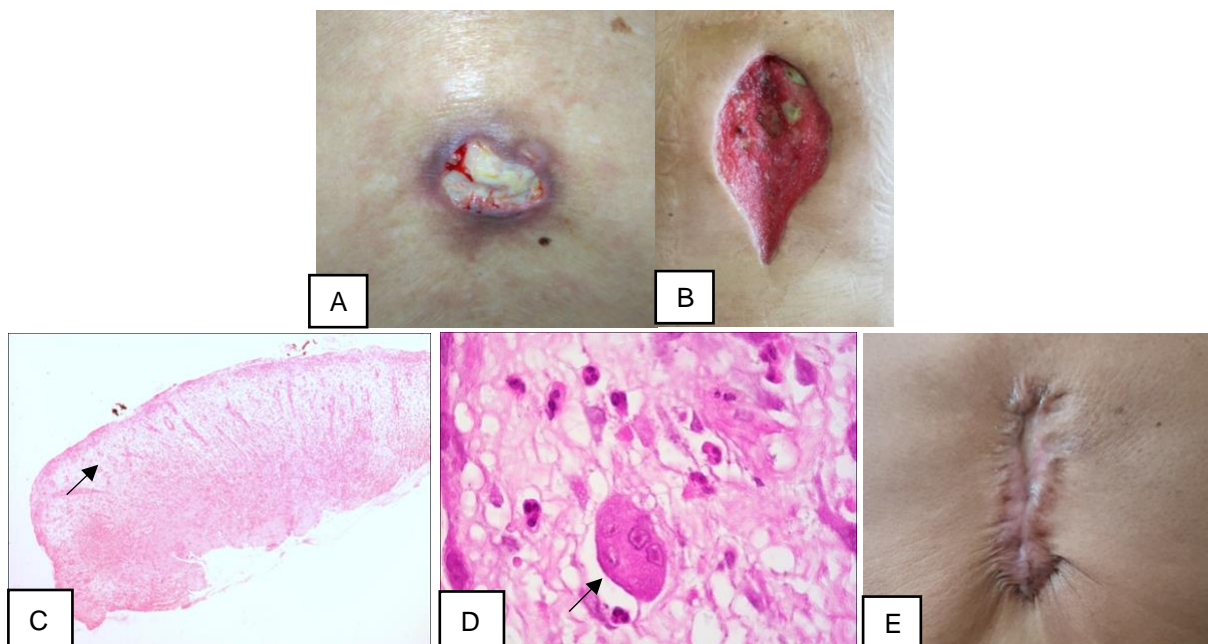
## Case 2

A 25-year-old woman presented with a 3-month history of a nonhealing wound on her right buttock. The patient had been taking mycophenolic acid thrice weekly for the treatment of pemphigus vulgaris. The patient had also been treated with 625 mg of amoxicillin-clavulanate TID for 7 days, and the wound had dried. On physical examination, the patient had a solitary, circumscribed, violaceous patch with brownish crusts on top (Figure 2A). A nontender inguinal lymph node measuring 1 cm in diameter was also noted on palpation. Histopathology result from the skin biopsy showed epidermal acanthosis with minor suprabasal clefts and dermal infiltration of lymphocytes, histocytes, polymorphonuclear cells (PMNs) with numerous Langhans giant cells (Figure 2B–C). Suppurative areas in the dermis were noted. AFB staining, culture, and PCR for *M. tuberculosis* from skin biopsy were negative. A diagnosis of tuberculosis verrucosa cutis was made, and antituberculosis medication was initiated. Upon treatment completion (after 12 months), the lesion showed significant improvement. However, the patient had intellectual impairment with neurotic excoriation, resulting in an inability to continue proper wound care (Figure 2D).



**Figure 2.** A. Before initiation of an antituberculosis drug regimen. B. Histopathological examination at 100x magnification revealing epidermal acanthosis with minor suprabasal clefts (arrow). C. Histopathological

examination at 400× magnification revealing Langhans giant cells (arrow). D. After 12 months of an antituberculosis drug regimen.



**Figure 3.** A. Before debridement surgery for tuberculous osteomyelitis. B. After debridement surgery. C. Histopathological examination at 100× magnification showing heavy edema of the dermis (arrow). D. Histopathological examination at 400× magnification revealing Langhans giant cells (arrow). E. After 12 months of an antituberculosis drug regimen

### Case 3

A 42-year-old man presented with a 1-month history of a painful exudative lump over his sternum that had become ulcerated. He was also on a multidrug therapy regimen for lepromatous leprosy. Chest CT scan revealed a soft tissue lesion with a cutaneous–subcutaneous defect and destruction of the corpus sternum. The patient was suspected to have tuberculous osteomyelitis under the cutaneous lesion. Physical examination of the sternum before debridement showed a solitary ulcer measuring 8 cm × 5 cm × 0.1 cm with a flat border and pus covering the lesion (Figure 3A). Axillary and cervical lymph nodes were not enlarged. Afterwards, the patient had debridement surgery (Figure 3B), during which tissue specimens were obtained for microbiological and histopathological examination. A PCR test for *M. tuberculosis* from skin biopsy was positive, but culture was negative. Histopathological examination revealed significant dermal edema with infiltration of inflammatory cells (i.e., lymphocytes, histiocytes, PMNs, and plasma cells), a proliferation of blood vessels, and the

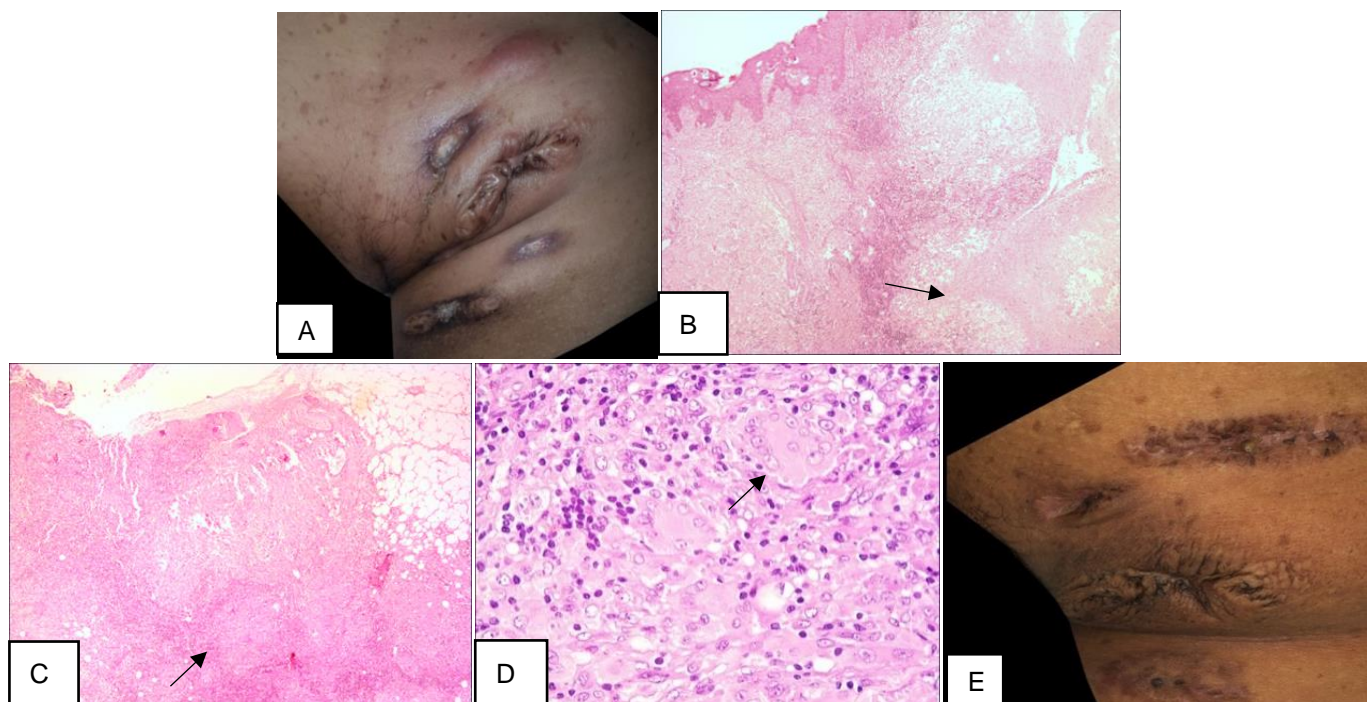
presence of giant cells (Figure 3C–D). Primary tuberculosis of the lung was excluded based on chest radiograph. The patient was diagnosed with scrofuloderma and treated with an antituberculosis regimen for 12 months. The lesion healed, leaving a painless hypertrophic scar (Figure 3E).

### Case 4

A 15-year-old woman presented with a 6-month history of multiple painless lumps on her left inguinal area, some of which had been ulcerating for the past 3 months. The patient had been self-treating with gentamicin ointment but noted only minor improvements. The patient reported a history of close contact with a classmate who had active lung tuberculosis. Physical examination revealed multiple circumscribed, erythematous nodules with multiple superficial ulcers surrounded by bright red areas on the left femoral, inguinal, and genitalia areas. Multiple scars were also found in the inguinal area (Figure 4A). Mantoux testing was highly positive with 20 mm of induration, and chest X-ray suggested lung tuberculosis. Histopathological examination revealed irregular acanthosis, discontinuous epidermis, and ulcers

filled with necrotic tissue on the epidermis. Lymphocyte infiltration and Langhans giant cells were found on the dermis (Figure 4B–D). PCR examination and culture in Löwenstein–Jensen medium tested positive for *M. tuberculosis*.

However, the patient's direct microscopic examination was negative for AFB. The patient was treated with a standard anti-tuberculosis regimen. After 3 months of therapy, her lesions showed significant clinical improvement (Figure 4E).



**Figure 4.** A. Before initiation of an antituberculosis drug regimen. B and C. Histopathological examination at 100× magnification revealing epithelioid granuloma in the dermis and deep dermis (arrow). D. Histopathological examination at 400× magnification showing giant cells (arrow). E. After 1 month of a standard antituberculosis drug regimen.

### Case 5

A 19-year-old woman presented with a 1-year history of an erythematous patch on her right thigh. The patch initially started as two lumpy masses on the upper part of her right thigh that subsequently became wounded and spread after the patient scratched the lesion. No history of trauma or injection to the femoral area was reported. The patient had previously been treated with oral and topical agents at a secondary referral hospital; however, very minimal improvement was observed. Physical examination revealed multiple, circumscribed, irregular, hyperpigmented, erythematous patches with coarse white scales and atrophic scars (Figure 5A). Histopathological examination revealed irregular epidermal acanthosis and spongiosis with severe dermal edema, a tuberculoid granuloma with numerous Langhans giant cells, and fibrosis consistent with lupus vulgaris (Figure 5B–C). However, culture and

PCR examination for *M. tuberculosis* were negative. The patient was diagnosed with lupus vulgaris, and clinical improvement was seen after 4 months of antituberculosis therapy (Figure 5D).

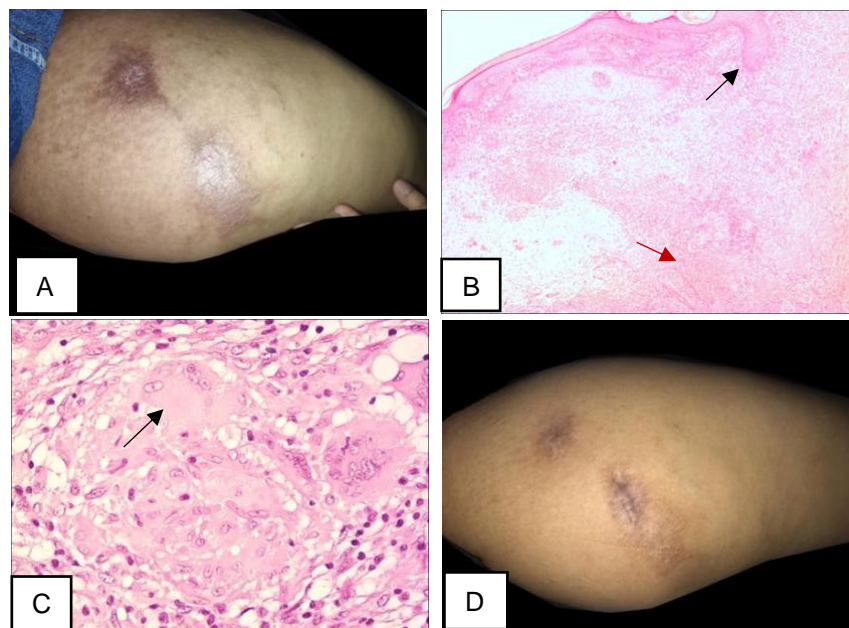
### Discussion

The diagnosis of cutaneous tuberculosis is fairly challenging. Because microbiological and molecular examinations may yield negative results, investigating the pathognomonic findings on each type of cutaneous tuberculosis during histopathological examination is essential to establish a correct diagnosis.<sup>4</sup>

The five cases presented in this article showed three types of cutaneous tuberculosis, including tuberculosis verrucosa cutis, scrofuloderma, and lupus vulgaris. The histopathological findings of our cases are in line with the study of Sharma et al.<sup>11</sup>

The histopathological features of tuberculosis verrucosa cutis comprise pseudoepitheliomatous hyperplasia, hyperkeratosis, and neutrophilic abscesses in the superficial dermis with several extensions through rete and epithelioid cells accompanied by some giant cells in the upper and mid dermis. Well-formed granulomas may be unseen. Although not all tuberculosis verrucosa cutis cases demonstrate neutrophilic abscesses, a

diagnosis of tuberculosis verrucosa cutis can still be established. The histopathological characteristics of scrofuloderma consist of substantial necrosis and abscesses in the deeper dermis along with tuberculoid granulomas and giant cells. The histopathology of lupus vulgaris includes tuberculoid granulomas, tissue necrosis, epidermal changes, and dermal fibrosis.



**Figure 5.** A. Before initiation of an anti-tuberculosis drug regimen. B. Histopathological examination at 100x magnification showing epidermal acanthosis (black arrow) and tuberculoid granuloma in the dermis along with fibrosis (red arrow). C. Histopathological examination at 400x magnification revealing giant cells (arrow). D. After 4 months of a standard antituberculosis drug regimen.

The typical clinical findings for tuberculosis verrucosa cutis include definite warty plaques with a predilection for forming on the extremities. However, growing evidence has demonstrated numerous atypical variants of tuberculosis verrucosa cutis, including the destructive papillomatous and sclerotic types, profuse granuloma, and even plantar keratoderma, as evidenced in the first case.<sup>12</sup> The supporting data confirming the diagnosis of tuberculosis verrucosa cutis in the first case are an inadequate clinical response of the lesion following numerous antibiotic therapies, histopathological examination revealing tuberculosis verrucosa cutis findings, and a satisfactory response after initiation of an antituberculosis drug regimen. Bacterial culture and PCR test were not performed on this patient because cutaneous tuberculosis was not initially suspected. Furthermore, mycobacterial cultures in

tuberculosis verrucosa cutis are frequently negative, as has been previously reported in the literature.<sup>13</sup>

In the second case, mycobacterial transmission could have been facilitated by the patient's tendency to pick her skin; tuberculosis verrucosa cutis often arises as a result of inoculation from an exogenous source. Another finding supporting the diagnosis of tuberculosis verrucosa cutis is the history of taking mycophenolic acid, which is an immunosuppressive agent, for pemphigus vulgaris treatment pemphigus vulgaris medication via consumption of mycophenolic acid, which is an immunosuppressive agent. Immunosuppressed patients are at increased risk of infection by opportunistic pathogens such as tuberculosis.<sup>6</sup> Other supporting findings include histopathological examination demonstrating Langhans giant cells



and significant clinical improvement after completion of antituberculosis treatment.<sup>14</sup> Although AFB staining, bacterial culture, and PCR showed negative results in this case, a diagnosis of tuberculosis verrucosa cutis could still be established because tuberculosis verrucosa cutis often displays negative result in these tests.<sup>13</sup>

As demonstrated in the third case, the diagnosis of scrofuloderma was established on the basis of a painful and exudative lump over the sternum that subsequently became ulcerated. Our findings are in agreement with the notion that scrofuloderma originates from the autoinoculation or contiguous expansion of *Mycobacterium*-infected deep tissues, such as bones, joints, or lymph nodes.<sup>6,7</sup> The patient's history of debridement following tuberculosis osteomyelitis on the sternum is an important detail supporting our diagnosis. Another noteworthy finding is a history of multidrug therapy for lepromatous leprosy. Concomitant infections of leprosy and cutaneous tuberculosis are rarely reported in the literature. A plausible explanation for dual *Mycobacterium* infection is impaired cell-mediated immunity in leprosy, which leads to either reactivation of latent tuberculosis infection or increased susceptibility to recent tuberculosis infection. The decrease in the inflammatory responses of chemokine ligand 2 (CCL2) and tumor necrosis factor- $\alpha$  in lepromatous leprosy have been postulated to lead to the uncontrolled development and spread of tubercle bacilli.<sup>15</sup> Another supporting finding in this patient is a positive result for PCR; although culture test showed a negative result, PCR is generally accepted to have higher sensitivity than culture.<sup>16</sup> The positive finding for PCR is suggestive for scrofuloderma because it belongs to the multibacillary group.<sup>13</sup>

Our fourth case demonstrated a patient with scrofuloderma, which is comparable with the previous case. As evidenced by both cases, the distinguishing clinical manifestations of scrofuloderma are the progressive enlargement of suppurative nodules, which eventually become ulcers draining a purulent or caseous discharge.<sup>2</sup> Scrofuloderma also frequently develops in certain areas containing infected lymph nodes, for instance, the neck, axillae, and inguinal area which then reaches the skin, as observed in this patient. Another prominent finding is the history of close contact with an active lung tuberculosis patient; indeed, the results of supporting examinations revealed lung tuberculosis. A number of reports have described the simultaneous occurrence of pulmonary tuberculosis and scrofuloderma.<sup>13,17</sup> Histopathological examination revealed an ulcer

filled with necrotic tissue on the epidermis and lymphocyte-infiltrated dermis accompanied by Langhans giant cells, which are suggestive for scrofuloderma.<sup>13,14</sup> These findings were confirmed by positive PCR and culture results because scrofuloderma is a multibacillary type of cutaneous tuberculosis. AFB staining was negative because of the low sensitivity of AFB for detecting tuberculous bacilli.<sup>18</sup>

The fifth case illustrated a patient with lupus vulgaris clinically manifesting as a 1-year history of erythematous patches on the right thigh. In most cases, lupus vulgaris occurs as a result of contiguous extension from the affected structure or lymphatic or hematogenous dissemination. As documented in this case, when the primary focus is unclear, reactivation of latent tuberculosis may result through silent bacteremia, which later inoculates the cutaneous structure.<sup>19</sup> In tropical areas, the most frequent predilection site of these patches is the lower extremities, as seen in this patient. In Western countries, these patches are commonly found on the head and neck.<sup>13</sup> The morphological features of lupus vulgaris can be divided into five distinctive patterns, including the plaque, ulcerative and mutilating, vegetative, tumor-like, and papular and nodular forms.<sup>16</sup> As evidenced by this case, lupus vulgaris can be observed in the plaque form, which manifests as multiple, circumscribed, irregular, hyperpigmented, erythematous patches with coarse white scales. Histopathological examination showed a tuberculoid granuloma with numerous Langhans giant cells and fibrosis because the local tissue response in lupus vulgaris often demonstrates a serpiginous quality that leaves scarring in the affected area.<sup>13,16</sup>

## Conclusion

Cutaneous tuberculosis in the presented cases was diagnosed on the basis of the results of clinical, histopathological, and microbiological examinations. Pathognomonic findings from histopathological examinations may assist physicians in diagnosing challenging cases of cutaneous tuberculosis. In addition, negative results on microbiological examinations do not necessarily exclude the diagnosis. Confirmation of clinical and histopathological findings could be objectively achieved through PCR. However, because of the resource-limited setting in low-income countries and wide-ranging sensitivity of PCR assays, physicians could rely on more cost-effective diagnostic modalities. As evidenced in the present study, the high positivity of clinicohistopathological correlations highlights the

importance of skin biopsy. Therefore, cutaneous tuberculosis could be correctly and efficiently diagnosed at an earlier stage by obtaining correlations between clinical and histopathological findings.

## Disclosure

Case number 1 has already been presented as a poster at the World Congress of Dermatology June 2019 in Milan, Italy.

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