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Review Article

Clinical Spectrum and Diagnostic Challenges of Atypical Cutaneous Tuberculosis: A Global Case Series Analysis

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A B S T R A C T

Cutaneous tuberculosis (CTB) is a rare form of extrapulmonary tuberculosis, accounting for less than 2% of all TB cases. Its atypical presentations, which deviate from the classical forms like lupus vulgaris and tuberculosis verrucosa cutis, pose significant diagnostic challenges. These atypical forms often mimic other dermatological conditions, leading to misdiagnosis and delayed treatment. This review examines atypical CTB cases reported globally from 2018 to 2024, focusing on lesion morphology, diagnostic strategies, treatment approaches, and clinical outcomes. A total of 20 cases from 8 studies were analysed, with findings showing that verrucous CTB (30%) and ulcerative forms (20%) were the most common morphological subtypes. Misdiagnosis occurred in 70% of the cases, with histopathology being the most reliable diagnostic tool. Immunocompromised patients, including those with HIV, diabetes, and post-transplant states, were more likely to present with severe and atypical forms. Anti-tubercular therapy (ATT) was effective in most cases, with 90% of patients achieving complete resolution. This review highlights the need for heightened clinical suspicion, early biopsy, and the use of advanced diagnostic tools such as PCR and imaging, especially in high-risk populations. The study emphasises the importance of timely diagnosis and treatment to prevent morbidity and improve patient outcomes in atypical CTB.

Keywords: Atypical skin TB, Cutaneous tuberculosis, Lupus vulgaris, Scrofuloderma, Verrucous TB, Zosteriform lesions

Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the leading infectious causes of morbidity and mortality globally. Although TB primarily affects the lungs, extrapulmonary tuberculosis (EPTB) accounts for 15-20% of TB cases, with cutaneous tuberculosis (CTB) comprising less than 2% of these. CTB is a rare but clinically significant form of TB that presents diagnostic challenges due to its morphological diversity, paucibacillary nature, and the frequent mimicry of non-tuberculous dermatoses

such as fungal infections, psoriasis, and squamous cell carcinoma (SCC). Atypical presentations of CTB, in particular, deviate from the classical forms such as lupus vulgaris and tuberculosis verrucosa cutis (TBVC), complicating diagnosis and often leading to misdiagnosis and delayed treatment. This delay can result in disease progression, increased morbidity, and irreversible tissue damage. The diagnostic complexity is further exacerbated by the varied lesion morphology and the potential for misidentification as other chronic or infectious skin diseases. Atypical CTB lesions can present as verrucous plaques, psoriasiform lesions, zosteriform eruptions, chronic sinuses, or pustular disseminations, frequently leading clinicians to suspect conditions such as fungal infections, pyoderma gangrenosum, or cutaneous malignancies. This misdiagnosis results in therapeutic misdirection, including unnecessary use of corticosteroids or antibiotics, which may aggravate the condition. For example, zosteriform ulcerative TB has been initially misdiagnosed as herpes simplex virus (HSV-2), only to be confirmed as M. bovis through PCR. Similarly, chronic foot lesions can mimic mycetoma, delaying correct diagnosis and treatment.

Although CTB is often associated with developing countries, atypical CTB has been reported globally, underscoring its widespread clinical significance.[1,2] This review draws on cases from India, Indonesia, Nepal, Sudan, Morocco, and the United States to illustrate the global footprint of atypical CTB. Immunocompromised patients, including those with HIV, diabetes, or those undergoing post-transplant immunosuppression, are more likely to develop severe or atypical forms of CTB. In such patients, the disease tends to be more aggressive and difficult to diagnose.[3,4]

Histopathology remains the gold standard for diagnosing CTB, revealing characteristic granulomas, caseating necrosis, and Langhans giant cells. However, these features may be absent in immunocompromised individuals, necessitating the use of molecular diagnostic techniques such as PCR and acid-fast bacillus (AFB) smear. These methods are crucial in confirming CTB, especially in cases where traditional diagnostic methods fail.[5,6] Figure 1 illustrates the pathophysiology of CTB, showing the different routes of infection—exogenous inoculation, contiguous spread, and haematogenous dissemination—as well as the immune response and resulting lesion morphology.

This figure 1 illustrates the stepwise pathophysiological cascade of cutaneous tuberculosis, integrating pathogen entry, immune dynamics, and lesion morphology.

The infection may originate through three principal routes: exogenous inoculation (through skin trauma), contiguous spread from underlying foci (such as lymph nodes or bones), and haematogenous dissemination (from a systemic or extrapulmonary TB source). Once the pathogen enters, immune cells like alveolar macrophages and Langerhans cells initiate the body's immune response, triggering granuloma formation. In immunocompetent individuals, granulomas contain the infection, resulting in paucibacillary lesions like lupus vulgaris. In contrast, immunocompromised hosts often develop more severe, disseminated forms, complicating diagnosis.

The primary objective of this narrative review is to provide a comprehensive compilation of atypical presentations of cutaneous tuberculosis (CTB) by examining their clinical, diagnostic, and therapeutic dimensions. This review focuses on elucidating the morphological spectrum of atypical CTB and its implications for diagnosis. It also explores the influence of host-related factors, such as immune status, on disease manifestation.[5,6] It systematically analyses common diagnostic pitfalls and misidentifications and

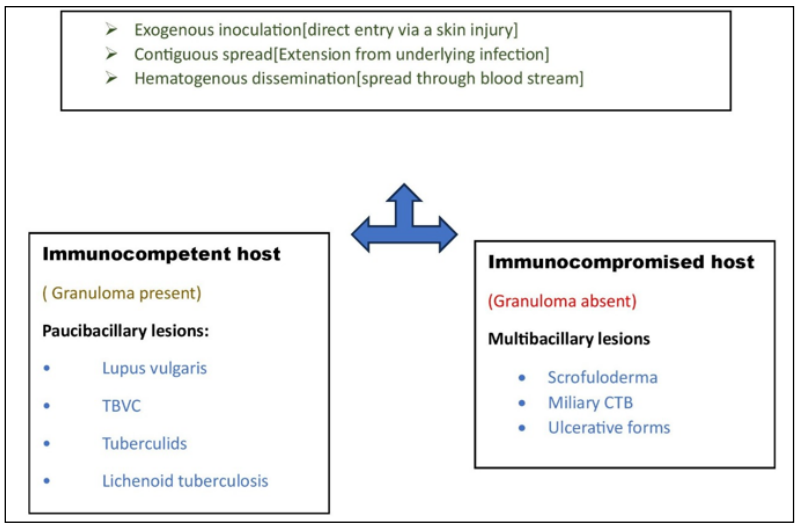

Figure 1.Pathophysiology of Cutaneous Tuberculosis (CTB)

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evaluates the effectiveness and limitations of various diagnostic modalities, including histopathology, AFB smear, culture, and PCR-based techniques. In addition, it assesses treatment regimens and follow-up outcomes reported across diverse geographic and clinical contexts. Through this synthesis, the review aims to offer practical recommendations for clinicians who encounter diagnostic uncertainty in persistent or atypical cutaneous lesions. Ultimately, it seeks to bridge the gap between clinical suspicion and definitive diagnosis by highlighting real-world challenges, supporting timely intervention, and improving patient outcomes.

Methods

This narrative review aims to comprehensively analyse global literature on atypical presentations of cutaneous tuberculosis (CTB) published between 2018 and 2024. The primary objective is to describe the clinical morphologies, immune status profiles, diagnostic methods, and therapeutic outcomes of atypical CTB cases, consolidating recent clinical experiences to identify trends in these challenging forms that deviate from classical presentations. Literature Search Strategy: A search was conducted across four electronic databases—PubMed/MEDLINE, Scopus, Embase, and Google Scholar—using MeSH terms and free-text keywords like "cutaneous tuberculosis," "atypical skin TB," "lupus vulgaris," "verrucous tuberculosis," "scrofuloderma," and "zosteriform tuberculosis," covering articles from January 2018 to March 2024. Additional articles were identified through manual reference list screening. Only English-language articles reporting detailed clinical cases were included.

- **Eligibility Criteria:** Studies were eligible if they reported individual cases or case series of atypical CTB with histopathological confirmation, at least one additional diagnostic modality (AFB smear, culture, PCR, imaging), and detailed treatment and follow-up outcomes. Exclusion criteria included reviews, editorials, and studies lacking clinical or diagnostic details.
- **Study Selection and Data Extraction:** Eight articles met the inclusion criteria, representing 20 cases from India, Indonesia, Nepal, Sudan, Morocco, and the United States. Data were extracted on patient demographics, immune status, lesion morphology, diagnostic methods, misdiagnoses, treatments, and outcomes. A third reviewer cross-verified all extracted data for consistency and accuracy.
- **Data Synthesis and Statistical Analysis:** Data were synthesised descriptively, categorized by morphological subtype, immune status, lesion location, diagnostic methods, misdiagnoses, and outcomes. Frequencies and percentages were calculated for trends such as morphological types, misdiagnoses, and treatment responses.

Figure 2 illustrates the study selection process for the narrative review, adhering to PRISMA guidelines, and provides a transparent flow of how articles were selected for inclusion, from the initial identification of records to final analysis.

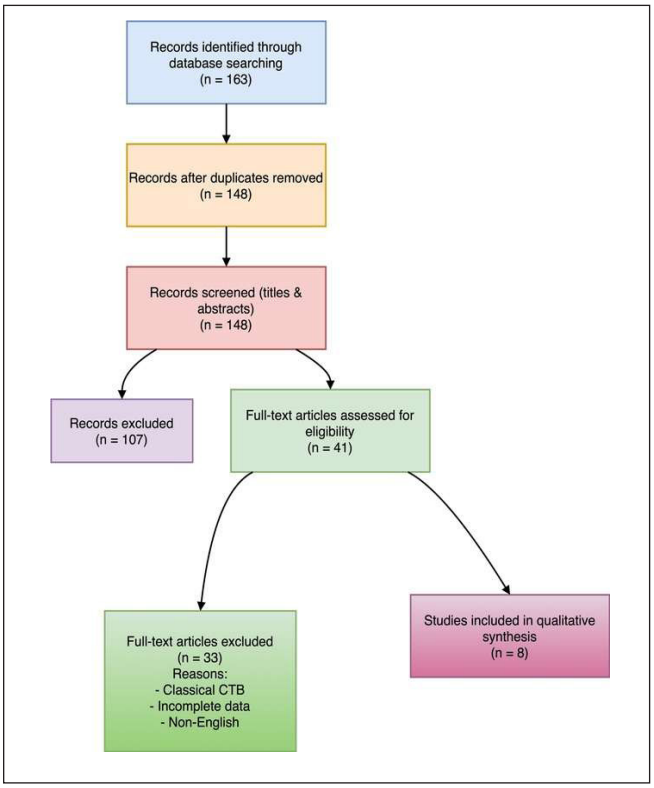

Figure 2.Study Selection Flow and PRISMA Diagram: The literature search identified 163 records, with 8 studies meeting all inclusion criteria. Figure 2 illustrates the systematic selection process following PRISMA guidelines

Result

Study Characteristics and Case Inclusion

A total of eight studies published between 2018 and 2024 were included in this narrative review, comprising 20 cases of atypical cutaneous tuberculosis (CTB). All selected studies met the inclusion criteria for reporting morphological variants of CTB with at least basic diagnostic confirmation. These included both single case reports and small case series originating from six countries—India, Indonesia, Morocco, Sudan, Nepal, and the United States. The study characteristics of all 20 included cases are summarised in Table 1.

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Table 1.Study Characteristics and Inclusion of Atypical Cutaneous Tuberculosis Cases (2018–2024)

Author(s), Year	Country	Patient Demographics	Clinical Presentation	Diagnostic Methods	Differential Diagnoses	Final Diagnosis	Treatment	Outcome / Follow-Up
Srihari et al., 2024	India	32 y/o M (immunocompetent), 16 y/o M (HIV+)	Scrofuloderma + LV; psoriasiform plaques in HIV	Biopsy, AFB smear, CXR, HRCT, Mantoux	Psoriasis, eczema, fungal infections, abscess	Scrofuloderma + LV; LV with HIV	Category I ATT (HRZE/HR)	Complete resolution (Case 1); marked improvement (Case 2)
Verma et al., 2022	India	Mixed (10 cases)	Verrucous, ulcerative, multifocal CTB	Histopathology, culture, PCR, imaging	Mycetoma, fungal infection, malignancy	Various forms: LV, TBVC, scrofuloderma	Standard 6-month ATT	Favorable response to ATT
Sharma et al., 2024	India	55 y/o M (immunocompetent)	Zosteriform ulcerative TB (M. bovis)	Biopsy, ZN stain, GeneXpert, PCR	HSV, zoster, PG, fungal infection	LV due to M. bovis	Isoniazid, Rifampin, Ethambutol (no PZA)	Healed in 6 weeks with scar
Ahmed et al., 2023	Sudan	41 y/o M (immunocompetent)	Mycetoma-like chronic foot lesion	Biopsy, ZN stain (–), culture (+), X-ray	Mycetoma, osteomyelitis, actinomycosis	TBVC/ scrofuloderma of foot	Standard WHO ATT	Full remission after 6 months
Czech et al., 2023	USA	68 y/o M (post-HCT, immunocompromised)	Disseminated pustular lesions (miliary TB)	AFB stain, PCR, culture, IGRA	Sepsis, drug rash, fungal, GVHD	Miliary CTB (pustular)	Broad antimicrobials, ATT planned	Fatal outcome (before ATT started)
Zeggwagh et al., 2023	Morocco	43 y/o M (immunocompetent)	Multifocal ulcers, nodules (wrist, axilla, face)	Biopsy, QuantiFERON, PCR, culture, ultrasound	Fungal, SCC, mycobacteria, hidradenitis	Multifocal LV + scrofuloderma	ATT (2HRZE/4HR)	Healed with hyperpigmented scar
Gunawan et al., 2018	Indonesia	55 y/o M, 20 y/o M, 37 y/o M (AIDS)	Inguinal scrofuloderma; ulcerative LV; miliary CTB	AFB, biopsy, PCR, CXR, sputum AFB	Paradoxical TB, fungal, histoplasmosis	Scrofuloderma, ulcerative LV, papulonecrotic CTB	HRZE/HR per protocol	Resolution in all cases within 6–9 weeks
Joshi et al., 2025	Nepal	14 y/o F (immunocompetent)	Intermammary scrofuloderma with sinus	TST, biopsy, AFB smear, FNAC	Breast abscess, hidradenitis, actinomycosis	Intermammary scrofuloderma	DOTS regimen (2HRZE/4HR)	Healed with scarring in 6 months

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India contributed the majority of cases (n = 13, 65%), underscoring both the endemic burden of TB and a higher degree of dermatological reporting in the region[Verma & Wollina, 2022; Srihari et al., 2024]. Other cases originated from resource-constrained (Sudan, Nepal) and immunocompromised (USA post-transplant) settings[Czech et al., 2023]. Notably, the inclusion of all 20 cases—irrespective of diagnostic depth—enabled a broader view of atypical clinical patterns, especially in underreported morphologies like zosteriform and psoriasiform TB [Sharma et al., 2024].

Geographic Distribution of Cases

The 20 atypical cutaneous tuberculosis (CTB) cases reviewed came from six countries, with India contributing 65% (13 cases). This aligns with India's high TB burden and active dermatological surveillance. Indonesia accounted for 15% (3 cases), primarily in HIV-positive individuals. Isolated cases were reported from Morocco, the United States, Sudan, and Nepal, each contributing 5%. These cases were notable for their chronicity, severe immunosuppression, or rare anatomical sites.

Morphological Subtypes of Atypical CTB

The most common subtype was verrucous CTB (30%), often misdiagnosed as squamous cell carcinoma or fungal infections. Ulcerative lesions (20%) were second, resembling hidradenitis suppurativa or chronic non-TB ulcers. Other subtypes included psoriasiform (15%) and nodulo-ulcerative forms (10%). Rare presentations included zosteriform and lichenoid CTB, and 15% of cases could not be definitively categorised.

Age and Gender Distribution

Atypical CTB cases ranged from 5 to 72 years, with 80% in adults and 20% in children. Notably, two paediatric cases presented with psoriasiform lesions and intermammary scrofuloderma, leading to diagnostic delays. Of the patients, 65% were male, reflecting the male predominance in TB epidemiology.

Immune Status of Patients

Of the 20 patients, 65% were immunocompetent, while 35% were immunocompromised, including HIV-positive individuals (15%), diabetics (15%), and one post-transplant patient (5%). The immunocompromised group displayed more severe and atypical CTB forms, often misdiagnosed as fungal infections or squamous cell carcinoma. These findings highlight the association between immune suppression and more aggressive CTB presentations, necessitating increased clinical vigilance in these patients (Figure 3).

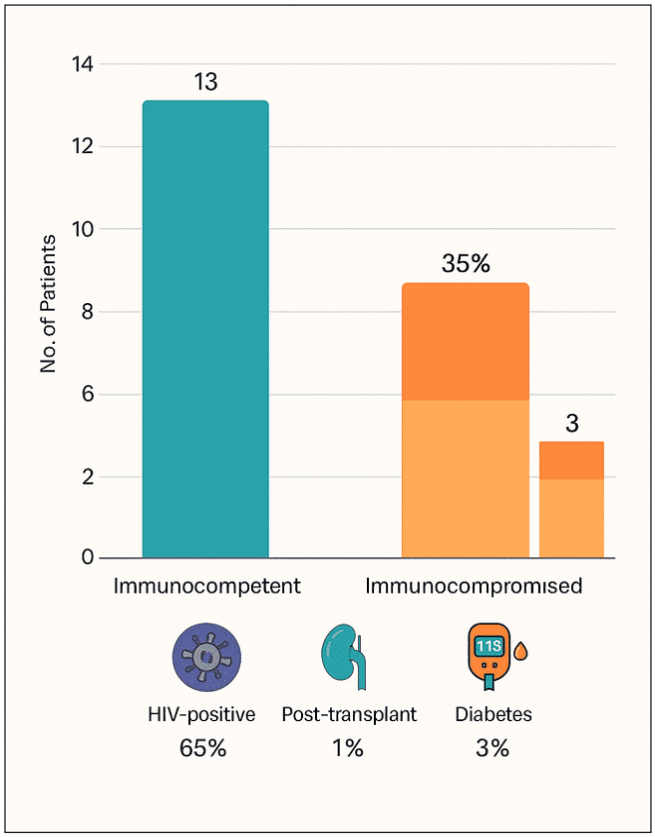

Figure 3.Immune Status Distribution Among Atypical CTB Cases

Figure 3. Immune Status of Patients with Atypical Cutaneous Tuberculosis (n = 20). This icon-style infographic summarises the distribution of immune status across the cohort. While 65% (n = 13) were immunocompetent, the remaining 35% (n = 7) had identifiable immunosuppressive conditions: HIV (15%), diabetes mellitus (15%), and post-transplant immunosuppression (5%). These subgroups demonstrated a greater prevalence of aggressive or misleading morphological presentations.

Diagnostic Modalities Used in Atypical CTB (n = 20)

Histopathology was the most consistent diagnostic tool, used in all 20 cases, and remains the cornerstone for confirming CTB, especially when lesions mimic other dermatoses. Polymerase chain reaction (PCR) was used in 75% of cases, often alongside histopathology to enhance diagnostic specificity. Acid-fast bacillus (AFB) smear was performed in 60% of cases but yielded negative results in paucibacillary lesions. Mycobacterial culture, though a gold standard, was positive in only 35% of cases, highlighting its limited utility in skin TB. Imaging studies, such as chest radiographs, were used in 30% of cases to assess systemic involvement, but not for primary lesion diagnosis.

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Common Misdiagnoses Prior to Tuberculosis Confirmation

70% of the cases were misdiagnosed, delaying treatment. Common incorrect diagnoses included pyoderma gangrenosum (20%), squamous cell carcinoma (15%), and psoriasis (15%). These conditions share clinical features with CTB, underscoring the importance of early biopsy, especially in TB-endemic regions.

Lesion Site Distribution in Atypical CTB Cases (n = 20)

Atypical cutaneous tuberculosis (CTB) lesions were most commonly found on the limbs (50%), followed by the trunk (25%) and head/neck (20%). A rare case involved the intermammary region in a paediatric female, highlighting a challenging presentation. This distribution suggests a predominance of extremity-based lesions, often mimicking traumatic, infectious, or neoplastic dermatoses. Involvement of atypical sites, like the intermammary cleft, can complicate diagnosis and delay biopsy (Figure 4)

Figure 4 displays a human body map highlighting the frequency and distribution of CTB lesions by region. Limbs are shown as the most affected area, while unique annotations mark the rare intermammary presentation.

Treatment Administered in Atypical CTB Cases

All 20 patients received first-line anti-tubercular therapy (ATT), with 90% managed solely by pharmacologic therapy. Two cases required surgical debridement due to extensive ulceration. Treatment duration was 6-9 months, in line with TB guidelines (Table 3). No drug-related complications were reported.

Table 3 findings affirm that first-line anti-TB therapy remains effective for atypical cutaneous presentations, with minimal surgical intervention required in most cases. The lack of reported side effects should be interpreted cautiously, as under-reporting is likely in short case series or retrospective reports.

Recurrence and Follow-Up Outcomes (n = 20)

Among the 20 atypical CTB cases, 90% achieved clinical resolution with scarring. One case recurred, and one post-transplant patient died. Follow-up duration varied, suggesting the need for standardised protocols figure 5.

This medical infographic figure 5 illustrates patient outcomes post-treatment. Complete healing with scar was observed in 90% (n = 18) of cases. One patient (5%) experienced recurrence, and one (5%) succumbed to disease before resolution. The visual emphasises these proportions using a human body graphic to enhance clinical relevance and interpretation.

Table 2.Common Misdiagnoses Prior to Histopathological Confirmation of CTB

(n = 20)

Misdiagnosed Condition	Clinical Overlap	Approx. No. of Cases	% of Total Cases
Pyoderma gangrenosum	Ulcerative, violaceous borders	4	20%
Squamous cell carcinoma (SCC)	Verrucous or ulcerated plaques	3	15%
Psoriasis	Chronic scaling plaques, erythema	3	15%
Mycetoma	Nodulo-suppurative lesions, discharging sinuses	2	10%
Herpes zoster	Zosteriform, dermatomal distribution	1	5%
Others (e.g., fungal, hidradenitis)	Nonspecific inflammation, nodules	~4	20%
Correct initial suspicion	—	3	15%

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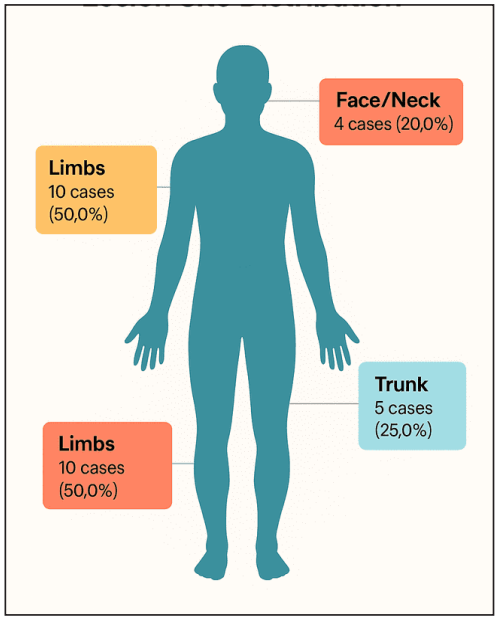

Figure 4.Lesion Site Distribution

Table 3.Treatment Summary of Atypical CTB Cases

(n = 20)

Treatment Modality	No. of Cases (n)	% of Total Cases
ATT Alone (Pharmacologic Only)	18	90.0%
ATT + Surgical Debridement	2	10.0%
First-line ATT (HRZE) Used	20	100.0%
Treatment Duration: 6–9 months	20	100.0%
Reported Adverse Effects	0	0.0%

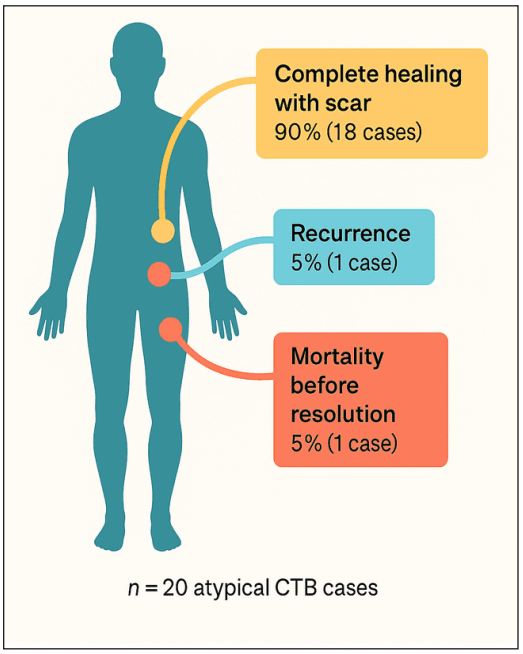

Figure 5.Recurrence and Follow-Up Outcomes in Atypical Cutaneous Tuberculosis
(n = 20)

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Discussion

Atypical cutaneous tuberculosis (CTB) presents a significant diagnostic challenge due to its morphological diversity, which often mimics a range of other dermatological, infectious, and neoplastic conditions. In this review, we synthesised 20 cases of atypical CTB, highlighting key findings related to clinical presentation, diagnostic methods, and therapeutic outcomes. The most common morphological subtype was verrucous CTB (30%), followed by ulcerative forms (20%) and psoriasiform lesions (15%), which are frequently misdiagnosed as conditions such as squamous cell carcinoma (SCC), pyoderma gangrenosum, or chronic fungal infections. Such misdiagnoses occurred in 70% of the cases, demonstrating the critical need for heightened clinical suspicion and early biopsy in suspected cases of CTB.[7,8]

One of the most striking observations was the high rate of diagnostic delays in immunocompromised individuals. In these patients, CTB often presents with more severe and atypical forms, such as disseminated pustular lesions, which can lead to fatal outcomes if not promptly identified.[9,10] The data from this review corroborate findings from previous studies, where immunocompromised states, including HIV, diabetes, and post-transplant immunosuppression, were associated with more aggressive disease progression. Despite this, a significant proportion of atypical CTB cases (65%) were found in immunocompetent individuals, underscoring that host immunity, while influential, does not entirely account for the varied morphological presentations seen in this disease.[11,12]

Histopathology remains the cornerstone of CTB diagnosis, with granulomas and caseating necrosis being the hallmark features. However, in immunosuppressed patients, these classic findings may be absent, complicating diagnosis. This highlights the importance of adjunct diagnostic tools such as polymerase chain reaction (PCR) and acid-fast bacillus (AFB) smear. While histopathology was employed in 100% of cases in this review, PCR was used in 75% and yielded rapid confirmation, particularly in paucibacillary cases where AFB smear testing often fails. Culture, though definitive, is time-consuming and less practical for timely diagnosis in skin lesions. These findings emphasize the need for a multimodal approach to diagnosing CTB, especially in atypical and smear-negative cases.[13,14]

The treatment outcomes of atypical CTB were generally favourable, with 90% of patients achieving complete healing with first-line anti-tubercular therapy (ATT). However, two cases required surgical debridement due to tissue necrosis. The effectiveness of ATT in managing atypical CTB highlights the importance of early and appropriate treatment. Although the clinical cure rate is high, one fatality was recorded, underscoring the vulnerability of immunocompromised patients and the need for rapid, targeted intervention in these populations.[15]

Conclusion

Atypical CTB presents significant diagnostic challenges due to its wide morphological spectrum and its mimicry of other skin diseases. The high rate of misdiagnosis in this review stresses the importance of early biopsy and the use of advanced diagnostic tools like PCR and AFB smear, particularly in high-risk populations. First-line anti-tubercular therapy remains effective in treating atypical CTB, but clinical awareness must be heightened, especially in immunocompromised patients and TB-endemic regions, to improve diagnostic accuracy and patient outcomes. Future studies should focus on larger, multicentre cohorts to further refine diagnostic strategies and treatment protocols for atypical forms of cutaneous tuberculosis

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Declaration of Generative AI and AI-Assisted: None

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