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Cutaneous tuberculosis, different clinical spectrum of the same disease: the importance of pre-test probability

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Abstract

Antecedents. This report presents three cases of Cutaneous tuberculosis CTB that were diagnosed at Calderon Hospital, Quito, Ecuador. The first case was Tuberculosis verrucosa cutis (TVC) in a 44-year-old man with circinated erythematous areas with ulcerated nodules and verruciform plaques from the right lower limb to the hip. The second case was Lupus Vulgaris (LV) in a 50-year-old female with one-year history of pruritic dermatosis in the left ciliary area. The third case was Scrofuloderma in a 23-year-old man with erythematous nodules that drain caseous material at neck, thorax and axillary region. Almost all laboratory tests that were available turned out to have limitations as a diagnostic tool. Conclusion. In immunocompromised and high-risk individuals with atypical lesions, it is important to correlate clinical and epidemiological characteristics with the pretest probability in order to optimize indicators and determine or exclude out the diagnosis.

Introduction

Tuberculosis (TB) is a public health problem because of its widespread prevalence, severe morbidity and high mortality. In 2020, TB was diagnosed in 9.9 million persons worldwide.^[1] Cutaneous tuberculosis (CTB) is a rare form of extrapulmonary tuberculosis that accounts for 1-1.5% of cases, the majority described in immunocompromised and high-risk population living in developing countries.^[2,3] *Mycobacterium Tuberculosis (Mtb)*, *Mycobacterium. Bovis (M. bovis)*, and occasionally BCG vaccine (an attenuated strain of *M. bovis*) are the etiological agents.^[2,3] CTB can resemble a number of inflammatory and neoplastic disorders and due to its high clinical polymorphism and non-specific primary skin lesions, it is difficult to diagnose.^[4,5] Several diagnostic techniques have been used to directly or indirectly detect *Mtb*. In the majority of developing nations, conventional solid-phase culture (Lowenstein-Jensen) remains the gold standard to diagnose TB; nevertheless, its usage in CTB is restricted due to the pathogens' lengthy development period.^[4] To address this limitation, new and more straightforward techniques, such as the automated liquid colorimetric culture (TK Medium), can be used to accelerate the diagnosis.^[6] Another direct diagnosis technique is the pathogen identification via microscopy based on Ziehl-Neelsen (ZN) and auramine-rhodamine staining.^[7] The indirect methods, such as Tuberculin skin test (TST), and Interferon-gamma release assays (IGRAs) challenge the immune system to determine if lymphoid T cells have been exposed to *Mtb*. TST includes antigens that are present in *Mtb* as well as *M. bovis*-BCG and other mycobacteria. As a result, this test has low specificity compared to the immunodiagnostic tests (IGRAs) which demonstrated to be capable to identify *Mtb* with high specificity.^[8]

Histopathology exhibits non-specific features of inflammation, characterized by granulomas, which are collections of histiocytes with multinuclear giant cells and other inflammatory cells like macrophages, lymphocytes, and plasma cells.^[9]

Finally, genetic diagnostic techniques such as polymerase chain reaction (PCR), Restriction Fragment Length Polymorphism (RFLP) and Mycobacterial Interspersed Repetitive Unit Variable Number Tandem Repeats (MIRU-VNTR) have emerged as important tools to diagnose infections, demonstrating enough discriminatory power to detect efficiently specific pathogens in tissues, secretions or fluids.^[2,4,5]

The lack of a rapid, sensitive, and accurate diagnostic test to demonstrate the etiologic agent in skin, which is aggravated in developing countries for different reasons beyond the technical ones, demand the integration of clinical and epidemiological likelihood (pre-test) for on-time treatment decisions using the best institutional guidelines and accessible multidrug approaches.^[10]

Case report 1

A 44-year-old male, farmer, presented at our outpatient department with two-year history of an ulcerated nodules and circinated erythematous areas, which together give a verruciform appearance in the right lower limb. Over a year, the verrucous plaque gradually progressed and coalesced into a big lesion, which expanded to the hip (Fig.1 A, B). He denied constitutional symptoms including fever or weight loss. There was no history of skin problems or TB among close contacts. The diagnostic tests for *Mtb* including tuberculin skin test (TST), bacilloscopy (BAAR), *Mtb* culture, and polymerase chain reaction (PCR) of skin were negative). Other tissue investigations included bacterial gram staining and fungal culture were negative. His blood test for venereal disease (VDRL) and the human immunodeficiency virus (HIV) showed negative results. A chest radiograph was performed to rule out the primary pulmonary and active TB, which showed no signs of infection. Histopathology revealed pseudoepitheliomatous hyperplasia, hyperkeratosis with granulomatous process and necrotic areas (Fig. 1C). Periodic acid-Schiff staining (PAS) was negative. However, the presence of acid-fast bacilli could be detected by Zielh-Neelsen test in skin (Fig. 1D)). The epidemiology, clinical characteristics of the lesions and histopathology supported the presumptive diagnosis of tuberculosis verrucosa cutis (TVC) that was treated according to the standard WHO recommendations.^[10,11] From the first month of treatment, a favorable evolution was already observed (Fig. 1E).

Case report 2

A 50-year-old female, health worker presented one-year history of pruritic dermatosis in the left

ciliary region. On physical examination, an infiltrated erythematous plaque with irregular edges with desquamation and central atrophy in the ciliary arch was observed (Fig 2A). Diascopy revealed the appearance of apple jelly (Fig. 2B). She denied constitutional symptoms including fever or weight loss. The patient has antecedents of hypertension but neither skin diseases nor close contact with TB. All diagnosis test for *Mtb* including periodic acid-Schiff stain (PAS), acid-fast stain (AFB), tuberculin skin test (TST), TB culture, polymerase chain reaction (PCR) and chest radiograph were negative. Histopathology revealed diffuse dermal lymphocytic infiltrate, granulomas with multinucleated giant cells sparing the hair follicles and negative Zielh-Neelsen. (Fig. 2C and D). The strong clinical suspicion (pre-test probability) supported the presumptive diagnosis of Lupus vulgaris (LV) and was treated according to the standard WHO recommendations.^[10,11] At the end of the treatment, a favorable evolution was observed (Fig. 2E).

Case report 3

A 23-year-old man with two-year history of erythematous nodules at the right neck, chest, and axilla, presented at the emergency room in poor general condition. He had antecedents of alcoholism and drug addiction, significant weight loss, diarrheal stools and melenas. The nodules worsen in recent months, which affect the contralateral side of the neck and thorax, draining purulent secretion, leaving painful fibrotic scars (Fig. 3 A, B and C). On physical examination, a cachectic and diaphoretic patient was observed, with bilateral edema in the lower limbs. Tuberculin skin test (TST) and bacilloscopy were negative. A chest radiography showed signs of primary pulmonary and active TB. Skin PCR for *Mtb* showed positive results. Histopathology revealed granulomas with Langhans-type giant cells, surrounded by crown of lymphocytes with necrosis and negative Zielh-Neelsen staining (Fig. 3D, 3E). A colonoscopy revealed nodular lesions in the cecum and ascending colon, whose biopsy reported granulomas with necrosis, suggestive of intestinal TB with negative Zielh-Neelsen and Periodic acid-Schiff staining (PAS) (Fig 3 F). Other laboratory test showed hemoglobin 8.6 g/dL (13.2 to 16.6 g/dL), creatinine 3.6 mg/dL (0.74 to 1.35 mg/dL), SOGT = 52 U/L (5 to 40 U/L) and SGPT = 59 U/L (7 to 56 U/L). Test for venereal disease (VDRL) and the human immunodeficiency virus (HIV) showed negative results. The clinical characteristics, complemented with laboratory tests, supported the diagnosis of disseminated Tuberculosis (miliary TB) and Scrofuloderma. The patient developed septic shock shortly after being admitted to the hospital, and due to his poor general health and adverse course of events, he passed away.

Discussion

Mtb-related skin lesions is challenging to distinguish from other dermatological disorders. The primary non-specific skin lesions may appear in the form of papules, vesicles, ulcers or plaques which frequently resemble other skin conditions such as granulomatous syphilis, leishmaniasis, discoid lupus erythematosus, psoriasis, Wegener's granulomatosis, tuberculoid leprosy, sarcoidosis, actinomycosis, mycetoma and other skin infections, making the diagnosis difficult.^[2,3]

CTB is prevalent in young adults and has a wide range of classifications as result of the significant clinical polymorphism.^[4] Depending on the route of infection and the pathogen burden on the skin, CTB is classified as exogenous and endogenous or multibacillary and paucibacillary.^[3] The most frequent manifestation of CTB, occurring in 59% of cases, is lupus vulgaris, followed by scrofuloderma.^[5]

We first described a case of tuberculosis verrucosa cutis (TVC), the most common paucibacillary variant in healthcare professionals and farmers (sensitized immunocompetent individuals) due to exogenous inoculation.^[12] As differential diagnosis, leishmaniasis, keratoacanthoma centrifugum, verruca vulgaris, hypertrophic lichen planus, and sporotrichosis were considered.^[13] The histology of skin lesions showed typical granulomas with necrotic areas and positive Ziehl-Neelsen staining demonstrating the presence of acid-fast bacilli in the biological material. We were able to highly suspect (pre-test likelihood) CTB thanks to the microscopic identification of the bacillus in the skin and the clinical presentation. As a result, we started the therapy according to the WHO recommendation, which worked satisfactorily. In the second patient the combination of clinical signs, dermoscopic examination (classic "apple-jelly" appearance) and the evidence of high prevalence of lupus vulgaris (59%) made us suspect of CTB disease.^[13] The positive clinical response to antituberculosis medication further confirmed the diagnosis in this case. Therapeutic trials with antituberculosis therapy are justified if clinical suspicion is strong.^[14] Due to the limitation of diagnostic tests for *Mtb*, the World Health Organization (WHO) have recently updated the guidelines for management of smear-negative and extrapulmonary TB. Hence, expanded clinical case definitions is used to circumvent the use of laboratory-based tests encouraging to use clinical case definitions.^[11] Lupus vulgaris (LV) is a paucibacillary form that may arise as a result of direct inoculation or hematogenous spread from a primary infection in a sensitive individuals, being the head and neck the common sites of lesions.^[3]

The third case describes a multibacillary form of CTB known as scrofuloderma, the most prevalent form of extrapulmonary TB in children and HIV-positive patients.^[15] This case presents an immunosuppressed patient due to alcoholism and drug abuse, HIV negative with high constitutional and nutritional impact, and multiple organ TB involvement (pulmonary, ganglion and

intestine). The diagnosis tests showed granulomas in histopathology and direct evidence of tuberculosis bacilli in tissue (positive PCR). The high pre-test probability combined with the 100% sensitivity and specificity of the PCR in this multibacillary form makes it possible to diagnose the disease with confidence (99% post-test probability).^[16] Tertiary syphilis, paracoccidioidomycosis, actinomycosis, hidradenitis suppurativa and lymphogranuloma venereum were all taken into consideration as differential diagnoses.^[17]

As seen by the three cases presented in this report, practically all established laboratory test revealed CTB diagnosis limitations. Depending on the setting, conventional microscopy's sensitivity for the direct detection of *Mtb* ranges from 20 to 80%, however it is described that fluorescence-based technique can increase the detection of paucibacillary infection.^[18] Conventional solid-phase cultures often appear positive after 21 days, while more recent, less complex automated liquid colorimetric culture techniques have the potential to diagnose illnesses in as little as 7 days.^[18] To maximize the culture diagnosis, the Center for Disease Control (CDC) advice combining liquid and solid-phase cultures

The new serologic and genotyping methods could open new diagnostic possibilities to detect this ambiguous disease with high sensitivity and specificity, which associated with the pre-test probabilities, will determine its diagnosis or exclusion. As an example, Interferon-gamma release assays (QFT-G and T-SPOT) have high sensitivity and specificity (from 89% to 100%) and have the advantage of determining whether a patient has latent or active infection since only T cells stimulated with ESAT-6 and/or CFP-10 release interferon-gamma (IFN-gamma) which is specific for active *Mtb*.^[5,19] In paucibacillary TB cases, nucleic acid amplification assays (PCR) are less sensitive (55% to 73%) and unable to distinguish living from dead mycobacteria.^[20] Additionally, other genotyping methods like RFLP and MIRU-VNTR have demonstrated to have sufficient discriminatory power to tracing transmission and determine phylogenetic of *Mtb*.^[2] Nevertheless, the use of new diagnostic methods is still restricted especially in developing countries due to the high running costs, the requirement for large amounts of genetic material, and necessity of well-equipped laboratory facilities.^[2]

Conclusions

A thorough history and meticulous physical examination in immunocompromised and high-risk patients with atypical lesions is required to diagnose cutaneous TB. Pre-test probability and new lab technology may help to address the existing inaccuracy of tests to identify CTB in underdeveloped countries, which usually results in a delayed treatment.

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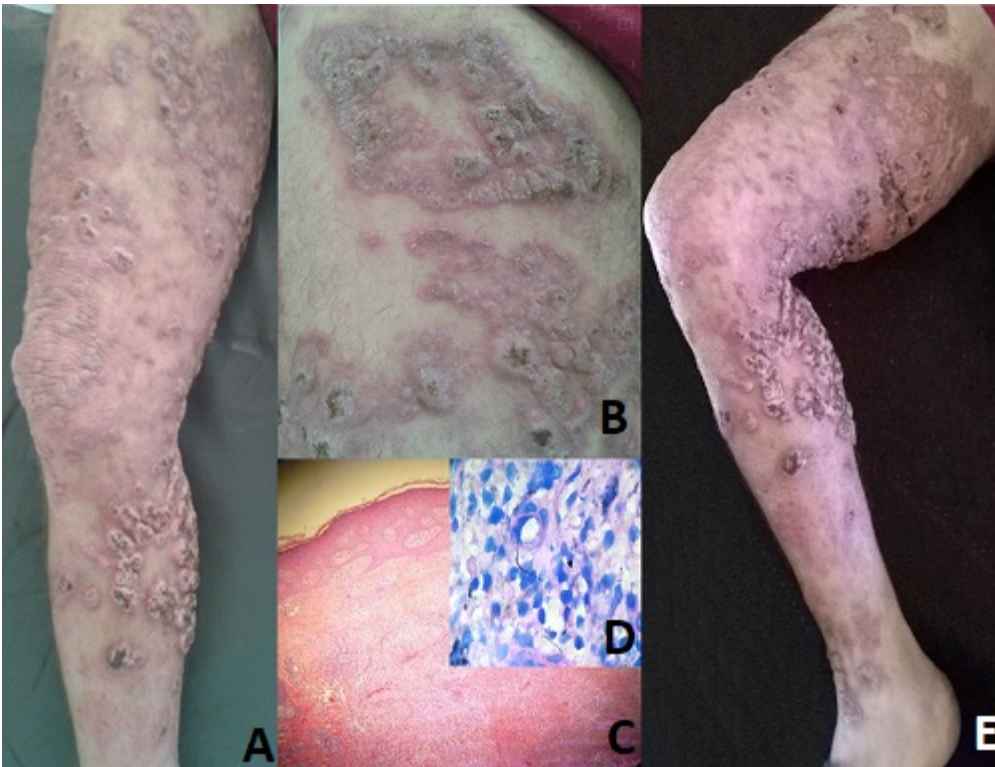


Figure 1. A) Verruciform dermatosis on the right lower limb. B) Approach granulomatous appearance, verruciform. C) Hematoxylin/eosin at 10x shows a granulomatous process. D) Zielh Neelsen stain positive for acid-fast bacilli (arrow). E) Verrucous tuberculosis decreased size and lesion hyperkeratosis after 1 month of treatment.

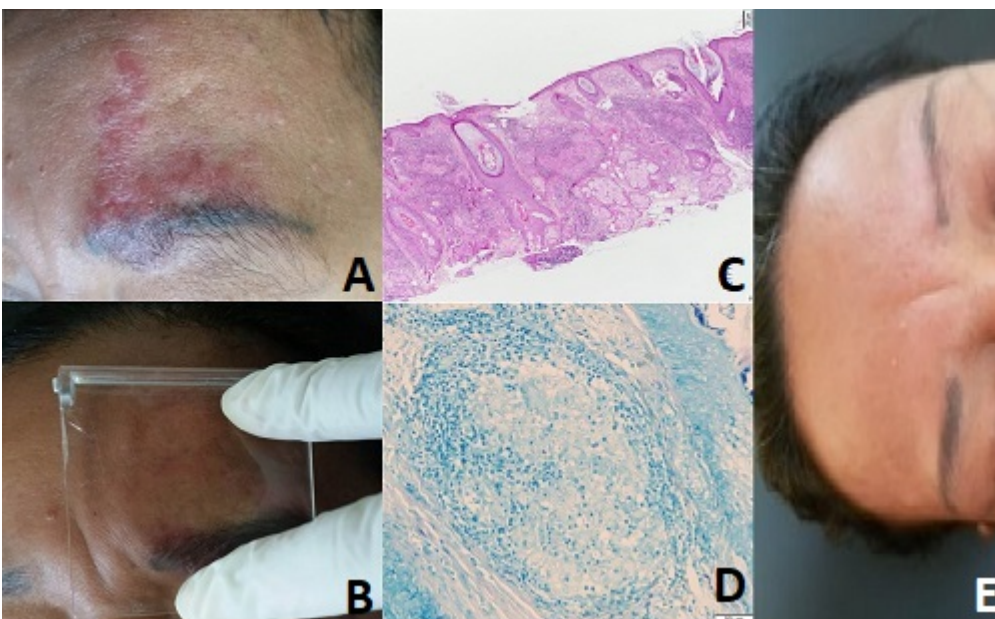


Figure 2. A) Erythematous plaque with irregular borders, desquamation on the ciliary arch. B) Diascopy positive. C) Dermis, numerous granulomas with epithelioid cells surrounded by abundant lymphocytic infiltrate and Langhans-type multinucleated giant cells. No necrosis is

evident. D) Zielh-Neelsen negative. E) Lesion resolution 6 months post- treatment.

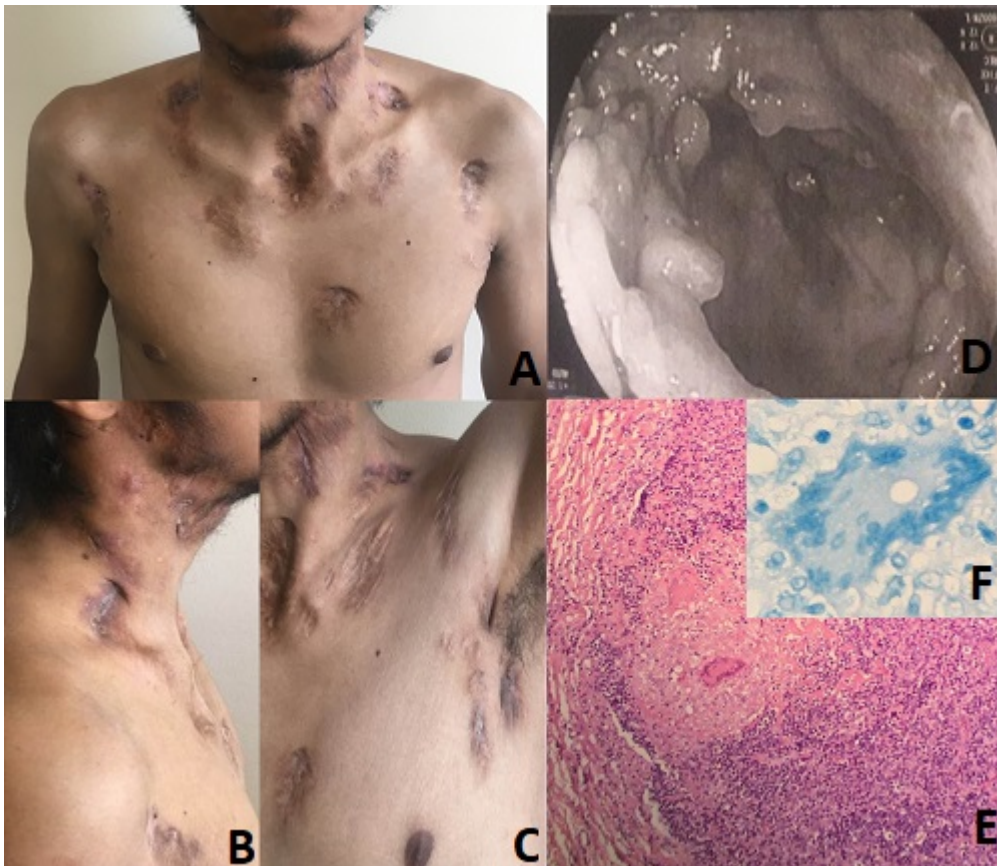


Figure 3. A) Fibrotic scars and erythematous nodules that drain caseous material from the neck and anterior chest. B) Neck scars. C) Lesions in the left axillary hollow. D). Nodules in colon and cecum in colonoscopy. E) Granulomas with Langhans-type giant cells, surrounded by a crown of lymphocytes with foci of necrosis. F) Zielh-Neelsen negative.

Table 1. Schematic information on the diagnosis test used for CTB.

	Age Gender	RX	BA AR	TS T	Zielh- Neels en	PC R	Histology	Diagnosis
Case 1	44/M	-	-	-	+	N/ A	Pseudoepitheliomatous hyperplasia, hyperkeratosis with granulomas, necrosis areas. Presence of tubercle bacilli.	Tubercul osis verrucosa cutis (TVC)
Case 2	50/F	-	-	-	-	N/ A	Diffuse dermal lymphocytic infiltrate, granulomas with multinucleated giant cells.	Lupus vulgaris (LV)

Case 3	23/M	+	-	-	-	+	Granulomas with Langhans-type giant cells, surrounded by lymphocytes crown and foci necrosis	Scrofuloderma
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Table 2. Clinical classification of CTB according to infection mechanism and pathogen load.

Infection mechanism	Clinical presentation
Exogenous inoculation	Tuberculosis verrucosa cutis Tuberculosis chancre Lupus vulgaris
Endogenous reinfection (lymphatic extension)	Lupus vulgaris
Endogenous reinfection (hematogenous extension)	Acute miliary tuberculosis Tuberculous gumma Lupus vulgaris
Endogenous reinfection (contiguous spread)	Scrofuloderma Orificial tuberculosis
Pathogen load	Clinical presentation
Paucibacillary	TB verrucosa cutis Lupus vulgaris Tuberculoid (Papulonecrotic tuberculid, Lichen scrofulosorum, Erythema induratum of Bazin)
Multibacillary	Tuberculous chancre Scrofuloderma Orificial tuberculosis Acute miliary tuberculosis Tuberculous gumma