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**Single Case**

# Intralesional Avirulent Bacillus Calmette-Guérin Injection as a Promising Method for the Treatment of Tuberculosis Verrucosa Cutis

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**Keywords**
Tuberculosis verrucosa cutis · Bacillus Calmette-Guérin · Immunotherapy

**Abstract**
Cutaneous involvement is a relatively uncommon manifestation of tuberculosis (TB), particularly outside the endemic regions. Cutaneous TB manifests itself in various clinical forms, depending on the host's immune status and mode of transmission. Nonetheless, the same treatment regimen is recommended for every subtype. Tuberculosis verrucosa cutis (TBVC) is a specific subgroup in which the affected persons are usually healthy adults who are vaccinated or exposed to mycobacteria during their occupational activities. These patients have the ability to launch a strong cellular immune reaction against mycobacteria. In this article, we present an elderly patient with a 4-year history of TBVC who was treated with intralesional injection of avirulent Bacillus Calmette-Guérin (BCG) and report our clinical observation on the inflammatory and healing process of the patient's lesion following the intralesional BCG injection.



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## Introduction

Tuberculosis (TB) is an infectious disease caused by a genetically homogenous group of *Mycobacteria*, known as *Mycobacterium tuberculosis complex* [1]. Despite being curable and preventable, TB continues to be a significant global health problem. One-quarter of the world's population is still infected with *M. tuberculosis*, the most common etiological agent for TB. Approximately 10 million new active cases are reported annually. TB ranks among the top ten causes of global deaths and is also the leading global cause of death due to a single microorganism [2, 3]. TB usually spreads via the airborne route. Lungs are the primary infection site for TB (pulmonary TB). However, organs other than the lungs can also be involved (extrapulmonary TB).

Various studies indicate that 20–53% of all TB cases present with extrapulmonary involvement [4]. Cutaneous tuberculosis (CTB) constitutes 1–2% of these extrapulmonary cases [5]. CTB can manifest in various forms, depending on the source of the bacilli (exogenous or endogenous), the route of transmission, and the host's immune status. Tuberculosis verrucosa cutis (TBVC) is an exogenous form of CTB seen in previously infected or vaccinated individuals with high or moderate immunity. TBVC can be self-limited, but there are reports of flexion-deformities, elephantiasis, and malign transformations in untreated cases [6–8]. Treatment options for all CTB forms are limited. All patients are treated with the same conventional oral therapy recommended by the World Health Organization for the treatment of pulmonary TB [4, 5].

Immunotherapy is a form of therapy that modifies patients' immune system to treat primarily oncological diseases. Although the roots of this concept (using the patient's own immune system to fight an active disease) can be traced back to the works of Dr. William Coley in the late 19th century, it is only recently that there has been a widespread emerging interest in it in dermatology [9]. The current main focus of dermatological immunotherapy is the treatment of melanoma, multiple warts, and alopecia areata [10–12]. In this paper, we report our clinical observation on the healing process of a patient with recalcitrant TBVC after intralesional injection of avirulent Bacillus Calmette-Guérin (BCG). At the end of our 40-day-long follow-up, we observed an 80% regression of the lesional area.

## Case Report

A 65-year-old male patient presented our clinic with a 4-year history of recalcitrant skin lesions. He was being treated as presumptive clinical diagnosis as verruca vulgaris with multiple topical therapies, including creams containing 5-fluorouracil, salicylate, retinoids, 40% urea, and cryotherapy. Despite the medical interventions, the lesion has been growing steadily. At the first visit, a well-demarcated, hyperkeratotic verrucous plaque on the thenar region of his left hand was observed. The plaque had a surface area of 10 $cm^2$ and was extending dorsally over the first interdigital fold (Fig. 1a). Except for the plaque, the patient's physical examination was unremarkable. On further questioning, the patient revealed that he had cared for a cow for a month for the religious "Feast of Sacrifice" 5 years ago. Due to the lesion's unresponsiveness to conventional verruca therapies, a tuberculin skin test (TST), a skin biopsy for histological examination, polymerase chain reaction, and culture were performed.

Histological sections showed epidermal hyperplasia and dermal noncaseous granulomas (Fig. 2a). TST resulted in 12-mm induration (Fig. 2b). The culture and polymerase chain reaction test results were positive for *M. bovis*. Based on clinical and laboratory findings, TBVC was diagnosed. Further diagnostic procedures revealed no other systemic involvement.

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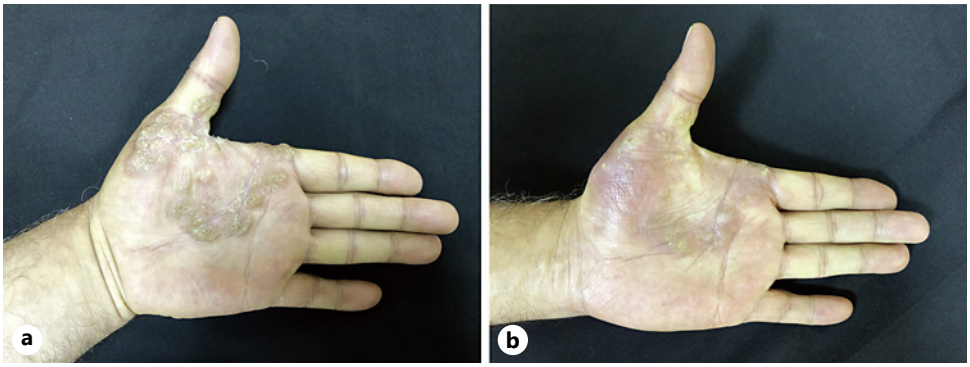


**Fig. 1.** TBVC First Day - Last Day comparison. **a** Well-demarcated thick hyperkeratotic verrucous plaque with a purplish base, extending from left thenar eminence to the first interdigital to the dorsum of the hand over the first interdigital fold at the time of admission. **b** Mild erythema and minimal residual areas at the 40th day.

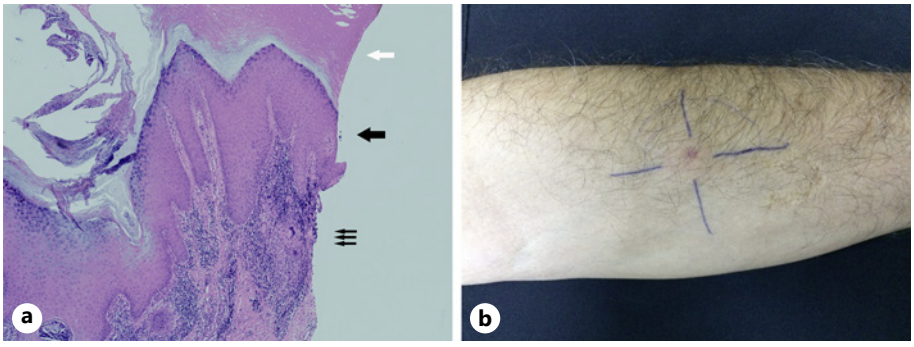


**Fig. 2. a** Biopsy from the plaque. Prominent thickening of stratum corneum (bold white arrow) and acanthosis (bold black arrow). Noncaseating granuloma with multinucleated Langhans cells in the center (three arrows). **b** A positive tuberculin skin test two days after the first visit, indicating the presence of reactive T-cells against mycobacterium.

Due to the patient's objection to therapy with a multiple drug regimen, an intralesional BCG injection was planned. A suspension from freeze-dried powder containing attenuated bacilli of *M. bovis* (prepared from a BCG culture [OncoTice®]) was prepared according to the manufacturer's instructions. 12.5 mg powderized BCG was diluted in 50 mL serum physiologic to obtain a suspension containing 0.4–1.6 × 107 CFU/mL. A total volume of 2,083 mL BCG was injected into a 10 $cm^2$-plaque intralesionally (0.2 mL per $cm^2$). The injected dose was calculated according to the ratio of one dose of OncoTice® to the mean urothelium surface area of an adult male without prostatic symptoms, which is 50 mL–240 $cm^2$ [13].

On the third day after the injection, an inflammatory reaction was observed. The plaque became edematous, erythematous (Fig. 3d–f). The patient had a fever of 38°C concurrently, which continued for one and a half day and was reduced with cold compresses. On the 10th day, erythema and edema were regressed, and the lesional area began to desquamate (Fig. 3g–i). On the 18th day, suppurative foci on the hand dorsum emerged and were drained by puncturing (Fig. 3j–l). Finally, on the 40th day, signs of acute inflammation were subsided without leaving any scars, and the lesional area shrank from 10 $cm^2$ to 2.0 $cm^2$ (Fig. 3m–o) (Fig. 1b). After that, the patient had to relocate to another city and was lost to our follow-up.

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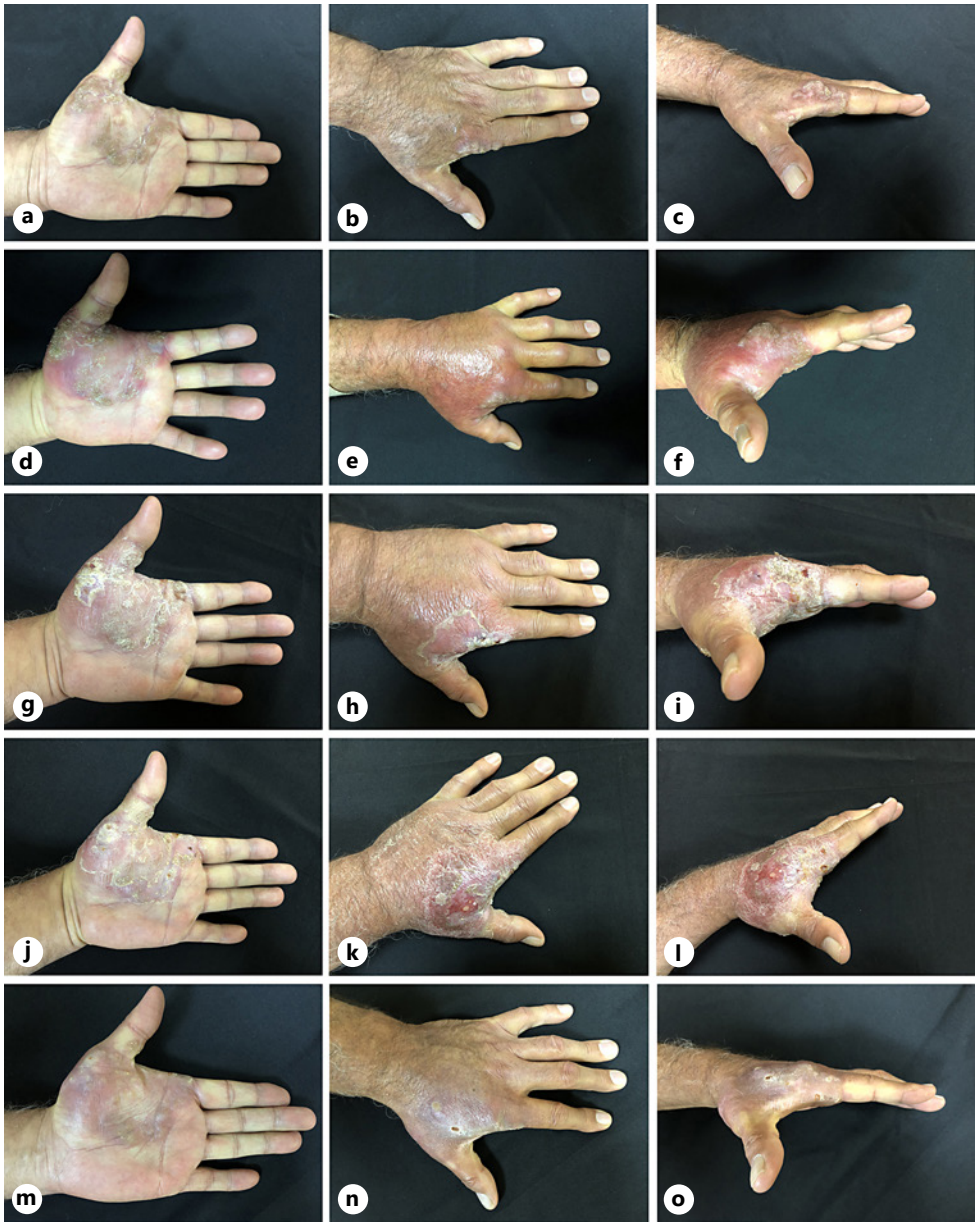


**Fig. 3.** Clinical follow-up. **a–c** (first row) Clinical appearance of the lesion before the BCG vaccination. **d–f** (second row) 3rd day after the injection. All the cardinal signs of acute inflammation were present. Localized erythema, edema can be seen in the photo. **g–i** (third row) 10th day after the injection. Regression of erythema of edema with concomitant desquamation. **j–l** (fourth row) 18th day. Emergence of a suppurative focus on the dorsum of the left hand. **m–o** (fifth row) 40th day. All signs of acute inflammation are diminished. Minimal residual areas of the verrucous plaque can be seen on the thenar eminence.

## Discussion

CTB defines a broad spectrum of skin diseases, ranging from highly contagious acute miliary TB with internal organ involvement and numerous mucocutaneous mycobacteria-rich lesions to TBVC with a solitary mycobacteria-poor cutaneous plaque and no systemic involvement. Regardless of the patient's immune status, mycobacterial burden, and degree

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of systemic involvement, the same regimen is recommended for all CTB cases, which is the standardized regimen recommended by the WHO for the treatment of new cases of pulmonary TB. This multi-drug regimen lasts 6 months and requires concomitant use of isoniazid (H), rifampin (R), pyrazinamide (Z), and streptomycin (E) in two phases; H + R + Z + E in the initial 8-week-long intensive phase and H + R during the following 16-week-long maintenance phase (2HRZE/4HR) [4, 5, 14]. Major disadvantages of this regimen are its long duration, the requirement to use multiple oral medications, and possible drug-related adverse reactions, which may lead to patients' noncompliance or failure in adherence to treatment.

TBVC is a specific subgroup of CTB. The patients with TBVC are usually vaccinated, healthy adults who are exposed to mycobacteria during their occupational activities (i.e., pathologists, laboratory personnel, dentists to *M. tuberculosis*; dairy farmers, butchers to *M. bovis*). These patients have the ability to launch a strong cellular immune reaction against mycobacteria, which can be observed clinically as strong positive reaction to TSTs and as well-formed granulomas in histopathological sections. These granulomas serve to the containment of the mycobacteria and prevent them from disseminating. Without treatment, TBVC can persist for years and may lead to some severe health problems, such as contractures of extremities, elephantiasis, and malign transformation into squamous cell carcinoma [6–8].

Kick-starting the immune memory may be beneficial for the treatment of TBVC patients, as seen in our case. We observed approximately 80% clearance of TBVC plaque in 40 days without any severe side effects, just after one injection. Therefore, we propose that intralesional BCG can be a useful therapeutic option for the treatment of TBVC. Intralesional BCG can shorten the duration of systemic therapy and so diminish the possibility of possible adverse drug side effects. Intralesional BCG can be used as a standalone agent or as an adjunct to classically recommended, systemic anti-TB multi-drug regimen. Intralesional BCG can also be helpful in treating other chronic mycobacteria-related diseases (i.e., lupus vulgaris, tuberculoid leprosy, sarcoidosis) or other skin diseases (i.e., cutaneous papillomavirus infections, advanced-stage basaliomas, and melanomas) in patients previously sensitized to BCG. Further studies are required to evaluate the validity of this proposal.

## Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local/national guidelines.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Özgür Gündüz (Ö.G.) established the diagnosis interpreted the patient's clinical findings and laboratory data regarding the dermatological disease. Ö.G. conceived of the presented idea. Ö.G. carried out the therapy. Ö.G. and Gülşah Koçak (G.K.) carried out the clinical follow-up. G.K. performed photographic documentation. Tuba Devrim (T.D.) performed the histological examination. Birgül Kaçmaz (B.K.) interpreted the microbiological data. Hülya Şimşek (H.Ş.) carried out bacterial cultures and polymerase reaction tests. Ö.G. wrote the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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