Case report

Interesting presentation of cutaneous tuberculosis on the face: a case report

Arada Ovattrakul and Pimsiri Poolsuwan
Institute of Dermatology, Ministry of Public Health

Abstract:

Cutaneous tuberculosis is a skin infection which is present in multiple subtypes. Lupus vulgaris is the most frequent cutaneous form. The clinicals of lupus vulgaris vary and sometimes mimick other skin conditions. A definite diagnosis depends on clinico-histopathological features and the presence of Mycobacterium tuberculosis.

We report an interesting clinical presentation of cutaneous tuberculosis on the face of a 28-year-old immunocompetent woman with a two-year history of progressive, non-healing, asymptomatic, papulopustular lesions and plaques on the nasal area with expanding lesions to the left medial cheek. The patient was previously diagnosed as rosacea fulminans with unsuccessful treatments and disease progression. Subsequently, the second time of the histopathological result showed pseudoepitheliomatous hyperplasia with tuberculoid granulomas in the dermis surrounded by lymphocytes and histiocytes. Tissue culture was positive for Mycobacterium tuberculosis. And QuantiFERON-TB Gold test also resulted in a positive. A chest radiograph was performed to exclude a pulmonary origin and revealed no sign of infection. The patient was treated according to the standard WHO recommendations.

Keywords: ● *Cutaneous tuberculosis* ● *Lupus vulgaris* ● *Tuberculoid granuloma* ● *Rosacea fulminans*

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Corresponding Author: Arada Ovattrakul Institute of Dermatology, Ministry of Public Health, Email: ployard@gmail.com

รายงานผู้ป่วย

อาการแสดงวัณโรคผิวหนังที่น่าสนใจ

อารดา โอวาทตระกูล และ พิมสิริ พูลสุวรรณ
สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

บทคัดย่อ

วัณโรคผิวหนังเป็นการติดเชื้อทางผิวหนังที่มีอาการแสดงได้หลากหลาย ชนิดที่พบได้บ่อยคือ Lupus vulgaris โดยการวินิจฉัยต้องอาศัยอาการแสดงทางคลินิค ร่วมกับผลจุลชีววิทยาและลักษณะทางพยาธิวิทยาที่บ่งบอกถึงการติดเชื้อวัณโรคกลุ่ม Mycobacterium spp.

รายงานฉบับนี้นำเสนออาการแสดงที่น่าสนใจของวัณโรคผิวหนังในผู้ป่วยหญิงชาวพม่า อายุ 28 ปี ไม่มีประวัติโรคประจำตัว มีผื่นลักษณะปื้นนูนหนาร่วมกับตุ่มหนอง ไม่เจ็บ ไม่คัน ผื่นเริ่มขึ้นบริเวณจมูกและลามไปบริเวณแก้มซ้ายในระยะเวลา 2 ปี ผู้ป่วยได้รับการวินิจฉัยครั้งแรกเป็นโรคผิวหนังอักเสบโรซาเซียชนิดรุนแรง (Rosacea fulminans) แต่ผื่นไม่ตอบสนองต่อการรักษา ผู้ป่วยจึงได้รับการตรวจประเมินอีกครั้งโดยผลทางพยาธิวิทยาพบลักษณะ pseudoepitheliomatous hyperplasia with tuberculoid granulomas และผลเพาะชิ้นเนื้อพบว่ามีเชื้อ Mycobacterium tuberculosis ร่วมกับ การตรวจพิเศษ QuantiFERON-TB Gold ได้ผลเป็นบวก ส่งตรวจเพิ่มเติมทางรังสีวิทยาไม่พบการติดเชื้อบริเวณช่องอก ผู้ป่วยรายนี้ได้รับการวินิจฉัยเป็นวัณโรคผิวหนังชนิด Lupus vulgaris และได้รับการรักษาตามแนวทางขององค์การอนามัยโลก (WHO)

คำสำคัญ: ● *วัณโรคผิวหนัง* ● *ลูปัสวัลการิส* ● *แกรนูโลมา* ● *ผิวหนังอักเสบโรซาเซียชนิดรุนแรง*

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ได้รับต้นฉบับเมื่อ 20 มีนาคม 2565 แก้ไขบทความ 31 มีนาคม 2565 ได้ตีพิมพ์เมื่อ 8 มิถุนายน 2565

ผู้นิพนธ์หลัก อารดา โอวาทตระกูล สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข Email: ployard@gmail.com

Introduction

Tuberculosis (TB) is a contagious disease that affects the entire world, caused by *Mycobacterium tuberculosis*. It is one of the most important public health issues, a persistent threat to health that disables and kills a number of people. In 2019, 1.4 million individuals died from TB, while 10 million developed active TB disease[19]. TB is also a significant public health problem in South-East Asia with the region's estimated 10.4 million active cases. While in 2016, calculating the death toll, the South-East Asia regions contributed to 85% of the overall global TB deaths[2]. The risk of contracting TB is determined by the presence of coexistence factors such as old age, immunocompromised host, and other comorbidities[3,5].

Cutaneous tuberculosis (CTB) is a relatively uncommon form of extrapulmonary TB, occurring at 8.4-13.7% of all TB cases. Although it is uncommon, given its global prevalence, clinicians must differentiate between the numerous clinical variants of cutaneous presentation and masquerading infections such as granulomatous syphilis, bacterial abscesses, leprosy, actinomycosis, mycetoma, sarcoidosis, and other skin conditions to mitigate missed or delayed diagnosis. Lupus vulgaris (LV) is the most frequent type of CTB. A slowly expanding plaque, characterized by a slightly raised border, central atrophy, and "apple jelly" crusting, is mainly located on the face or neck[3].

Case report

A 28-year-old Burmese female was presented at our outpatient department with a two-year history of localized, persistent, asymptomatic, well-defined, infiltrative, telangiectatic, yellowish to erythematous, crusted, papulopustular skin lesions on the nasal area. Over a year, the lesion gradually progressed and coalesced into plaques measuring 4×3 cm and expanding to the left medial cheek. She complained of flushing which was exacerbated by spicy diets and sunlight exposure.

She denied constitutional symptoms, including fever, weight loss, and previous trauma, and there was no history of insect bites or TB among close contacts. No history of family members was presented with any skin conditions. A year ago, a skin biopsy was performed at the previous hospital. Histopathology revealed a non-specific granulomatous formation. All laboratory investigations for cutaneous infection were negative. She was diagnosed with rosacea fulminans and treated

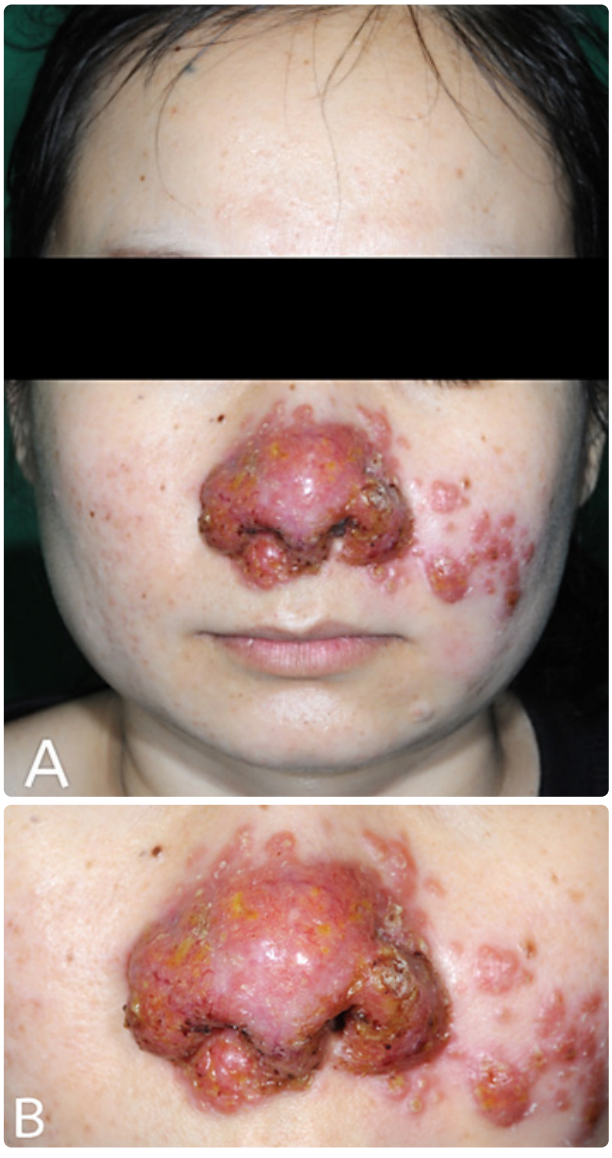

Figure 1 Localized, well-defined, asymptomatic, firm, infiltrative, yellowish to erythematous crusted plaques on the nasal area measuring 4×3 cm with expanding lesions on medial side of the left cheek. (**A, B**)

with 10 mg/day of oral Isotretinoin for a month without clinical improvement before the patient lost follow-up.

On the first visit at our hospital, the patient was 22-week pregnancy with a history of progressive lesions on the face. A physical examination was conducted, which revealed normal lymph nodes and respiratory system. However, she denied any additive skin biopsy and other investigations. She was clinically diagnosed as rosacea fulminans and treated with a first-line regimen of topical metronidazole gel twice daily, combined with oral azithromycin 500 mg/day, a pregnancy categories B medication. Regrettably, she lost follow-up from our hospital and went for an alternative treatment. She was given an unknown intramuscular medication every four days for eight times, the lesion persisted. During that period, her pregnancy was terminated for an unknown cause.

Four months later, on the second visit at our hospital, her skin lesion progressed gradually without pain or cutaneous ulcer. A chronic infection was highly suspected, and an incisional skin biopsy was performed. Histopathology, the epidermis showed irregular acanthosis with pseudoepitheliomatous hyperplasia. The dermis exhibited tuberculoid granulomatous formation, infiltrating lymphocytes and histiocytes extending to the subcutaneous fat. The laboratory investigations for *M. tuberculosis* included polymerase chain reaction (PCR), periodic acid-Schiff stain (PAS), Gomori-methenamine silver stain (GMS), acid-fast stain (AFB), and modified acid-fast stain (MAFB). Other tissue investigations included bacterial gram stain and bacterial culture, and fungal culture were negative. Her blood test for the human immunodeficiency virus showed a negative result. A few weeks later, the TB culture demonstrated the presence of *M. tuberculosis*. Then QuantiFERON-TB Gold was performed to assess lymphocytes' reactivity to TB-specific antigens, which was likewise positive.

The clinical, laboratory, and histopathology also supported the diagnosis of LV. A chest radiograph was performed to rule out the primary pulmonary TB, which showed no sign of infection. She was finally diagnosed as LV and treated according to the standard WHO recommendations. An intense phase of oral rifampicin, isoniazid, pyrazinamide, and ethambutol was used for the first two months, followed by a four-month maintenance phase of rifampicin and isoniazid.

Discussion

Robert Koch identified and isolated *M. tuberculosis* in 1882. It is an obligate intracellular, aerobic, straight, or slightly curved, immobile, non-sporulating pathogen ranging from 1 to 10 cm in length and 0.2 to 0.6 cm in width. It is an acid-fast bacillus capable of survival and multiplication inside macrophages[6]. Various mechanisms of the disease have been identified. Chen, et al. proposed that: "proteins are essential antigens of *M. tuberculosis* and can induce T-cell immune responses and other allergic reactions, including late-onset hyperreactive cell immune responses"[18]. CTB is considered a spectrum disease based on bacteriological, histopathological, and immunological characteristics[5].

LV is the most prevalent variant, accounting for around 59% of CTB cases. LV occurs in previously sensitized individuals with a high level of TB sensitivity. It is a chronic, progressive, paucibacillary form of CTB that is most prevalent among previously sensitized individuals. Most cases are caused by hematogenous or lymphatic seeding. Occasionally, LV manifests itself over the site of primary infection, in a scrofuloderma scar, or following recurrent bacillus Calmette Guérin vaccines[5]. These lesions are typically present as isolated plaques or nodules, including some ulceration and scarring; they typically appear on diascopy as "apple jelly" nodules and are most frequently found on the face or neck. LV has

been described in various variants including plaque-type, ulcerative form, vegetative form, tumor-like, and papulonodular form. Moreover, nasal ulceration, and eventual destruction of the cartilaginous component of the nasal septum had been reported[13,14]. Due to a variety of clinical manifestations, many cases remain delayed diagnosed for years[4]. Up to 10% of long-term LV patients develop malignancy[15]. On rare occasions, squamous cell carcinoma has been reported with long-term untreated LV on the face[16].

Numerous diagnostic techniques have been utilized to diagnose TB based on clinical symptoms and adjunctive tests. The standard *M. tuberculosis* direct test, also known as bacilloscopy, is used to detect the pathogen in smears of biological material stained with particular procedures, the most frequently used of which is the Ziehl-Neelsen technique. *M.tuberculosis* culture is the gold standard method for identifying pathogens and their drug sensitivities; however, the pathogens' long growth period and the low sensitivity of culture result from tissue samples add to further challenges in prompt and accurate diagnosis of CTB. Culture on solid media, such as Löwenstein-Jensen and Ogawa-Kudoh, of material from lesions demonstrates growth detection in 14 to 30 days[7].

Tuberculin Skin Test (TST) involves intradermally injecting 0.1 mL of tuberculin, purified protein derivatives (PPD) derived from an attenuated strain of *M. tuberculosis*, and reading the induration diameter after 48 to 72 hours; a positive interpretation occurs when the induration diameter exceeds 10 mm. In LV, the TST becomes positive in 2-10 weeks following infection and the reaction has a sensitivity of 33-96% and 62.5% specificity with a cut-off of 10 mm; however, the sensitivity exceeds 97% in an unvaccinated population[17]. The reaction is a classic example of a delayed hypersensitivity reaction, in which sensitized T cells are recruited and release the lymphokine. Interferon Gamma-Release-Assay, an FDA-approved immunological test, has been widely used. The QuantiFERON-TB Gold and EliSpot assays quantify TB sensitizations by determining the quantity of INF gamma produced by lymphocytes in response to TB-specific antigens[12]. QuantiFERON-TB Gold has a sensitivity of 89% and a specificity of 99%, respectively, while EliSpot has 98.8% sensitivity and a specificity of 100%. Unlike the TST, it detects disease in patients who have had the BCG vaccine (latent infection) as well as current infection[8]. Depending on availability, nucleic acid amplifications are available. The PCR assay improved sensitivity and specificity in identifying CTB. The detection of the *Mycobacterium genus* utilizing bacterial 16S ribosomal DNA and PCR assays is now considered a milestone in the diagnosis of TB.[9]

Histopathology of LV is characterized by pseudoepitheliomatous hyperplasia, tuberculoid granuloma in the dermis, surrounded by lymphocytes, epithelioid histiocytes, plasma cells, and Langhans-type multinucleated giant cells. Other histological changes are occasionally found, including adiponecrosis, regions of caseation necrosis,

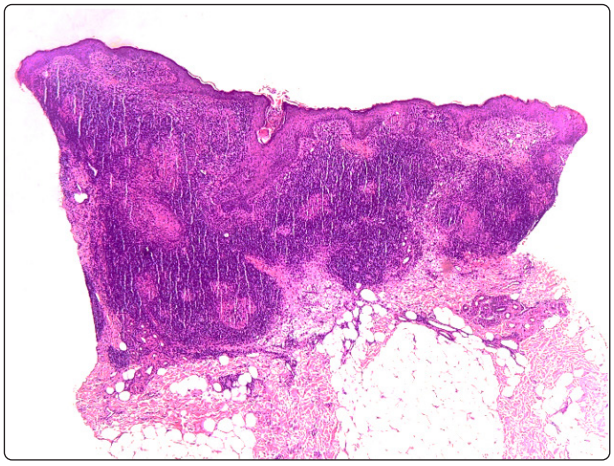

Figure 2 Histopathological examination shows irregular acanthotic epidermis with pseudoepitheliomatous hyperplasia. The whole dermis exhibits tuberculoid granulomatous formations with partial subcutaneous involvement. (H&E, 10X)

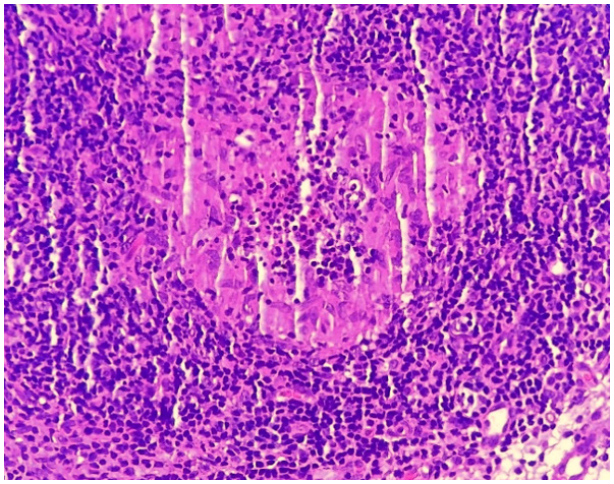

Figure 3 Histopathological examination reveals packed tuberculoid granulomas in the dermis with epithelioid histiocytes and lymphocytes. (H&E, 40X)

and vasculitis affecting the arteries and veins of adipose tissue. Fibrosis has also been seen in lesions with extended periods. Histopathology of a skin biopsy indicates granulomatous lesions consistent with those seen in various cutaneous disorders, including cutaneous leishmaniasis, tuberculoid leprosy, superficial granulomatous pyoderma, cutaneous sarcoidosis, and chromomycosis. Meanwhile, no precise definition of CTB in terms of histopathology has been proposed; however, the characteristic features of well-formed granulomas with or without caseous necrosis and the presence of poorly formed granulomas with intense caseous necrosis would help differentiate types of CTB[10]. The diagnosis is based on clinical signs, histological examination, and additional tests.

Isoniazid, rifamycin, pyrazinamide, and ethambutol are the first line of WHO recommendations of anti-TB medications, for all kinds of CTB. The intensive phase begins and lasts for two months, followed by a four-month maintenance phase[3].

Finally, LV was confirmed in our case by the second histopathological results, which showed tuberculoid granulomas. Additionally, the presence of *M.tuberculosis* from the mycobacterial culture and the result of Quanti-FERON-TB Gold were positive. LV may be initially caused by either hematogenous, lymphatic spread, direct infection, or reinfection[1]. Since no evidence of endogenous source was found, direct infection, re-infection, or latent TB was suggested. Standard treatments of anti-TB regimen were prescribed for this patient and the outcome of the treatment is under follow-up.

Our case presented an interesting clinical and complicated diagnosis of LV. The patient primarily received a misdiagnosis as rosacea fulminans that may share similar features. There is no previous report of similar cases of LV clinically mimicking as rosacea fulminans. Therefore, a proper skin biopsy with adequate evaluations of the infection should be established. And our case suggests repeating skin biopsy and re-evaluation which is recommended in a complicated case.

Statement of Ethics

The patients in this manuscript have given written informed consent to publication of their case details.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

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Data Availability Statement

This article does not constitute a data-sharing article because no new data were created or evaluated.

References

1. *Bravo FG, Gotuzzo E. Cutaneous Tuberculosis. Clin Dermatol 2007;25 (2):173-80.*
2. *World Health Organization. Global Tuberculosis Report 2017: Leave no one behind Unite to end TB. Geneva:WHO; 2017.*
3. *Van Zyl L, du Plessis J, Viljoen J. Cutaneous Tuberculosis overview and current treatment regimens. Tuberculosis (Edinb). 2015;95(6):629-38.*
4. *Turan E, Yurt N, Yesilova Y, Celik O. Lupus vulgaris diagnosed after 37 years: A case of delayed diagnosis. Dermatol Online J. 2012;18(5):13.*

5. *Khadka P, Koirala S, Thapaliya J. Cutaneous Tuberculosis: Clinicopathologic Arrays and Diagnostic Challenges. Dermatol Res Pract. 2018;2018:7201973.*
6. *Murray JF. Die historische Entwicklung der Tuberkulose seit Robert Kochs Entdeckung des Tuberkelbazillus 1882 [Historical development of tuberculosis since Robert Koch's discovery of the tubercle bacillus in 1882]. Pneumologie. 2007;61(12):764-70. German.*
7. *Dias M, Bernardes Filho F, Quaresma M, Nascimento L, Nery J, Azulay D. Update on cutaneous Tuberculosis. An Bras Dermatol. 2014;89(6):925-38.*
8. *Almaguer-Chávez J, Ocampo-Candiani J, Rendón A. Panorama actual en el diagnóstico de la tuberculosis cutánea [Current panorama in the diagnosis of cutaneous tuberculosis]. Actas Dermosifiliogr. 2009;100(7):562-70. Spanish.*
9. *Abdalla CM, de Oliveira ZN, Sotto MN, Leite KR, Canavez FC, de Carvalho CM. Polymerase chain reaction compared to other laboratory findings and to clinical evaluation in the diagnosis of cutaneous tuberculosis and atypical mycobacteria skin infection Int J Dermatol. 2009;48 (1):27-35.*
10. *Santos JB, Figueiredo AR, Ferraz CE, Oliveira MH, Silva PG, Medeiros VL. Cutaneous tuberculosis: diagnosis, histopathology and treatment - part II. An Bras Dermatol. 2014;89(4):545-55.*
11. *Chougule A, Chatterjee D, Yadav R, Sethi S, De D, Saikia U. Granulomatous Rosacea Versus Lupus Miliaris Disseminatus Faciei—2 Faces of Facial Granulomatous Disorder: A Clinicohistological and Molecular Study. Am J Dermatopathol. 2018;40(11):819-23.*
12. *Conlledo R, Guglielmetti A, Sobarzo M, Woolvett F, Bravo F, González S, et al. Lewandowsky's Rosaceiform Eruption: A Form of Cutaneous Tuberculosis Confirmed by PCR in Two Patients. Dermatol Ther (Heidelb). 2015;5(1):67-76.*
13. *Warin AP, Jones EW. Cutaneous tuberculosis of the nose with unusual clinical and histological features leading to a delay in the diagnosis. Clin Exp Dermatol. 1977;2(3):235-42.*
14. *Fine RM, Meltzer HD. Psoriasiform lupus vulgaris: a case report. Int J Dermatol. 1970;9(4):273-7.*
15. *Ljubenovic MS, Ljubenovic DB, Binic II, Jankovic AS, Jancic SA. Cutaneous tuberculosis and squamous-cell carcinoma. An Bras Dermatol. 2011;86(3):541-4.*
16. *Miyake T, Uhara H, Ishii N, Okuyama R. Squamous cell carcinoma arising from lupus vulgaris with a > 60-year history. Int Cancer Conf J. 2017;6(3):135-7.*
17. *Frankel A, Penrose C, Emer J. Cutaneous Tuberculosis: a practical case report and review for the dermatologist. J Clin Aesthet Dermatol. 2009;2(10):19-27.*
18. *Chen Q, Chen W, Hao F. Cutaneous tuberculosis: A great imitator. Clin Dermatol. 2019;37(3):192-9.*
19. *WHO. Global Tuberculosis report 2020. Geneva: World Health Organization; 2020.*