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CASE REPORT

A Rare Paradoxical Reaction in Cutaneous Tuberculosis: Insight from a Case of Lupus Vulgaris

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Introduction: Lupus vulgaris (LV) is the most common form of paucibacillary cutaneous tuberculosis (TB), which is treatable with antituberculosis treatment (ATT). Otherwise, paradoxical reaction (PR) is an adverse clinical consequence of restoring the specific antigen immune response elicited by ATT.

Case Presentation: We report a case of PR in a 20-year-old female patient with LV, who had previously completed treatment for meningitis and lymphadenitis TB and had a history of juvenile idiopathic arthritis (JIA). Initially, the patient presented with reddish papules on the neck, which appeared four months before consultation. The skin lesions progressively enlarged and failed to heal completely despite treatment, accompanied by knee joint pain. Physical examination revealed well-defined reddish-brown plaques measuring 1.5×1×0.1 cm on the neck and 5×3×0.5 cm beneath the right chin with gyrate borders. Diascopy tests revealed an "apple jelly" sign, while dermoscopy demonstrated yellowish-white globules on a pinkish-red background. Histopathological examination revealed tuberculoid granulomas, Langhans giant cells, and epithelioid cells with caseous necrosis. Based on these findings, a diagnosis of LV was established. However, bacteriological culture and polymerase chain reaction (PCR) testing showed no evidence of *Mycobacterium tuberculosis*. After three weeks of category I ATT, the skin lesions worsened and enlarged, suggesting the development of PR. The lesions subsequently improved two weeks after initiating additional therapy with 8 mg methylprednisolone twice daily and showed significant improvement following the addition of 200 mg hydroxychloroquine once a day.

Conclusion: Although PR is rare, it should be considered in patients who demonstrate clinical deterioration after ATT. Clinicians should be aware of its occurrence in cutaneous TB, particularly LV, to ensure timely recognition and appropriate management.

Keywords: antituberculosis treatment, cutaneous tuberculosis, lupus vulgaris, paradoxical reaction

Introduction

Tuberculosis (TB) is an infectious disease primarily caused by *Mycobacterium tuberculosis hominis* (*M. tuberculosis*), though it can also be due to *M. bovis* and *M. africanum*.[1] Based on World Health Organization (WHO) estimates, Indonesia ranks second worldwide in TB burden, with an incidence rate of 354 per 100,000 population in 2021.[2] According to the 2023 Indonesian Health Profile, West Java Province reported the highest number of TB cases, totaling 212,613.[3]

The most prevalent type of TB is pulmonary TB, although extrapulmonary TB is also frequently observed. Extrapulmonary TB can affect various organs such as the pleura, abdomen, bones and joints, liver, spleen, lymph nodes, meninges, and skin.[4] Cutaneous TB is a rare form of extrapulmonary TB, representing 1–3% of cases.[4–6] In high-prevalence countries, cutaneous TB accounts for approximately 2% of dermatology consultations.[5] Lupus vulgaris (LV), the most common form of paucibacillary cutaneous TB in Europe, India, Nepal, and China, is typically seen in patients with moderate to high immunity to *M. tuberculosis*.[1,4,7–9] It primarily affects females more than males and is often associated with lower social and economic status.[1] LV lesions have several clinical forms and are most commonly

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located on the head and neck. They typically appear in those who are highly sensitive to tuberculin and generally occur in individuals previously sensitized to the bacteria.[7,9]

Diagnosis of cutaneous TB is challenging due to the low sensitivity and specificity of standard tests. Clinicians often need to use multiple tests in conjunction with thorough clinical assessment.[4,7] Culture and polymerase chain reaction (PCR) are useful but may yield negative results. In such cases, clinical suspicion supported by histopathology and therapeutic response to antituberculosis treatment (ATT) can establish the diagnosis.[9]

A paradoxical reaction (PR) is a clinical worsening or appearance of new lesions during ATT despite initial improvement.[9] It is uncommon but should be considered in patients who, despite an initial adequate response to treatment, experience clinical or radiological deterioration or the emergence of new lesions.[10] It occurs in about 10–15% of patients with TB and is considered a delayed hypersensitivity response to tuberculoproteins released from dead bacilli.[11] PR usually develops within weeks to months after starting therapy and often resolves with corticosteroids without altering ATT.[10,12] We report a case of LV complicated by PR in a young female patient who had previously completed treatment for tuberculous meningitis and lymphadenitisTB.

Case Presentation

A 20-year-old female presented with painless, non-itchy erythematous plaques on the neck and beneath the right chin, which initially appeared as reddish papules four months prior to consultation. The lesions gradually enlarged into erythematous plaques and did not respond to prior treatment. She had a history of meningitis and lymphadenitis TB, both declared cured after adequate ATT. She also had a history of JIA during childhood and occasionally complained of knee joint pain.

Physical examination revealed two well-defined erythematous plaques on the neck and beneath the right chin with gyrate borders (Figure 1a). Diascopy tests demonstrated an “apple jelly” sign (Figure 1b), and dermoscopy examination demonstrated yellowish-white globules with a pinkish-red background (Figure 1c). The tuberculin test was positive. However, the Ziehl-Neelsen staining was negative.

Histopathological examination revealed tuberculoid granulomas, Langhans giant cells, and epithelioid cells with caseous necrosis (Figure 1d–f). However, bacterial culture, PCR, fine needle aspiration biopsy (FNAB), and sputum examination were negative for *M. tuberculosis*. The anti-human immunodeficiency virus (HIV) antibody test was also negative. Based on these findings, a clinical-histological diagnosis of LV was established.

The patient was treated with category I ATT. After two weeks of treatment, the skin lesions decreased in size. However, in the third week, she developed abrupt worsening of the lesions (Figure 1g), while her general condition remained good. Based on these conditions, a PR was suspected. Two weeks after initiating 8 mg of methylprednisolone twice daily, the lesions began to improve. Significant improvement was observed after starting 200 mg of hydroxychloroquine (HCQ) for joint pain, without altering the ATT regimen. After several weeks of combined corticosteroid and HCQ therapy, the lesions regressed markedly (Figure 1h), supporting the diagnosis of ATT-induced PR in LV.

Discussion

Extrapulmonary TB may occur through direct inoculation, spread from adjacent sites, or hematogenous dissemination.[13,14] According to WHO, about 15% of new TB cases are extrapulmonary, and 1–2% of these involve the skin, which is commonly found worldwide, particularly in developing and tropical countries.[7,15–18] Cutaneous TB, a chronic skin infection caused mainly by *M. tuberculosis* (rarely *M. bovis* or BCG vaccine), is divided into exogenous (eg, TB chancre, TB verrucosa cutis) and endogenous types (eg, LV, scrofuloderma, TB gumma).[16,19] LV is the most common form, representing up to 59% of cutaneous TB, usually in females and young adults aged 15 to 24 years. Lesions often appear on the head and neck as reddish-brown plaques with gyrate borders.[1,13,16,20,21] In this case report, the patient was female, 20 years old, with clinical presentation of LV.

Lupus vulgaris occurs in individuals with moderate to high immunity, usually after prior exposure to TB, and presents with diverse clinical manifestations, most often as solitary and asymptomatic lesions.[7,9,13,22–24] There are five main types of LV: plaque, ulcerative/mutilating, vegetative, tumor-like, and papular/nodular.[16,23] The most common sites for this condition include the face, neck, lower arms, chest, trunk, and legs.[25–27] Lesions typically begin as reddish-brown, soft or friable macules or papules with a smooth or hyperkeratotic surface, later progressing into elevated plaques with a deeper

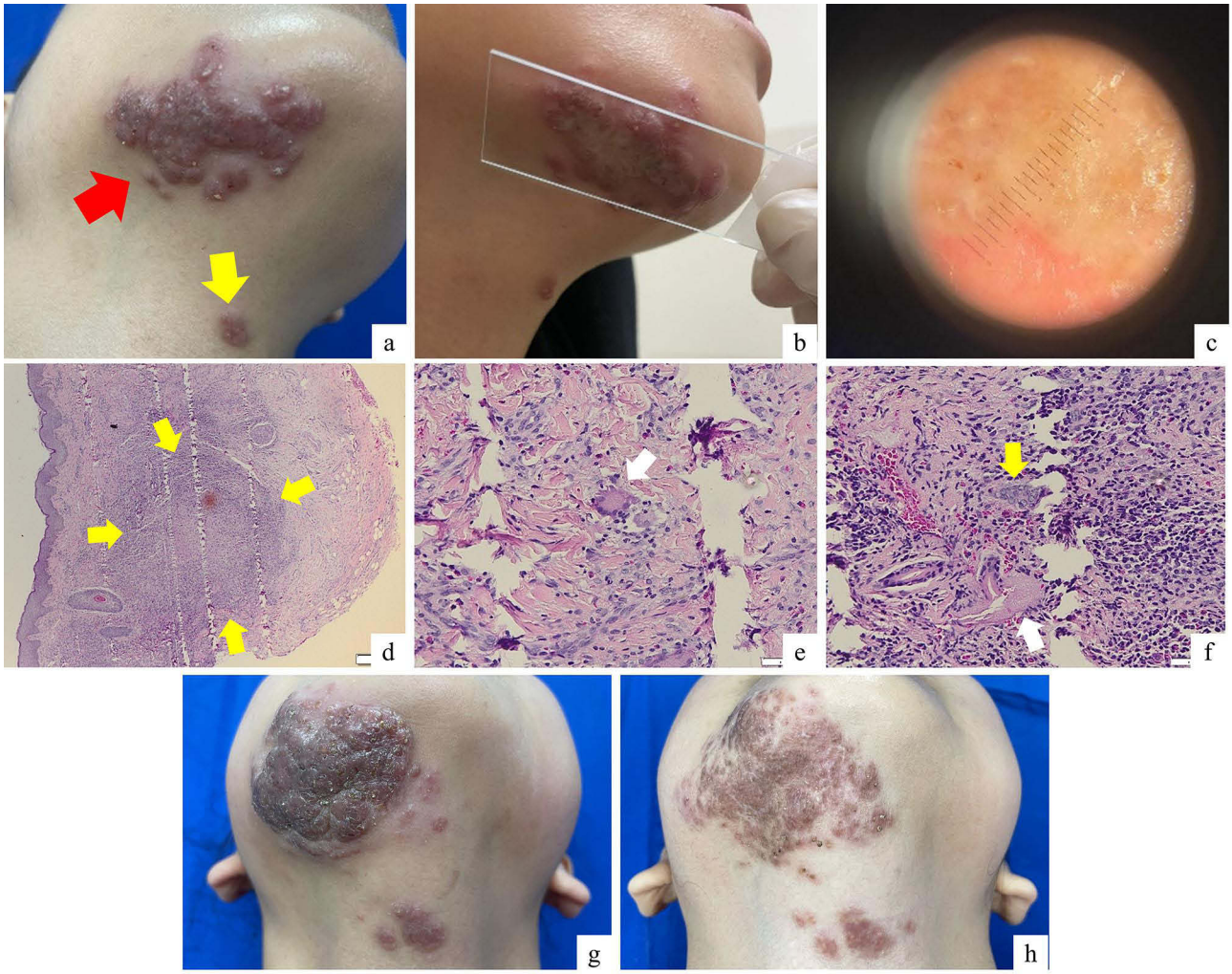

Figure 1 Initial lesions at the first visit showed (**a**) well-defined erythematous plaques, measuring 1.5×1×0.1 cm on the neck (yellow arrow) and 5×3×0.5 cm beneath the right chin (red arrow). (**b**) Diascopy test showed "apple jelly" sign. (**c**) Dermoscopy examination showed yellowish-white globules and a pinkish-red background. Histopathology features at 100× magnification showed (**d**) granuloma tuberculoid in the upper and mid dermis (yellow arrow), (**e**) Langhans giant cell (white arrow), (**f**) epithelioid cells (yellow arrow) and caseation necrosis (white arrow). (**g**) Appearance of skin lesions with severe inflammatory reaction; erythematous plaques became swelling and enlarged three weeks after starting ATT. (**h**) Skin lesions smaller and deflated after several weeks of additional corticosteroid and HCQ treatment, while ATT treatment was continued.

brownish color. Borders may appear gyrate due to involution in one area and expansion in another. The hypertrophic variant presents as a soft nodule or plaque with a hyperkeratotic surface.[15] LV may also coexist with TB at other sites, with 40% of cases associated with lymphadenitis, 30% with scrofuloderma, and 10–20% with pulmonary or skeletal involvement.[13] In this case, the patient had a history of meningitis and lymphadenitis TB and developed reddish-brown plaques on the neck and chin, consistent with LV.

Furthermore, diascopy and dermoscopy can serve as diagnostic or supportive tools in various infectious skin conditions, including LV. LV lesions typically show the characteristic "apple jelly" sign on diascopy.[15,28,29] Dermoscopic findings often include a pinkish-red background indicating inflammation, superficial scaling suggestive of hyperkeratosis, and yellowish-white globules representing granulomas.[29] In this patient, diascopy revealed a positive "apple jelly" sign, while dermoscopy demonstrated yellowish-white globules and a pinkish-red background, supporting the diagnosis of LV.

Although cutaneous TB may present with diverse histopathological features, it typically shows granulomas composed of epithelioid cells, mononuclear cells, plasma cells, and Langhans giant cells, with or without caseous necrosis.[25,30,31] In LV, the epidermis may be hyperplastic, atrophic, or ulcerative, and multiple tuberculoid granulomas with caseous

necrosis are often found in the superficial dermis.[25,32,33] In this patient, histopathology revealed tuberculoid granulomas with epithelioid cells, Langhans giant cells, and caseous necrosis, consistent with LV.

The diagnosis of LV is based on absolute and relative criteria. Absolute criteria involve detecting *M. tuberculosis* through bacterial culture or PCR.[13] Mycobacterial culture remains the gold standard for diagnosis and for monitoring drug-resistant strains. However, the bacillary load in cutaneous TB is much lower than in pulmonary TB.[34] Since LV is a paucibacillary form of infection, cultures and PCR are often negative.[5,28,35] Relative criteria include a relevant medical history, clinical findings, evidence of active TB in other organs, positive bacteriological tests, supportive histopathological results, a positive tuberculin test, and a favorable response to ATT.[13,15,36] Negative bacteriological or tuberculin results do not exclude the diagnosis, as LV is frequently diagnosed through clinicopathological correlation.[13,36] In this case report, the tuberculin test was positive with an induration of 15 mm, while culture and PCR were negative. The diagnosis of LV was established based on clinical features, diascopy and dermoscopy findings, tuberculin testing, and histopathological results.

The treatment of cutaneous TB follows the same principles as pulmonary and other extrapulmonary TB. According to the Indonesian Guidelines for the National TB Control Program (2020), extrapulmonary TB should be treated with the category 1 ATT regimen.[13] This consists of a 2-month intensive phase with rifampicin, isoniazid, ethambutol, and pyrazinamide, followed by a 4-month continuation phase with rifampicin and isoniazid.[25,37] Treatment duration for extrapulmonary TB may extend beyond 6 months, sometimes up to 12 months.[38] In this case, the patient received category 1 ATT for 12 months.

During effective TB treatment, patients may experience unexpected worsening of clinical manifestations, which can be difficult to distinguish from treatment failure. This phenomenon, known as a paradoxical reaction (PR), is an undesirable consequence of the restored antigen-specific immune response induced by therapy.[9] It is characterized by clinical or radiological worsening of pre-existing TB lesions or the appearance of new ones in patients receiving ATT who initially showed improvement.[39–41] PR involving the skin has been mostly described in miliary TB, with only two reported cases in cutaneous TB (tuberculosis cutis verrucosa and LV). Both are paucibacillary forms occurring in individuals with good host immunity.[42] The incidence of PR varies across populations, affecting about 18% of HIV-positive patients after starting antiretroviral therapy (ART) and 10–25% of HIV-negative patients.[40,43,44] In HIV-negative individuals, PR occurs in approximately 2.4% of pulmonary TB cases but is significantly more common in extrapulmonary TB, ranging from 16–50%.[44,45] PR has been reported as early as two weeks and as late as 18 months after initiating ATT, with about two-thirds occurring within the first 1–4 months.[12,40] In this case, the patient was HIV-negative with cutaneous TB presenting as LV. The lesions improved during the first two weeks of ATT but worsened in the third week, suggesting a PR.

The exact mechanisms of PR in HIV-negative patients remain unclear. *M. tuberculosis* employs several strategies to evade the host immune system. Live bacilli can alter cell-mediated immunity by blocking phagosome–lysosome fusion in macrophages or reducing MHC-II expression on dendritic cells.[44] When bactericidal therapy is initiated, immune rebound may occur, possibly exacerbated by the release of *M. tuberculosis* antigens during macrophage lysis, which may explain the worsening of clinical symptoms.[39,44]

Diagnosing PR remains a major clinical challenge. Although its definition and pathogenesis are better understood, no rapid or reliable test exists to confirm the diagnosis.[46] Diagnosis is based on several criteria: initial improvement of TB-related symptoms or radiographic findings after appropriate ATT, followed by paradoxical worsening at the original site or new locations; absence of factors that compromise drug efficacy; and exclusion of other causes of deterioration.[9,47] A diagnosis can only be made after eliminating other possible causes of the symptoms, such as superinfection, inadequate TB therapy, poor adherence to treatment, side effects of the medication, improper drug absorption, and the development of resistance to tuberculostatic agents.[9] Drug-resistant cutaneous TB is usually paucibacillary, making isolation of the organism uncommon and reducing diagnostic sensitivity and specificity. Resistance is therefore often suspected clinically, particularly when there is no response to first-line therapy and systemic symptoms such as malaise, fever, weight loss, anorexia, or new ulceration occur.[48] The clinical spectrum of PR often involves multiple organs, with manifestations such as enlargement of existing skin lesions, new cold abscesses, erythematous or purpuric papules, painful muscle swelling, or abscesses in the abdominal and chest walls.[44,46] In this case, the paucibacillary nature of the disease meant that laboratory tests did not detect *M. tuberculosis*, and FNAB excluded other infections. The patient received adequate category 1 ATT per the Indonesian Guidelines for TB Control 2020 and was adherent to therapy. Because systemic symptoms and signs of resistance were absent, the worsening skin lesions were attributed to PR triggered by ATT for LV.

At present, there are no specific guidelines for managing PR.[47] Typically, paradoxical clinical deterioration after initiating ATT is self-limiting and does not require discontinuation or modification of therapy.[9] Most patients with cutaneous TB respond within five to six weeks, consistent with earlier studies reporting that nearly all patients improve after this period.[49–52] Corticosteroids may be added or their dosage increased while continuing ATT in patients experiencing PR. Their rationale is to reduce inflammation as ATT eradicates the pathogens.[9,12] Corticosteroid use during PR is generally safe and beneficial, with no significant complications reported.[46,47] In severe, progressive, or persistent cases, oral or parenteral prednisone at 1–2 mg/kg/day for 4–6 weeks, or until symptoms resolve, is recommended.[9,53] HCQ is a mild and safe disease-modifying antirheumatic drug, initially used for rheumatoid arthritis (RA) but most effective in systemic lupus erythematosus (SLE), where it reduces flares, improves survival, and enhances prognosis. Although its precise mechanism is unclear, HCQ exerts anti-inflammatory and immunomodulatory effects partly by inhibiting toll-like receptor (TLR)7 and TLR9 signaling, thereby reducing type-1 interferon transcription.[54] In this case, the patient's skin lesions improved after additional therapy with 16 mg methylprednisolone daily (equivalent to 0.5 mg/kg prednisone) without altering ATT. Two weeks after corticosteroid initiation, the lesions became smaller, deflated, and free of discharge or ulceration. HCQ (200 mg daily) was subsequently added to address joint pain suspected to be related to JIA and to enhance the anti-inflammatory effect for PR. Marked improvement following corticosteroid and HCQ therapy confirmed that the patient experienced a PR induced by ATT for LV. This case report has several limitations, including the absence of rapid molecular testing to confirm the presence of *M. tuberculosis* and the lack of long-term follow-up data.

Conclusion

LV is the most prevalent form of cutaneous TB in young females. Paradoxical reaction in LV is a rare condition that may occur after initiation of ATT. Clinicians should be aware of PR in cutaneous TB, particularly LV, and consider relevant factors when making the diagnosis. This case report highlights PR in LV to emphasize the importance of timely recognition and appropriate management.

Abbreviations

ART, antiretroviral therapy; ATT, antituberculosis treatment; BCG, Bacillus Calmette Guerin; DNA, deoxyribonucleic acid; FNAB, fine needle aspiration biopsy; HCQ, hydroxychloroquine; HIV, human immunodeficiency virus; JIA, juvenile idiopathic arthritis; LV, lupus vulgaris; MHC-II, major histocompatibility complex-II; M. Tuberculosis, *Mycobacterium tuberculosis*; PCR, polymerase chain reaction; PR, paradoxical reaction; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis; TLR, toll-like receptor; TVC, tuberculosis verrucosa cutis; WHO, World Health Organization.

Ethical Approval

Ethical review and approval were required to publish the case details in accordance with the local legislation and institutional requirements. This study ethics approval was obtained from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung with the registry number DP.04.03/D.XIV.6.5/513/2024.

Consent for Publication

The patient provided written informed consent for the publication of their anonymized case details. The patient has given written consent for the publication of their case report and images, with personal identifiers removed to ensure privacy. We confirm that consent was obtained following ethical standards and the patient was fully informed and agreed to the use of their medical information without conditions. Approval has been obtained from Dr. Hasan Sadikin General Hospital to publish the case details.

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Disclosure

The authors have no competing interests to declare.

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