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Case Report

Successful Treatment of Relapse Cutaneous Tuberculosis on Pregnant Woman with Ethambutol Allergic

Keberhasilan Tatalaksana Tuberkulosis Kulit Kambuh pada Wanita Hamil dengan Alergi Ethambutol

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Abstract

Tuberculosis infection among pregnant women often reveals unspecific clinical manifestations, and cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis. The aim of this case report is to manage well Extra-Pulmonary tuberculosis manifestation, especially in pregnant women. A Pregnant woman with a gestational age of 6-7 weeks complained of red spots on cheeks. One year ago, the patient suffered cutaneous tuberculosis and was only treated with Rifampicin, Isoniazid, and Levofloxacin; pyrazinamide and ethambutol were not given due to a strong suspicion of allergy. Physical examination revealed plaque with scales, and PCR examination revealed Mycobacterium tuberculosis. She suffered relapse of cutaneous tuberculosis and was given rifampicin, isoniazid, and pyrazinamide. After 2 weeks the skin lesion improved significantly, and ethambutol was added to the regimen. The patient suffered from drug eruption, ethambutol was discontinued, and the skin lesion disappeared after four months of treatment. The regiment was continued for one year; showed better condition and delivered a healthy baby boy. Cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis (1-1.5%) and is hard to diagnose and treat, especially in pregnant women. Allergic to one of its drugs can increase its risk of being resistant and increase its mortality and morbidity. As conclusion, prompt treatment is needed for tuberculosis patients, especially pregnant women. Early detection and examinations are required to diagnose it properly.

Keywords*: cutaneous; tuberculosis; pregnant woman; allergy*

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Abstrak

Infeksi Tuberkulosis pada wanita hamil sering menunjukkan manifestasi klinis yang tidak spesifik, dan tuberkulosis kulit merupakan tuberkulosis ekstra paru dengan insidensi yang jarang. Tujuan penulisan laporan kasus ini untuk memberikan penanganan yang tepat bagi manifestasi tuberkulosis Extra-Paru, terutama wanita hamil. Wanita dengan usia kehamilan 6-7 minggu datang mengeluhkan bercak merah pada kedua pipi. Satu tahun yang lalu, pasien menderita tuberkulosis kulit dan hanya diobati dengan Rifampicin, Isoniazid, dan Levofloxacin; pirazinamid dan etambutol tidak diberikan dikarenakan dugaan alergi. Pada pemeriksaan saat ini ditemukan plak bersisik dan pemeriksaan PCR ditemukan *Mycobacterium tuberculosis.* Tuberkulosis kulit kambuh pada pasien ini dan diputuskan untuk diberi rifampisin, isoniazid, dan pirazinamid. Setelah 2 minggu lesi kulit membaik secara signifikan, dan ethambutol ditambahkan ke dalam regimen. Pasien mengalami erupsi obat, ethambutol diputuskan untuk dihentikan, dan lesi kulit menghilang setelah empat bulan pengobatan. Regimen tersebut kemudian dilanjutkan selama satu tahun dan pasien menunjukkan kondisi yang lebih baik serta melahirkan bayi laki-laki yang sehat. Tuberkulosis kulit merupakan bentuk tuberkulosis ekstra paru dengan insidensi yang jarang (1-1,5%) dan sulit didiagnosis serta ditatalaksana, terutama pada wanita hamil. Alergi terhadap salah satu pengobatan dapat meningkatkan risiko resistensi sekaligus meningkatkan mortalitas dan morbiditasnya. Sebagai simpulan, penanganan yang cepat dan tepat sangat diperlukan bagi penderita TBC, terutama ibu hamil. Deteksi dan pemeriksaan dini diperlukan sehingga diagnosis dapat ditegakkan dengan baik.

Kata kunci: kulit; tuberkulosis; wanita hamil; alergi

Introduction

Tuberculosis (TBC) infection is an infectious disease caused by the Rod-type bacteria, *Mycobacterium tuberculosis*. Mostly, the type of tuberculosis infection is a pulmonary infection, but it can be an extrapulmonary type too.[1] In 2018, around 10 million people worldwide suffered from tuberculosis.[2] The exact number of pregnant women with tuberculosis is unknown.[3] Still, in 2011 the number was estimated at around 192.100 to 247.000 cases, with the highest number in Africa and Southeast Asia.[4]

The clinical picture of tuberculosis in pregnancy is often atypical and difficult to diagnose; this results in delayed treatment given to pregnant women which will provide poor therapeutic results.[4] Cutaneous tuberculosis is a relatively rare disease among other extrapulmonary tuberculosis diseases; the incidence ranges from 1 to 1.5% [3,5]. The lupus vulgaris form of cutaneous tuberculosis is hard to detect, even on histopathology examination.[3]

If a pregnant woman has been diagnosed with tuberculosis, then therapy should be given immediately and should not be delayed. First-line treatment is safe for pregnant women with tuberculosis.[4] There are several compelling reasons why early treatment of pregnant women with tuberculosis is necessary. First, tuberculosis infection can increase the risk of complications in pregnancy and premature birth. Both pregnant women with tuberculosis infection can give birth to babies with less weight and some defects and increased infant mortality. Third, Tuberculosis

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patients, including pregnant women, can be a source of transmission to the surrounding environment.[4,6]

We present you a case of successful treatment for a pregnant woman who had relapsed cutaneous tuberculosis in rare lupus vulgaris form and was allergic to ethambutol. The aim of this case report is to manage well Extra-Pulmonary tuberculosis manifestation, especially in pregnant women. Prompt Diagnosis and treatment are required to improve patient's quality of life.

Case

A 34-year-old pregnant woman came to our hospital with major complaints of painless red spots on her face for one month, and it was getting worse. On physical examination, we found an erythematous plaque with squama on the right cheek, left temporal, and forehead and no other abnormal signs in other body parts. She was expecting her third child and her gestational age was seven weeks. She had a history of cutaneous tuberculosis one year before and finished her treatment; pyrazinamide and ethambutol were not given due to a strong suspicion of allergy to these drugs and no trace of the lesion after the treatment. She was also diagnosed with Synovitis Tuberculosis Knee Joint a year ago and had no complaints after the treatment.

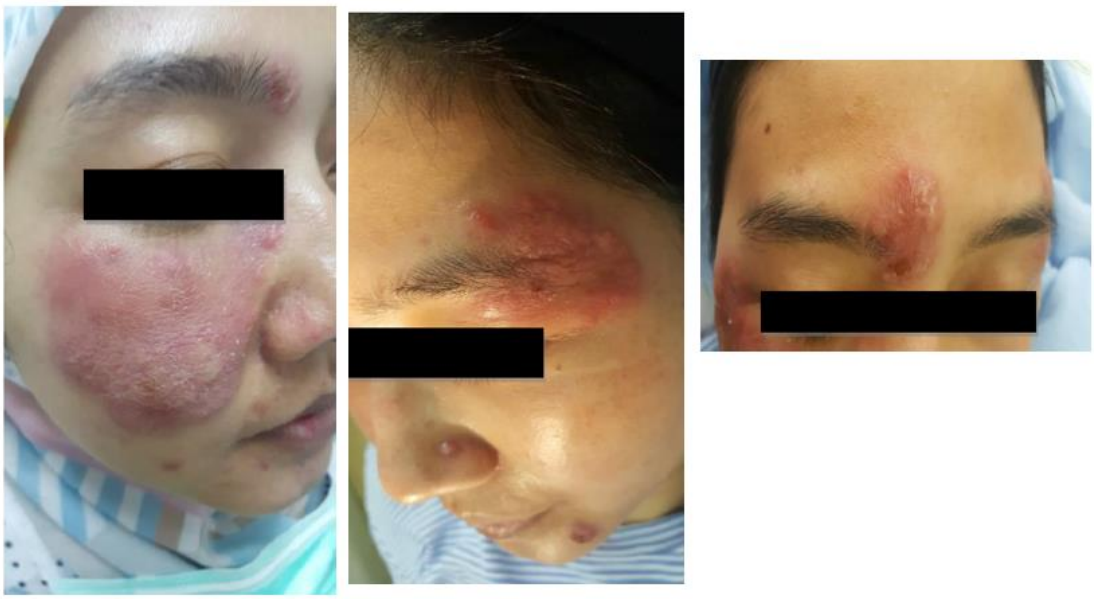

Figure 1 Day 0 Skin Conditions, Showed Erythematous Lesions on Face

We suspected a relapse of cutaneous tuberculosis she had before with lupus vulgaris form of cutaneous tuberculosis, so we did a punch biopsy on the lesion. The result was unspecified, and we did not find the *Mycobacterium tuberculosis* bacilli, so we continued with the Polymerase Chain Reaction (PCR) test on skin tissue. The result was positive for *Mycobacterium tuberculosis*.

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Her Purified Protein Derivative (PPD) Skin Test was also positive. One week later, we removed the thread we used for the biopsy with her last skin condition had crust and pustules.

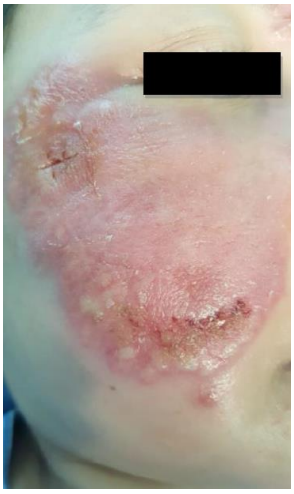

Figure 2 Skin Condition after We Removed the Thread Used for Biopsy

We immediately started the regimen for her treatment with rifampicin(R), isoniazid(H), and Pyrazinamide(Z) with a lower dose. We also added pyridoxine. One week later, she showed better skin condition. On physical examination showed macula and plaque erythema with squama. We planned to titrate on pyrazinamide dose based on her skin condition later.

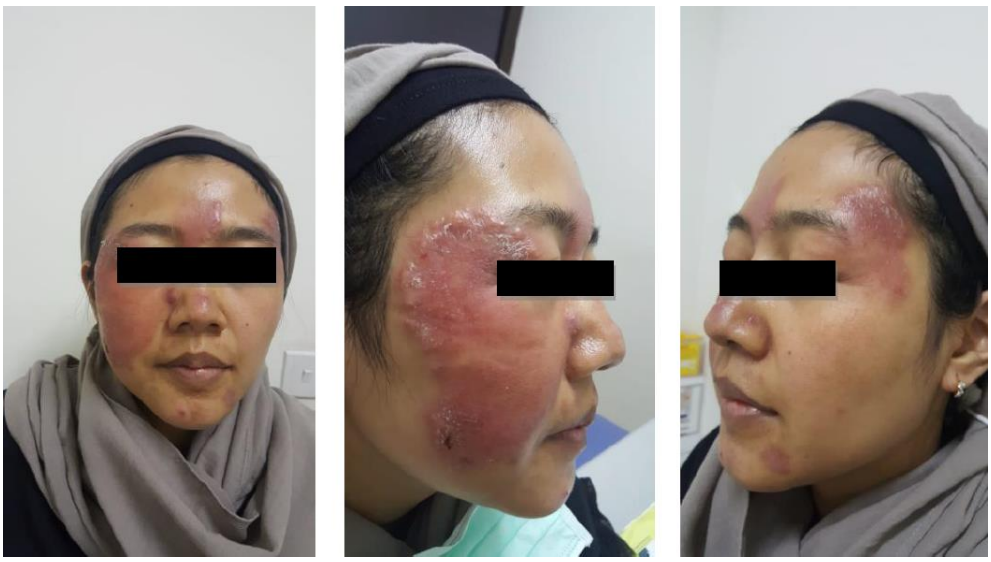

Figure 3 Skin Condition after One Week Treatment.

On her second week of treatment, she showed less erythematous skin condition. We decided to continue her treatment with rifampicin, Isoniazid, Pyrazinamide full dose, and ethambutol lower dose.

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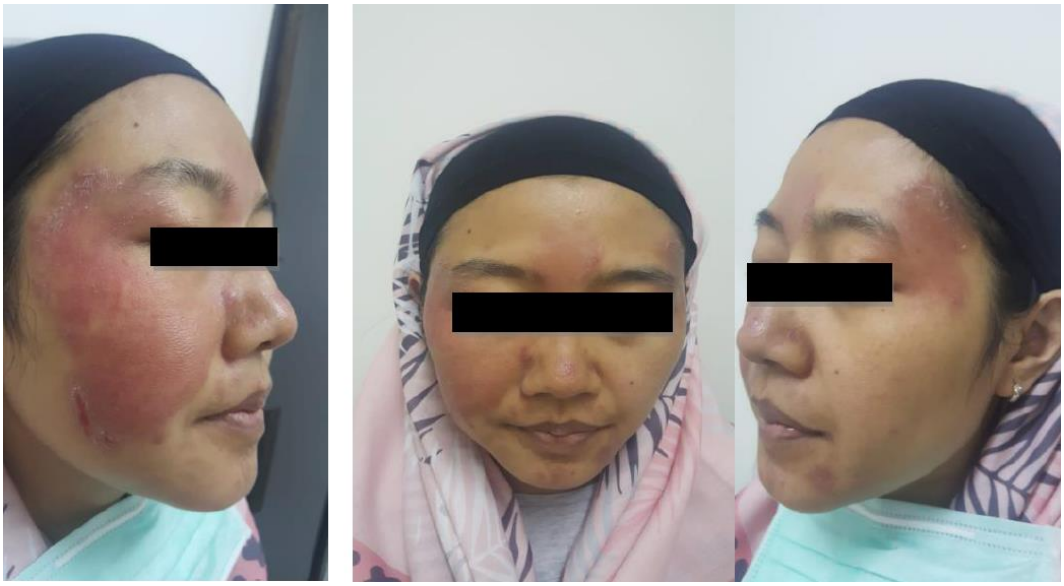

Figure 4 Skin Condition on Two weeks Treatment

Six days later, she complained she had pruritus on her lesion and all over the body; she had drug eruption because of ethambutol. We stopped ethambutol, continued her other treatments, and gave her an antihistamine. After that, her complaint of pruritus was gone. We continued her treatments with rifampicin and isoniazid. She came to our hospital on her four months treatment for follow up. On physical examination showed: Macula hyperpigmentation and hypertrophic scar. Her skin condition showed less erythematous and no pruritus complaints at the end of her intensive treatment for anti-tuberculosis drug regimens.

Figure 5 Skin Condition on Four months Treatment

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One month later, she gave birth to a healthy baby boy with a 3.7 kg weight with normal delivery. She showed better skin condition during her nine months of treatment, and we continued her treatment for the next three months. Her total duration of treatments was twelve months, and at the last follow-up, she showed good skin condition and no complaints of having pruritus, pain, or anything on the skin and other parts of the body.

Figure 6 Skin Condition on the last Treatment and Follow Up

Discussion

Tuberculosis is still a problem in developing countries[7], and Indonesia still faces a significant challenge in reducing the tuberculosis infection rate, requiring special attention. It also carries a high burden of morbidity and mortality.[1] We know that over the past decade, Indonesia has made good progress in reducing the incidence of tuberculosis infection and achieving a highly successful rate of tuberculosis treatment. We are also working to eliminate the remaining tuberculosis infection in every province. Aside from all achievements, tuberculosis infection still becomes a burden for developing countries, and Indonesia ranked third in infection rate among the top thirty countries with high tuberculosis burden, not to mention Indonesia still has a high incidence rate of multidrug-resistant tuberculosis (MDR-TB) infection.[8]

Pregnancy carries its own risk of having a tuberculosis infection for pregnant women and infants. The presence of tuberculosis infection during pregnancy, delivery, and post-partum can result in unfavourable outcomes. Non-specific symptoms related to physiological pregnancy response can make diagnosing tuberculosis infection challenging and difficult. Standard practice

and screening for diagnosing tuberculosis in pregnant women is needed and should be established well in the general population, especially in countries with high tuberculosis burden.[4] Tuberculosis in pregnancy is associated with an increased risk of spontaneous abortion, perinatal mortality, and low birth. The baby also has a high risk of congenital tuberculosis due to maternal hematogenous spread.[1] Despite all the risks, this patient delivered a healthy normal-weight baby.

A study in South Africa by Martie *et al.* mentioned that pregnant women, especially those who were drug-resistant, have a high risk of having unfavorable birth outcomes; from their study, favorable birth outcomes have been reported in 88% of the total population, but 12% of the population had unfavorable birth outcomes which were two miscarriages or abortions and one stillbirth. Not to mention the adverse event that those women should carry. [6] Although, in this case, this patient had a relapse cutaneous tuberculous, she was rifampicin sensitive and had an excellent response to the anti-tuberculosis drugs regimen.

Cutaneous tuberculosis is an uncommon manifestation and a rare form of tuberculosis infection. Only 1-2% of the population suffer from this manifestation of extrapulmonary tuberculosis. We can find more cutaneous tuberculosis infections in countries with a high incidence rate of human immunodeficiency virus (HIV) infection or where the population is immunodeficient for other reasons.[9] The pathogenesis of cutaneous mycobacterial infections is rather hard to explain. Still, recently, studies mentioned that the infection comes from the hematogenous dissemination route, spread from regional or local infection from other parts of the body, or it can be from direct inoculation into the skin and soft tissues.[10]

The diagnosis of this patient was made based on history, physical examination, and Polymerase Chain Reaction Test (PCR), which was positive for *Mycobacterium tuberculosis*. The patient was also getting better with the anti-tuberculosis drug regimen. Cutaneous involvement occurs in 1–2% of tuberculosis cases, a rare form of extrapulmonary infection. Lupus vulgaris is one of the cutaneous tuberculosis forms and often occurs in people previously sensitized to *Mycobacterium tuberculosis*.[11] Cutaneous tuberculosis is often underdiagnosed because we are unaware of *Mycobacterium tuberculosis* infection and are limited in examination and laboratory facilities. Lesions owing to cutaneous tuberculosis are highly variable. Culture and a series of biomolecular testing are beneficial in identifying the mycobacterium tuberculosis but sometimes are limited and hard to do. PCR-based DNA sequencing and homology comparisons are best for pathological organism identification.[12]

Because of the varied clinical spectrum and rarity of cutaneous tuberculosis, high suspicion and prompt judgment are needed to identify skin lesions. We should do a biopsy for histopathology even though, in some cases, histopathology only shows non-specific inflammation

without granuloma formation.[13] Finding bacilli in a cutaneous tuberculosis lesion is a challenge. Considering that atypical erythema nodosum and non-specific appearance are not uncommon, and histopathology may not be so specified, we as health practitioners should think about any possible test as a basis for diagnosis, tuberculin skin test, chest radiograph, and collect material for histopathological examination and did detection of Mycobacterium tuberculosis DNA by polymerase chain reaction (PCR) can help to diagnose and deliver prompt treatment to the patient.[14]

Cutaneous tuberculosis has a wide variety of clinical presentations and classifications. Most cases of cutaneous tuberculosis are lupus vulgaris, scrofuloderma, miliary tuberculosis, and orifical tuberculosis.[3] This case is about lupus vulgaris type form. Infection can occur through exogenous routes, cutaneous inoculation, or endogenous ones and often result from secondary infection from other body parts, like contiguous involvement of the skin overlying subcutaneous focus, most commonly tuberculous lymphadenitis or tuberculosis of the bones and joints. It may also be from epididymis tuberculosis or pulmonary tuberculosis.[15] This also explains why this patient got cutaneous tuberculosis in the first place.

Lupus vulgaris is one cutaneous tuberculosis form that mainly occurs in previously sensitized individuals. It is formed because of delayed hypersensitivity reaction and results positively in the tuberculin (PPD) test,[3] which explains why the PPD test in this patient was positive. It may also develop secondarily to other cutaneous tuberculosis forms, like verrucosa cutis, scrofuloderma, or inoculation. Infection often occurs endogenously, through a lymphohematogenous route or by continuity, and rarely via exogenous routes. In histopathology, the epidermis is atrophic or hypertrophic, sometimes featuring acanthosis, papillomatosis, and even pseudoepitheliomatous hyperplasia. If tuberculous granulomas are present, it is often accompanied by Langhans giant cells and granulomas, and we often do not find any *Mycobacterium tuberculosis* bacilli. Mycobacterial culture is often negative.[16] This also manifests as latent nodules, annular plaques, or accompanied by hypertrophic or vegetative lesions, and women suffer most from this clinical form.

The American College Physician (ACPP) recommends that a standard Tuberculosis treatment be divided into two phases: initial and continuation. The most frequent predilections are lower extremities, buttocks, and trunks.[17] So, the predilection of this case on the face is quite rare because we often find cutaneous tuberculosis in the trunk or extremities. The principle of cutaneous tuberculosis's treatment as extrapulmonary tuberculosis is the same as pulmonary tuberculosis and should be paid attention to. The patients should get prompt treatment without interruption so that resistance does not quickly occur, treatment must be in combination, and at

least two bactericidal drugs are selected.[18] The treatment goals are to cure the disease, prevent drug resistance, prevent a recurrence, and break the chain of transmission.

The administration of anti-tuberculosis drugs in Indonesia follows the 2020 National Tuberculosis Management Guidelines from the Ministry of Health of the Republic of Indonesia (MOH), which consists of categories I and II. Treatment of category I tuberculosis is divided into two stages. In the initial or intensive stage, patients received RHZE drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) every day for two months, while in the following stage received two kinds of medicines consisting of rifampicin and isoniazid, given every day for four months. The anti-tuberculosis medications are provided in one pack regiment and consist of a combination of four or two types of drugs in one tablet.[19] Treatment's continuation phase lasts for nine to twelve months to eradicate the remaining bacteria.

The patient's compliance is essential and the leading role in eradicating tuberculosis infection.[9] This patient also received the treatments in two following stages, the intensive stage and the following stage for twelve months, following the guidelines that cutaneous tuberculosis can be given the regiments up to twelve months. The patient is allergic to ethambutol, so she was treated with three kinds of drugs, rifampicin, isoniazid, and pyrazinamide. Rifampicin and isoniazid are the first-line anti-tuberculosis strategies and are usually combined with pyrazinamide and ethambutol. Mainly, ethambutol's side effect is optic nerve damage, skin rash, and, rarely, liver injury. The adverse effects of pyrazinamide are arthralgia, decreased appetite, liver injury, and skin rash and pruritus in some cases.[20] We should be careful when choosing the patient's treatment. The baby was born with normal deliveries in good health.

Immunity status of the patient, overall health including comorbidities, the type, and severity of the disease, patient's compliance of the treatment, the treatment's duration and side effects concluded the patient's treatment.[9] This patient had a successful treatment result, despite her pregnancy and allergic condition. It is also challenging to diagnose rare extrapulmonary tuberculosis, especially in pregnant women. We also find it challenging to choose a prompt treatment based on her pregnancy and relapse conditions, especially when she was allergic to ethambutol. But it was a successful treatment with good results, both on her skin and her baby.

Conclusion

Cutaneous tuberculosis is a rare extra pulmonary tuberculosis and is often underdiagnosed. It is hard to perform an adequate examination, and the results are often unspecified, while it has high mortality and morbidity, especially in pregnant women.

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Tuberculosis in pregnancy also carries its own risk, so we should give prompt treatment so the patient can get better and have safe labour.

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