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Lupus Vulgaris Treated Successfully with Modified Anti-Tuberculosis Regimen in a Drug-Induced Liver Injury Patient: A Case Report

İlaca Bağlı Karaciğer Hasarı Olan Bir Hastada Modifiye Antitüberküloz Rejimi ile Başarıyla Tedavi Edilen Lupus Vulgaris: Olgu Sunumu

Adnan et al. Managing Lupus Vulgaris with Hepatotoxicity

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Abstract
Lupus vulgaris is a form of cutaneous tuberculosis (TB) that commonly affects the face and neck. It is typically treated with standard anti- TB therapy (ATT). However, adverse drug reactions may alter treatment strategies. We report a case of female with red plaque on the left cheek, diagnosed as lupus vulgaris. Standard ATT was initiated but subsequently discontinued due to signs and symptoms of drug-induced liver injury (DILI). The treatment regimen was modified to levofloxacin, ethambutol, and streptomycin, with the gradual reintroduction of rifampicin. Reintroduction of isoniazid led to intolerance symptoms and therefore discontinued. The patient declined reintroduction of pyrazinamide due to fear of recurrence of the same symptoms. Consequently, modified regimen of levofloxacin, streptomycin, ethambutol, and rifampicin was continued in intensive phase, followed by rifampicin and ethambutol in continuation phase. Marked clinical improvement was observed. This case demonstrates successful individualized management of lupus vulgaris with a modified regimen in the setting of DILI, representing the first reported use of this approach.
Keywords: Antituberculous drugs, cutaneous tuberculosis, drug-induced liver injury, hepatotoxicity, lupus vulgaris

Öz
Lupus vulgaris, genellikle yüz ve boyun bölgelerini tutan bir kutanöz tüberküloz formudur. Bu durum genellikle standart anti-tüberküloz tedavisi (ATT) ile tedavi edilir. Ancak, advers ilaç reaksiyonları tedavi stratejisinin değiştirilmesini gerektirebilir. Sol yanakta eritematöz plak bulunan bir kadın hastada lupus vulgaris tanısı konulan bir olguyu sunuyoruz. Standart ATT başlatılmış, ancak ilaca bağlı karaciğer hasarı (drug-induced liver injury, DILI) belirti ve bulgularının ortaya çıkması üzerine tedavi sonlandırılmıştır. Tedavi rejimi daha sonra levofloksasin, etambutol ve streptomisin içerecek şekilde modifiye edilmiş, rifampisin ise kademeli olarak yeniden tedaviye dahil edilmiştir. İzoniazidin yeniden başlanması intolerans semptomlarına yol açmış ve bu nedenle tedavi kesilmiştir. Hasta, pirazinamidin yeniden başlanmasını reddetmiştir. Bu nedenle, yoğun fazda levofloksasin, streptomisin, etambutol ve rifampisinden oluşan modifiye rejim sürdürülmüş; ardından idame fazında rifampisin ve etambutol ile tedaviye devam edilmiştir. Belirgin klinik iyileşme gözlenmiştir. Bu olgu, DILI varlığında modifiye edilmiş bir rejim ile lupus vulgarisin bireyselleştirilmiş tedavisinin başarısını vurgulamaktadır.
Anahtar Kelimeler: Anti-tüberküloz tedavi, kutanöz tüberküloz, ilaca bağlı karaciğer hasarı, hepatotoksisite, lupus vulgaris

Introduction

Lupus vulgaris is a chronic, progressive form of cutaneous tuberculosis (TB) that typically develops in individuals with moderate to high immune competence[1]. Predilection of lupus vulgaris includes face and neck. Lupus vulgaris can be caused by the spread of TB through the bloodstream, lymphatic system or by directly extending from adjacent infected organ[2]. The typical manifestations are well-demarcated reddish-brown plaques or nodules and apple-jelly sign. The treatment of lupus vulgaris typically involves the standard anti-TB therapy (ATT). However, this case reports the first

successful use of a combination regimen of levofloxacin, ethambutol, streptomycin, and rifampicin for lupus vulgaris in the setting of drug-induced liver injury (DILI).

Case Report

A 53-year-old female presented with a thick, red plaque on her left cheek, the patient reported occasional pruritus. The lesion had been present for one year prior to hospital admission. The lesion did not worsen with sun exposure. There was no associated numbness. The patient denied any history of irritation from topical substances and had no history of chronic cough, weight loss, or a diagnosis of pulmonary TB. There was no family history of similar symptoms. Physical examination was unremarkable, except for multiple erythematous plaques with telangiectasia on the left cheek. Histopathological examination revealed epidermal atrophy with parakeratosis and focal lymphocytic exocytosis. The superficial to deep dermis and superficial subcutis showed confluent granulomatous infiltrates composed of epithelioid histiocytes and Langhans-type giant cells, surrounded by lymphocytes. No caseating necrosis was observed. These findings were consistent with lupus vulgaris.

The patient was referred to the pulmonology clinic and started on standard multidrug regimen. The intensive phase regimen consists of rifampicin, isoniazid, pyrazinamide, and ethambutol. After two weeks of therapy, the patient developed severe nausea, and liver function test level was found to be elevated more than five times the upper reference limit (Table 1). The bilirubin and aspartate aminotransferase (AST) values were not obtained before the first line regiment initiation due to limited coverage from insurance. The patient had no history of alcohol consumption. She was diagnosed with DILI, and the standard regimen was discontinued. The treatment was modified to a non-hepatotoxic regimen consisting of levofloxacin 750 mg (11.7 mg/kg), ethambutol 1000 mg, and streptomycin 1000 mg intramuscularly (15.62 mg/kg).

Rifampicin was subsequently reintroduced after two weeks of alternative regimens, with close monitoring for signs of hepatotoxicity and serial assessment of liver function parameters to evaluate for DILI associated with first-line standard ATT. The initial dose of rifampicin was 450 mg daily for one week. During this period, liver function tests improved and approached the normal range. The rifampicin dose was then increased to 600 mg daily, followed by the addition of isoniazid at a dose of 360 mg daily for one week. However, shortly after the reintroduction of isoniazid, the patient developed palpitations, nausea, and vomiting. The drug was discontinued based on suspicion of isoniazid allergy or intolerance. The patient declined reintroduction of pyrazinamide due to concerns about potential adverse effects.

The intensive phase of treatment was completed using levofloxacin, streptomycin, ethambutol, and rifampicin. Continuation phase regimen was comprised of rifampicin 600 mg and ethambutol 1000 mg, which was given for 7 months, bringing the total treatment duration to 9 months. There were no adverse events during this phase. By the end of the treatment, the patient demonstrated significant clinical improvement with thinning of the lesion and resolution of erythema (Figure 1). This case illustrates a successful alternative regimen for lupus vulgaris in a patient who developed DILI from the standard ATT.

Discussion

Lupus vulgaris is paucibacillary form of cutaneous TB. Histopathology of lupus vulgaris shows epithelioid cells, macrophages, and Langerhans giant cells[3]. Caseating granuloma is rarely seen in lupus vulgaris. These findings are in accordance with the result of patient histopathology. Cutaneous TB, including lupus vulgaris, is treated with standard Fixed Dose Combination of ATT. The first line treatment should be taken for at least 9 months which was divided into two phases, intensive and continuation. The intensive phase consists of a two-month regimen comprising rifampicin, isoniazid, pyrazinamide, and ethambutol. However, liver injury is one of the possible side effects. The incidence rate of DILI is 2-28%[4]. Pyrazinamide is the most common causative drug for DILI among the other drugs in first line ATT[5]. In one study assessing serious adverse events associated with pyrazinamide during first-line ATT, hepatotoxicity was identified as the most frequent adverse effect, accounting for 44.5% of cases[6].

Elevation of liver enzymes of more than five times is an indication to stop the hepatotoxic medicine (rifampicin, isoniazid, pyrazinamide). Rifampicin should be reintroduced with low dose and slowly titrated. The patient tolerated the full dose of rifampicin; therefore, rifampicin was continued, and isoniazid was subsequently reintroduced. However, following the reintroduction of isoniazid, the patient exhibited signs of drug intolerance, including palpitations, nausea, and vomiting. Based on the symptoms, Isoniazid hypersensitivity was suspected. According to literature, 73.7% of hypersensitivity reactions with first-line ATT occurred within the first week of treatment and presentation may vary. Nausea and vomiting are found in immediate-type of hypersensitivity[7]. However, the data regarding skin rash, eosinophilia, and specific immunological test result were not available. Thus, the palpitation, nausea, and vomiting should be categorized as intolerance to the side effects of isoniazid.

Second-line drugs of cutaneous TB include aminoglycosides and quinolones[8]. According to Indonesian National guideline of TB, regimen of fluoroquinolone, ethambutol, and streptomycin may be administered when the patient has liver impairment[9]. This is consistent with other literature, which states that if discontinuing ATT is not safe, an alternative regimen can be administered. The regimen consists of non-hepatotoxic drugs: streptomycin, ethambutol, and fluoroquinolone[4]. The dose of streptomycin and levofloxacin are based on patient body weight. According to the World Health Organization guidelines for the management of TB, streptomycin is administered at a recommended dosage of 10–15 mg/kg body weight per day. The standard therapeutic dose is 15 mg/kg, with a maximum daily dose not exceeding 1,000 mg[9]. Previous case report has demonstrated successful treatment of multidrug-resistant lupus vulgaris using regimens including kanamycin, cycloserine, moxifloxacin, linezolid, clofazimine, para-aminosalicylic acid, and pyridoxine[10].To the best of the author's knowledge, this is the first case report to describe the successful treatment of lupus vulgaris using an alternative regimen consisting of levofloxacin, ethambutol, streptomycin, and rifampicin. This regimen may be beneficial for patients with similar experiences of liver injury associated with standard ATT and suspected isoniazid hypersensitivity.

Conclusion

Hepatotoxicity caused by anti-TB treatment may alter the management course of lupus vulgaris. A modified regimen consisting of levofloxacin, streptomycin, ethambutol, and rifampicin resulted in satisfactory resolution of the cutaneous lesion in patient with DILI.

Ethics

Informed Consent: The patient was informed in detail about the study, and written informed consent was obtained for the publication of this case report and any associated images for scientific purposes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.D.S.F.A., M.M., E.M., Concept: F.D.S.F.A., Design: F.D.S.F.A., Data Collection or Processing: F.D.S.F.A., M.M., E.M., Analysis or Interpretation: F.D.S.F.A., M.M., E.M., Literature Search: F.D.S.F.A., Writing: F.D.S.F.A., M.M., E.M.

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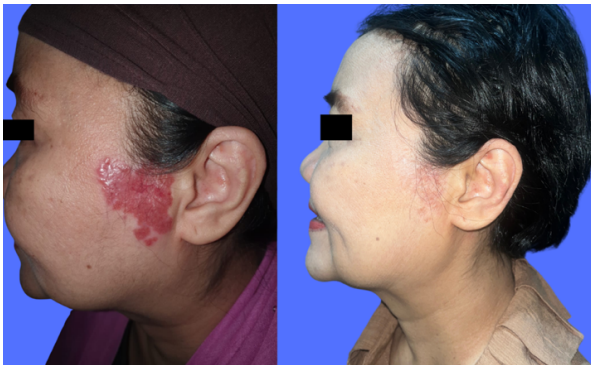

Figure 1. Skin lesion before and after treatment.

Table 1. Course of liver function tests.

Parameters	Upper reference limit	Before initiation of 1st line regiment	After initiation of 1st line regiment	After 1-week of levofloxacin, ethambutol, and streptomycin for a week	After 1-week of additional rifampicin
ALT	55	34	142	95	50
AST	34	-	194	67	33
Total bilirubin	1.2	-	0.9	0.36	0.45
Indirect bilirubin	0.8	-	0.48	0.18	0.21
Direct bilirubin	0.5	-	0.42	0.18	0.24

ALT, alanine aminotransferase; AST, aspartate aminotransferase.