Original Article

Antitubercular drug-induced lichen planus: A case study with a mini literature review

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Abstract

Introduction: Drug-induced lichen planus is a cutaneous adverse effect that manifests as a systemic eruption of flat-topped, erythematous, or violaceous papules resembling lichen planus on the trunk and extremities. Although antitubercular therapy has been linked to cutaneous hypersensitivity reactions, the literature on such cases is scarce. Here, we present a case to contribute to this field, reporting on its presentation and management, and reviewing previous case studies. **Case Report:** Our patient, a 63-year-old male, presented with black pigmented patches on the skin, having been diagnosed with pulmonary tuberculosis and on antitubercular therapy for the past two months. A diagnosis of ATT-induced lichen planus was made, and all ATT was stopped. The patient was treated with antihistamines, apremilast, tacrolimus, and corticosteroids, and rechallenge of each drug was performed consecutively. No new lesions appeared after rechallenge with isoniazid and rifampicin. However, ethambutol was not reintroduced due to strong suspicion, by exclusion, that it was the offending agent, whereas on rechallenge with isoniazid and rifampicin, the patient's skin lesions gradually improved with eventual resolution of hyperpigmentation. **Discussion and Conclusion:** Lichenoid drug eruptions are characterized by type IV hypersensitivity reactions, and rechallenge is required to ensure safer treatment since the risk of disseminated and multi-drug-resistant tuberculosis increases with the cessation of antitubercular therapy.

Keywords: Antitubercular drugs, drug induced, India, lichenoid reaction, tuberculosis

Introduction

Lichen planus represents a collection of persistent inflammatory conditions impacting the stratified squamous epithelium. Lichenoid eruptions have been linked to various factors including viral infections, contact allergens, and multiple medications. Although this affliction affects individuals of all races, it is primarily observed in young adults between the ages of 20 to 40 years; however, it can occur across all age groups. Notably, the prevalence of this condition stands at 2.4% in the general population and is three times more common in women than in men.[1]

One of the manifestations of drug-induced lichen planus involves a cutaneous adverse effect characterized by a systemic eruption of flat-topped erythematous or violaceous papules that resemble lichen planus on the trunk and extremities. This disorder also includes a lattice-like network of white lines known as Wickham striae, which overlays the lesions but is most prominently observed on the buccal mucosa where erosions may also manifest.

Classic cutaneous lichenoid eruptions have been associated with several medications such as ACE inhibitors, antimalarials,

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penicillamine, thiazide diuretics, beta-blockers, and antitubercular drugs. On the other hand, oral lichen planus reactions may be triggered by allopurinol, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), and ketoconazole. Similarly, photo-distributed lichenoid drug eruptions can arise due to carbamazepine, chlorpromazine, ethambutol, diltiazem, tetracyclines, and thiazide diuretics.

Although cutaneous hypersensitivity reactions have been linked to antitubercular therapy, the literature describes only a scant number of cases. In this case report, we aim to contribute to the existing knowledge base by presenting a case with its associated clinical features and our approach to managing the condition. Additionally, we provide a brief review of the prior case studies on this topic.

Case description

A 63-year-old male presented at the pulmonology outpatient clinic, complaining of cough, loss of appetite, and left-sided chest discomfort. The patient had a history of hypertension and was taking amlodipine 5 mg. No prior history of allergic tendencies or skin disorders was reported. Following diagnosis of pulmonary tuberculosis, the patient was initiated on antitubercular treatment (ATT), which comprised rifampicin, isoniazid, and ethambutol for two months.

Two months after beginning ATT, the patient returned to the clinic, describing a new onset of skin rashes, hair loss, and black-pigmented patches on the skin lasting one month. A physical examination revealed violaceous eruptions over the patient's anterior chest, back, hands, and legs [see Figure 1]. A diagnosis of ATT-induced lichen planus was subsequently made, with rifampicin, ethambutol, or isoniazid being the suspected offenders. All antitubercular drugs were discontinued, and the patient was prescribed hydroxyzine 10 mg, liquid paraffin, and clobetasol ointment.

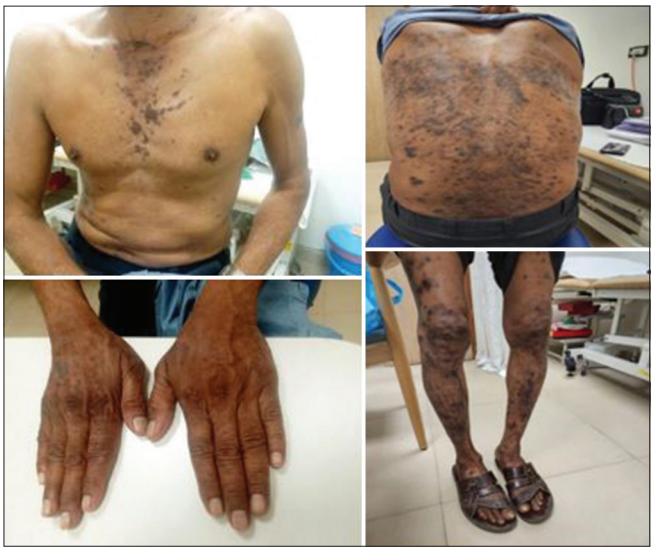

Figure 1: Violaceous eruptions over the patient's anterior chest, back, hands, and legs

Two weeks later, the patient's condition had improved and a modified ATT regimen, comprising levofloxacin 500 mg and linezolid 600 mg, was initiated. Unfortunately, after a month, the patient developed oral lesions and reported slow resolution of existing lesions. A chest radiograph revealed persistent centrilobular emphysematous changes in the bilateral lower lobes and a few enlarged subcentimetric superior mediastinal lymph nodes. The patient was treated with a combination of prednisolone 10 mg, fluticasone cream, apremilast 10 mg, and triamcinolone acetonide oral paste, while continuing with levofloxacin and linezolid.

After four months of discontinuing ATT, the patient showed signs of recovery, and plans for reintroduction of antitubercular medications were initiated. Individual drugs were reintroduced consecutively, while monitoring for any new lesions. Following 1.5 months of initiating rifampicin, no new lesions were observed, and the oral lesions appeared to be subsiding. Subsequently, isoniazid 300 mg was added to the regimen [see Figure 2]. Serial blood tests performed including a complete hemogram, liver function test, and renal function tests were all within the normal limits.

The patient returned for follow-up after one month, reporting joint pain that was likely attributed to the levofloxacin therapy. However, there were no new complaints of exacerbation in skin rashes. Consequently, the treatment plan was modified to discontinue the use of levofloxacin while adding pyrazinamide 750 mg to the regimen [see Table 1 for detailed timeline].

Due to strong index of suspicion of ethambutol being the culprit drug and prior case reports showing ethambutol

Table 1: Timeline of events

TIME RANGE	EVENTS
18th March, 2022	Patient visits with complaints of left sided pneumonia.
31st March, 2022	Pulmonary Tuberculosis diagnosed.
01st April, 2022	Patient started on ATT consisting of rifampicin, isoniazid and ethambutol.
May June, 2022	ATT therapy continued.
22nd July, 2022	Diagnosis of drug induced lichen planus made and all ATT stopped.
5th August, 2022	Lichen planus recovering.
2nd September, 2022	Patient complains of oral lesions.
22nd September, 2022	Patient complains of slow resolution of existing lesions.
16th November, 2022	Lichen planus recovering well and rechallenge with rifampicin 450mg.
12th January, 2023	No new lesions upon rechallenge with rifampicin. Isoniazid 300mg added to the regimen.
03rd February, 2023	No new lesions on rechallenge with isoniazid. Levofloxacin induced joint pain reported. Levofloxacin stopped and pyrazinamide 750mg introduced. No rechallenge done with ethambutol due to strong index of suspicion for being the culprit drug.

Figure 2: No new lichenoid eruptions after reintroduction of rifampicin and isoniazid

induced lichenoid drug eruptions, it was not reintroduced in the challenge regimen. The patient's skin lesions gradually started to improve and only hyperpigmentation was left, which also significantly improved with treatment as compared to prior lesions. With all other drugs reintroduced, the patient completed 9 months of antituberculosis treatment (isoniazid, rifampicin, and pyrazinamide). Repeat CT scan of the chest showed no new lesions and insignificant mediastinal lymphadenopathy with no feature suggestive of active disease. The antituberculosis treatment regimen was stopped subsequently.

Prior case studies

This is a brief compilation of the previous case studies on this topic from the last 10 years. (See Table 2 for summary)

1. Pathave H, Dongre A, Gund G, Goutham S, Nayak C (2022)[2]: A 40-year-old woman presented with pruritic, elevated lesions, and red, scaly skin that persisted for 15 days. These skin lesions appeared after two months of receiving rifampicin, ethambutol, and isoniazid as part of the antitubercular treatment for pulmonary tuberculosis. Upon cutaneous examination, the patient had numerous flat-topped papules and plaques on the scalp, face, and trunk of both upper and lower limbs. Biopsy results revealed interface dermatitis, lymphocytic lichenoid infiltration with eosinophils, and spongiosis, supporting the diagnosis of lichenoid drug eruption. The patient was treated with oral corticosteroids and methotrexate with gradual tapering, and emollients were prescribed for symptom relief. Within a month, the lesions showed a noticeable decrease in size, but unfortunately, the patient did not follow up.
2. Pathave H, Dongre A, Gund G, Goutham S, Nayak C (2022)[2]: A 35-year-old woman with a cold abscess of tuberculosis (TB) on her chest was treated with a four-drug antitubercular therapy (ATT) for three months. However, she developed violaceous scaly elevated lesions all over her body two months after starting the treatment. A cutaneous examination revealed violaceous papules and plaques with scaling and coalesce on the lips, upper extremities, and trunk. The biopsy showed a band-like infiltrate of lymphocytes in the superficial dermis with upper dermal edema, parakeratosis, and spongiosis, leading to a diagnosis of lichenoid drug eruption. After cessation of ATT, the lesions healed with postinflammatory hyperpigmentation. The patient was treated with corticosteroids that was continued for the remainder of the course of ATT.
3. Singh P, Nathiya D, Jain S, Raj P *et al.* (2020)[3]: A 63-year-old man who was undergoing ATT for pulmonary tuberculosis and transverse myelitis for the past four months. He developed a scaly, itchy rash on his bilateral extremities, but his face was unaffected. Upon physical examination, the presence of several violaceous papules and plaques of various sizes that were coalescing in some spots was noted. The rash was polymorphic, confluent, and erythematous, but spared the oral mucosa. The patient was given a two-week break from the antitubercular regimen, and each individual medication was reintroduced consecutively one week later in the following order: ethambutol, pyrazinamide, rifampicin, and finally isoniazid. Notably, the patient did not develop any skin lesions prior to the isoniazid challenge. However, after reintroducing isoniazid, he immediately developed similar lesions with severe itching. He received treatment with a tapering course of steroids. The diagnosis of isoniazid-induced lichenoid drug eruption was subsequently made.
4. Bhanja B.D, Sil A, Panigrahi A, Chakraborty S (2020)[4]: A 45-year-old man with sputum-positive pulmonary tuberculosis was treated with isoniazid and rifampicin for a month. After two weeks, he developed pruritic generalized skin eruptions. The histopathological analysis of the lesion revealed hyperkeratosis, basal cell degeneration, an upper dermal band-like infiltrate composed of mononuclear cells and eosinophils, multiple colloid bodies, melanin incontinence, and sparse deep dermal perivascular infiltration. These findings were consistent with lichenoid drug eruption (LDE). The patient was taken off of isoniazid and rifampicin and was put on topical powerful steroid and an oral antihistaminic. Rifampicin and isoniazid were restarted, but when the daily dosage of rifampicin reached 450 mg, fresh skin lesions appeared across the trunk. Rifampicin-induced

Table 2: Summary of prior case studies

Case report	Age (in years)	Gender	Presentation	Diagnosis	Treatment	Offending antitubercular agent
1. Pathave H *et al* (2022)	40	Female	Pruritic, elevated lesions and red, scaly skin	Biopsy	Corticosteroids, methotrexate	Undetermined; patient lost to follow up
2. Pathave H *et al* (2022)	35	Female	Violaceous, scaly, elevated lesions	Biopsy	Corticosteroids	Undetermined; patient received corticosteroids while completing the course of ATT
3. Singh *P et al* (2020)	63	Male	Violaceous, scaly, itchy rash	Clinical	Corticosteroids	Isoniazid
4. Bhanja B.D *et al* (2020)	45	Male	Generalized pruritic skin eruptions	Biopsy	Corticosteroids, antihistaminic	Rifampicin
5. Sheema Ali (2020)	55	Female	Violaceous, pruritic eruptions	Clinical	Corticosteroids, antihistaminic	Isoniazid
6. Jakyoung Kim *et al* (2017)	38	Male	Hyperkeratotic, scaly lesions	Clinical	Only discontinuation of offending agent	Second line ATT: cyclosporine
7. Jun Seo S *et al* (2016)	73	Female	Generalized macules and papules	Biopsy	Only discontinuation of offending agent	Ethambutol
8. Shahul H.A *et al* (2014)	65	Male	Generalized itchy skin lesions	Biopsy	Only discontinuation of offending agent	Rifampicin
9. Ji-Won B *et al* (2013)	52	Male	Violaceous rash	Biopsy	Corticosteroids, antihistaminic	Undetermined

LDE was identified as the cause based on the histological analysis, clinical characteristics, and suggestive history.

5. Sheema Ali (2020)[5]: A middle-aged woman of 55 years presented with pruritus and numerous violet-colored macules and plaque eruptions in areas of her body that were exposed to sunlight. These skin abnormalities manifested approximately two months after she commenced the 4-FDC (fixed drug dosage combination) therapy, which comprises of rifampicin, isoniazid, pyrazinamide, and ethambutol hydrochloride, prescribed for the management of pulmonary tuberculosis. At the fourth week of therapy, she reported itching, which subsequently progressed to symmetrical erythematous papules affecting her entire body. Upon re-administration of the medication, it was discovered that she had an isoniazid sensitivity. The patient continued taking rifampicin and other medications for another six months. She received treatment for the lichenoid drug eruption with antihistamines, topical corticosteroids, liquid paraffin, and multivitamins.
6. Jakyoung Kim, Shinyoung Park, Chul Min Jung *et al.* (2017)[6]: A 38-year-old male suffering from pulmonary tuberculosis, who had been undergoing ATT treatment for four months, was hospitalized owing to generalized pruritus. During the first two months of treatment, he was administered isoniazid, rifampin, ethambutol, and pyrazinamide, following which he received second-line anti-TB drugs such as ethambutol, levofloxacin, and cycloserine. Upon clinical examination, the patient displayed Wickham striae on the buccal mucosa and extensive hyperkeratotic lesions with scales covering his entire body. The lichenoid skin lesions experienced an immediate improvement upon discontinuation of the anti-TB medicines. No additional anti-TB drugs were prescribed thereafter, and the patient was monitored for a year, during which there was no recurrence of tuberculosis or exacerbation of the skin lesion. Cycloserine was correctly identified as the culpable drug in this patient, through patch test and the lymphocyte transformation test (LTT).
7. Jun Seo S, Hong C.K, In Ro B, Chang Y.C (2016)[7]: A 73-year-old female patient who developed generalized macules and papules that persisted for 15 days after undergoing ATT for four months. Upon clinical examination, the patient's entire skin surface exhibited polygonal, flat papules with an erythematous to violaceous hue, with histopathological results similar to those of lichen planus. The skin lesions were aggravated, and new ones formed during an ethambutol provocation test. Upon discontinuation of the patient's tuberculosis treatment with ethambutol, the skin lesions gradually subsided. A diagnosis of ethambutol-related lichenoid drug eruption was confirmed.
8. Shahul H.A, Manu M, Mohapatra A *et al.* (2014)[8]: A 65-year-old male patient who experienced generalized, itchy skin lesions over a period of one month while undergoing isoniazid, rifampicin, ethambutol, and pyrazinamide treatment for positive pulmonary tuberculosis smear. Physical examination revealed several erythematous, itchy eruptions on the patient's back, anterior chest, and arms, and punch biopsy of the skin lesion confirmed the diagnosis of lichenoid drug eruptions. Upon cessation of the antituberculosis treatment, the lesions gradually disappeared, and subsequent resumption of isoniazid, ethambutol, and pyrazinamide did not cause any intolerance in the patient. However, when the daily dosage of rifampicin was increased sequentially and reached 300 mg, new lesions reappeared, leading to withdrawal of rifampicin while continuing with the other drugs. The patient was diagnosed with rifampicin-induced lichenoid eruptions.
9. Ji-Won B, Chan-Y.B, Choi G.S, Shin J (2013)[9]: A 52-year-old male presented with left neck lymphadenopathy and chronic cough. Pulmonary tuberculosis was subsequently diagnosed and promptly treated with a combination of isoniazid,

ethambutol, rifampin, and pyrazinamide. Due to detected isoniazid resistance in sputum cultures, levofloxacin was prescribed instead. Two weeks after initiation of antitubercular medication, the patient developed a violaceous to erythematous rash. Physical examination revealed hyperpigmented lesions on the tongue, oral mucosa, and generalized dusky purpuric to hyperpigmented macules, as well as some lichenoid papules. A punch biopsy of the affected skin revealed extensive basal cell vacuolar degeneration and satellite cell necrosis, leading to the diagnosis of a lichenoid drug eruption.

Discussion

The incidence of lichenoid drug eruption remains unknown, though it appears to occur more frequently observed in young adults between the ages of 20 to 40 years; however, it can occur across all age groups and a slight predominance in women. This affliction affects individuals of all races.[1].

Lichenoid drug reactions affect the dermis and may trigger a type IV hypersensitivity reaction and TNF alpha, which in turn triggers keratinocyte apoptosis through CD 8+ cytotoxic T cells. This inflammatory cascade then affects melanocytes, leading to excessive melanin production and resulting in hyperpigmentation. Histologic analysis usually shows irregular thickening of the stratum granulosum, destruction of the stratum basale, and alteration or loss of rete ridges, resulting in a saw-tooth appearance.

The onset of lichenoid eruptions following administration of the offending drug can vary from a few weeks to a year. In this particular case, the eruption started occurring approximately one month after initiating antituberculosis therapy. The eruptions can present either as a localized or generalized distribution, with a fairly symmetrical distribution. Unlike lichen planus, the lesions of lichenoid drug eruptions typically occur on the extensor aspects of the extremities and dorsal aspects of the hands. In this case, the patient experienced black pigmented breakouts over their hands, legs, back, and anterior chest.

While lichen planus can be diagnosed clinically, a biopsy may be necessary in cases of atypical presentation. In this instance, the diagnosis of drug-induced lichen planus was based on the patient's history, morphology of skin lesions, and the relation between rechallenge and recurrence of lesions.

Once drug-induced lichen planus is detected, treatment involves withdrawing the suspected drug and administering high-dose topical corticosteroids such as fluocinonide or clobetasol.[10,11] In cases where topical corticosteroids are ineffective, calcineurin inhibitors may be used. Severe and widespread eruptions may require oral prednisone therapy for three to six weeks. In this particular case, the patient was administered hydroxyzine, apremilast, tacrolimus, and corticosteroids. Triamcinolone acetonide oral paste was also used to manage oral lesions.

Discontinuation of antitubercular therapy poses a considerable threat in the form of disseminated and multi-drug-resistant tuberculosis. In order to mitigate this risk, rechallenging is a viable option that can aid in identifying the problematic drug and reinstating a safer ATT regimen. In our study, no new lesions appeared after rechallenge with isoniazid and rifampicin. However, ethambutol was not reintroduced due to strong suspicion, by exclusion, that it was the offending agent, whereas on rechallenge with isoniazid and rifampicin, the patient's skin lesions gradually improved with eventual resolution of hyperpigmentation.

A note on the role of primary care physicians

The WHO TB statistics for India for 2021 give an estimated incidence figure of 2.14 million cases. This is a rate of 210 per 100,000 population.[12] Wide spread misuse of antitubercular drugs has also resulted in emergence of drug-resistant TB including multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) globally. Primary care physicians often serve as the first point of contact for individuals seeking medical assistance. Their role is pivotal in the diagnosis, treatment initiation, monitoring, follow-up, education, and counseling of patients with tuberculosis. We believe this research article to be meaningful in bringing awareness to one of the cutaneous reactions to antitubercular agents and the method of reintroduction of these medications in order to avoid the emergence of resistant or disseminated TB.

Conclusion

In the case report, ethambutol was deemed to be the most likely offending agent for the lichenoid skin eruptions. No new lesions appeared after rechallenge with isoniazid and rifampicin, whereas on rechallenge with isoniazid and rifampicin, the patient's skin lesions gradually started to get better, with gradually resolving hyperpigmentation.

Among the cutaneous adverse reactions linked to antitubercular treatment, lichenoid drug eruptions make up approximately 10%.[13] Typically, the management of lichenoid drug eruptions involves the administration of oral and topical corticosteroids. In this particular case, the patient was treated with corticosteroids, antihistamines, and phosphodiesterase inhibitors.

Although ethambutol is commonly associated with optic neuritis and peripheral neuropathy, there is limited research on the incidence of lichenoid eruptions resulting from its use. As such, we aim to contribute to the existing literature by presenting this particular finding.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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