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Unfamiliar territory of a familiar drug: INH-induced erythroderma

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Abstract:

Tuberculosis is a major cause of ill health, and one of the top ten causes of death worldwide. Treatment with multiple first-line drugs is the standard recommended treatment for drug-sensitive tuberculosis. Isoniazid (INH) is an important component of first-line therapy. Erythroderma is a rare but serious adverse drug reaction. We report here a case of a 64-year-old man who presented with generalized itchy, red-colored scaly lesions associated with extensive skin peeling after 8 weeks of antitubercular treatment (ATT). After the withdrawal of ATT, skin lesions improved along with symptomatic treatment. On sequential rechallenge with INH, the patient developed a recurrence of skin lesions, which confirmed the diagnosis of INH-induced erythroderma.

Keywords:

Antitubercular treatment, cutaneous adverse drug reaction, erythroderma, isoniazid

Introduction

Tuberculosis is a common infectious disease in developing countries. According to the World Health Organization, India featured among the eight high TB burden countries and contributes one quarter (26%) of all TB cases worldwide.^[1] The treatment regimen with multiple first-line antitubercular agents (rifampicin, isoniazid, pyrazinamide, ethambutol) remains a standard treatment for tuberculosis. Good bacteriological diagnosis and compliance to treatment are the main

components for a successful outcome. Adverse drug reaction (ADR) is defined as "A response to a drug which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function."^[2] ADR is associated with treatment disruption followed by treatment failure and acquired drug resistance (MDR TB) and an increased number of deaths. The common ADR associated with first-line drugs are arthralgia, allergic reaction, hepatotoxicity, and neurological and gastrointestinal

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disorders. Cutaneous adverse drug reactions (CADRs) are well-known undesired side effects of antitubercular treatment (ATT) drugs. It can range from mild pruritus to life-threatening toxic epidermal necrolysis. It needs discontinuation of treatment and complicates the treatment. The reported incidence of CADRs with pyrazinamide, streptomycin, ethambutol, rifampicin, and isoniazid is 2.38%, 1.45%, 1.44%, 1.23%, and 0.98%, respectively.^[3] Although the incidence of CADRs is rare with isoniazid, our patient had it in the form of exfoliative dermatitis.

Case Report

A 64-year-old man was diagnosed with a case of extrapulmonary tuberculosis by a local physician when he was evaluated with left lower chest wall swelling, weight loss, and loss of appetite. Ultrasonography showed ill-defined heterogeneous area of 54 mm×23 mm in the left lower chest involving intra- and intermuscular planes along the rib. Another similar lesion (44 mm×10 mm) was noted even behind the rib. Histopathology of the lesion confirmed it as caseous necrotizing granulomatous inflammation consistent with tuberculosis. He was started on first-line antitubercular drugs as per the directly observed treatment, short course regimen. After 8 weeks of ATT, he consulted a dermatologist with complaints of acute onset erythema with severe itching and extensive skin peeling. Then, ATT was withheld. One week after stopping the ATT, he presented to us with healed skin lesions, no organomegaly or history of any other drug intake, preexisting dermatitis, and exposure to chemical precipitants of dermatitis. He is a known diabetic with good glycemic control. Family history was negative for similar conditions or skin disorders. Laboratory investigations were normal, and HIV-ELISA was nonreactive.

Although there are no set guidelines for rechallenge, ethambutol was initiated because the incidence of CADRs is more with ethambutol (1.44%) than isoniazid (INH) (0.98%).^[3] Therefore, we decided to challenge with the more common drug than uncommon drug. Our patient tolerated ethambutol well, and there were no CADRs with ethambutol. As CADRs are expected to occur within 72 h in a majority of cases with extra precaution, INH was initiated on the fifth day with a dose of 300 mg.^[4] Within 48 h, the patient witnessed the recurrence of the skin lesions. The dermatological evaluation showed >90% body involvement except for the scalp. Skin lesions are nonuniform erythematous scaly lesions associated

with extensive skin peeling [Figs. 1, 2]. INH was stopped and symptomatic treatment was initiated with antihistaminic and topical emollients. The patient improved over a 2-week span with a reduction in erythema and skin peeling. The patient was prescribed modified ATT with the replacement of INH with levofloxacin.

Discussion

Erythroderma is also called exfoliative dermatitis. It is a severe and potential life-threatening condition that presents with diffuse erythema and scaling involving >90% of body surface area. Von Hebra first described the erythroderma in 1868.^[5] The pathogenesis of erythroderma is incompletely understood. The increased mitotic rate and decreased transit time of epidermal cells through the skin layers resulted in exfoliation.

Erythroderma is a clinical sign or presentation of a wide range of cutaneous and systemic diseases such as psoriasis or atopic dermatitis, drug hypersensitivity reaction, and rarely Sezary syndrome, which is a leukemic subtype of cutaneous T cell lymphoma.^[6] Drug-induced erythroderma is noted with phenylbutazone, hydantoin derivatives, carbamazepine, sulfonamide, penicillin, cimetidine, diltiazem, dapson, allopurinol, gold salt, and lithium.^[7] The incidence of CADR with first-line ATT drugs is 5.7%. Of all the first line ATT drugs, CADR is least common with INH (0.98%).

The latent period between the intake of the drug and the onset of the rash varies between 3 and 150 days, but the mean duration is 33 days. Our patient developed the erythroderma 60 days after the initiation of ATT. Predisposing factors for the CADs are HIV infection, polypharmacy, advanced age, autoimmune disease, renal or liver impairment, diabetes, smoking, and consumption of alcohol.^[3] The female gender is more vulnerable to CADRs than the male gender with a ratio being 1.2:1, and the mean age group is 50 years. CADR is more common in pulmonary tuberculosis than extrapulmonary tuberculosis. TB lymphadenitis is the most common type of extrapulmonary tuberculosis.^[4] Our patient had TB lymphadenitis, and he had the risk factors of diabetes and advanced age.

Erythroderma is associated with significant morbidity and mortality in addition to the risks inherent to the underlying disease and its therapy. The rapid and extensive exfoliation of the skin layers causes significant loss of proteins, amino



Figure 1: Non uniform scaly plaques on the face, trunk and upper limbs



Figure 2: Exfoliative eruptions leading to severe sloughing of the epidermis

acids, and nucleic acids. Thermoregulatory disturbances such as fever, chills, and superimposed bacterial infections are reported. In severe cases, it can cause hypovolemia, high-output cardiac failure, anemia, electrolyte disturbance, and rarely acute respiratory distress syndrome.^[8]

Drug causality can be identified by different methods such as provocation test including prick test, lymphocyte transfusion test, oral provocation test (OPT), or rechallenge.^[9] OPT is a gold standard test because of the lack of sensitivity or availability of the other tests in resource constraint settings. Rechallenge is defined as a controlled administration of a drug to diagnose drug hypersensitivity reaction.^[10] As there are no set guidelines for the sequence of rechallenge, we initiated ethambutol first followed by INH on the fifth day. As rechallenge reactions occur within 72 h in >90% of

the cases, we chose to rechallenge INH on the fifth day.^[4] As expected, our patient had a recurrence of skin lesions in <72 h. The complete resolution of skin lesions after withdrawal suggests that INH is the causative agent. Modified ATT was prescribed with 800 mg ethambutol, 450 mg rifampicin, and 750 mg levofloxacin for the continuation phase.

Conclusion

Although INH-induced erythroderma is a rare but potentially fatal adverse drug reaction. Oral provocation (OPT) or re-challenge is the recommended standard testing to identify the offending drug. Withdrawal of the offending drug along with supportive treatment improves the outcome. Replacing the offending drug can reduce the risk of ATT interruption and resistance.

Informed Consent

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Conflicts of interest

There are no conflicts of interest.

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Authorship Contributions

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