Acquired Ichthyosis in an Active Case of Tuberculosis Receiving ATT

Dear Editor,

First line anti-tubercular therapy (ATT) with rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin is the cornerstone of the treatment.[1] The most common adverse reactions (ADRs) observed with the ATT are gastrointestinal, nervous, ophthalmic, and dermatological in nature. ADRs produce significant challenges to the physician and patients both and can lead to compromised regimens, treatment discontinuation, drug resistance, and subsequent treatment failure.[2] Long list of cutaneous ADRs secondary to ATT includes urticarial and maculopapular rash, Lichenoid Drug Eruptions (LDEs), acute generalized exanthematous pustulosis, exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome/toxic epidermal necrolysis.[1] Herein, we are discussing a case of acquired ichthyosis (AI) in a patient receiving ATT.

A 72-year-old male patient being treated for pulmonary tuberculosis (TB) with ATT in continuation phase was presented to our dermatology outpatient with complaints of severe itch, dryness, and generalized flaking of the skin since one month. On examination, there was fine scaling and xerosis over the trunk. Scratch marks in crisscross pattern were present over back [Figure 1]. Patient had greyish-brown ichthyosiform scaling over lower limbs and gluteal region [Figures 1 and 2]. Few ichthyosiform scales were sparsely scattered over the chest and abdomen. Head, neck, face, and genitals were spared. Nails were shiny with a smooth surface. Mucosal and lymph nodes examination was normal. In addition, he also had multiple, grayish to violaceous, hyperkeratotic papules to plaques distributed over abdomen, bilateral flanks, and bilateral lower limbs [Figures 1 and 2]. Clinical history revealed prolonged cough and intermittent mild grade fever for more than 2–3 months in past for which he consulted at a government health facility. Documentation of the visit revealed radiological and microbiological confirmation of tuberculosis four months back. Since then, patient reported uninterrupted intake of ATT for last four months. He had no complaints of itching and noticed no changes in his skin during the first two months of the treatment. However, in the following month he gradually developed generalized dryness and grayish-brown scaling associated with multiple, thickened, lesions over lower limbs and abdomen. There was no history of any atopic diathesis (asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis), and also patient did not report occurrence of similar symptoms in past. There was history of weight loss of 4–5 kilograms during last few months. There was no history of similar symptoms in the close family. Based on clinico-morphological details and close association with history of drug intake and an active infectious disease, acquired ichthyosis and LDE secondary to ATT in the setting of active pulmonary TB were considered as the most probable diagnosis. Laboratory tests revealed normocytic, normochromic anemia (hemoglobin 11 g/dL), slight elevation in liver enzymes with alanine amino transferase at 49 IU/L (n <41), and aspartate amino transferase at 73 IU/L (n <50). Serum T3/T4/TSH levels were within normal limits, and anti-thyroid peroxidase antibodies were not detected. Ultrasonography of abdomen, radiological survey (CT chest) did not reveal added abnormalities indicative of any concealed systemic illness. Patient was screened for co-existing viral infections, and there were no serological evidences of Human Immunodeficiency Virus (HIV)/Hepatitis B/Hepatitis C infection. Two skin punch biopsies from separate sites (leg and abdomen) were taken. Histopathological examination

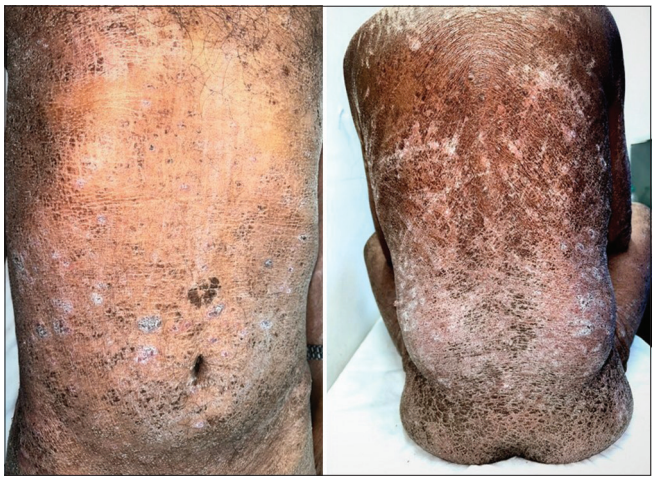

Figure 1: Fine scaling, xerosis, and multiple violaceous papules to plaques over abdomen and back along with scratch marks in crisscross pattern over back. Grayish-brown ichthyotic scaling is seen over lower back in the right half of the image

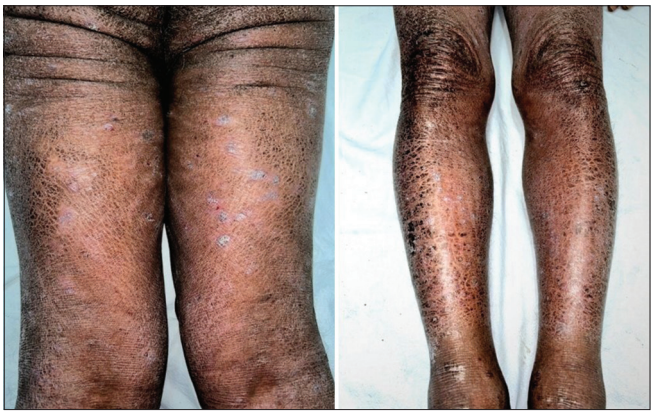

Figure 2: Multiple discrete lesions of lichenoid drug eruption are present over posterior aspect of thighs. Multiple, grayish-brown ichthyotic scales over bilateral lower limbs

of biopsies from leg and abdomen reaffirmed the presence of acquired ichthyosis (AI) and lichenoid drug eruption, respectively [Figure 3]. While LDE is well known to occur secondarily to ATT, acquired ichthyosis is not. We considered that ichthyosis could be due to either the ATT or the tuberculosis itself. After discussing with chest and TB experts, we stopped Isoniazid and started the modified ATT regimen including (levofloxacin, rifampicin). Patient was advised to apply emollients creams. No topical/oral corticosteroids were given. During the next 15 days with modified ATT, patient improved with significant decrease in pruritus and scaling making ichthyotic lesions much less noticeable [Figure 4]. Lesions of LDE became slightly flatter, and characteristic pigmentation of LDE was more appreciable at this stage [Figure 4]. Patient was advised to continue the modified regimen until the completion of ATT as reappearance of the symptoms could have the negative impact on the compliance of the patient to ATT. We could not examine the patient after the completion of the ATT with modified regimen. Naranjo algorithm was used to predict the causal association between the presenting Cutaneous adverse drug reactions (CADRs) and most likely culprit drug.[3]

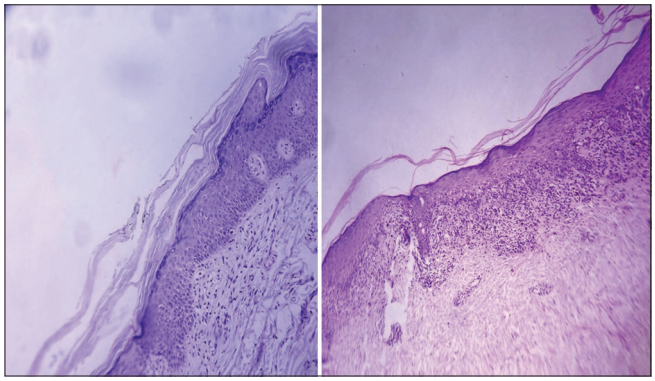

Figure 3: Left half of the image showing histopathological changes of acquired ichthyosis in form of epidermis with orthokeratotic hyperkeratosis, mounds of keratohyalin granules, thinned out granular layer, and sparse chronic inflammation in superficial dermis. Right half of the image shows changes of lichenoid drug eruption in form of epidermis with hyperkeratosis and irregular acanthosis and saw toothing of rete ridges. Dermo-epidermal junction has band like lymphocytic infiltrate. Occasional eosinophils are also present. (H and E, 10x)

Incidence of ADRs to anti-TB, particularly first line drugs have been reported to vary widely, ranging from 8.4% to 53.5%.[4] The time period between the initiation of drug and onset of rash ranges from days to years, with most cases occurring within 2 months. Lesions usually resolve gradually on withdrawal of offending drug, occasionally with post-inflammatory hyperpigmentation.[5]

Etiological spectrum of AI is very wide and varies from infectious diseases and drugs to malignancies, but it has no or little place neither in long list of ADRs of ATT nor in the cutaneous manifestations of tuberculosis. We could only find a handful of literature suggesting development of AI secondary to ATT or the tuberculosis itself.[6-9] The rare case of acquired ichthyosis secondary to isoniazid was reported by Kouismi *et al.* in 2013.[10] Ichthyosis has also been reported to develop secondary to several other medications [Table 1].[11] Ichthyosis in tuberculosis can arise secondary to either ATT or the primary infection itself.[7] In our case, patient had symptoms (chronic cough, intermittent low-grade fever) pointing toward a chronic illness for 2–3 months before he was diagnosed with the

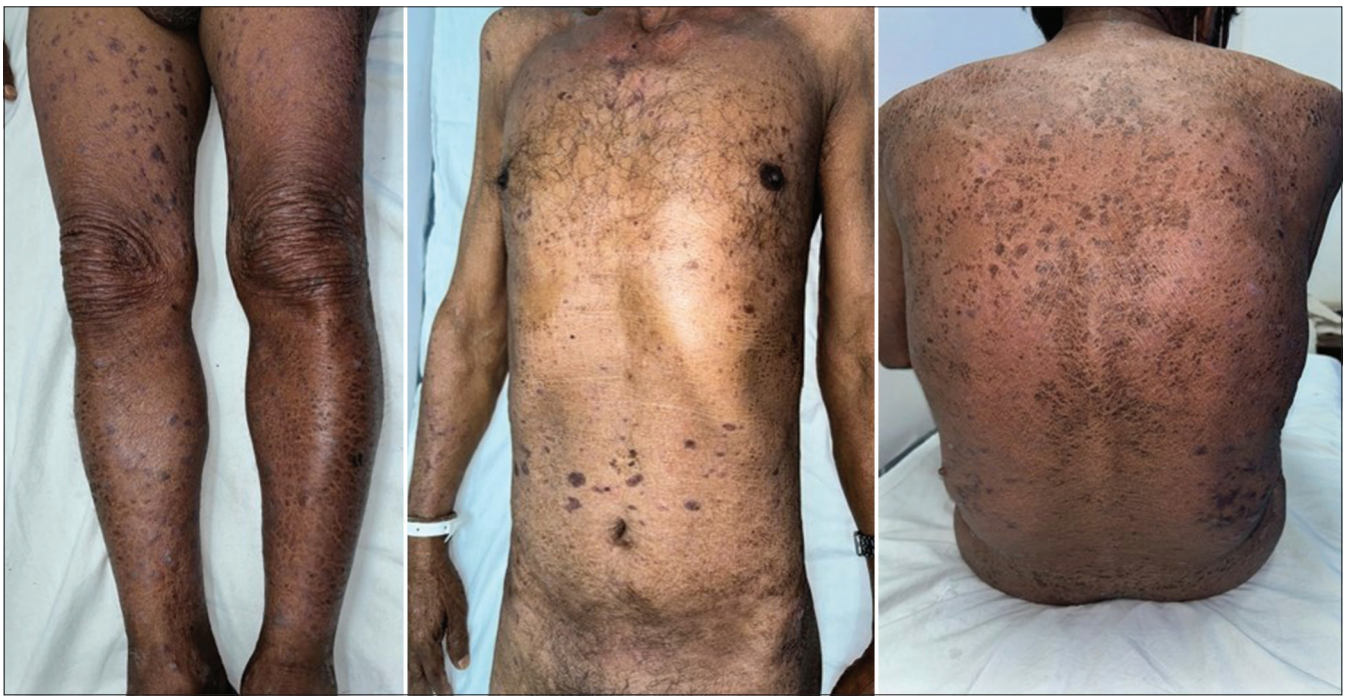

Figure 4: Decrease in scaling of acquired ichthyosis and flattened out lesions of lichenoid drug eruption 15 days after starting the modified ATT

Table 1: Medications implicated in acquired ichthyosis[11]

Cimetidine
Clofazimine
Hydroxyurea
Cholesterol-lowering agents
Nicotinic acid
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
Triparanol, and
Rarely used medications such as butyrophenon, dixyrazine, maprotiline, and nafoxidine.

tuberculosis. He apparently had no cutaneous symptoms during this period but started to develop ichthyotic lesions two months after the ATT was started. Patients of adult onset AI should always be extensively evaluated to rule out any underlying metabolic disorder, malignancy, infectious diseases (HIV), and connective tissue disorders. Association of Hodgkin's lymphoma with AI is well established. AI has been observed in up to 30% of the patients of HIV.

Naranjo algorithm is used to assess the casual association of ADRs and drugs. However, in case of combination regimens as in ATT it is challenging to conclusively indicate any single drug as causality of adverse reactions. Based on the previous reports on acquired ichthyosis, resolution of symptoms on withdrawal of isoniazid, and a score of 5 on Naranjo's algorithm, isoniazid was the considered as the most likely culprit drug. Pathomechanism of ichthyosis secondary to isoniazid is not clearly understood. However, isoniazid induced vitamin B6 deficiency and subsequent peripheral neuropathy has been speculated to play a significant role in the development of xerotic skin lesions.[10] Moreover, rarely peripheral neuropathy can also present with autonomic disturbances (e.g., dysregulated sweating).[12] All these factors can contribute to development of the ichthyosis in patients receiving isoniazid, which can be further aggravated by associated weight loss, malnutrition, and the tuberculosis itself. In addition, as LDE also started to improve on stopping the isoniazid, it was also considered as the most likely cause of the LDE in this patient. However, the role of rifampicin cannot be completely ruled out in the causation of the LDE. Tuberculosis outcomes are better if re-challenge is undertaken and only the offending drug is removed from the treatment regimen.

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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Conflicts of interest

There are no conflicts of interest.

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