Brief Report

A case series of generalized lichenoid drug eruption due to anti-tubercular drugs: Treated with immunosuppressant's while continuing anti-tubercular therapy

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Abstract

The spectrum of tuberculosis-associated cutaneous adverse drug reactions (ADRs) is wide and includes Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and generalized lichenoid drug eruption (LDE). LDE constitutes less than 10% of the total incidence of anti-tubercular drug induced cutaneous ADRs. In any type of drug reaction there is a prompt need of withdrawal of suspected drugs and institution of aggressive treatment of ADRs with proper control of underlying primary disease. Herein, we present a case series of five cases of generalized LDE due to anti tubercular therapy (ATT), in whom cutaneous lesions were managed with oral immunosuppressants while continuing ATT.

Keywords: Anti-tubercular therapy (ATT), lichenoid drug eruption (LDE), systemic immunosuppressants

Introduction

Lichenoid drug eruption (LDE) can be defined as lichen planus-like rash caused by drugs.[1] The diagnosis of LDE can be made on the basis of a clinical presentation of lichenoid skin lesions often a larger in size, less monomorphic and more prone to be eczematous, coalescing morphology and associated with desquamation in contrast to that of lichen planus; most of them do not show Wickham's striae, involvement of nails and mucous membrane is rare. In LDE, the rash can be limited to a small area or can be extended to the whole body (generalized). Histopathologically, LDE shows spongiosis, absence of wedged shape hypergranulosis, focal parakeratosis, necrotic keratinocytes in all layers of epidermis, and a deeper perivascular and periadnexal infiltrates of lymphocytes and eosinophils. ATT induced adverse drug reactions (ADRs) may result in interruption and change of treatment, that may lead to treatment failure, development of drug resistance, relapse and the transmission of disease.[2] The threat of transmission makes prompt resumption of therapy necessary, but the limited number of effective anti-tuberculosis drugs complicates management. We present a case series of generalized LDE related to anti-tuberculosis drugs in which the offending drug could not be definitively identified and therapy was continued successfully under the cover of systemic immunosuppressant's.

Case Reports

Case 1

A 35-years old lady presented with reddish to violaceous scaly raised lesions all over the body of two months duration. She was on ATT (rifampicin, isoniazid, ethambutol and pyrazinamide) from the past three months for cold abscess of tuberculosis (TB) on chest. Cutaneous examination revealed multiple violaceous papules and plaques with scaling and coalescing at places on trunk [Figure 1a & b], upper and lower extremities (predominantly extensor aspect) and lips.

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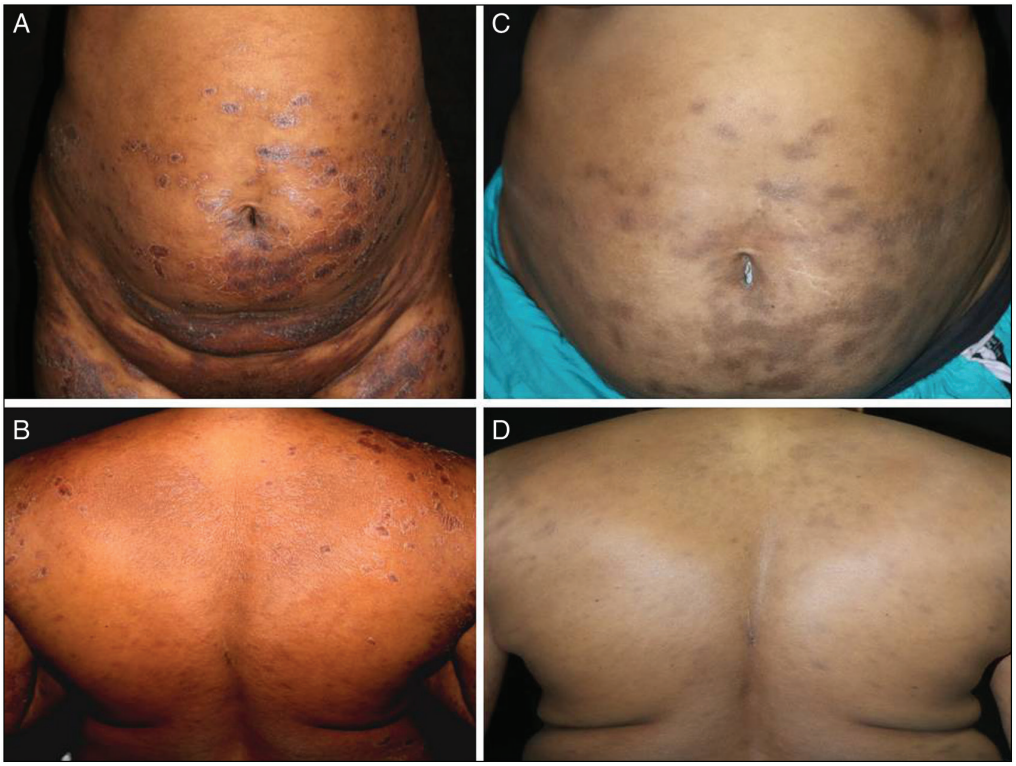

Figure 1: Case 1- (a and b) Multiple violaceous to hyperpigmented papules and plaques on abdomen and back (c and d) After treatment postinflammatory hyperpigmentation

Biopsy from the plaque showed bandlike infiltrate of lymphocytes in the superficial dermis, parallel to the epidermis with upper dermal edema and parakeratosis, spongiosis with few necrotic keratinocytes in upper epidermis. Hence, LDE was diagnosed. Complete blood count (CBC), liver function tests (LFT) and renal function test (RFT) were normal. Human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) and venereal disease research laboratory (VDRL) test were negative.

She received ATT for nine months and oral corticosteroids was started after one month of ATT (i.e. after eruption of LDE lesions) at 0.5 mg/kg/day dose with emollient and oral antihistaminics and followed up every 2 weeks with slow tapering. Oral corticosteroid was continued for about eight months of total ATT course with tapering doses without interruption and discontinued after one month of completion of ATT and subsidence of skin lesions. She was received 10 mg corticosteroid (low dose) for last two months of ATT. Post ATT, lesions resolved with post inflammatory hyperpigmentation [Figure 1c & d] without any complications and corticosteroid was stopped after continuing 5 mg dose for one more month after ATT completion.

Case 2

A 74 years old man presented with generalized dark scaly lesions [Figure 2a & b] for two months. The lesion had developed two months after starting TB treatment (rifampicin, isoniazid, ethambutol and pyrazinamide) for pulmonary TB. A private practitioner had stopped TB treatment at the onset of the lesions, but they recurred on reinitiating the drugs. Around the time of presentation to the private practitioner he was diagnosed with rifampicin and isoniazid resistance and assessed as multidrug resistant-tuberculosis (MDR-TB). He was started on injection kanamycin, tablet moxifloxacin, tablet ethambutol, tablet cycloserine and injection pyrazinamide.

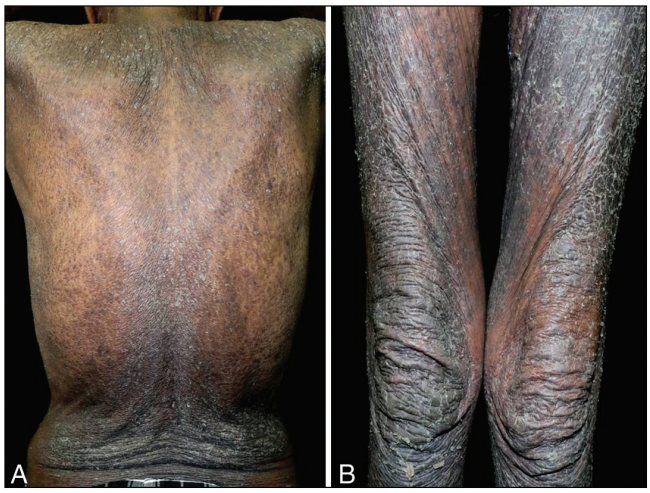

Figure 2: Case 2- (a and b) Multiple violaceous to hyperpigmented papules and plaques with scaling on trunk and extremity

Cutaneous examination revealed multiple violaceous to hyperpigmented scaly papules and plaques, coalesced at places on trunk [Figure 2a], extremity [Figure 2b], head and neck.

Biopsy from plaque showed lymphocytic lichenoid infiltrate with eosinophils and spongiosis with necrotic keratinocytes in upper epidermis. CBC showed anemia (Hemoglobin: 8 gm/dL, normal range for men: 14–17.5 gm/dL), LFT and RFT were in normal range. HIV, HbsAg, HCV and VDRL were negative. On clinico-histopathological correlation diagnosis of LDE secondary to ethambutol or pyrazinamide was made.

He was prescribed oral corticosteroids (prednisolone) 1 mg/kg/day with other symptomatic treatment in form of topical emollient, oral antihistaminics and followed up every two weeks with tapering of prednisolone. There was an improvement in the skin lesions in form of flattened plaques and no new lesions 15 days after starting corticosteroid. Then corticosteroid was tapered by 10 mg every two weeks for one month then by 5 mg every two weeks; unfortunately he passed away during hospital admission due to disseminated multi-organ MDR-TB. We could not confidently comment about reason for dissemination of TB; but multidrug resistant could be one reason rather than corticosteroid therapy as we tapered it very early and maintained on very low dose (5 mg).

Case 3

A 40 years old lady came with itchy red scaly raised lesions all over the body since 15 days. She developed skin lesions after two months of continuation phase (rifampicin, ethambutol, isoniazid) of ATT for pulmonary TB. Cutaneous examination revealed multiple scaly violaceous flat topped papules and plaques on scalp, face, trunk [Figure 3a] extensor aspect of both upper and lower limbs [Figure 3b].

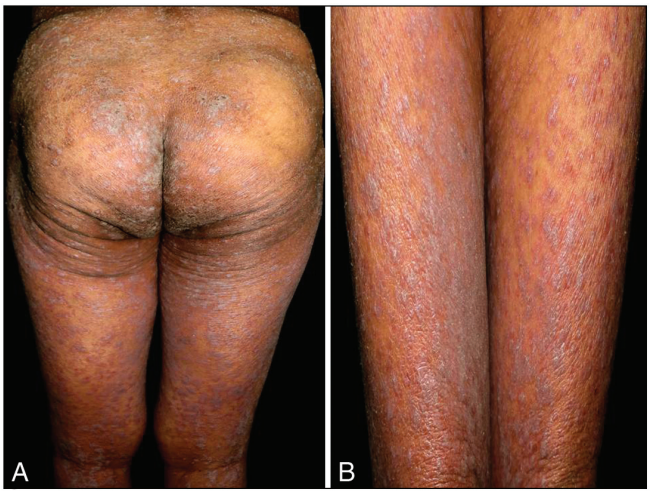

Figure 3: Case 3- (a and b) Multiple eczematous erythematous to purplish plaques and papules on buttocks, abdomen and thigh

Biopsy from lesion showed interface dermatitis, lymphocytic lichenoid infiltrate with eosinophils and spongiosis [Figure 4a & b]. A diagnosis of LDE was established based upon the clinical presentation, pathological findings, and temporal relationship between the treatment of tuberculosis and appearance of skin lesions. CBC, LFT and RFT were normal. HIV, HbsAg, HCV and VDRL were negative.

She was prescribed oral corticosteroids (0.5 mg/kg/day) with fast tapering within three weeks and methotrexate (12.5 mg/week) which was gradually tapered, with symptomatic treatment in form of emollient and oral antihistaminics. Within a month lesions noticeably decreased; hence after three weeks we fast tapered corticosteroid to 5 mg and kept methotrexate 10 mg/week but unfortunately she did not follow up after that.

Case 4

A 60 years old lady came with dark raised lesions with thickening of skin and scaling with itching all over body since past two months. She had no history of photosensitivity or joint pain. She was on ATT (rifampicin and isoniazid) continuation phase since last four months for pulmonary TB. Cutaneous examination revealed multiple hyperpigmented hyperkeratotic scaly plaques on trunk [Figure 5a], scalp and neck [Figure 5b] sparing palms, soles and mucosae. Nails were normal.

Biopsy from hyperpigmented hyperkeratotic plaque showed lichenoid interface dermatitis, pigment incontinence and eosinophilic spongiosis with multiple necrotic keratinocytes in upper epidermis [Figure 6a & b]. On basis of clinical and histopathological findings a diagnosis of LDE was made. CBC, LFT and RFT were normal. HIV, HbsAg, HCV and VDRL were negative.

Patient was started on emollients, oral antihistaminics and oral corticosteroids (prednisolone) 1 mg/kg/day.

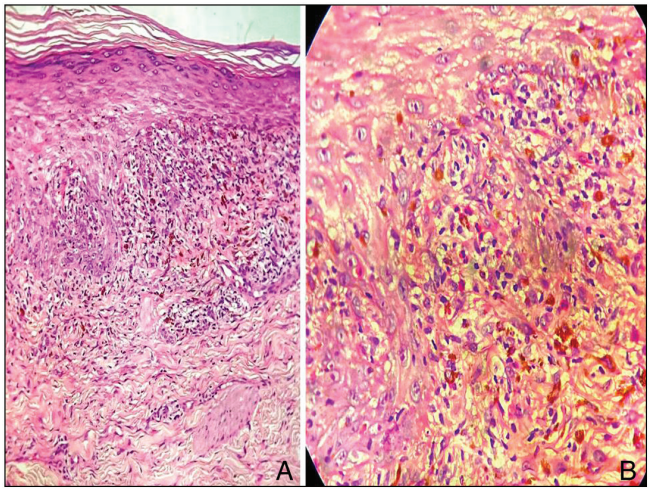

Figure 4: (a) Biopsy showing interface dermatitis, lymphocytic lichenoid infiltrate and pigment incontinence (H and E, x10). (b) Moderate spongiosis with multiple eosinophils in upper dermis (H and E, x40)

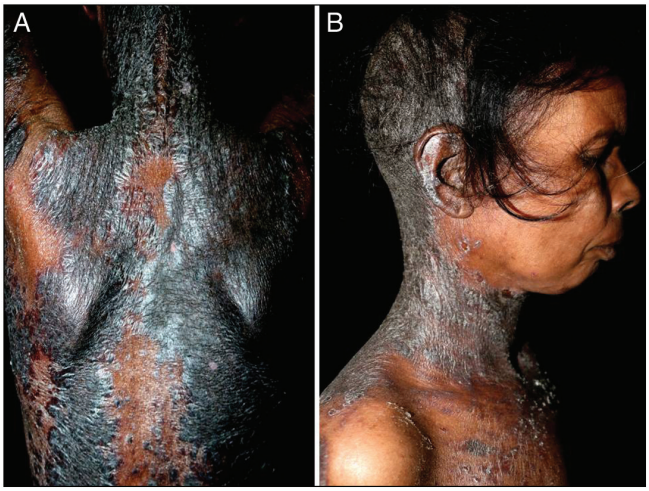

Figure 5: Case 4- (a and b) Multiple confluent hyperpigmented plaques with white shiny scaling on abdomen, back, neck and scalp

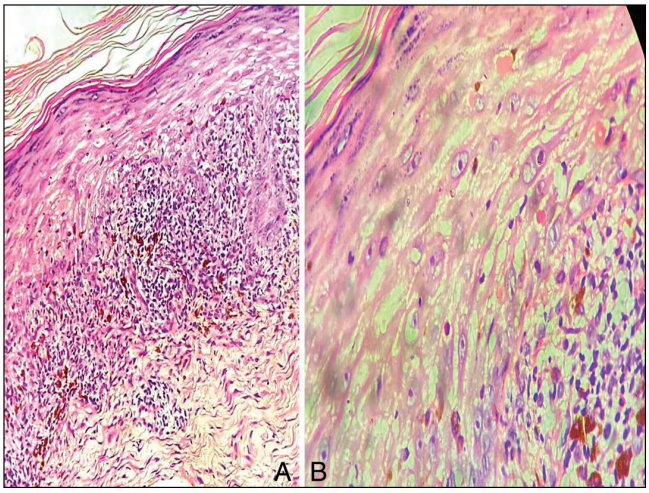

Figure 6: (a) Biopsy showing lichenoid interface dermatitis and pigment incontinence (H and E, x10). (b) Moderate eosinophilic spongiosis with multiple necrotic keratinocytes in upper epidermis (H and E, x40)

After about 5 weeks she had noticeable improvement in skin lesions and steroid was tapered to 20 mg once daily and was kept on same dose for one more month then tapered to 10 mg which was continued till completion of ATT. Once ATT was completed, lesions started to resolve spontaneously and reached a plateau, for which oral methotrexate 12.5 mg once a week was started and corticosteroid was stopped. She was followed up every 2 weeks. Lesions resolved with residual hyperpigmentation without aggravation of underlying TB; then methotrexate was tapered and stopped in next two months.

Case 5

A 56 years old male presented with dark coloured raised lesions with itching all over the body since one and half months. She developed skin lesions after one and half months of continuation phase of ATT (rifampicin and isoniazid) for pulmonary TB. Cutaneous examination showed multiple violaceous to hyperpigmented plaques with scaling on trunk, extremity [Figure 7a & b] sparing palms, soles and mucosae.

Biopsy from plaque showed lichenoid interface dermatitis, mid-dermal perivascular infiltrate, moderate spongiosis, focal parakeratosis and necrotic keratinocytes in upper epidermis. On basis of clinical and histopathological findings a diagnosis of LDE was made. CBC, LFT and RFT were normal. HIV, HbsAg, HCV and VDRL were negative.

He was started on oral corticosteroid (prednisolone) 0.5 mg/kg/day and antihistaminics with emollients. The dose of corticosteroid was tapered to 25 mg after four weeks with 5 mg twice weekly tapering and then maintained on 10 mg till completion of ATT. During treatment he didn't show any complications and his skin lesions were also well controlled [Figure 7c & d]. Post ATT, skin lesions started to resolve spontaneously and oral steroid was stopped within one month of completion of ATT.

Discussion

LDE is a condition that is well characterized both clinically and histopathologically.[3] It is characterized by a symmetric flat-topped, erythematous or violaceous papules and plaques which resembles lichen planus and presents on the trunk and extremities. They may rarely progress to exfoliative dermatitis and tend to be extensive or generalized.[2]

LDE constitutes less than 10% of the total incidence of anti-tubercular drug induced cutaneous ADRs.[4] Isoniazid, rifampin, pyrazinamide, and ethambutol have been reported to be culprit agents for LDE.[5-7] The incidence rate of rifampicin-induced cutaneous ADRs is about 1.23%.[8] Lichenoid drug eruption is infrequent and uncommon indicative of isoniazid induced cases of 0.98% incidence for cutaneous adverse reactions.[7]

The pathogenesis of LDE is thought to involve T cell mediated autoimmune damage of basal keratinocytes induced by the inciting drugs.[9] One hypothesis suggests the formation of a hapten, which becomes antigenic or immunogenic by covalently binding to a larger protein or peptide, thereby activating T cells, and subsequently eliciting an immune response.[9] It shows type IV hypersensitivity, TNF-α-triggering keratinocyte apoptosis through CD8+ cytotoxic T cells.[10] As LDE develops as a result of autoreactive T cells directed against a drug major histocompatibility complex (MHC) antigen complex, so that keratinocytes and Langerhans cells are viewed by the immune system as 'non-self'. Hence, systemic immunosuppressant's are helpful in LDE.

LDE even if generalized or severe, it doesn't presents with systemic involvement like Stevens Johnson syndrome/toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. All five cases described here didn't have systemic involvement which made it easier to continue ATT.

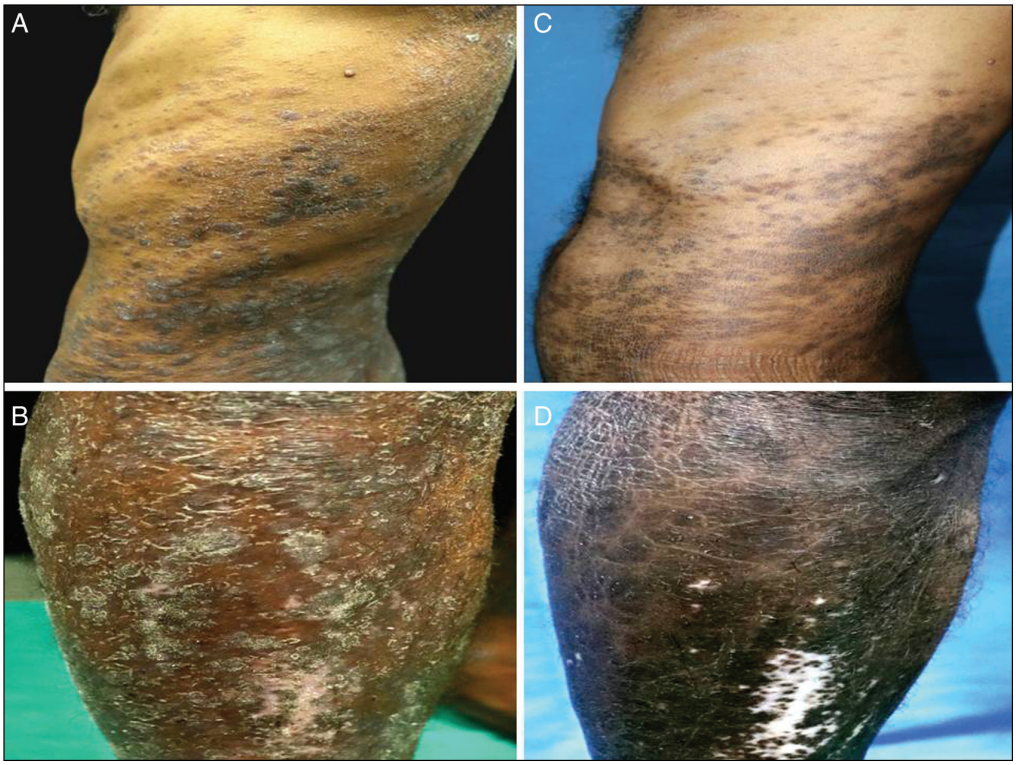

Figure 7: Case 5- (a and b) Multiple violaceous to hyperpigmented scaly papules and plaques on trunk, lichenified on leg (c and d) After treatment postinflammatory hyper- and depigmentation

Histopathologically, lichenoid interface dermatitis, focal parakeratosis, necrotic keratinocytes with exocytosis of lymphocytes, eosinophilis, a deeper perivascular and periadnexal infiltrate are signs more typical of LDE.[11]

The time period between the initiation of drug and onset of rash ranges from days to years, with most cases occurring within 2 months.[2] The lesions usually resolve spontaneously on withdrawal of offending drug, occasionally with postinflammatory hyperpigmentation. As ATT is always group of antitubercular drugs; it become big challenge to identify specific offending drug.

Drug re-challenge is considered definitive for identifying culprit drug; however, it is time-consuming, not always reproducible and contraindicated in severe reaction.[12] This approach also increases the risk of inducing additional and possibly a fatal ADRs. The other option is desensitization that is defined as loss of response after prolonged or repeated application of stimulus.[13] In all our five cases we continued ATT in spite of LDE and no one of our patient showed aggravation or exacerbation of skin lesions which is due to systemic immunosuppressant treatment and possibly due to desensitization to causative drug.

The lack of acute markers, insidious onset of the rash, and varying intervals between drug initiation and a clinically detectable rash make it difficult to establish a temporal relationship with the drug and ascribe causality in LDE. This is more so in patients receiving multiple drugs. The limited number of effective anti-tuberculosis drugs, the cessation of which is associated with a higher mortality, increased risk of drug resistance, longer duration of therapy and public health concerns, make it necessary to balance the interruption of therapy against treating through the ADRs.[14,15]

The first-line therapy usually used for LDE is topical steroids. Data supporting the use of retinoids, systemic steroids, and other immunosuppressants in LDE are available.[16] Cutaneous drug reactions due to ATT are mostly need treatment including topical emollients, oral antihistaminics and topical steroids; but when skin lesions become generalized or ATT needs to continue in spite of drug reactions then systemic steroids and/or immunosuppressant's needed with continuing ATT regimen. Lehloenya *et al.*[17] had presented a case of severe LDE related to antituberculosis drugs in which the offending drug could not be definitively identified and therapy was continued successfully under the cover of topical steroids and phototherapy. Phototherapy is one treatment option for LDE which is also used in atopic dermatitis and lichen planus; but it takes time to resolve lesions and if not properly supervised then there is always possibility of precipitation of skin lesions with fissuring; as happened in above mentioned case[17] due to excessive sun-exposure, problematic in non-compliant patient and eczematous morphology of LDE is also limits its use.

In all our five cases of generalized LDE, we started systemic immunosuppressant's (corticosteroid or/and methotrexate) while continuing ATT. We started corticosteroids with 1 mg/kg to 0.5 mg/kg dose in all cases which was tapered in short duration and maintained with 10 mg once daily till completion of ATT. All patients showed improvement in skin lesions in an average 3–5 weeks of post corticosteroid treatment. In our second case who was died due to MDR-TB, skin lesions were lichenified and thick on whole body including scalp with bilateral leg oedema; hence oral corticosteroid was planned in treatment and tapered twice weekly to maintained on 10 mg after 5 weeks of initiation of LDE treatment. It is quite obvious that steroid can cause immunosuppression but due to severity of LDE and need of continuing ATT especially in MDR-TB; we started him on corticosteroids which was tapered very early to maintained on low dose (10 mg) to avoid immunosuppression and aggravation of underlying TB. Our third case was started on corticosteroid with methotrexate in which steroid was used to rapidly control skin lesions and was tapered fast in first three weeks and methotrexate (10 mg) continued once weekly with low dose (5 mg) of corticosteroid; with such treatment regimen also the skin lesions were well under controlled. Our fourth case was started on corticosteroid (1 mg/kg/day) and tapered after significant improvement to low dose (10 mg/kg/day) which was continued till completion of ATT and then as lesions became plateau, we treated him with methotrexate without corticosteroid. Due to extensive cutaneous involvement, scarring alopecia, and slow resolution of lesions in our two cases (case 3 and 4), oral methotrexate was started. As there was significant and noticeable but incomplete resolution of skin lesions even after 3–5 weeks of initiating corticosteroids almost in all cases; we continued corticosteroids in low dose (10 mg/kg/day) till completion of ATT.

Due to the prolonged latency between initiation of therapy and onset of rash, one may not recognize the drug as a causative factor. Hence, high index of clinical suspicion is required for appropriate diagnoses and management of such cases.

Conclusion

ATT should be continued irrespective of cutaneous drug reactions like LDE as there are limited ATT drugs and stopping ATT can lead to drug resistance, increased treatment duration and mortality. Hence a good balance of continuing ATT therapy and treating the cutaneous lesions has to be there. All our five cases were treated with systemic corticosteroids or/and methotrexate along with continuation of ATT medications and except second case no mortality occurred. The mortality was attributed to MDR-TB and not to immunosuppressant treatment or LDE.

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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