Zinc-Responsive Acral Hyperkeratosis: A Report of a Rare Entity

Abstract
Chronic acral hyperkeratotic dermatosis includes several conditions such as lichen simplex chronicus (LSC), hypertrophic lichen planus (HLP), psoriasis vulgaris (Ps), acral acanthosis nigricans, acquired zinc deficiency, and necrolytic acral erythema (NAE). LSC, Ps, and HLP respond to conventional treatments such as topical corticosteroids, immuno-modulators such as tacrolimus, and oral methotrexate. Zinc-responsive acral hyperkeratosis is a novel entity that resembles the above-mentioned diagnoses clinically but fails to respond to the above treatment options. NAE is a rare condition, commonly associated with hepatitis C virus infection and manifest similar clinical features of zinc-responsive acral hyperkeratosis, but differs histopathologically. Both conditions show a good response to oral zinc supplementation. As there is a paucity of literature on zinc-responsive acral hyperkeratosis, we are highlighting the case.

Keywords: Acral hyperkeratosis, hepatitis C infection, necrolytic acral erythema, zinc

Introduction
Zinc-responsive acral hyperkeratosis presents typically with persistent, well-defined hyperpigmented plaques distributed symmetrically over acral regions of the body. Necrolytic acral erythema (NAE) is the closest mimicker of this entity and can be differentiated on the basis of histopathology. Herein, we report a case of zinc-responsive acral hyperkeratosis which responded well to zinc therapy.

Case Report
A 57-year-old male presented to us with dark-colored, mildly itchy, dry, scaly raised lesion over both hands for 4 months. He was treated with potent topical steroids, emollients, tacrolimus, and oral methotrexate in the past without any relief. Cutaneous examination revealed bilaterally symmetrical well-demarcated hyperpigmented plaques over the dorsum of hands [Figure 1]. General and systemic examination was normal. Palms and soles, oral mucosa, hair, and nail examination revealed no abnormality, and Auspitz sign was negative. We kept the differential diagnosis of lichen simplex chronicus (LSC), psoriasis vulgaris (Ps), acral acanthosis nigricans (AN), acquired zinc deficiency, NAE, and zinc-responsive acral hyperkeratosis. All routine laboratory investigations such as lipid profile, kidney function test, and blood sugars were unremarkable except for liver function test which shows low serum albumin of 2.9 g/dl [normal range = 3.4–5.4 g/dl]. His alkaline phosphatase level was within normal range. HIV, hepatitis B, and C serology were negative. Serum zinc levels could not be performed due to financial constraints. Histopathology showed hyperkeratosis, focal parakeratosis, and acanthosis with a prominent granular layer. Dermis showed a sparse perivascular mononuclear infiltrate of lymphocytes [Figure 2]. Since histopathological findings were not consistent with the clinical diagnosis of AN, Ps, LSC, and NAE, a therapeutic trial of oral zinc was given with 200 mg of zinc sulfate three times daily for 3 weeks along with 10% urea containing emollient. At 3 weeks, the follow-up patient noticed a good therapeutic response to oral zinc with flattening of plaques [Figure 3a and b]. Thus, based on history, skin biopsy, and excellent response to oral zinc, a final diagnosis of zinc-responsive acral hyperkeratosis was made. The patient was asked to continue oral zinc 200 mg two times a day for the next 3 weeks. After 6 weeks of treatment, we observed 60–70% improvement in the lesion [Figure 4a and b]. He is still under treatment.
Kowe, et al.: A rare case of zinc-responsive acral hyperkeratosis

Discussion

We report a rare entity with a unique clinical presentation of symmetric acral hyperkeratotic plaques of long duration which is responsive to oral zinc supplementation. This entity is found to be refractory to different modalities of treatment. In 2015, Ghosh et al.\textsuperscript{[1]} reported a series of 10 patients with psoriasiform lesions over acral regions of the body (8 patients had lesions over dorsum of hands only and 2 patients with lesions over both dorsum of hands and feet) who were nonreactive to hepatitis C and on histopathology showed hyperkeratosis, acanthosis, prominent granular layer, and dermal infiltrate and who were resistant to conventional treatment but showed significant improvement on oral zinc therapy which they labeled as zinc-responsive acral hyperkeratotic dermatosis. In Ghosh et al.’s study, 8 out of 10 patients showed normal serum zinc levels and only 5 patients had associated systemic abnormalities. Our patient had involvement of dorsum of hands only. NAE is clinically identical to zinc-responsive acral hyperkeratosis and also responds to zinc therapy. It was first described by el Darouti and Abu el Ela in 1996, in Egypt, which belongs to the group of other necrolytic erythema which includes necrolytic migratory erythema, acrodermatitis enteropathica, pellagra and biotin, and essential fatty acid deficiencies.\textsuperscript{[2,3]} The exact etiopathogenesis of NAE is unknown; however, hepatocellular dysfunction, hyperglucagonemia, hypoaminoacidemia, hypoalbuminemia, zinc deficiency,
Table 1: Differential diagnosis of chronic acral hyperkeratotic dermatosis

| Diagnosis                        | Clinical features                                                                 | Histopathology                                                                 |
|----------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Psoriasis ([12])                 | Pruritic well-defined, symmetrical erythematous plaques with silvery-white scaling over extensor surface of the body. Auspitz sign positive. Involvement of scalp, joint, and nails often present | Hyperkeratosis, parakeratosis, absent granular layer, acanthosis with regular elongation of the rete ridges, suprapapillary thinning of epidermis, papillary dermal edema with dilated capillaries surrounded by lymphocytic infiltrate. Munro microabscesses in the stratum corneum, spongiform pustules of Kogoj in the spinous layer |
| Hypertrophic lichen planus ([13])| Pruritic violaceous, shiny verrucous plaques usually present over shins. Wickham striae, mucous membrane, and nail involvement seen often present | Compact orthokeratosis, wedge-shaped hypergranulosis, irregular acanthosis, vascular degeneration of basal layer, band-like dermal lymphocytic infiltrate |
| Lichen simplex chronicus ([4])   | Severely pruritic, symmetrical hyperpigmented, lichenified plaques most commonly over shins | Hyperkeratosis interspersed with parakeratosis, acanthosis with irregular elongation of the rete ridges, wedge-shaped hypergranulosis, slight spongiosis, and sparse perivascular lymphocytic infiltrate in dermis |
| Chronic eczema ([15])            | Ill-defined pruritic scaly plaques mostly over acral regions. Unilateral and sometimes lichenified | Hyperkeratosis, parakeratosis, wedge-shaped hypergranulosis, focal spongiosis, acanthosis. Sparse inflammatory infiltrate in dermis |
| Acral acanthosis nigricans ([16])| Hyperpigmented, thickened, velvety plaques over dorsum of hands and feet | Hyperkeratosis, papillomatosis, irregular acanthosis, slight hyperpigmentation of basal layer, upward finger-like projection of dermal papillae, horn pseudocysts can be seen |
| Necrolytic acral erythema ([9])  | Well-circumscribed, symmetrical dusky to violaceous plaques with or without scaling with a rim of erythema over acral areas. Sometimes vesiculation or bulla formation can be seen | Hyperkeratosis with psoriasiform hyperplasia, necrotic keratinocyte with vascular degeneration, parakeratosis, papillomatosis, focal hypergranulosis, pigment incontinence, inflammatory cells in papillary dermis |
| Acquired zinc deficiency ([10])  | Acral, periorificial, and ano-genital erythematous scaly sharply demarcated patches, alopecia, paronychia, and transverse ridging of nails | Necrosis, confluent parakeratosis, hypogranulosis, psoriasiform hyperplasia, vacuolization, and ballooning degeneration |
| Zinc-responsive acral hyperkeratosis | Bilaterally symmetrical well demarcated hyperpigmented scaly plaques over dorsum of hands and feet | Hyperkeratosis, focal parakeratosis, acanthosis with normal granular layer, and intact basal cell layer. Sparse perivascular mononuclear infiltrate of lymphocytes in the dermis |

and diabetes are postulated mechanisms for the pathogenesis. Normally albumin sequesters the fatty acids released from tissue membranes and makes them inaccessible to further degradation to metabolic products such as prostaglandins. Thus, hypoalbuminemia results in high levels of prostaglandins which further induces the inflammatory process in NAE. Also, it is responsible for zinc deficiency as albumin is the main carrier of zinc. Our patient lacks any such systemic abnormality; however, his serum albumin level was slightly on lower side. NAE is characterized clinically by well-circumscribed dusky to violaceous symmetrical plaques with or without scales with a rim of erythema distributed exclusively over acral areas such as the dorsal surface of hands and feet. Severe cases may present as vesiculation and pustules. Nails, hairs, and mucous membranes are usually spared. Most of the time it is asymptomatic but some patients may complain of burning sensation. Though our patient had clinical resemblance with NAE but lacks vesiculation and pustules. Abdallah et al.,[4] in 2005, reported NAE as a cutaneous marker of hepatitis C virus (HCV) infection. He studied a total of 30 patients with NAE and all were positive for hepatitis C virus serology. However, there are cases of seronegative NAE reported in the recent past.[1-8] This suggests that NAE could be an isolated phenomenon as a result of zinc metabolism dysregulation rather than a result of HCV infection itself. Histopathology of NAE shows psoriasiform hyperplasia, hyperkeratosis, parakeratosis, papillomatosis, focal hypergranulosis, pigment incontinence, inflammatory cells in the papillary dermis, and necrotic keratinocytes.[9] Thus, the presence of necrotic keratinocyte and vascular degeneration in basal cells helps in the diagnosis of NAE. Our patient was seronegative for HCV and lacks necrotic keratinocytes and vascular degeneration on histopathology, thus ruling out seronegative NAE. Though we could not know about serum zinc level of our patient, it can be normal, high, or low as reported by the study of Ghosh et al.[1] Another differential that responds to oral zinc is acquired zinc deficiency which is usually associated with Gastro-Intestinal disorders (malabsorptive syndromes, pancreatic disease, cirrhosis, blind-loop syndrome), diet (high phytate intake, alcoholism, total parenteral nutrition, severely restrictive diets, anorexia, bulimia), trauma (burns, postsurgery), malignancy, renal disorders (tubular disease, nephrotic syndrome, dialysis), drug (anti-metabolites, chelators), diabetes mellitus, hemolytic anemia, and pregnancy/lactation.[10] It typically involves acral, periorificial, and anogenital area as erythematous, well-demarcated eczematous plaques. Nail involvement reveals paronychia with transverse ridging. Hairs may be dry, brittle, lustreless with occasional banding.[10] Our patient had exceptional involvement of.
Thus, while diagnosing this condition, we should rule out its mimickers such as Ps, LSC, eczemas, acral AN, hypertrophic lichen planus, acquired zinc deficiency, and NAE [Table 1].[9,10,12-16] Conclusion
Practicing dermatologists should be aware of this new entity as it is chronic, refractory, and resistant to conventional treatments but responds to simple modality like zinc supplementation, thus increasing patient compliance. We understand that further studies are required with a large number of cases as it is an underreported entity.

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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