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Seronegative necrolytic acral erythema: A report of two cases and literature review

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Abstract

Necrolytic acral erythema (NAE) is a newly described entity, seen in patients infected with hepatitis C virus. It is characterized by its distinguishing acral distribution, psoriasiform skin eruption and histological features. Its etiopathogenesis is not fully understood though hypo amino academia, hyperglucagonemia and zinc deficiency are considered as probable causes. In 1996, El Darouti and Abu el Ela first described this entity in seven Egyptian patients with hepatitis C virus (HCV). Since then, several small studies and cases have been reported around the world. Nevertheless, it may occur independently without HCV association as a few cases have been reported recently. We report two seronegative cases of NAE, which responded dramatically with oral zinc therapy. This suggests that NAE could be an isolated clinical subset.

Keywords: Hepatitis, hyperkeratotic plaques, necrolytic erythema, zinc dysregulation

INTRODUCTION

Necrolytic acral erythema (NAE) is a rare diagnostic cutaneous sign of HCV infection, first reported in Egypt.[1] Initially, it was seen in seven Egyptian patients in association with hepatitis C infection. Clinically, it is characterized by pruritic, symmetric, well-demarcated, hyperkeratotic, erythematous-to-violaceous, lichenified plaques with a rim of dusky erythema on the dorsal aspects of the feet and hands.[2] Subsequently, several others have described the same dermatologic findings without associated HCV infection. Here, we report two seronegative cases of NAE.

CASE REPORT

Patient 1

A 24-year-old male patient presented with a history of skin lesions on legs since three weeks. Skin lesions were associated with burning sensation. Cutaneous examination showed well-demarcated, erythematous to hyperpigmented, hyperkeratotic plaques involving both the dorsa of feet and index fingers [Figure 1]. Multiple flaccid vesicles and bullae were also seen. Laboratory studies including complete hemogram and liver function tests were within normal limits except for serum albumin levels, which were slightly low. The patient tested seronegative for hepatitis C virus, although he had history of jaundice one month back. Serum zinc level was low at 54.56 μg/gL (reference range, 70–120 μg/dL). Histopathological examination of the lesion showed hyperkeratotic epidermis with focal parakeratosis, irregular acanthosis, and elongated rete ridges [Figure 2]. In the dermis, peri-adnexal and perivascular lymphocytic infiltration along with extravasation of red blood cells were seen. Based on the patient's low serum zinc levels and

clinicopathologic correlation, the diagnosis of NAE was established. At his initial visit, the patient was started on zinc supplementation and showed near complete resolutions of lesions in two weeks.

Patient 2

A 40-year-old male patient presented with complaint of asymptomatic skin eruption on the feet since five months. No history of any chronic illness such as diabetes mellitus, liver diseases was noted. He had been treated with topical steroid with no clinical improvement of the lesions. On examination, there were well-defined hyperkeratotic, hyperpigmented plaques on the dorsa of both feet including the malleoli [Figure 3]. Soles, nails, upper extremities, and mucous membranes were normal. Lab investigations were with normal limits, except for the low serum zinc levels. Serum antibodies against HCV were negative. Skin biopsy and histopathological study could not be done in this patient. Oral zinc supplementation showed complete clearance of skin eruptions in four weeks in this patient.

DISCUSSION

NAE is a rare condition, almost exclusively associated with hepatitis C infection.[1] It presents as a psoriasiform eruption mainly over the acral sites. Other sites of involvement are knees, thighs, abdomen, and genitalia. Palms, soles, nail bed, nail plates, and mucous membrane are usually spared in this condition.

Although majority of patients reported earlier tested positive for hepatitis C infection, there are a few reports of seronegative NAE [Table 1]. We found only four previous reports of necrolytic acral erythema with seronegativity for hepatitis C infection (based on a search of the Pubmed database). Males and females were equally affected in these previous reports. The clinical features of these patients were similar to those with seropositive NAE.[1,3,4,5]

The etiopathogenesis of NAE is not known yet; hypo-aminoacidemia, hypoalbuminemia, hyperglucagonemia, and zinc deficiency are considered probable causes. Hepatocellular dysfunction may result in hypo-aminoacidemia and hyperglucangonemia. Hypo-aminoacidemia may induce epidermal protein depletion which leads to necrolysis. High serum glucagon level yields greater amount of arachidonic acid and its metabolites, which induce inflammatory changes of NAE.[6] Albumin sequesters the fatty acids released from tissue membranes, making them inaccessible to further degradation to metabolic products such as prostaglandins. Hypoalbuminemia leads to the appearance of higher levels of prostaglandins, which would induce inflammatory process in NAE. And it causes deficiency of zinc as albumin is the main carrier of zinc. The exact role of zinc deficiency in NAE is not unknown, although there are reports of improvement of skin eruptions of NAE with zinc supplementation.[7]

NAE is clinically characterized by three stages of evolution: Initial acute stage characterized by scaly, erythematous papules that may have a dusky hue and deep-red center. Appearance of flaccid blisters and erosions may be seen in this stage; fully developed stage showing confluence of erythematous to violaceous lichenified plaques with sharply defined margins surrounded by adherent scales. In late stage, progressive thinning with increased hyperpigmentation is seen. In some cases, crusting and erosion ensues in this stage. [8] During the late stage, spontaneous remission or an exacerbation (flare) may occur.

Histopathologically, acute NAE demonstrates acanthosis, individual keratinocytes necrosis, confluent upper epidermal necrosis with necrosis tracking perpendicular to the surface of the epidermis, probably along the course of the acrosyringia, and a superficial and deep perivascular infiltrate of lymphocytes. Chronic lesions demonstrate parakeratosis, irregular acanthosis, papillomatosis, epidermal pallor, and a superficial and deep perivascular inflammatory infiltrate.

The differential diagnosis includes psoriasis, hypertrophic lichen planus, atopic dermatitis, necrolytic migratory erythema, and other necrolytic erythemas. Psoriasis can be easily excluded clinically by the absence of silvery white scales and Auspitz sign, and histopathologically by the absence of dyskeratotic cells and spongiosis.[4] Other necrolytic erythemas such as acrodermatitis enteropathica, biotin deficiency, and pellagra can be easily differentiated from NAE clinically by specific predilection of sites, periorificial and mucosal involvement, associated systemic symptoms, more erythematous, blistering and erosive lesions, and less common hyperkeratotic and verrucous lesions.

Treatment of NAE includes supplementation of oral zinc. Response to oral zinc is very dramatic (similar results in index case seen) and seen within few weeks of oral therapy.[7] Treatment of NAE in patients seropositive for hepatitis C is the definitive treatment (interferon-alpha with or without ribavirin) and has led to improvement of skin disease in the majority of patients.[9,10] Supplementation of oral aminoacids, systemic and topical corticosteroids have minimal role in the treatment of NAE.[11] Manzur *et al*. reported successful use of topical tacrolimus in NAE with complete resolution of lesions within 4 weeks of application.[12]

World Health Organization estimated the global prevalence of hepatitis C as 3% and approximately 170 million persons at risk of fulminant hepatitis.[13] Seroprevalence of HCV infection among the general population is 1.8% as revealed by studies in India.[12]

NAE is a rare cutaneous marker for systemic disease that requires a high index of clinical suspicion for diagnosis. Recognition of this condition is important as early intervention of undetected HCV infection with antivirals may decrease the morbidity and prevents the clinical outcomes such as chronic hepatitis, hepatic cirrhosis, and hepatocellular carcinoma.

Although majority of cases reported by Abdallah *et al*.,[8] El-Gandhour *et al*.,[14] and Nofal *et al*.[6] tested positive for hepatitis C infection, there are few reports of NAE without any association with this infection.[3,4,15] This suggests that NAE could be an isolated entity as a result of dysregulation in zinc metabolism, rather than a result of hepatitis C infection itself. This is evidenced by the dramatic response with oral zinc therapy in the index cases with negative serology for HCV.

These reports also support the view that seronegative necrolytic acral erythema may be a distinct clinical subset.[5]

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Conflicts of interest

There are no conflicts of interest.

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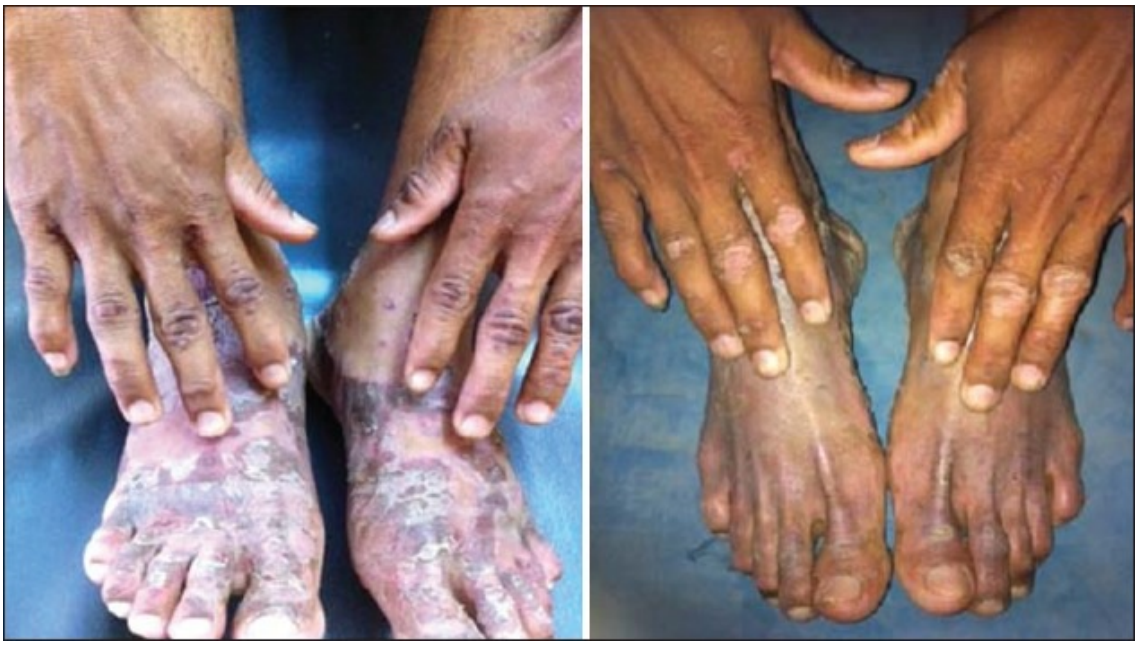
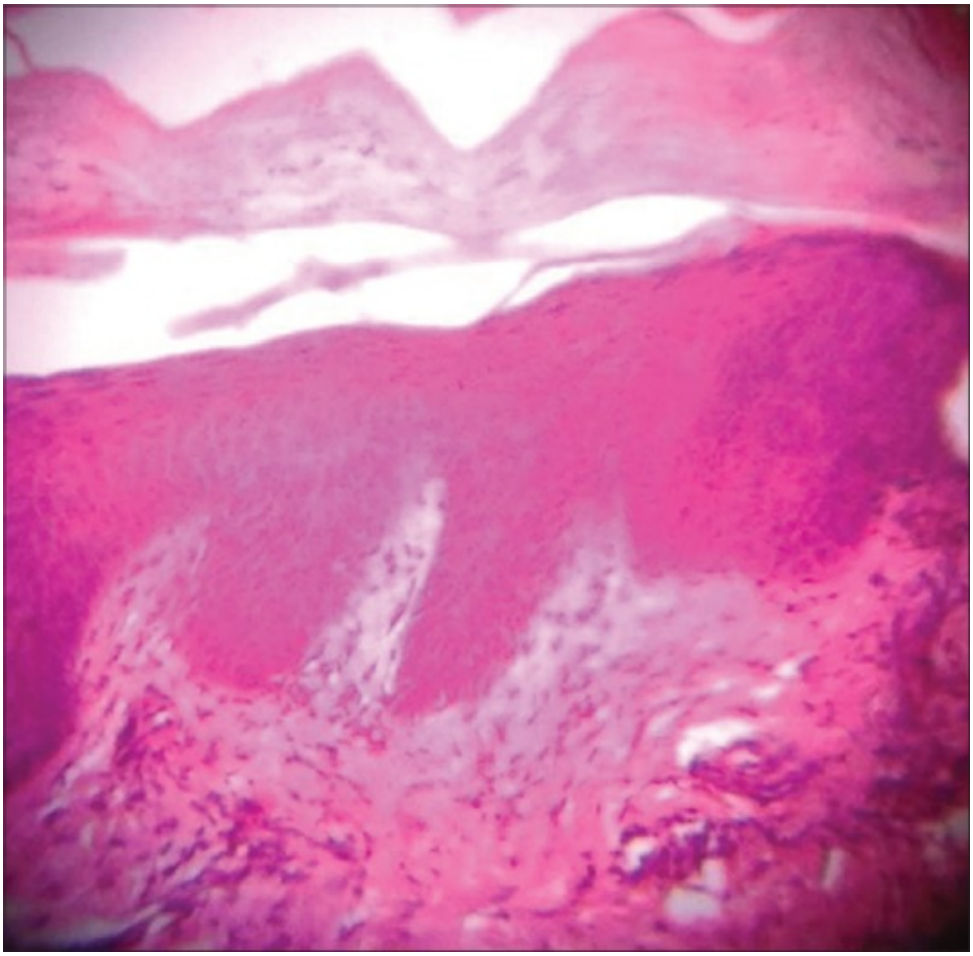
Figures and Tables

Figure 1



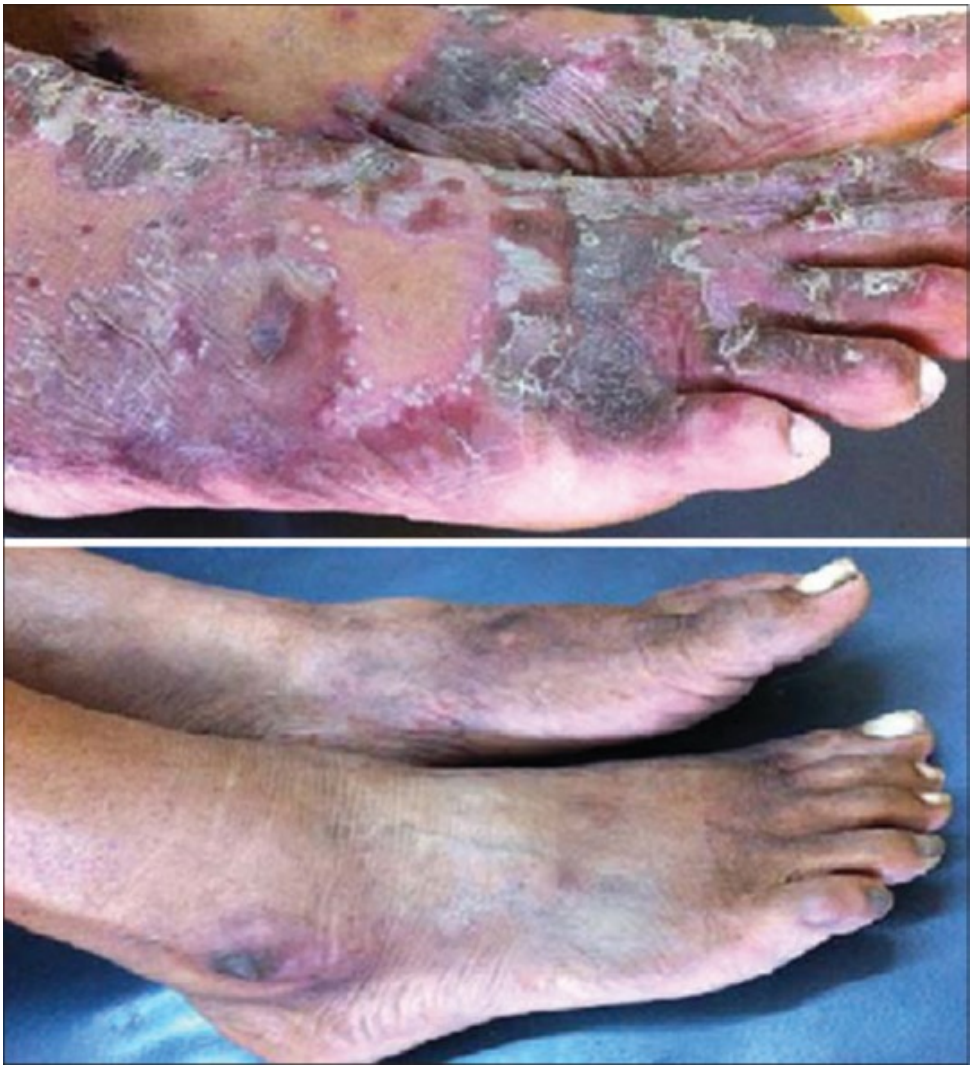
Well-demarcated, erythematous to hyperpigmented, hyperkeratotic plaques involving both the dorsa of feet and index fingers. Near complete clearance of skin eruption after two weeks of zinc therapy

Figure 2



Low power view shows hyperkeratosis, focal parakeratosis, irregular acanthosis and elongated rete ridges. (10×, H and E stain)

Figure 3



Clinical picture of well-defined hyperkeratotic, hyperpigmented plaques with violaceous hue on the dorsa of both feet. Complete resolution of eruption after four weeks of treatment

Table 1

Reference	Age	Sex	Duration	Site	Initial presentation	Symptoms	HPE findings	Serum zinc levels	Underlying disorder	Treatment given	Course
Present case 1	24 year	M	3 weeks	Dorsa of feet and index fingers	Well-defined, erythematous plaques with vesicles and bullae	Burning sensation	Hyperkeratosis, irregular elongated rete ridges	Low	-	Oral zinc	Near complete resolution
Present case 2	40 year	M	5 months	Dorsa of feet	Well-defined hyperpigmented plaques	Asymptomatic	Not done	Low	-	Oral zinc	Complete clearance
Nikam *et al.* 2009[3]	38 year	M	1 year	Dorsa of feet and fingers, shin	Well-defined hyperpigmented, hyperkeratotic, minimally scaly plaques	Extremely pruritic	Regular psoriasiform hyperplasia without spongiosis and necrotic keratinocytes in spinous layer	Normal	Down's syndrome	Oral zinc acetate 100 mg TID for 8 weeks	Complete resolution, recurrence
Nikam *et al.* 2009[3]	25 year	F	1.5 year	Dorsa of feet and finger webspaces	Well-defined, hyperpigmented, hyperkeratotic scaly plaques	Pruritic	same	Not done	-	Oral Zinc	Complete resolution
Wu *et al.* 2009[4]	32 year	F	4 months	Dorsa of feet, hands and elbow	Small, erythematous, serpiginous, inflammatory bordered plaques	Asymptomatic	Diffuse parakeratosis, hypogranulosis, psoriasiform hyperplasia, dyskeratotic keratinocytes	Low-453 µg/dL	SLE with lupus nephritis	Withdrawal of steroids	Rapid resolution, recurrence
Panda *et al.* 2009[5]	68 year	M	2 months	Dorsa of feet and hands	Well-defined, erythematous, scaly, crusted plaques with few linear eroded or ulcerated areas with pitting pedal edema	Burning sensation; tenderness	Hyperkeratosis, acanthosis, spongiosis and proliferated capillaries	Borderline-60 mg/dL (60-120 mg/dL)	Diabetes mellitus and hypertriglyceridemia	Oral zinc sulfate 200 mg twice daily	Near complete resolution

Seronegative necrolytic acral erythema- review of reported cases