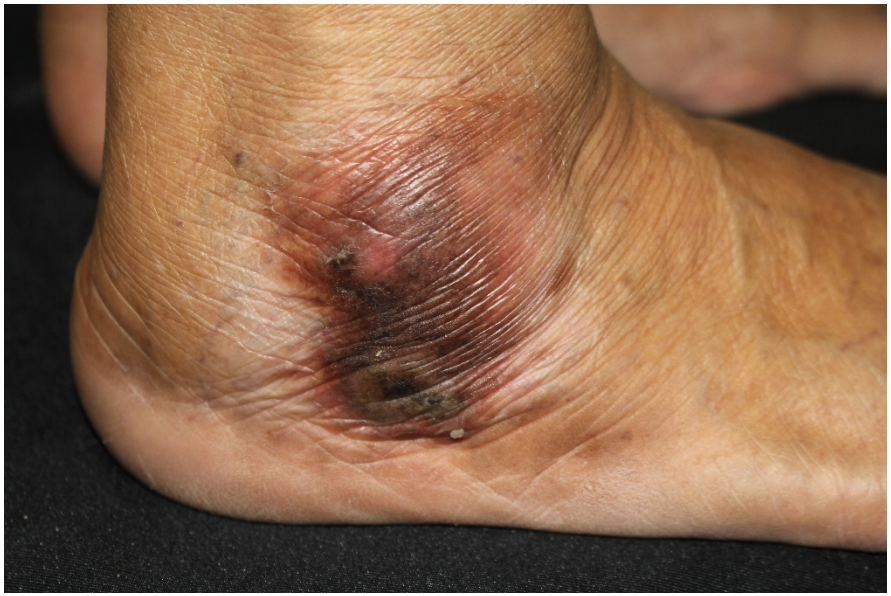
Case 26
A 64 year-old Thai woman from Bangkok
Chief complaint: Bilateral pruritic rashes on lateral malleolus for 7 months



Present illness:
The patient had chronic mildly pruritic brownish to erythematous rashes on both lateral malleolus for 7 months. She had been treated with 0.05% clobetasol propionate ointment and intralesional triamcinolone acetonide with minimal improvement. She denied previous trauma before the onset of rashes. No history of significant weight loss.

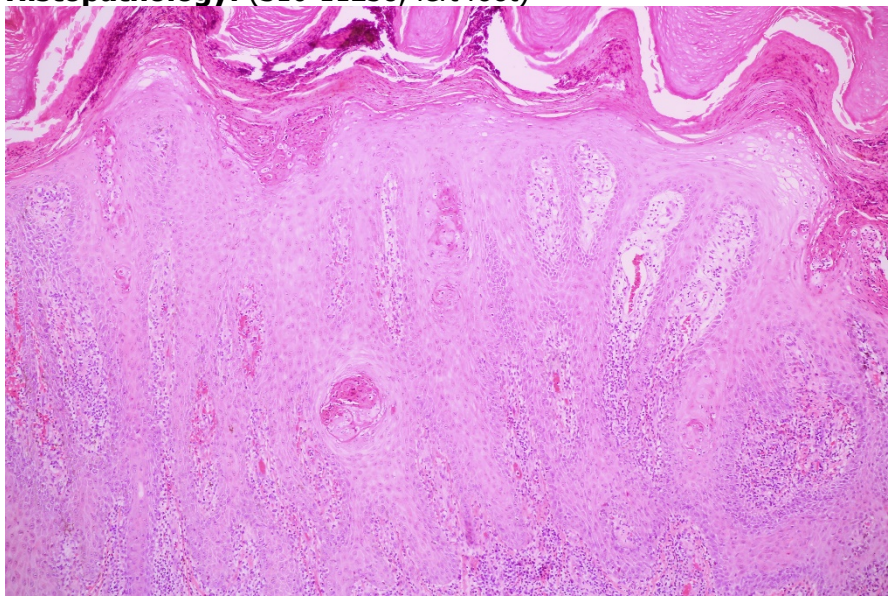
Past history:
There was no underlying disease or any current medication.

Physical examination:
HEENT: Not pale, no jaundice, thyroid gland not enlarge
Heart and lung: Normal
Abdomen: No palpable mass, no hepatosplenomegaly

Dermatological examination:
- Bilateral well-defined brownish hyperkeratotic plaques with erythematous rim on both lateral malleolus

Nail and scalp: Normal

Histopathology: (S16-11238, left foot)



- Compact hyperkeratosis and mounds of parakeratosis with neutrophils. Absence of granular layer with pale and vacuolated keratinocytes in the superficial epidermal layer and scattered necrotic keratinocytes.

- Papillated psoriasiform epidermal hyperplasia. Dense inflammatory-cell infiltrate of mainly lymphocytes and extravasated erythrocytes with dilated capillaries in the papillary dermis.

Laboratory:

- Anti-HCV: Negative
- Zinc level: 71 ug/dL (70-120 ug/dL)
- FBS: 107 mg/dL

Diagnosis: Necrolytic acral erythema (NAE)

Treatment: Zinc sulphate (110) 1 tab PO bid, Doxepin (25) 1 tab PO hs, 0.05% Betamethasone dipropionate/3% salicylic acid ointment apply bid

Presenter: Ploychompoo Srisuwanwattana, MD
Consultant: Vasanop Vachiramon, MD

Discussion:

Necrolytic acral erythema (NAE), first described in 1996 by el Darouti M et al, is a distinctive skin disorder associated with hepatitis C virus (HCV) infection.[1] NAE almost exclusively associated with HCV, nevertheless, 6 cases of NAE have been reported in the absence of HCV infection[2-6] and one case report following hepatitis B virus (HBV) vaccination.[7] The pathogenesis of is unknown, but it is thought to be related to zinc dysregulation, which can occur as a result of HCV–induced metabolic alteration.[8] NAE is associated with decreased serum and skin zinc levels.[9] Characteristic features of NAE include sharply marginated scaly erythematous to hyperpigmented plaques predominately on lower extremities.[10] The most common location is feet follow by lower legs, knees, thighs, genitalia, buttocks and abdomen. Involvement of upper extremities generally mild and limited. Head and neck, palms, soles, nails and mucous membrane was spared.[10] Initial stage is presented with scaly erythematous papules or plaques with deep red to violaceous at center. Sharply demarcated scaly erythematous to violaceous lichenified plaques could be found in fully developed lesion. Superficial epidermal necrosis was occasionally observed over the dusky portions of the lesion. The plaque remained unchanged for months and were associated with pruritus. In late stage the lesions became progressively thinner with some crusting and erosion. Remission and exacerbation of disease occurred spontaneously.[10]

The differential diagnosis include psoriasis, other necrolytic erythema, including necrolytic migratory erythema (NME) which associated with glucagonama, acrodermatitis enteropathica or acquired zinc defficiency, pellagra, biotin and essential fatty acid deficiency.

Histological findings are similar to those necrolytic erythema characterized by initially acanthosis, epidermal spongiosis and a superficial perivascular dermatitis. Fully developed form, exhibits psoriasiform hyperplasia and prominent papillomatosis with parakeratosis, subcorneal pustules, epidermal pallor and necrotic keratinocytes. Confluent necrosis of the keratinocytes in the upper parts of the epidermis may lead to cleft formation. Vascular ectasia, papillary dermal inflammation and pigment incontinence are also seen.[11] The presence of foci of epidermal dyskeratosis and pallor helps to differentiated from psoriasis.

Histological findings in our patient consistent with necrolytic erythema. She had negative serology for HCV infection with low normal plasma zinc level. However, we did not evaluated glucagon, niacin, and biotin level due to the limitation in laboratory process. Dermatitis of niacin deficiency usually present in photo-exposed areas and may accompany with diarrhea and dementia. However, such features have not been found in our patients. This patient

denied history of weight loss and she generally well, her fasting blood sugar was in normal range. Therefore, glucagonoma which characterized by glucagon overproduction is less likely. Acquired zinc deficiency which manifested as eczematous rash preferentially on acral and periorificial area are indistinguishable from NAE histologically. However, acquired zinc deficiency is less likely in this patient due to normal zinc level.

Treatment of NAE is difficult and resistant to most topical and systemic agents. Available treatment options mostly depend on case reports or small case series. Complete or partial resolution have been reported with interferonα-2b and/or ribavirin.[12] Topical corticosteroids result in transient improvement. Systemic corticosteroids showed inconsistent benefit ranged from no response to completely resolution.[12] Benefit on intralesional triamcinolone acetonide could not be proven. Oral zinc supplement at dosage of 220 mg twice a day mostly showed partial response followed by complete or near complete response and no response.[12] Improvement of NAE after zinc supplementation has been reported from both low and normal zinc level.[12] Topical tacrolimus and combination of zinc, vitamin B1 and B6 have been shown complete response in few patients.[12, 13]

References

1. el Darouti M , Abu el Ela M. Necrolytic acral erythema: a cutaneous marker of viral hepatitis C. Int J Dermatol 1996;35:252-6.
2. Liu A, Erickson CP, Cockerell CJ , Hsu S. Necrolytic acral erythema: a case not associated with hepatitis C infection. Dermatol Online J 2008;14:10.
3. Wu YH, Tu ME, Lee CS , Lin YC. Necrolytic acral erythema without hepatitis C infection. J Cutan Pathol 2009;36:355-8.
4. Nikam BP. Necrolytic acral erythema seronegative for hepatitis C virus--two cases from India treated with oral zinc. Int J Dermatol 2009;48:1096-9.
5. Panda S , Lahiri K. Seronegative necrolytic acral erythema: a distinct clinical subset? Indian J Dermatol 2010;55:259-61.
6. Das A, Kumar P , Gharami RC. Necrolytic Acral Erythema in the Absence of Hepatitis C Virus Infection. Indian J Dermatol 2016;61:96-9.
7. Pernet C, Guillot B, Araka O, Dereure O , Bessis D. Necrolytic acral erythema following hepatitis B vaccination. Br J Dermatol 2014;171:1255-6.
8. Najarian DJ, Lefkowitz I, Balfour E, Pappert AS , Rao BK. Zinc deficiency associated with necrolytic acral erythema. J Am Acad Dermatol 2006;55:S108-10.
9. Moneib HA, Salem SA , Darwish MM. Evaluation of zinc level in skin of patients with necrolytic acral erythema. Br J Dermatol 2010;163:476-80.
10. Abdallah MA, Ghozzi MY, Monib HA, Hafez AM, Hiatt KM, Smoller BR et al. Necrolytic acral erythema: a cutaneous sign of hepatitis C virus infection. J Am Acad Dermatol 2005;53:247-51.
11. Abdallah MA, Ghozzi MY, Monib HA, Hafez AM, Hiatt KM, Smoller BR et al. Histological study of necrolytic acral erythema. J Ark Med Soc 2004;100:354-5.
12. Tabibian JH, Gerstenblith MR, Tedford RJ, Junkins-Hopkins JM , Abuav R. Necrolytic acral erythema as a cutaneous marker of hepatitis C: report of two cases and review. Dig Dis Sci 2010;55:2735-43.
13. Manzur A , Siddiqui AH. Necrolytic acral erythema: successful treatment with topical tacrolimus ointment. Int J Dermatol 2008;47:1073-5.