Necrolytic acral erythema was first described in 1996 by physicians in Egypt, M. El Darouti and M. Abu El Ela. Reports have continued to link hepatitis C with NAE. Necrolytic acral erythema manifests as well-circumscribed, dusky erythematous plaques with adherent scale. While the plaques are psoriasiform, they do not manifest an Auspitz sign as would be seen with psoriasis. Patients with active necrolytic acral erythema report burning or pruritus. It is limited to an acral distribution and, in most cases, is associated with hepatitis C infection.

Several cases of necrolytic acral erythema have occurred in patients without hepatitis C. This suggests that necrolytic acral erythema might be a result of zinc dysregulation, rather than...
a result of hepatitis C infection itself.

Authors debate whether necrolytic acral erythema is a distinct entity or a subtype of necrolytic migratory erythema. However, the distinct appearance and usual coincidence with hepatitis C infections suggests that it is a unique entity. It has been speculated that viral load and viral genotype might play a role in NAE.⁶

Pathophysiology

The pathophysiology of this condition is uncertain. Proposed theories for the cause of necrolytic acral erythema describe alterations in some metabolic factor, many of which are seen in other necrolytic erythemas, including necrolytic migratory erythema, pellagra, essential fatty acid and biotin deficiency, and acrodermatitis enteropathica. The hypothesized causes for the metabolic alteration include hypoalbuminemia, hypoaminoacidemia, low zinc level, increased glucagon, liver dysfunction, or diabetes. Only hepatitis C is universally present in all persons with necrolytic acral erythema.

An odd fact is that no cases of necrolytic acral erythema have been reported in Japan, which has a high seroprevalence rate of hepatitis C.

History

Patients with necrolytic acral erythema present with a 1-month to 2-year history of a rash on the dorsum of the feet, which may or may not also involve the hands. In many cases, it has been unresponsive to topical steroids.

Patients do not necessarily give a history of hepatitis C. Necrolytic acral erythema may be the presenting sign. Patients may report a burning sensation, especially when walking or standing. Sometimes, necrolytic acral erythema lesions are pruritic. The most common area of origination of the rash is the dorsal aspect of the great toe. It also occurs on the shins. In 43 of 44 reported cases, necrolytic acral erythema did not affect the palms or soles, the nail bed, nail plate, or mucous membranes.

Williams⁸ reported a case of necrolytic acral erythema in an adolescent boy with a history of infection with hepatitis C virus; he had hepatic fibrosis, hypertension, and thrombocytopenia.
The patient developed a pruritic eruption on his face, trunk, genitals, and extremities, and the eruption had a predilection for bony prominences. This patient did not respond to topical steroids, antihistamines, topical barrier repair creams, narrow-band UV-B therapy, or tar baths. A skin biopsy specimen demonstrated a nonspecific psoriasiform dermatitis consistent with necrolytic acral erythema. Hepatitis C virus RNA polymerase chain reaction studies showed 974,000 IU/mL (<50) and hepatitis C virus RNA genotype 1b.

Janjua\(^9\) noted a 45-year-old man who developed well-defined erythematous hyperpigmented keratotic pruritic plaques on the dorsa of his feet and the lateral aspect of his ankles; he was determined to have necrolytic acral erythema.

**Physical**

Dusky, red erythematous plaques are present bilaterally on the dorsum of the feet and toes. These may extend around to the skin overlying the Achilles tendon and up the lower leg, as depicted in the image below.

The dorsum of the hands may or may not be involved. The lesions are clearly demarcated from uninvolved skin by a dark red border. The surface may be scaly, eroded, or velvety. Thick hyperkeratosis is sometimes present. Active lesions often include flaccid blisters. Edema may or may not be present.

Abdallah et al\(^10\) describe stages of the lesions:

1. Initial stage: Erythematous papules or plaque with scale are present and have a dusky or eroded center.
2. Fully developed stage: A confluence of papules and plaques with sharply defined margins and adherent scale develops. Increased hyperpigmentation and decreased redness may be present. Lesions may be lichenified. Pustules also may occur at this stage.
3. Late stage: Thinning of lesions occurs, with continued hyperpigmentation. Demarcation continues, followed by spontaneous relapse and remission.
As a general rule, necrolytic acral erythema does not affect the palms or soles, the nail bed, nail plate, or mucous membranes. Hivnor et al\textsuperscript{11} reported a single case in which the plaques extended proximally to the thighs. This patient also had hyperkeratosis of the palms and soles and involvement of the face. While multiple biopsy specimens confirmed necrolytic acral erythema histologically, it is not clear whether these biopsy specimens were taken from the typical locations of necrolytic acral erythema or if the palms and soles were also included in the biopsy specimen.

Other disorders that can be seen in persons with hepatitis C should be considered as possible epiphenomena. These include the following:

- Lichen planus
- Porphyria cutanea tarda
- Palpable purpura/leukocytoclastic vasculitis
- Spider telangiectasias
- Vitiligo
- Polycythemia nodosa
- Erythema multiforme
- Urticaria
- Erythema nodosum

**Causes**

The cause is uncertain, but a metabolic alteration due to hepatocellular degeneration from hepatitis C infection is proposed. Many hypotheses describe deficiencies similar to those of the other necrolytic erythemas; histological features are similar among necrolytic acral erythema and other nutrient deficiencies. Note the following:

- el Darouti and Abu El Ela\textsuperscript{1} suggested that the increased levels of glucagon seen in persons with liver disease allow for "potentiation" of arachidonic acid after trauma.

- High glucagon levels alone may allow for greater arachidonic acid potentiation, which may induce inflammatory changes and necrosis in the epidermis.
- Low amino acid levels may lead to epidermal protein depletion and necrolysis.
- Low albumin levels have also been postulated as causative. Albumin sequesters fatty acids and helps regulate prostaglandin levels. High levels of prostaglandins as a result of low levels of albumin may induce inflammation.
- Low zinc levels have also been proposed as a cause. Because albumin is the main carrier of zinc in plasma, these 2 may be interrelated.
- Diabetic microangiopathy also may play a role; 4 of 5 necrolytic acral erythema patients described by Nofal et al\textsuperscript{12} also had diabetes.
Laboratory Studies

Hepatitis A, B, and C serologies: These are the most important tests because necrolytic acral erythema (NAE) has a high association with hepatitis C.

Assess liver function, including aspartate aminotransferase, alanine aminotransferase, bilirubin, protein, albumin, and alkaline phosphatase values. Some authors believe the lesions are most active during the active stage of hepatitis. The severity of the lesions does not correlate with the severity of the hepatitis.

Serum zinc, serum glucagon, and serum amino acid levels: These values have been reduced in some reported cases. Zinc deficiency associated with necrolytic acral erythema was noted by Najarian et al.\textsuperscript{13}

Serum glucose and hemoglobin A1C levels: Consider performing these tests because necrolytic acral erythema may be more common in persons with diabetes and hepatitis C.

Najarian et al has associated hypozincemia and hyperzincuria with necrolytic acral erythema.\textsuperscript{14}

Imaging Studies

CT scanning of the liver and pancreas can be considered as an ancillary assessment. In some reported cases, the pancreas was imaged, most likely because some believe necrolytic acral erythema is a subset of necrolytic migratory erythema, a condition indicative of pancreatic glucagonoma. No pancreatic masses were found any of the patients imaged.

Procedures
Consider skin biopsy to substantiate the diagnosis of necrolytic acral erythema. Consider liver biopsy to assess the status of hepatitis and before the institution of hepatitis C treatment.

**Histologic Findings**

Necrolytic acral erythema is perhaps best defined clinically rather than histologically. Bentley et al noted a case of necrolytic acral erythema without classic histology findings, which responded to oral zinc therapy.\(^{15}\)

In 2004, Abdallah et al\(^ {10}\) noted the following histopathological features:

- Early stage - Nummular dermatitis–like moderate and regular acanthosis, as follows:
  - Variable spongiosis
  - Inflammatory infiltrate
  - Pigment incontinence
  
  - Fully evolved stage - Psoriasiform epidermal hyperplasia, as follows:
    - Marked papillomatosis
    - Parakeratosis
    - Focal hypergranulosis
    - Pigment incontinence
    - Occasional subcorneal pustules
    - Epidermal pallor
    - Vascular ectasia
    - Infiltrate of inflammatory cells in the papillary dermis
    - Necrotic keratinocytes - Sometimes become confluent in the upper epidermis, sometimes tracking along the acrosyringium

- Late stage samples - Minimal-to-moderate acanthosis, as follows:
  - Minimal-to-moderate inflammatory cell infiltrate
  - Pigment incontinence

Others have noted epidermal necrosis with or without blister formation; vacuolar degeneration of the basal layer; and psoriatic changes with acanthosis, papillomatosis, hyperkeratosis, and parakeratosis. All of these are commonly found in persons in deficient nutritional states. Dermal findings have included a nonspecific superficial perivascular and interstitial lymphocytic dermatitis.

El-Ghandour et al\(^ {7}\) noted that electron microscope examination of patients with necrolytic acral
Necrolytic acral erythema demonstrated clumped tonofilaments in the keratinocytes, yet hepatitis C virus RNA could not be detected in the plaques of necrolytic acral erythema.

**Medical Care**

The optimal treatment for necrolytic acral erythema (NAE) is the optimal treatment of hepatitis C—combination therapy with interferon and ribavirin. In one patient, ribavirin in addition to the interferon alfa therapy improved the necrolytic acral erythema despite the presence of a continued high viral load.

Oral zinc replacement has been successful in some cases.\(^4,16\) Interferon alfa monotherapy has been reported to be effective treatment.\(^4\)

Amino acid replacement therapy, both orally and parenterally, has yielded some improvement. Disease response to corticosteroid therapy (ie, topical, intralesional, and systemic) has been poor. No benefit has been seen with topical tar or tetracycline.

El-Ghandour et al\(^7\) noted in their series of 23 Egyptian patients that interferon alfa combined with ribavirin caused regression of the plaques of necrolytic acral erythema in 3 patients and complete clearance in 1 patient. Oral zinc administration induced some improvement in the appearance of the skin in some patients.

**Surgical Care**

A surgical approach has not been shown to be therapeutically beneficial.

**Consultations**

Consultation with an infectious disease specialist, gastroenterologist, or hepatologist may be helpful for management of the hepatitis C. Consultation with a dermatologist may be helpful for diagnosis and management of cutaneous findings.

**Diet**

Supplementation with zinc and amino acids has shown benefit.
Activity

No restrictions on activity are needed for persons with this condition.

Medication

The goal of treatment is to decrease the burning and pruritus and improve the appearance of the lesions of necrolytic acral erythema. Zinc sulfate, amino acid supplementation, and interferon alfa have been successful in treating necrolytic acral erythema. Topical tacrolimus has been reported as an effective treatment for necrolytic acral erythema.

Minerals

Act as enzyme cofactors and are required in metabolic processing.

Zinc supplements

Use sulfate or gluconate zinc salt. Zinc sulfate 4.4 mg = 1 mg of elemental zinc. Zinc gluconate 7.1 mg = 1 mg of elemental zinc.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

Effective zinc sulfate dose used in studies: 440 mg PO qd (single dose or divided) for 100 mg/d of elemental zinc

Pediatric

General supplementation: 1-2 mg/kg/d elemental zinc; dose not documented in 12-year-old treated with zinc
Necrolytic acral erythema

- Dosing
- Interactions
- Contraindications
- Precautions

May reduce penicillamine and tetracycline effects

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in patients with renal impairment

Interferons

Naturally occurring compounds that have both antiviral and immunomodulatory effects.

Peginterferon alfa-2a (Pegasys)

Used in combination with ribavirin to treat patients with chronic hepatitis C who have
Necrolytic acral erythema = اﻠﻨﻬاﻴاﺖ ﻋﻠﻰ اﻠاﻨﺤﻠاﻠﻴﺔ اﻠﻨﺨرﻴﺔ اﻠﺤﻤاﻤﻰ

Compensated liver disease and have not previously received interferon alfa. Consists of interferon alfa-2a attached to a 40-kd branched PEG molecule. Predominantly metabolized by the liver.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

180 mcg SC qwk

Pediatric

Not established

- Dosing
- Interactions
- Contraindications
- Precautions

Theophylline may increase toxicity by reducing clearance; cimetidine may increase antitumor effects; zidovudine and vinblastine may increase toxicity

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; decompensated liver disease; significant preexisting psychiatric disease; ongoing or recent alcohol use; platelet count <70,000/µL

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Insomnia; mental dysfunction (eg, mood dysfunction, depression, psychosis, aggressive behavior, hallucinations, violent behavior, suicidal ideation, suicide attempt, suicide, homicidal ideation [rare]), even without previous history of psychiatric illness; flulike symptoms; rash and pruritus; anorexia; neutropenia; thrombocytopenia; thyroid dysfunction; retinal abnormalities

Peginterferon alfa-2b (PEG Intron)

*Escherichia coli* recombinant product. Used to treat chronic hepatitis C in patients not previously treated with interferon alfa who have compensated liver disease. Exerts cellular activities by binding to specific membrane receptors on cell surface, which, in turn, may suppress cell proliferation and may enhance phagocytic activity of macrophages. May also increase cytotoxicity of lymphocytes for target cells and inhibit virus replication in virus-infected cells.

- Dosing
- Interactions
- Contraindications
- Precautions

**Adult**

Inject SC qwk for 1 y using weight-based dosing

37-45 kg: 40 mcg (0.4 mL of 100 mcg/mL)
46-56 kg: 50 mcg (0.5 mL of 100 mcg/mL)
57-72 kg: 64 mcg (0.4 mL of 160 mcg/mL)
73-88 kg: 80 mcg (0.5 mL of 160 mcg/mL)
89-106 kg: 96 mcg (0.4 mL of 240 mcg/mL)
107-136 kg: 120 mcg (0.5 mL of 240 mcg/mL)
137-160 kg: 150 mcg (0.5 mL of 300 mcg/mL)

**Pediatric**
Necrotic acral erythema

Not established

- Dosing
- Interactions
- Contraindications
- Precautions

Concurrent administration with IL-2 may increase nephrotoxicity; theophylline, zidovudine, and vinblastine may increase toxicity; cimetidine may increase antitumor effects

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; autoimmune hepatitis; pancreatitis; colitis

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Considered to have abortifacient potential; reduce starting dose by 50% or discontinue if serious adverse reactions develop during course of treatment (may reinitiate treatment if adverse reaction abates or decreases in severity); fatal and nonfatal pancreatitis or ulcerative and hemorrhagic colitis reported; life-threatening or fatal neuropsychiatric events may occur; severe suppression of bone marrow function may occur, sometimes resulting in severe cytopenias; may cause, headache, flulike symptoms, or myelosuppressive, pulmonary, thyroid, cardiovascular, or infectious disorders
Nucleoside Analogs

Drugs that interfere with the production of DNA and RNA.

Ribavirin (Virazole)

Antiviral nucleoside analog. Chemical name is $D$-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide. Given alone, has little effect on the course of hepatitis C. When given with interferon, significantly augments rate of sustained virologic response.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

10.6 mg/kg PO qd or divided bid

Pediatric

Not established