The Necrolytic Erythemas: A Continuous Spectrum?

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The necrolytic erythemas is a group of disorders with similar histologic and clinical features. The objective of this case report is to present a patient with features of both necrolytic migratory erythema (NME) and necrolytic acral erythema (NAE). These 2 entities appear more likely to be on a spectrum caused by the same underlying process of abnormal liver function and glucagon metabolism.

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The necrolytic erythemas is a group of disorders with similar histologic and clinical features. We describe a patient who presented with the coexistence of necrolytic acral erythema (NAE) and necrolytic migratory erythema (NME), which are likely on a spectrum caused by the same underlying process.

Case Report

A 53-year-old woman presented with erythematous hyperpigmented plaques on the ankles and dorsal feet of several weeks' duration with extensive desquamation of the palms and soles bilaterally (Figure 1). The skin lesions were tender, most notably on the distal extremities, and the patient reported a burning sensation on her hands and feet. She was treated with clobetasol propionate ointment 0.05% under occlusion with some improvement. The patient's medical history was remarkable for hepatitis C virus (HCV) infection, renal failure on hemodialysis, diabetes mellitus, hypertension, diarrhea, and gastric stapling in 1982.

Over the next 8 months, her course was complicated by admissions for myocardial infarction, third degree atrioventricular block, and deep vein thrombosis of the left arm. The patient developed diffuse alopecia, stomatitis, and considerable weight loss. Bullae subsequently appeared on her distal extremities and an erosive dermatitis previously localized to her hands and feet began to involve the back, legs, face (Figure 2), and genitalia. Hyperpigmented plaques with desquamation were noted periorificially and perianally as well as in the inguinal flexion crease (Figure 3). These lesions displayed an undulating temporal pattern. She was treated with zinc supplementation without substantial improvement.

Laboratory results included the following levels: plasma zinc within reference range; elevated plasma glucagon, 201 and 147 pg/mL (reference range, 20–100 pg/mL); negative transglutaminase; elevated chromogranin A, 440 µg/L (reference range, 6–39 µg/L). Serum studies conducted prior to dialysis showed the following results for amino acids: histidine, 46 µmol/L (reference range, 72–184 µmol/L); threonine, 6 µmol/L (reference range, 6–225 µmol/L); tyrosine, 16 µmol/L (reference range, 34–112 µmol/L); valine, 80 µmol/L (reference range, 119–336 µmol/L); leucine, 54 µmol/L (reference range, 72–201 µmol/L); tryptophan, 4 µmol/L (reference range, 10–140 µmol/L); lysine, 50 µmol/L (reference range, 118–296 µmol/L); 3-aminoisobutyric acid, 24 µmol/L (reference range, 0 µmol/L). Abdominal computed tomography revealed a questionable mass in the head of the pancreas, but follow-up magnetic resonance imaging was normal with no evidence of malignancy. Further workup for malignancy including an octreotide scan was normal.

Histologic examination showed hyperkeratosis with extensive subcorneal and intraepidermal clefting. There was minimal inflammatory infiltrate with necrosis and pallor of the overlying epidermis (Figure 4). Direct immunofluorescence was negative.

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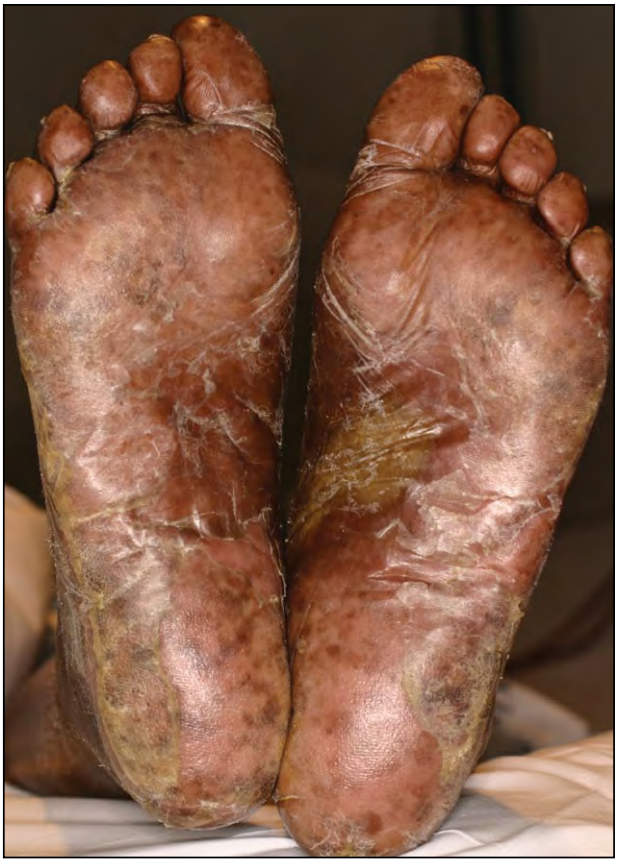

Figure 1. A 53-year-old woman with erythema and desquamation that initially presented on the soles.

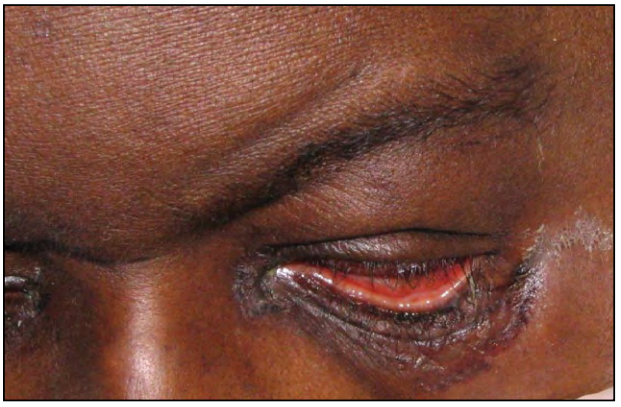

Figure 2. Erosive dermatitis that progressed to involve the face.

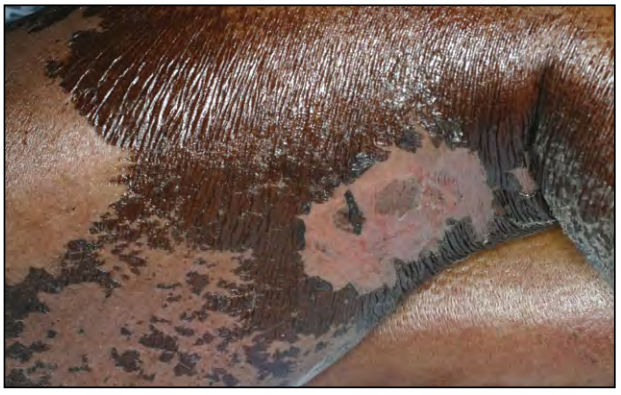

Figure 3. Progressive desquamation involving the lower extremity.

Based on clinicopathologic correlation and laboratory studies, the patient was diagnosed with a necrolytic erythema. Total parenteral nutrition with amino acid supplementation was instituted and bullae formation ceased by day 3. The patient had complete clearance of her skin lesions by day 8 of treatment and was without reoccurrence 6 months later with continued total parenteral nutrition at dialysis. The patient was lost to follow-up.

Comment

The necrolytic erythemas is a group of disorders with similar histologic and clinical features consisting of acrodermatitis enteropathica, NME, NAE, biotin deficiency, pellagra, and essential fatty acid deficiency.

Traditionally the necrolytic erythemas are differentiated on the basis of their cutaneous distribution and underlying biochemical abnormalities, but there is evidence of overlap between them. We believe that our patient manifested characteristics of both NAE and NME at different times and demonstrated the coexistence of these 2 entities. Her disease initially resembled the acral lesions of NAE but transitioned into the more extensive lesions of NME as her diarrhea and other nutritional deficiencies worsened.

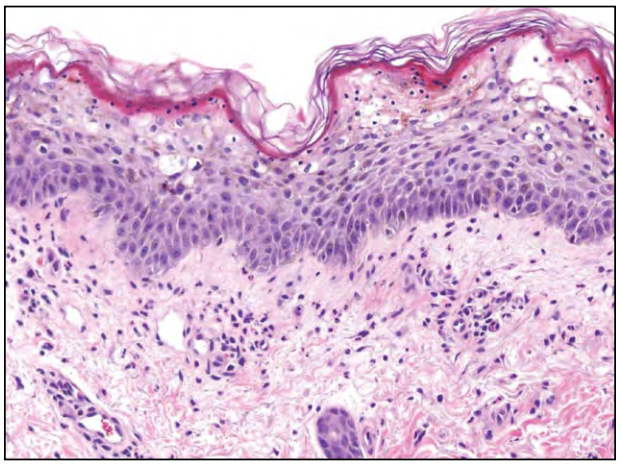

Figure 4. Subcorneal and intraepidermal pallor with minimal inflammation (H&E, original magnification ×200).

Necrolytic acral erythema was originally reported by el Darouti and Abu el Ela[1] in 1996 and has since been described as a cutaneous marker for HCV,[2] though 1 case without HCV has been reported.[3] Necrolytic acral erythema classically presents with tender erythematous or violaceous plaques in an acral distribution preferentially involving the dorsal surface, though palm and sole involvement, as seen in our patient, has been described.[4] Although histologically the entities are indistinguishable, NAE differs by its lack of annular lesions and restriction to acral extremitites.[5]

Necrolytic migratory erythema is the cutaneous manifestation of both the glucagonoma and pseudoglucagonoma syndromes. Glucagonoma syndrome is caused by a pancreatic alpha cell tumor, whereas pseudoglucagonoma syndrome is the existence of NME in the absence of a glucagon-secreting neoplasm.[6] The pseudoglucagonoma syndrome has been attributed to other pathologic processes such as hepatitis, cirrhosis, pancreatic disease, nutritional deficiencies, malignancies, celiac sprue, inflammatory bowel disease, generalized malabsorption, or intravenous glucagon.[7] Necrolytic migratory erythema presents as erythematous plaques on any part of the body but most commonly appears on the buttocks, inguinal flexion crease, perineum, and extremities. Bullae are not uncommon initially, and the lesions have a waxing and waning temporal pattern. In addition to the skin findings, NME is associated with cheilitis, glossitis, diabetes mellitus, deep vein thrombosis, and decreased serum amino acids.[8]

The etiology of the necrolytic erythemas remains unclear. There have been many different mechanisms implicated in NME including hepatic impairment, as well as deficiencies of essential fatty acids, amino acids, and zinc. Given their associations with liver dysfunction, low amino acids, and similar treatment responses, NME often is used as a model for NAE. We believe that the pathophysiology of NAE may be based on a similar mechanism as NME.

One of the first hypotheses proposed for the pathophysiology of NME was based on the observation that the cutaneous lesions of patients with glucagonomas improved after surgical resection and normalization of their serum glucose levels. Subsequent treatment successes have been reported using somatostatin analogues to inhibit glucagon secretion.[9] Glucagon levels in patients with pseudoglucagonoma syndrome have been described as within reference range or elevated; however, these elevated values were still markedly lower than the measured glucagon levels in patients with glucagonoma syndrome.[10] Glucagon is produced by pancreatic islet cells as well as some enterochromaffin cells of the gut and is degraded in the liver. In cases of liver disease, the capacity to degrade glucagon is diminished, which leads to increased serum glucagon levels as well as abnormal distribution of the 4 different glucagon fractions.[6] Most reported cases of NME in pseudoglucagonoma syndrome have some degree of hepatocellular dysfunction, and it has been postulated that impairment of hepatic glucagon metabolism may result in the cutaneous findings.[7] Small increases in glucagon levels can result in increased arachidonic acid and its metabolites such as prostaglandins, which may lead to the inflammatory changes seen in NME.[11] Although NAE typically has been associated with glucagon levels within reference range, almost all reported cases have some degree of hepatic impairment secondary to infection with HCV.[12] The decreased liver function could produce abnormal glucagon fractions resulting in cutaneous lesions, even in cases with serum glucagon levels within reference range, which may explain why treatment of HCV with interferon and subsequent improvement in hepatic function may lead to improvement of skin disease.[2]

Treatment with amino acid supplementation has been described with some success in both of the necrolytic erythemas, thereby implicating an amino acid deficiency in their pathogenesis.[1] Three of the original 6 cases of NAE described by el Darouti and Abu el Ela[1] as well as most patients with NME have decreased amino acid levels. Both acute and chronic hepatocellular disease can have increased or normal amino acid levels in the early stages, but as the damage becomes more extensive, there is a concomitant decline in serum amino acids.[13] The extent of skin involvement in the necrolytic erythemas may be associated with the degree of liver disease. The liver damage in HCV can be indolent at times, and as subtle nutritional deficits are not noticeable at the early stage, early HCV-induced liver damage may manifest as the lesser involved acral lesions of NAE. In contrast, more severe hepatic impairment may result in the extensive skin involvement that characterizes NME.

The concept of overlap has been previously proposed, with some authors considering classic NAE to be an NME variant termed *acral necrolytic migratory erythema*.[14,15] Our patient shows a variable clinical expression of disease that evolved from a pattern more consistent with NAE to a pattern more consistent with NME, which may indicate that variations in liver function and nutritional deficiencies can cause the varying skin lesions of NAE and NME. Although more than one biochemical abnormality may contribute to the pathophysiology of the necrolytic erythemas, both conditions

show an association with liver disease and decreased amino acid levels, which leads us to believe that the 2 entities do in fact represent a spectrum of the same underlying process.

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