# Necrolytic Migratory Erythema Associated With a Metastatic Neuroendocrine Tumor

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*Necrolytic migratory erythema (NME) is a skin condition historically associated with pancreatic glucagonomas. Rarely it occurs in the absence of a pancreatic tumor, which has been described as pseudoglucagonoma syndrome. We describe a woman with a metastatic neuroendocrine tumor who developed NME 6 years after diagnosis of the tumor. Her laboratory data revealed essential fatty acid deficiency and a high level of glucagon. Although the pathogenesis of NME is not completely understood, zinc, essential amino acid, and fatty acid deficiencies have all been postulated as possible causative factors.*

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Necrolytic migratory erythema (NME) historically has been associated with pancreatic glucagonomas and elevated serum levels of glucagon. However, neither a glucagonoma nor hyperglucagonemia are necessary for the development of the disease. The presence of NME in the absence of a pancreatic tumor has been described as pseudoglucagonoma syndrome.[1,2] In such cases, the disease has been associated with intestinal malabsorption disorders; cirrhosis; pancreatitis; and specific nutritional deficiencies including zinc, essential amino acid, and fatty acid deficiencies.[1,3-5] There also have been reports of NME-like skin lesions induced by chemotherapy treatments with epidermal growth factor (EGF) receptor inhibitor gefitinib[6] as well as intravenous glucagon treatment of hypoglycemia.[7]

Although the exact pathogenesis of NME is unclear, 4 main pathogenic mechanisms have been proposed in the literature, including glucagon excess; multifactorial malnutrition; liver dysfunction; and increased levels of inflammatory mediators in the skin, mainly arachidonic acid and its inflammatory metabolites, prostaglandins, and leukotrienes.

We present a case of NME in a patient with a metastatic neuroendocrine tumor of unknown primary origin, which was clinically consistent with a carcinoid. According to a PubMed search of articles indexed for MEDLINE using the terms *necrolytic migratory erythema* and *neuroendocrine tumor,* only 2 other similar cases have been reported in the literature; Marko et al[8] and Appetecchia et al[9] described a patient with NME associated with metastatic neuroendocrine hepatic tumors of unknown origin.

## Case Report

A 52-year-old woman presented with a pruritic rash on the trunk and extremities of 10 days' duration and progressive swelling of the left lower extremity with serous discharge. Her medical history revealed a metastatic small cell neuroendocrine tumor of unknown primary origin that was diagnosed 6 years prior and was believed to be a carcinoid. At the time of presentation she was undergoing therapy with atiprimod for

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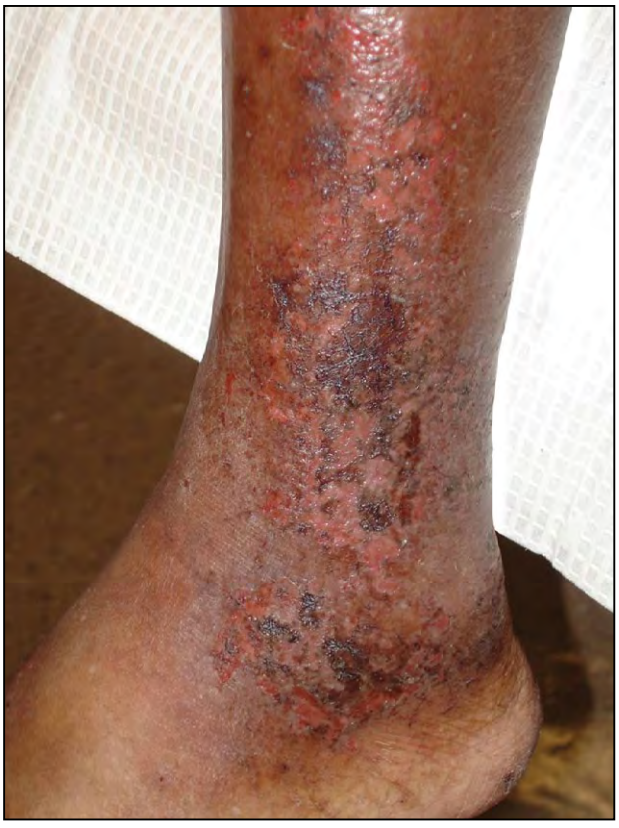

Scaling erythematous plaques over the left lower extremity characteristic of necrolytic migratory erythema.

20 days as part of a clinical trial of chemotherapy for metastatic carcinoid syndrome.

Focused physical examination revealed a chronically ill, cachectic woman with several eczematous excoriated plaques on the abdomen, forehead, and all 4 extremities. The left lower extremity demonstrated pitting edema with fluid-filled vesicles, crust, and serous discharge (Figure).

Punch biopsies (3 mm) of lesions on the left shin and periumbilical area were performed. Histologic sections showed parakeratosis accompanied by epidermal pallor and vacuolation as well as a superficial perivascular dermatitis with a mixed infiltrate. These histologic features were suggestive of NME.

Extensive laboratory workup revealed microcytic anemia (hemoglobin, 8.7 g/dL [reference range, 14.0–17.5 g/dL]; hematocrit, 25.8% [reference range, 41%–50%]; mean corpuscular volume, 75.2 fL [reference range, 80–100 fL]); low octanoic acid (7 nmol/L; reference range, 8–47 nmol/L); low γ-linolenic acid (12 μmol/L; reference range, 16–150 μmol/L); and borderline α-linolenic acid (50 μmol/L; reference range, 50–130 μmol/L). Zinc, insulin, and gastrin levels were all within reference range. A low 5-hydroxyindoleacetic acid level (1.6 mg/24 h; reference range, 2–6 mg/24 h) and a high glucagon level (272 pg/mL; reference range, 4–130 pg/mL) was notable. A prior glucagon level in February 2004 was 3789 pg/mL.

The patient was hospitalized and treated with intravenous vancomycin for presumed secondary cellulitis of the left leg, with substantial improvement of the edema and rash on the left leg. Three weeks later she presented with painful genital and perianal superficial erosions. Burow solution compresses along with topical steroids and an antifungal agent were initiated. Unfortunately, the patient died 2 months later due to complications of her underlying malignancy.

## Comment

We hypothesize that the NME in our patient was triggered by the high glucagon levels associated with the tumor and possibly, in part, by the low levels of fatty acids found in the laboratory workup. Because the patient received atiprimod 20 days prior to presentation, this chemotherapy agent was explored as a possible etiology. However, an association between NME and atiprimod does not exist. Atiprimod acts on multiple pathways involved in tumor growth, invasion, and metastasis, primarily by downregulation of JAK2 (Janus tyrosine kinase)–STAT (signal transducer and activator of transcription) pathway.[10]

Although gefitinib, an EGF receptor inhibitor used for cancer treatment, has been reported to induce NME by altering skin homeostasis through inhibition of the EGF receptor,[6] we do not believe that atiprimod triggered NME in this patient because it acts via a different pathway of tumor inhibition.

Necrolytic migratory erythema is a great source of morbidity in patients, as it forms coalescent areas of blistering and scaling, producing progressively disabling pain and pruritus.[1] Treatment often is focused on removing the underlying glucagon-secreting tumor, but such therapy has been suboptimal. Peripheral infusion of amino acids and fatty acids has been reported to be effective in inducing complete resolution of NME in a patient with subnormal amino acids and normal fatty acid levels.[11] Interestingly, at the end of treatment, a gradual decrease in fatty acid levels was noted, while there was no change in serum amino acid levels,[11] suggesting that disease may be related to levels of amino acids or fatty acids directly in the skin rather than in the serum.

The diagnostic and prognostic potential of NME is well-established in glucagonoma syndrome, as it is a common finding at presentation.[12] Furthermore, NME often precedes the onset of systemic symptoms, providing an early clue in the detection of glucagonoma syndrome.[13] In patients with pseudoglucagonoma syndrome, the skin disease is present for at least 1 year before a correct diagnosis is made.[8]

A previously reported case of NME associated with neuroendocrine tumors demonstrates some similarities to our patient. Because there was no confirmation of the presence of a pancreatic tumor, 2 years elapsed before a tentative diagnosis of a glucagon-secreting tumor was made in that case,[8] which highlights the importance of a correct and expedient diagnosis of NME because it may provide an important clue for the early detection of glucagonomas and extrapancreatic glucagon-secreting tumors.

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