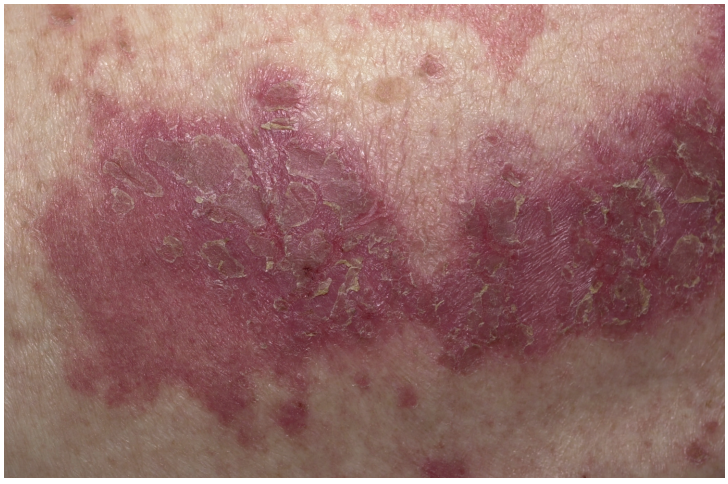
What Is Your Diagnosis?



A 58-year-old woman with bipolar disorder and recent weight loss presented with a 2-year history of a pruritic and painful rash involving her extremities, face, and trunk.

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The authors report no conflict of interest.

The Diagnosis: Necrolytic Migratory Erythema Associated With a Glucagonoma

A 58-year-old woman presented with a diffuse, macular, scaling, erythematous, eczematous eruption; some flaccid bullae also were present. The rash started on her extremities and subsequently spread to her face (Figure 1) and trunk (Figure 2). The rash improved temporarily when she was treated with oral antibiotics. She also reported a 60-lb weight loss over 6 months and a 6-week history of weakness, fatigue, anemia, and diarrhea. Ten years earlier, the patient was diagnosed with bipolar disorder and treated with lithium carbonate and antipsychotic agents. Despite treatment, the patient reported a 1-year "loss of reasoning."

A skin biopsy specimen obtained at an outside institution was interpreted as showing features of erythema multiforme. A second skin biopsy specimen obtained by one of the authors showed extensive erosion and thinning of the epidermis, with an overlying crust of neutrophils and parakeratosis, loss of the granular cell layer, and slight pallor of the upper epidermis. A mixed acute and chronic inflammatory cell infiltrate was present beneath the eroded zone (Figure 3). These findings were considered consistent with necrolytic migratory erythema (NME) in the context of the patient's history and clinical findings. Results from laboratory studies showed a plasma glucagon level of 279 pg/mL (reference range, 46–166 pg/mL). A computed tomographic scan confirmed a 49×39-mm mass arising from the tail of the pancreas with no associated lymphadenopathy. Following a hemipancreatectomy and splenectomy, plasma glucagon levels fell to 40 pg/mL and the rash completely resolved within days. The histology of the pancreatic tumor was that of an islet cell tumor and tumor cells stained positively with an antibody to glucagon (Figure 4). Six weeks after surgery, the patient regained 25 lb and was able to discontinue lithium carbonate and antipsychotic agents she had taken for many years.

A glucagonoma is a rare endocrine tumor arising from alpha cells of the pancreas.[1-3] The tumor typically occurs in middle-aged or elderly individuals, with a median age of 54 years.[3] Wermers et al[2] found a mortality rate of 43% (9/21) in patients with glucagonoma syndrome, with tumor-related death occurring approximately 5 years after diagnosis. Glucagonoma syndrome includes weight loss, NME, glucose intolerance, anemia, stomatitis, aminoaciduria, thromboembolism, gastrointestinal

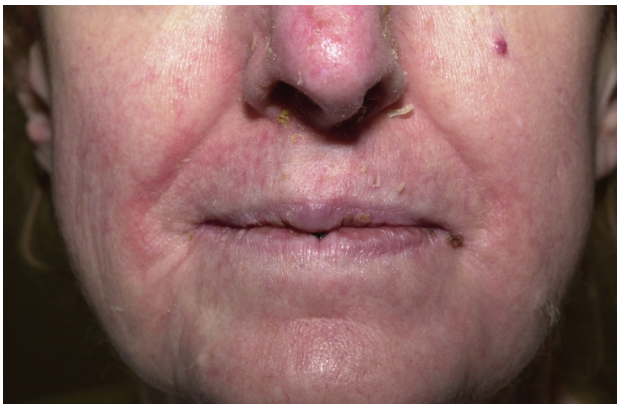

Figure 1. Perioral macular erythematous lesions with greasy scaling.

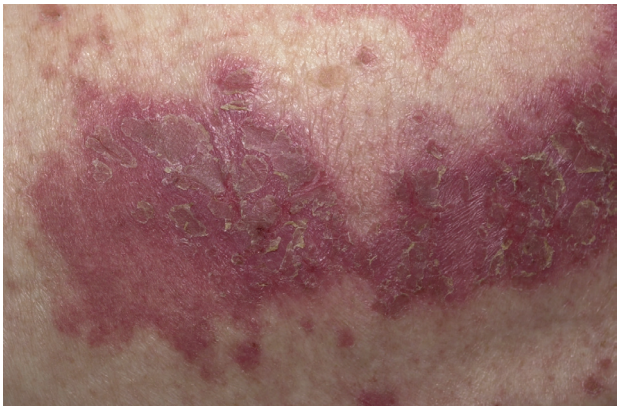

Figure 2. Truncal macular erythematous lesions with waxy scaling.

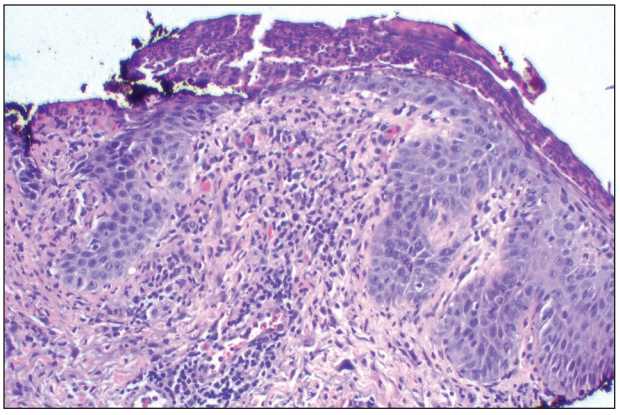

Figure 3. Skin biopsy specimen showed extensive erosion of the epidermis, with an overlying crust of neutrophils, loss of the granular cell layer, slight pallor of the upper epidermis, and a mixed dermal infiltrate (H&E, original magnification ×100).

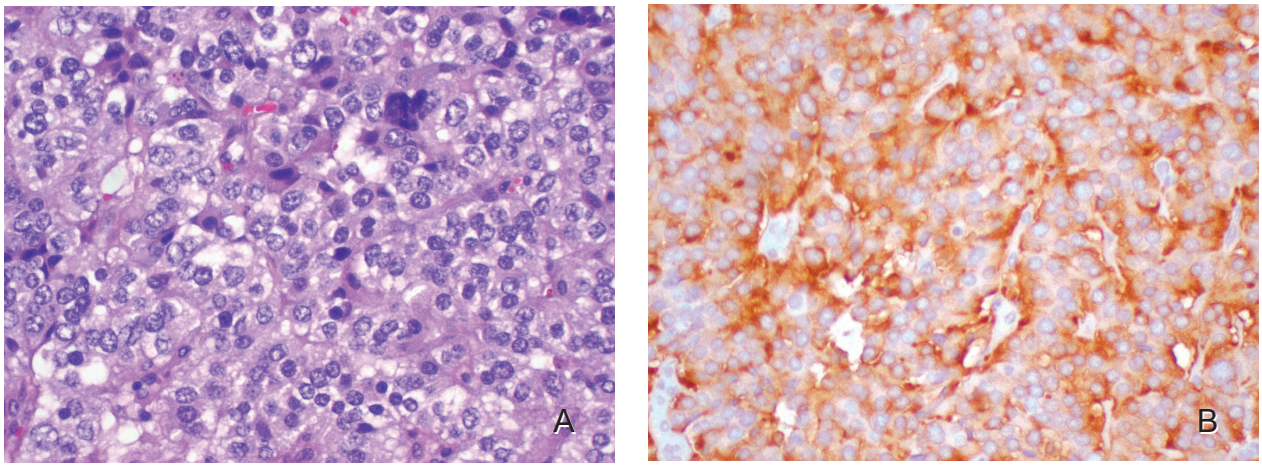

Figure 4. Biopsy specimen of the pancreatic tumor composed of pleomorphic pancreatic islet cells (H&E, original magnification ×200)(A). Using the immunoperoxidase technique, tumor cells stained positively with an antibody to glucagon (original magnification ×200)(B).

disturbances, neuropsychiatric features, and increased serum glucagon levels.[1,3-6] In a review, 67% (14/21) of patients with glucagonoma syndrome presented with NME.[2]

Becker et al[7] first described NME associated with an islet cell tumor in 1942. The intensely pruritic and often painful eruptions occur as spontaneous exacerbations and remissions lasting about 10 days.[8,9] Typical lesions present as erythematous patches that blister centrally, erode, and then crust. Annular plaques, flaccid vesicles and bullae, purpura, papules, and oozing dermatitis also have been reported in patients with NME. Hyperpigmentation occurs after resolution, and a peripheral collarette of scale remains on active margins.[10] Our patient had involvement of the characteristic areas, including the trunk, buttocks, lower extremities, perineum, and perioral areas.[3,10] A review of patients with NME noted that oral and genital mucosal involvement was a constant feature.[10]

Histopathologic changes of NME are varied and include epidermal necrosis, pallor of the upper epidermis, loss of the granular cell layer, epidermal hyperplasia, and papillary dermal edema with vascular dilation.[10,11] However, biopsy specimens do not always have features suggestive of NME; therefore, multiple biopsies are recommended.[10] Our patient's first skin biopsy specimen did not show histologic features characteristic of NME, while the second biopsy specimen was more suggestive of NME.

There are several theories on the pathogenesis of NME, but Tierney et al[9] identified 4 main mechanisms. The first theory of NME pathogenesis is that glucagon excess is the primary cause. If glucagonomas are surgically removed or treated with octreotride acetate, a glucagon antagonist, the NME skin lesions resolve, which is evidence for this theory on NME pathogenesis.[8,12] However, rashes associated with NME are not confined exclusively to patients with elevated glucagon levels.[8] A second theory suggests that malnutrition plays a major role. Similar skin lesions are seen with zinc, protein, selective amino acid, or essential fatty acid deficiencies.[10,12-14] Third, liver dysfunction also has been theorized as a cause of NME. The liver normally functions in the degradation of glucagon, and liver dysfunction has been observed with most cases of NME associated with glucagonoma.[9,10] There also is evidence suggesting that increased levels of glucagon may cause an elevated level of inflammatory mediators in the skin. The fourth theory on the pathogenesis of NME is increased levels of inflammatory mediators such as arachidonic acid and its metabolites (prostaglandins and leukotrienes) may cause NME.[15]

There have been reports of NME that are not associated with glucagonoma. Pseudoglucagonomas occur in association with other malignancies, such as cirrhosis, hepatitis, celiac sprue, inflammatory bowel disease, pancreatitis, generalized malabsorption syndromes, and zinc and fatty acid deficiencies.[9]

Diagnosis of glucagonoma can be achieved with imaging techniques such as a computed tomographic scan, ultrasonography, positron emission tomography, and selective angiography.[1,6] If necessary, needle biopsy can confirm the diagnosis. The only treatment that offers a chance for cure is complete surgical excision of the tumor.[2] Sites of metastasis include the liver, peripancreatic lymph nodes, bones, adrenal body, kidneys, and lungs. For patients with liver metastasis, pancreatectomy, hepatic artery embolization, liver transplant, and a debulking operation can be performed. Due to the slow growth

of glucagonomas, even those with extensive disease may achieve postoperative improvement of symptoms for a prolonged period.[2] Scintigraphy with a somatostatin analogue, indium In 111 diethylenetriamine pentaacetic acid N-terminal D-phenylalanine octreotide, has been used postoperatively to monitor recurrence or disease spread.[6] Symptomatic treatment includes octreotide acetate for weight loss, abdominal pain, and diarrhea, and blood transfusions may be required to correct anemia.[1] There have been reports of improvement after intravenous administration of fatty acids, amino acids, or oral zinc supplementation,[12,13] which supports the theory of malnutrition-related NME pathogenesis.

In summary, we report a patient with weight loss, fatigue, anemia, diarrhea, mental alteration, and a distinctive rash caused by NME. The clinical appearance of the rash and the histopathologic findings led to the detection of a glucagon-secreting pancreatic tumor. Her signs and symptoms cleared completely after surgical excision of the glucagonoma.

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