Case Letter

Necrolytic Migratory Erythema: A Common Cutaneous Clue of Uncommon Syndromes

To the Editor:

A 60-year-old man presented with a recurrent cutaneous eruption on the lower legs, feet, arms, and perianal and genital areas of 5 months' duration. The patient's medical history indicated hypertension and recently diagnosed type 2 diabetes mellitus (DM). On review of systems the patient reported vague recurrent abdominal pain and diarrhea over the last few months for which he had never been evaluated.

On physical examination the patient had a skin eruption with annular erythema demonstrating central pigmentation and scaly erythematous borders located over the face, shins, and feet (Figure 1). Signs of inflammatory dermatitis with angular cheilitis as well as scaly, erosive, and crusted plaques and fissures around the nose, mouth, and forehead also were present (Figure 2). There was a cyclic, waxing and waning pattern in the course of the eruption. The patient reported burning and itching over the areas of erythema. Generally, he appeared cachectic and malnourished with psychomotor retardation and symptoms of depression. He had been seen on a few occasions in our dermatology department and was treated with antibiotics as well as oral and topical corticosteroids.

Laboratory testing revealed normochromic normocytic anemia, hyperglycemia, and normal serum zinc levels. Skin biopsy showed epidermal hyperplasia; parakeratosis; rare dyskeratosis; infiltration by neutrophils, mostly on the upper zones of the dermis; and occasional perivascular lymphocytic infiltrate. The skin biopsy proved to be otherwise nondiagnostic. Thoracic computed tomography was normal. Abdominal computed tomography revealed an enhancing well-circumscribed lesion in the body of the pancreas with mild enlargement of the head and body of this organ. His liver, spleen, kidneys, and adrenals appeared normal. Hormonal analysis showed that levels of glucagon (390 pg/mL [reference range, 59–177 pg/mL]), pancreatic polypeptide (600 pmol/L [reference range, 0–100 pmol/L]), gastrin (180 pg/mL [reference range, 0–100 pg/mL]), and vasoactive intestinal polypeptide (75 pmol/L [reference range, 0–30 pmol/L]) were all elevated. Somatostatin receptor scintigraphy of the pancreas showed increased uptake in the area of the documented lesion.

The patient underwent resection of the pancreatic tumor. Biopsy confirmed the presence of glucagonoma. Subsequently he was treated with somatostatin analogues and diet supplementation

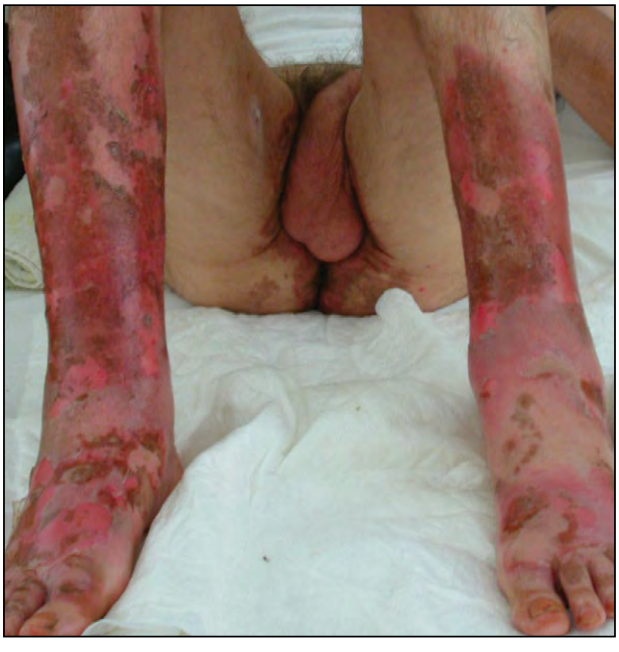

Figure 1. Scaly erythematous plaques over the shins and feet.

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The authors report no conflict of interest.

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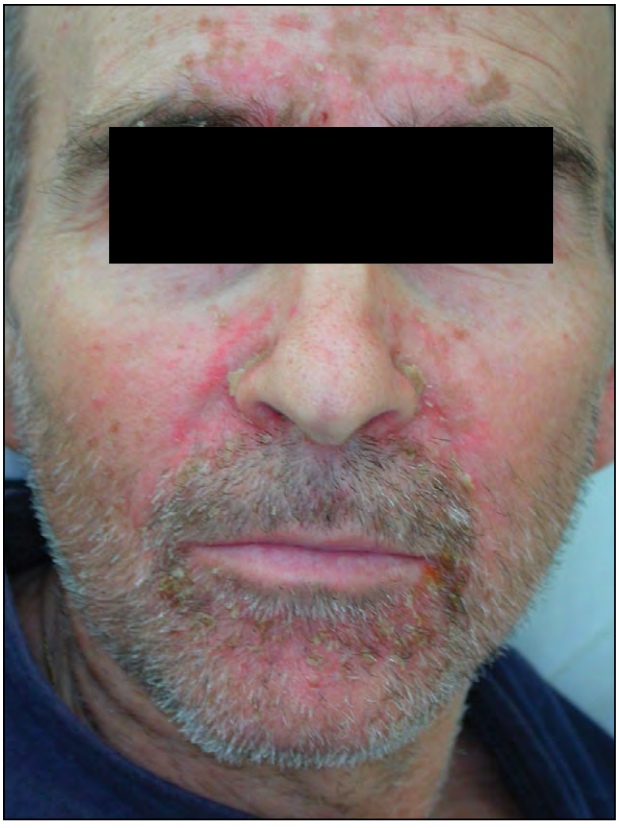

Figure 2. Angular cheilitis as well as scaly erosive, and crusted plaques and fissures around the nose, mouth, and forehead.

with amino acids and zinc. His cutaneous lesions gradually improved and he has remained stable on follow-up.

Glucagonoma syndrome (GS) is a rare paraneoplastic disease of pancreatic alpha cells resulting from excessive secretion of glucagon. Islet cell carcinomas account for approximately 1.3% of pancreatic cancers, and most patients have advanced disease at the time of diagnosis.[1] Few cases of GS have been reported in the literature.[2] The incidence of the disease is estimated to be 1 in 20,000,000 per year. The prevalence of the disease is equal in women and men and most commonly encountered in adults aged 50 to 59 years. In patients diagnosed with glucagonomas, at least 50% of tumors are metastatic at the time of diagnosis.[3]

The basic clinical features of the disease are cutaneous eruptions, glucose intolerance or DM, weight loss, anemia, diarrhea, thromboembolism, and neuropsychiatric symptoms. Necrolytic migratory erythema (NME) is an initial feature in 70% of cases. Excessive glucagon induces hypoaminoacidemia, which is thought to lead to NME. Liver disease as well as fatty acid and zinc deficiency states also may contribute to the pathogenesis of the skin eruption. Necrolytic migratory erythema is characterized by bouts of irregular erythema in which flaccid vesicles and bullae develop and subsequently erode and become crusted. The center of the lesions heals, sometimes leaving areas of hyperpigmentation. Lesions often are pruritic and painful and can be secondarily infected with bacteria or fungi. The dermatosis typically evolves in 7 to 14 days.[2] The typical feature in skin biopsy is necrolysis of the upper epidermis with vacuolated keratinocytes.[4] Psoriasiform epidermal hyperplasia, hypogranulosis, and thickened stratum corneum with parakeratosis, as well as perivascular lymphohistiocytic infiltrate in the superficial dermis, are characteristic histopathologic features. Multiple biopsies may be required to confirm diagnosis because histologic examination may show nonspecific dermatitis.

The diagnosis of GS is suggested when increased plasma glucagon levels are found along with the characteristic skin rash and DM. In a study by Kindmark et al[5] of 23 patients with diagnosed GS, only 22% (5/23) developed DM prior to the diagnosis. Necrolytic migratory erythema was diagnosed or clinically suspected in 52% (12/23) of patients, and 78% (18/23) had metastatic disease to the liver at the time of diagnosis.[5] A review of 21 patients with GS by Wermers et al[6] showed that all patients had metastatic disease at presentation and 9 died of disease complications 4.9 years after initial presentation. Twelve patients were alive after an average follow-up of 3.7 years.[6] However, Dourakis et al[7] reported the case of a patient who survived for 21 years after initial diagnosis of GS with concurrent liver metastases.

Pseudoglucagonoma syndrome (PGS) may be encountered in conditions such as liver disease, inflammatory bowel disease, pancreatitis, celiac sprue, zinc, and other nutritional deficiencies[8] (Table 1). It may be associated with elevated serum glucagon levels in up to half of patients,[18] but glucagon levels in these cases are not typically elevated at the same proportion as in glucagonoma. This feature along with the underlying pathology defines the major differences between the 2 syndromes (Table 2). Pseudoglucagonoma syndrome shares a similar pathogenic origin of skin lesions with GS. The rash of NME in patients with PGS is clinically and histologically identical to patients with GS and both are frequently associated with nutritional deficiencies.

Glucagonoma syndrome and PGS are rare syndromes that are easily overlooked. The characteristic rash frequently is unrecognized and the histologic examination is nonspecific. Recognition of the specific cutaneous features, thorough investigation and

Table 1.
Reported Cases of Pseudoglucagonoma Syndrome

Reference (Year)	No. of Patients	Associated Disease
Chiyomaru et al[9] (2010)	1	Cholangiocarcinoma
Muller et al[10] (2008)	1	Opiate dependency
Baricault et al[11] (2006)	1	Waldmann disease (primary intestinal telangiectasia)
Nakashima et al[12] (2006)	1	Short bowel syndrome
Kitamura et al[13] (2005)	1	Hepatitis B virus
Technau et al[14] (2005)	1	Myelodysplastic syndrome
Bak and Ahn[15] (2005)	1	Malnutrition
Hivnor et al[16] (2004)	1	Hepatitis C virus
Echenique-Elizondo et al[17] (2004)	2	Acute pancreatitis

Table 2.
Suggested Differences Between Glucagonoma and Pseudoglucagonoma Syndrome

Glucagonoma Syndrome	Pseudoglucagonoma Syndrome
Pancreatic tumor	Other diseases (eg, malabsorption, malnutrition, liver diseases)
Higher glucagon levels	Glucagon levels usually not as high
NME resolves by surgery, somatostatin analogues, chemotherapy, and diet supplementation	NME resolves by treatment of the underlying condition

Abbreviation: NME, necrolytic migratory erythema.

assessment of the patient's medical history, and use of detailed imaging may more securely lead to the diagnosis of these uncommon syndromes.

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