Clinical Vignettes

Putting the Pieces Together: Necrolytic Migratory Erythema and the Glucagonoma Syndrome

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Glucagonomas are slow-growing, rare pancreatic neuroendocrine tumors. They may present with paraneoplastic phenomena known together as the “glucagonoma syndrome.” A hallmark sign of this syndrome is a rash known as necrolytic migratory erythema (NME). In this paper, the authors describe a patient with NME and other features of the glucagonoma syndrome. The diagnosis of this rare tumor requires an elevated serum glucagon level and imaging confirming a pancreatic tumor. Surgical and medical treatment options are reviewed. When detected early, a glucagonoma is surgically curable. It is therefore imperative that clinicians recognize the glucagonoma syndrome in order to make an accurate diagnosis and refer for treatment.

KEY WORDS: glucagonoma; neuroendocrine tumors; necrolytic migratory erythema.

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Pancreatic neuroendocrine tumors (PNETs) are rare tumors representing <5 % of all pancreatic malignancies.^{1,2} PNETs are classified by the hormonal products that they produce. A glucagonoma is an extremely rare variant in which glucagon is the primary hormonal product. Hyperglucagonemia may result in the “glucagonoma syndrome,” characterized by a rash known as necrolytic migratory erythema (NME), diabetes mellitus, and other features. NME is characteristic of a glucagonoma, and may be a useful early clue to the diagnosis.³

In this paper, we describe a patient with a glucagonoma that eluded diagnosis for many years, despite having NME and many of the other characteristic features of the

glucagonoma syndrome. We will describe NME, the glucagonoma syndrome and how to recognize and treat these rare tumors.

KEY POINTS

1. Glucagonomas are rare pancreatic neoplasms that are often heralded by a characteristic rash (NME) and diabetes mellitus, among other symptoms.
2. NME is characterized by erythematous, well-demarcated plaques that are pruritic and painful, and often involve the intertriginous areas, perineum, and buttocks.
3. The diagnosis of a glucagonoma requires an elevated serum glucagon level and imaging confirming a pancreatic tumor.

CASE

A 63-year-old woman with a history of unexplained chronic dermatitis was admitted to the inpatient medicine service for acute cellulitis. Her past medical history was notable for depression, anxiety, and chronic diarrhea, which had been diagnosed as irritable bowel syndrome. She had also recently been diagnosed with Lewy body dementia.

Three years prior to admission, she was seen in Dermatology clinic for evaluation of a pruritic rash of her groin, abdomen, axillae, gluteal region, calves and ankles that had been present for several years. She was found to have well-demarcated, erythematous plaques in these regions. Biopsy of a lesion revealed “spongiotic dermatitis” and she was treated with topical steroids. Over time, the rash would remit and recur. The patient underwent allergen patch testing, which was negative, and repeat biopsies confirmed the initial diagnosis. A year later, she was noted to have worsening lesions in the gluteal cleft and trunk. The differential diagnosis at that time included irritant dermatitis from diarrhea and zinc deficiency. A zinc level returned low

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(53 $\mu\text{g/dL}$, normal range 60–120 $\mu\text{g/dL}$) and she was diagnosed with zinc deficiency dermatitis and prescribed supplementation.

Several months later she was noted to have progressive memory impairment, personality changes, weight loss and falls, and was diagnosed with Lewy body dementia. She was moved to a care facility where she continued to receive zinc supplementation and topical steroids for her dermatitis. One month prior to admission, she was seen again by Dermatology, at which time her skin findings consisted of erythematous, crusted thin plaques distributed over the intertriginous skin of the groin and buttocks, scattered on the trunk, and found on the perioral skin, hands and feet (Figs. 1 and 2). Tiny fragile vesicles were observed at the margins of several plaques. Scattered, hyperpigmented patches were noted on both legs (Fig. 3, right leg). Based on these findings, necrolytic migratory erythema (NME) was considered and a glucagon level was obtained. It returned elevated at 1810 ng/L (normal 40–130 ng/L), and a referral to Endocrinology was made. Prior to being evaluated by Endocrinology, she developed an abrupt worsening of pain and redness in her left leg, and presented to the hospital.

On admission, she had stable vital signs. In addition to the findings noted in clinic, the skin exam revealed a well-demarcated, warm, brightly erythematous plaque on the left shin and foot that was felt to be consistent with cellulitis (Fig. 3). Pertinent features of the neurologic examination included intact orientation, irritability and agitation, difficulty following commands, difficulty naming common objects, and impaired short-term memory. She denied visual or auditory hallucinations. There was no muscular rigidity, though there was a mild resting tremor.

Admission laboratories demonstrated hyperglycemia (Table 1), hypoalbuminemia (2.3 g/dL, normal 3.5–4.7 g/dL), anemia (hemoglobin 10.8, normal range 12–16 g/dL) and a normal white blood cell count. Serum glucagon levels were elevated, as were levels of chromogranin A, a serum tumor marker for neuroendocrine tumors

Figure 2. Photo from dermatology clinic showing papules along the corners of the mouth.

(Table 1).⁴ A glycosylated hemoglobin was elevated at 6.6 % (normal < 5.7 %) and the patient was diagnosed with diabetes mellitus. Dermatology and Endocrinology were consulted and a repeat skin biopsy showed “confluent parakeratosis, spongiosis, and keratinocytic pallor with necrosis in the upper spinous layers,” findings consistent with a diagnosis of NME.

A contrast-enhanced CT of the chest and abdomen confirmed a 4.6×3.8×4.4 cm enhancing pancreatic tail mass, as well as left femoral and right iliac venous thromboses and multiple pulmonary emboli. Hematology/Oncology and General Surgery were consulted. The patient was started on intravenous antibiotics and a heparin infusion. Her cellulitis improved and, due to the extensive nature of her thromboses, an inferior vena cava filter was placed in anticipation of surgery. On hospital day nine, she underwent laparoscopic distal pancreatectomy and splenectomy. Pathology confirmed a pancreatic neuroendocrine carcinoma with evidence of vascular and perineural invasion, consistent with a diagnosis of a glucagonoma.

Her post-operative course was complicated by a pancreatic fistula that resolved with non-operative care. Her glucagon levels dropped dramatically post-operatively (Table 1). Her skin lesions were noted to begin improving

Figure 1. Photo from dermatology clinic showing friable, erosive, erythematous plaques with crusting and scale on the lower back and gluteal region.

Figure 3. Photo on admission to the hospital showing acute left lower extremity cellulitis, as well as erythematous thin plaques with scale present on the right lower extremity and scattered hyperpigmented patches at the site of prior disease activity.

Table 1. Laboratory Values on the Day of Hospital Admission and Hospital Day 12 (Post-Operative Day 3)

Serum laboratory studies	Admission values	Post-operative values	Normal values
Glucose (mg/dL)	154	91	60–99
Glucagon (ng/L)	3000	304	40–130
Chromogranin A (ng/mL)	383	113	< 96
Gastrin (pg/mL)	38	—	< 101
Vasoactive intestinal peptide (pg/mL)	< 5	—	< 62
5-HIAA (mg/g cr)	8	—	< 15
Plasma metanephrines (nmol/L)	< 0.10	—	< 0.50
Plasma normetanephrines (nmol/L)	1.25	—	< 0.90
Calcitonin (pg/mL)	< 2.0	—	< 5.3a

almost immediately after surgery (Fig. 4). A repeat CT scan 3 months later revealed two sub-centimeter liver lesions concerning for metastases. An octreotide scan confirmed increased activity in the right hepatic lobe lesion, and she was started on monthly octreotide-LAR injections for metastatic disease. Currently, more than 1 year post-operatively, her cognition has improved significantly and her skin lesions have resolved, leaving behind some chronic scarring.

DISCUSSION

Glucagonomas are extremely rare tumors, comprising only 2–5 % of all islet cell tumors.^{2,5} They can occur alone or may be associated with multiple endocrine neoplasia type 1 (MEN1) syndrome.² The diagnosis of a glucagonoma requires an elevated serum glucagon level (usually 500–1,000 pg/mL) and imaging confirming a pancreatic tumor. A single glucagon measurement is not

Figure 4. Photo on post-operative day 3 showing resolution of cellulitis, as well as evidence of healing of the NME (for example lateral aspect of the right shin and dorsum of right foot).

adequately sensitive for the diagnosis, and specificity can be hindered by secondary glucagon elevations in the setting of sepsis, acute myocardial infarction, renal failure, and other disorders.^{1,6}

Glucagonomas are often heralded by paraneoplastic phenomena. The key features of the “glucagonoma syndrome” are NME and diabetes mellitus. NME is the most specific feature of the syndrome, and is the presenting symptom in approximately 70 % of patients.^{3,6} NME is felt to be due to hypoaminoacidemia or other nutritional deficiencies invoked by hyperglucagonemia, though the exact pathogenesis remains unclear.^{7–9} NME has also rarely been reported in the absence of a pancreatic tumor.⁹ This so-called “pseudo-glucagonoma” syndrome has been seen in association with intestinal malabsorption disorders, cirrhosis, and other diseases.¹⁰

The diagnosis of NME can be challenging, both clinically and histologically. Clinically, the skin eruption is characterized by a pattern of spontaneous remissions and exacerbations. The typical lesions are intensely erythematous, well-demarcated plaques.^{9,11} NME can be highly pruritic and painful, and classically involves the intertriginous areas, perineum, and buttocks. There may be fragile, transient vesicles and bullae that leave erosions when damaged and hyperpigmentation when healed. Angular cheilitis and painful glossitis are common mucocutaneous manifestations. The clinical differential diagnosis for this rash includes contact dermatitis, intertrigo, inverse psoriasis, zinc deficiency, and other nutritional deficiencies. Secondary infections, such as cellulitis, are common.^{9,12}

Histologically, the hallmark of NME is necrosis of the upper spinous layer (hence the term “necrolytic”),¹³ though this finding is nonspecific and may be absent or only focally present on biopsy. Even when present, the histologic differential diagnosis includes other more common mimickers such as zinc deficiency, niacin deficiency (as seen in pellagra), and necrolytic acral erythema (seen in the setting of chemotherapy), which are indistinguishable by histopathology alone. To complicate matters further, a mild zinc deficiency is often seen in conjunction with NME.¹⁴

Diabetes mellitus is another common finding and case studies suggest that between 76 and 94 % of patients with glucagonomas will eventually develop the disease.^{6,9} The diabetes associated with glucagonomas has been described as mild and easily controlled.⁶ Hyperglucagonemia, in combination with elevations in other hyperglycemic hormones (adrenocorticotrophic hormone, vasoactive intestinal peptide, somatostatin, etc.), is the likely precipitant.⁶ The other, less common features of the glucagonoma syndrome include anemia, weight loss, gastrointestinal symptoms, thromboembolic phenomena and hypoaminoacidemia.⁹ Twenty percent of patients with glucagonomas will also exhibit neurologic and/or psychiatric disturbances such as dementia, psychosis, agitation, paranoid delusions, ataxia, and hyperreflexia.^{6,15–17} The mechanism of these changes

is unknown; however, patients can have considerable improvement in their symptoms with treatment.^{6,15–17} Our patient's marked cognitive improvement after surgery and treatment strongly suggests that her neuropsychiatric symptoms were due to the glucagonoma, and not Lewy body dementia.

While in many ways our patient had a classic presentation of a glucagonoma, the diagnosis was missed for nearly 3 years. Delays in diagnosis are common for this slow-growing tumor. In a recent case series of six patients with glucagonomas, the median time from onset of tumor-related symptoms to diagnosis was 39 months.³ In another case series, the diagnosis was made a median of 4 years after the development of NME or diabetes mellitus alone, but much more rapidly once the combination of NME and diabetes developed.⁶ Thus, the combination of NME and diabetes appears to be a useful diagnostic clue to an underlying glucagonoma. Delays in diagnosis have been attributed to the extreme rarity of the tumor, under-recognition of the dermatologic presentation, the difficulty making the diagnosis of NME on biopsy, and the lack of specificity of the other symptoms.^{3,6}

Glucagonomas are generally large (> 4 cm) at the time they are discovered and most are metastatic.^{18–20} As in our patient, most are located in the distal pancreas.¹⁹ CT or magnetic resonance imaging is recommended to identify the number and location of tumors. Endoscopic ultrasound (EUS) may provide additional visualization and can be combined with fine needle aspiration for diagnostic purposes.²¹ Somatostatin receptor scintigraphy may be obtained if there is concern for distant disease.^{22,23}

Tumor stage at the time of diagnosis is highly correlated with survival. In a study utilizing Surveillance, Epidemiology, and End Results (SEER) data, patients with localized disease had a mean survival of 102 months compared to a median of 24 months in patients with distant disease (median data unavailable for localized disease).²⁰ Regardless of SEER stage, patients who underwent resection had significantly longer median survival than patients who were recommended for, but did not undergo surgery (114 months compared to 35 months, respectively, $p < 0.001$). Taken together, these findings suggest that patients with PNETs (including glucagonomas) enjoy a distinct survival benefit when diagnosed with localized disease, and/or when they undergo surgery even when diagnosed with later stages of disease.²⁰ Post-surgical surveillance consists of imaging and glucagon levels at 3 and 6 months post-resection, and every 6 to 12 months thereafter.²⁴

Patients with metastatic disease may experience symptoms related to ongoing hormone secretion. Somatostatin, a polypeptide produced by gastrointestinal paracrine cells, inhibits the release of hormones such as glucagon, gastrin, and insulin. Long-acting somatostatin analogs (such as octreotide-LAR) provide good control of symptoms and are generally well tolerated.^{9,25,26} Octreotide-LAR has also

been shown to delay tumor growth in other types of neuroendocrine tumors, though this benefit remains to be proven in glucagonomas.²⁶ Limited metastatic disease (usually hepatic) is often treated with a combination of local directed therapy (e.g. surgery, radiofrequency ablation, or chemoembolization) in addition to medical management.^{27–29} Systemic chemotherapy may also be warranted. There has been a surge of interest in molecularly targeted therapies for neuroendocrine tumors. Two positive prospective randomized phase III trials have led to the recent FDA approval of sunitinib (an oral multi-targeted tyrosine kinase inhibitor) and everolimus (an oral mTOR serine-threonine kinase inhibitor) for the treatment of low-grade to intermediate-grade metastatic PNETs, including glucagonomas.^{18,30}

In summary, we present a case of a patient with an unexplained rash (in retrospect, classic NME), dementia and chronic diarrhea, all found to be due to a glucagonoma. Her later findings of diabetes mellitus, anemia, cheilitis and thromboembolic disease are also likely attributable to the underlying tumor. Primary care providers should be familiar with NME, albeit rare, as it may be the first and only manifestation of the glucagonoma syndrome.¹³ The combination of NME and diabetes should further heighten suspicion for this rare tumor. Multidisciplinary management is recommended and early surgical intervention is essential.^{1,13} Medical therapy is warranted to treat symptoms and manage metastatic disease, and molecularly targeted therapies may hold future promise for these rare tumors.

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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