Case Report

DIAGNOSTIC CHALLENGE OF GLUCAGONOMA: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Objective: To report the diagnostic difficulties encountered in a case of glucagonoma.

Methods: We provide a literature review and present the clinical findings, pertinent laboratory data, and results of related studies in a patient with a glucagonoma.

Results: A 54-year-old-man, with no relevant history of endocrine disorders, presented to the hospital with a 5-year history of recurrent stomatitis and glossitis, a more recent weight loss of 11.5 kg, and recurrent pruritic maculae on the scalp in conjunction with raised erythematous maculae in the scrotal region and perineum that gradually migrated to the distal extremities, becoming bullous and painful. The patient was hospitalized, and because of the dermatologic findings suggestive of necrolytic migratory erythema, the presence of a glucagonoma was suspected. His blood glucose levels were in the normal range. Glucagon levels were found to be elevated, and imaging studies confirmed the presence of an enlarged mass in the pancreatic tail, without evidence of extension to surrounding structures. Liver metastatic lesions were also excluded. After surgical removal of the tumor, the skin and oral mucosal lesions disappeared spontaneously. The histologic appearance and immunohistochemical staining results confirmed the diagnosis of a glucagonoma. Subsequently, all related symptoms resolved, and the glucagon levels normalized.

Conclusion: The diagnosis of glucagonoma is often delayed. Clinicians should be aware of the unusual initial manifestations of this tumor and the potential for less than a full spectrum of the characteristic features of the glucagonoma syndrome. **(Endocr Pract. 2006;12:422-426)**

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INTRODUCTION

Glucagonomas are rare islet alpha-cell tumors of the pancreas. They are the third most common neuroendocrine tumor, after insulinomas and gastrinomas, and are often malignant at the time of diagnosis. Occasionally, they may be part of the multiple endocrine neoplasia type 1 syndrome or von Hippel-Lindau disease (1). The prevalence is equal in women and men, and occurrence is most common in the sixth decade of life. At least 50% of these tumors have associated metastatic lesions at the time of diagnosis (2). The natural history of this tumor is not well known, but early detection is important in view of the malignant course of the disease. Frequently, diagnosis is a challenge because some patients may not have the characteristic features of the "glucagonoma syndrome," a term coined by Mallinson et al (2) in 1974. This syndrome is characterized by mild hyperglycemia, the cutaneous manifestation of necrolytic migratory erythema, and hypoproteinemia related to malnutrition. Clinical signs and symptoms include weight loss, anemia, stomatitis, thromboembolic disease, gastrointestinal and neuropsychiatric disturbances, onychoschizia, and dyspareunia (3).

CASE REPORT

A previously healthy 54-year-old-man, with no relevant personal or familial medical history of endocrine disorders, was admitted with a 5-year history of painful recurrent stomatitis and glossitis of unknown cause. During the previous 2 years, he had lost 11.5 kg and had become malnourished. Concomitantly, recurrent pruritic maculae had also developed on the scalp, and raised erythematous maculae had developed in the scrotal region and perineum, had gradually migrated to the distal extremities, and had become bullous and painful. The skin lesions broke down spontaneously and ultimately healed, leaving residual areas of hyperpigmentation (Fig. 1). Eventually, these lesions developed secondary bacterial and fungal infections that were treated appropriately. A clinical and histopathologic diagnosis of psoriasis was established after assessment by several dermatologists. The patient had received numerous unsuccessful treatments elsewhere, including vitamin supplementation,

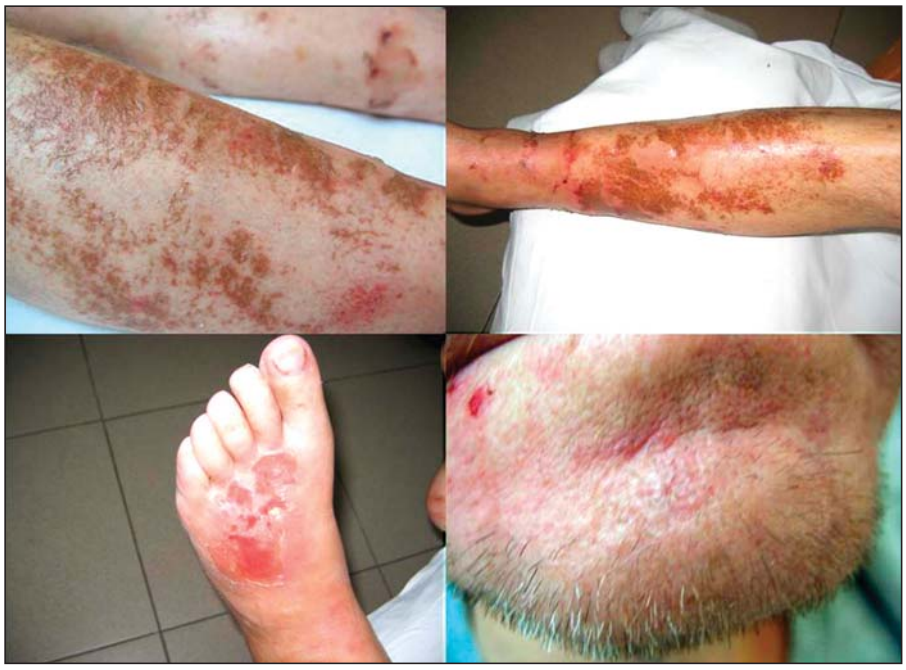

Fig. 1. Migrating areas of erythema with active borders, forming blisters that healed with hyperpigmentation (necrolytic migratory erythema) in 54-year-old male study patient.

coriodermina, and ozonotherapy. (Coriodermina is a placenta-derived factor that inhibits psoriasis crises by regulating epidermal cell reproduction rate. Its mechanism of action is the stimulation of neuropeptides and cytokines. Ozonotherapy is an alternative procedure used to regulate immune response in some autoimmune diseases and, theoretically, as a regenerator of tissues including skin.)

A dermatologist referred the patient to our institution with a presumptive diagnosis of necrolytic migratory erythema. Physical examination revealed a thin man with glossitis, stomatitis, and a geographic tongue. He had annular erythematous maculae, vesicles, and erosions involving the perineal area and the distal extremities as well as nonpainful bilateral leg edema (distal bilateral deep venous thrombosis was confirmed by Doppler ultrasonography).

Pertinent laboratory data included the following: blood glucose 94 mg/dL, serum albumin 3.0 g/dL, hemoglobin 12.3 g/dL, and erythrocyte sedimentation rate 22 mm in 1 hour. The results of the rest of the clinical chemistry, hematologic, and renal and liver blood tests were normal.

Because of the characteristic skin lesions among the differential diagnoses, the presence of a glucagonoma was suspected. The fasting serum glucagon level was found to be elevated at 490 pg/mL (normal range, 46 to 186). Serum levels of the vasoactive intestinal polypeptide, pancreatic polypeptide, corticotropin, and insulin were within normal ranges.

Abdominal ultrasonography, computed tomography, and magnetic resonance imaging (Fig. 2) showed a neoplasm located in the distal pancreas. No liver metastatic lesions were observed. The patient underwent a distal pan-

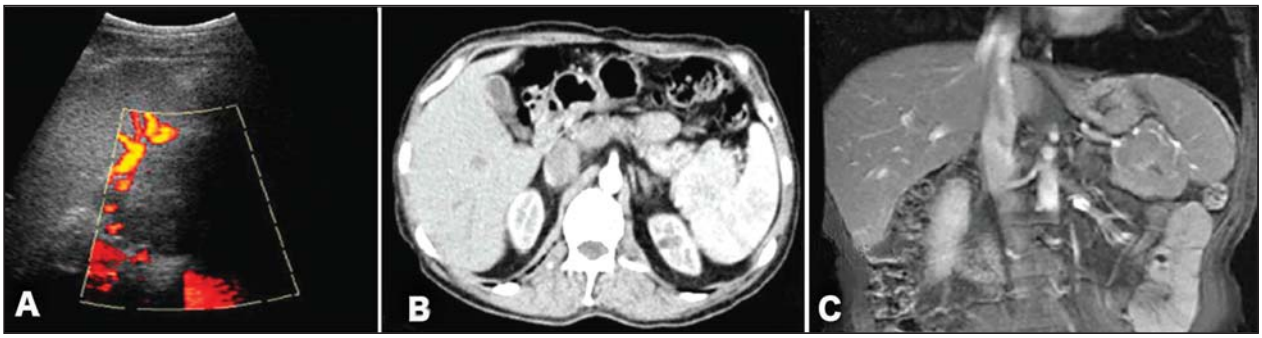

Fig. 2. Diagnostic procedures in study patient. *A*, Ultrasonography of abdomen, showing hypoechoic, well-marginated mass in pancreatic tail with no significant blood flow. *B*, Computed tomography of mass in pancreatic tail, demonstrating enhancement during arterial phase after intravenous contrast injection. Course of splenic artery is inside the tumor. *C*, Coronal T1-weighted magnetic resonance imaging of pancreatic tail. Considerable enhancement was evident after intravenous contrast injection, characteristic of neuroendocrine tumors. No metastatic lesions were identified.

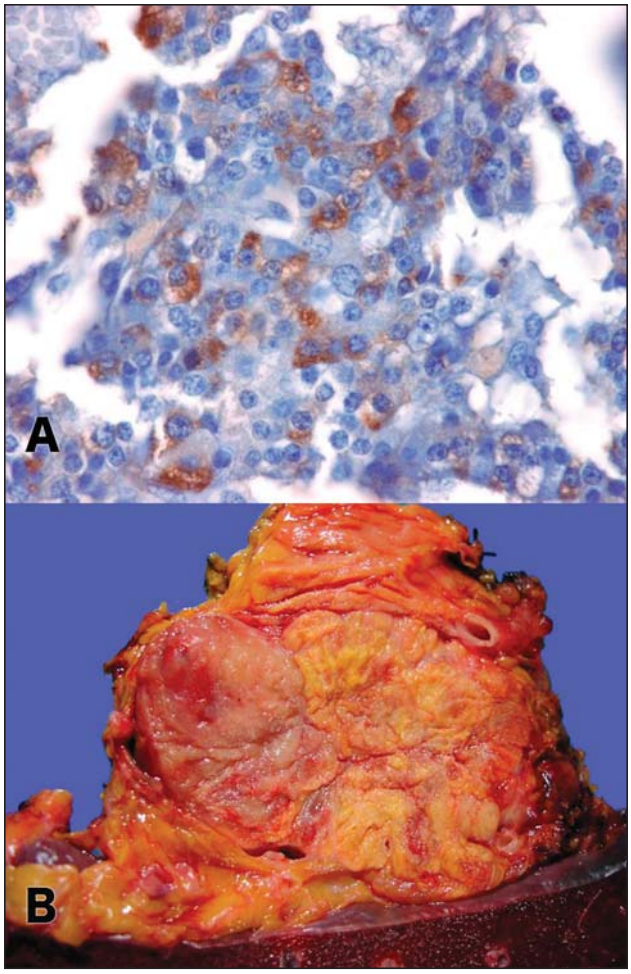

Fig. 3. *A*, Histologic appearance of neoplasm, with solid and trabecular growth patterns and abundant blood vessels. The cells are monotonous, with round nuclei and granular chromatin. They are immunoreactive for glucagon. (Original magnification ×100.) *B*, Gross tumor mass in distal pancreas, with well-defined borders and pink-to-tan color, characteristic of a neoplasm with neuroendocrine differentiation.

createctomy with complete removal of the tumor and splenectomy.

The tumor (5.0 by 6.8 cm) had well-defined borders and a pink-to-tan color, characteristic of a neuroendocrine tumor. The microscopic features showed a tumor with a solid and trabecular growth pattern and abundant blood vessels; the monotonous cells had round nuclei and granular chromatin and were immunoreactive for glucagon (Fig. 3).

The dermatologic manifestations completely disappeared 2 days postoperatively (Fig. 4). The patient was dismissed from the hospital after 5 days of anticoagulant therapy, a high-protein diet, and administration of vitamin and zinc supplements. Subsequently, all symptoms resolved, and glucagon levels returned to the normal range (47 pg/mL).

DISCUSSION

As this case illustrates, making the diagnosis of a glucagonoma can be a clinical challenge. This patient had most of the characteristic features of the glucagonoma syndrome except for diabetes or mild hyperglycemia (found in 75% of cases) and diarrhea caused by hypersecretion of gastrin, vasoactive intestinal polypeptide, or serotonin (which was within the normal range in the current patient). In common with other similar cases, our patient had undergone extensive assessment and previous treatment by numerous physicians without satisfactory results and had been given a diagnosis of psoriasis.

In most patients with glucagonoma, the clinical presentation and histologic analysis of the skin lesions should support the diagnosis of a necrolytic migratory erythema, particularly when the classic pattern of acral or periorificial lesions evolving in recurrent crops, with an annular and migratory distribution, is present. The mucocutaneous manifestations, as occurring in the current case, can precede the diagnosis of the pancreatic neoplasm by several years (4-7). After removal of the tumor, the clinical abnormalities—particularly the glossitis, the stomatitis, and the necrolytic migratory erythema—tend to disappear, probably as a result of the reduction in the plasma glucagon levels (8). A similar clinical response has been observed after administration of a glucagon antagonist.

The differential diagnoses include psoriasis, the necrolytic acral erythema associated with hepatitis C infection, pseudoglucagonoma associated with intestinal malabsorption disorders (that is, celiac sprue), cirrhosis, inflammatory bowel disease, pancreatitis, malignant lesions, acrodermatitis enteropathica, essential fatty acid deficiency, annular chronic lupus erythematosus, drug reactions, contact dermatitis, and other nutritional deficiency syndromes such as vitamin and mineral deficiencies—for example, vitamin B_3 (niacin), vitamin B_2 (riboflavin), vitamin B_6 (pyridoxine), and zinc (9,10).

Becker et al (11) first described the characteristic dermatitis, necrolytic migratory erythema, in 1942. This rare skin condition consists of migrating areas of erythema (located mainly in the groin, extremities, thighs, buttocks, and perineum), which form blisters that heal with hyperpigmentation (12-14). Angular cheilitis, glossitis, and stomatitis are commonly present (15). The skin disorder is thought to be attributable to secondary hypoaminoacidemia (especially deficiency of histidine and tryptophan) and malnutrition, which leads to epidermal protein depletion and necrolysis. Histologically, the lesions are characterized by parakeratosis with the loss of the granular layer, necrosis, and separation of the upper epidermis with vacuolation of the keratinocytes, dyskeratotic keratinocytes, and neutrophils in the upper epidermis (16).

Several diagnostic procedures are useful for localizing the tumor and for excluding metastatic involvement:

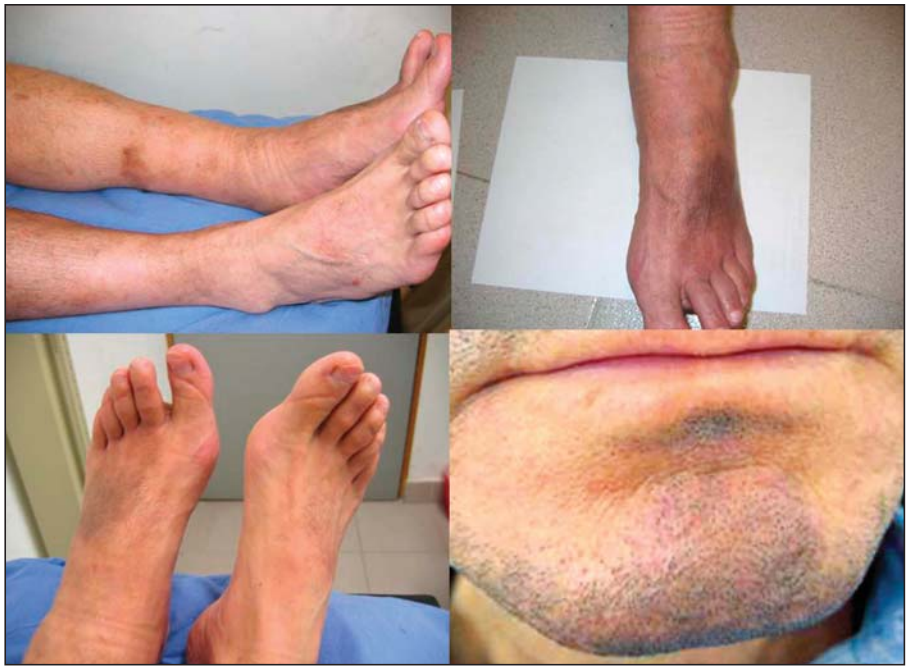

Fig. 4. Complete resolution of skin lesions 2 days after resection of the patient's glucagonoma. (See Figure 1 for initial appearance of lesions.)

ultrasonography, computed tomography, magnetic resonance imaging, angiography, endoscopic ultrasonography, and somatostatin receptor scintigraphy. Because of the rarity of these tumors, the sensitivity and specificity of these studies have not been established. In addition, a few published reports have supported the use of ^{111}In-diethylenetriamine pentaacetic acid (pentetic acid), N-terminal D-phenylalanine octreotide, and ^{18}F-fluorodeoxyglucose positron emission tomography (17-19).

Glucagonomas usually metastasize to the liver, regional lymph nodes, or bone (20), and in such cases, chemoembolization may help to control symptoms. Patients with liver metastatic lesions may need parenteral nutrition, oral zinc supplements, intravenously administered amino acids, and essential fatty acid supplementation (21). These treatment options are suboptimal and often useful for only brief periods. The antiproliferative potency of somatostatin and its analogues in experimental tumor models has prompted several studies in patients with metastatic endocrine tumors that are unresponsive to conventional chemotherapeutic protocols. Stabilization of tumor growth lasting several months to a few years has been the most favorable result, occurring in 30% to 70% of patients (22).

The current patient seems to be free of metastatic disease. Nevertheless, close follow-up is necessary (23).

CONCLUSION

The diagnosis of glucagonoma is often delayed. This situation prevails not only because of the unusual presentation and the lack of clinical suspicion but also because of the potential absence of some of the characteristic features of the glucagonoma syndrome.

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