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Multidisciplinary Approach to Glucagonoma: A Case Report

CASE REPORT
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ABSTRACT

Glucagonomas, a rare subset of pancreatic neuroendocrine neoplasms (PNETs) originating from alpha cells of the pancreas, secrete glucagon and represent less than 10% of PNETs, with an incidence of 0.01-0.1 per million population per year. Often metastatic at diagnosis, glucagonomas commonly present with dermatological symptoms, notably necrolytic migratory erythema (NME), leading to diagnostic delays. Effective management necessitates a multidisciplinary approach. We report a case of a 26-year-old woman with itchy, coin-sized lesions, initially misdiagnosed as erythema multiforme and treated with topical corticosteroids. Recurrence of symptoms, weight loss, night sweats, nail changes, and gastrointestinal issues led to further investigation. Elevated glucagon (700 pg/mL) and chromogranin A levels (>700 ng/mL) confirmed glucagonoma. Imaging revealed multiple hepatic and pancreatic lesions. The treatment included lanreotide, peptide receptor radionuclide therapy (PRRT), distal pancreatectomy, and splenectomy. Despite 6 PRRT cycles and additional chemotherapy, recurrent liver metastases necessitated ongoing management and potential liver transplantation. This case emphasizes the importance of early NME recognition and a multidisciplinary approach involving dermatology, endocrinology, pathology, radiology, surgery, nuclear medicine, medical oncology, and interventional radiology for effective glucagonoma management.

Keywords: Glucagonoma, multimodal therapy, necrolytic migratory erythema, neuroendocrine tumors

Introduction

Glucagonomas are a type of well-differentiated neuroendocrine neoplasm originating from pancreatic alpha cells, classified under pancreatic neuroendocrine neoplasms (PNETs). These tumors, which secrete glucagon, constitute less than 10% of PNETs, with an incidence of 0.01-0.1 per million people annually.[1]

Often, glucagonomas are metastatic at diagnosis, presenting as gastro-endocrinological malignancies. However, patients typically seek medical help for necrolytic migratory erythema (NME), a dermatological symptom that causes diagnostic and treatment delays.[2] Effective management requires a multidisciplinary approach, highlighting the need for collaborative clinical practice. This case study details a patient who initially presented with dermatological symptoms and ultimately needed a liver transplant after 5 years of treatment. Written informed consent was obtained from the patient, who agreed to participate in the study.

Case Presentation

A 26-year-old woman presented at Hacettepe University Hospital's dermatology clinic with itchy, coin-sized lesions (Figure 1A). Diagnosed with erythema multiforme, she was prescribed Clobetasol (50 mg). While corticosteroid treatment resolved the lesions, they reappeared upon discontinuation. About a year later, with worsening lesions (Figure 1B), night sweats, and a 10 kg weight loss, she sought further medical attention. She reported nail changes, nausea, and vomiting but no polyuria or polydipsia. A skin biopsy confirmed NME, with glucagon levels at 700 pg/mL (normal <100 pg/mL) and chromogranin A >700 ng/mL (normal <98 ng/mL). Pathology indicated a well-differentiated grade 2 neuroendocrine tumor with Ki-67 staining of 5%-6%. Immunohistochemistry showed diffuse positivity for pan keratin, CAM5.2, synaptophysin, and INSM1, and cytoplasmic staining for chromogranin and glucagon. Genetic testing found no MEN1 mutation, leading to a glucagonoma diagnosis.

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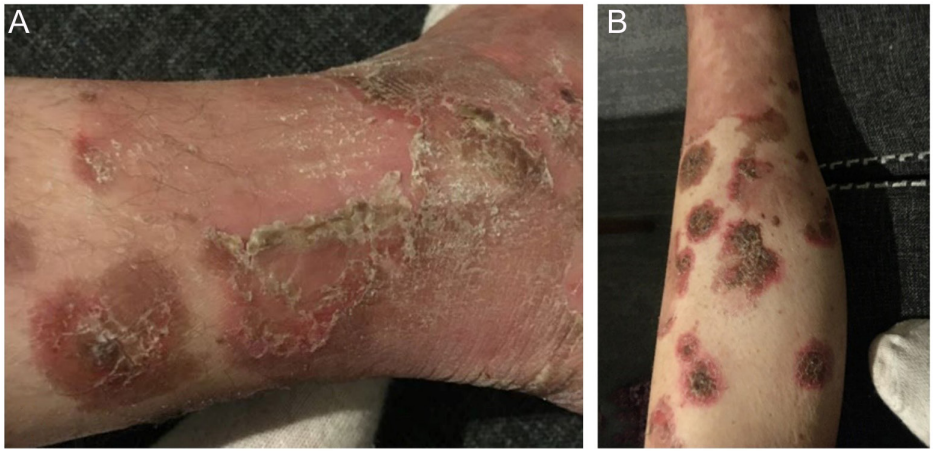

Figure 1. Lesions of the patient. A. Lesions at the initial appearance. B. Reappeared lesions after 1 year.

68-Gallium DOTATATE positron emission tomography–computed tomography (PET–CT) imaging revealed multiple liver lesions and a 3.7 × 2 cm mass in the pancreatic tail (Figure 2A), consistent with metastatic neuroendocrine tumors, including a 5 cm lesion in the liver dome. The pancreatic tail appeared lobulated, indicating tumor involvement. Before liver biopsy, lanreotide was administered to reduce hepatic vascularization. Liver fine needle aspiration biopsy confirmed well-differentiated neuroendocrine neoplasms. Following kidney function assessment, the patient received 90Y-DOTATOC (120 mCi) as the first cycle, then 177Lu DOTATATE (200 mCi) for the second to fourth cycles (Figure 2B-E). Post-treatment Ga-68 PET/CT imaging showed high-intensity uptake in the pancreas tail (Figure 2F). Liver lesions decreased in size but maintained uptake. An additional cycle of 90Y-DOTATOC (120 mCi) and 177Lu DOTATATE (190 mCi) was administered. After 6 radionuclide therapy cycles, Ga-68 DOTATATE PET imaging indicated stable disease (Figure 2G).

The patient then underwent distal pancreatectomy, splenectomy, and liver metastasectomy, with ablation of 3 liver metastases. Post-surgery, due to emerging liver metastases, she began a regimen of capecitabine, temozolomide, and bevacizumab. After nine chemotherapy cycles, CT imaging revealed new necrotic liver areas and a hypervascularized 2.2 × 2.5 cm lesion in the dome. Thirteen chemotherapy cycles were planned. Under intraoperative ultrasound, percutaneous microwave ablation (MWA) was performed on 1 lesion in liver segment 8, 3 in segment 4, 1 at the segment 4-8 junction, and 1 in the left lobe.

MAIN POINTS

- Glucagonoma, a rare pancreatic neuroendocrine tumor, often presents with necrolytic migratory erythema, which can delay diagnosis and treatment.
- Early detection is crucial, as most glucagonomas are metastatic at diagnosis, requiring a multidisciplinary approach involving dermatology, endocrinology, radiology, and oncology.
- Peptide receptor radionuclide therapy, combined with surgery, chemotherapy, and local ablation, can stabilize metastatic disease, but recurrence remains common.
- In advanced cases with liver metastases, liver transplantation may become necessary despite extensive multimodal treatment.

Discussion

Patients diagnosed with glucagonoma typically present at the clinic with NME, diabetes mellitus, weight loss, anemia, glossitis, cheilitis, and angular stomatitis as the most common symptoms. Additionally, less frequently observed symptoms include diarrhea, deep vein thrombosis, and various neuropsychiatric conditions.[2]

We conducted a literature review on the clinical manifestations of glucagonoma cases reported from 2018 onwards, supplementing the 2018 review by Song et al.[2] Using a comparable methodology with Song et al, the search terms Glucagonoma OR (((hyperglucagonemia OR (secreting AND glucagon)) AND (pancreatic AND (((tumor OR neoplasm) OR cancer) OR carcinoma))) were utilized. Data were retrieved from PubMed and included if patients were diagnosed with glucagonoma based on pathological findings or if they exhibited glucagonoma syndrome accompanied by elevated blood glucagon levels. Articles were also required to provide specific patient information, such as age, sex, and clinical symptoms. Through this approach, 35 new cases were identified. Among these 35 cases, the incidence of typical clinical findings was as follows: NME in 77.1% (27/35), weight loss in 40.0% (14/35), diabetes in 28.5% (10/35), glossitis/angular stomatitis in 25.7% (9/35), anemia in 20.0% (7/35), diarrhea in 14.2% (5/35), deep vein thrombosis (DVT) in 11.4% (4/35), and psychiatric symptoms in 8.5% (3/35).

The review by Song et al included data from a 1998 review by Soga et al,[3] which encompassed 425 patients with reported symptoms. By incorporating the 35 new cases from our review, the total number of patients is now 460. Among these 460 cases, the incidence of typical clinical findings was NME in 81.9% (377/460), diabetes in 65.4% (301/460), weight loss in 58.6% (270/460), anemia in 47.3% (218/460), and glossitis/angular stomatitis in 40.0% (184/460).

Diagnosis requires identifying clinical NME, elevated serum glucagon levels, and confirming a glucagon-secreting pancreatic islet cell tumor.[4] The definitive diagnostic method is selective visceral angiography, which helps detect liver metastases. However, due to availability and cost, initial diagnostics typically include ultrasound, with additional methods such as magnetic resonance imaging or PET–CT scans.[5] For our patient, we measured plasma glucagon levels and

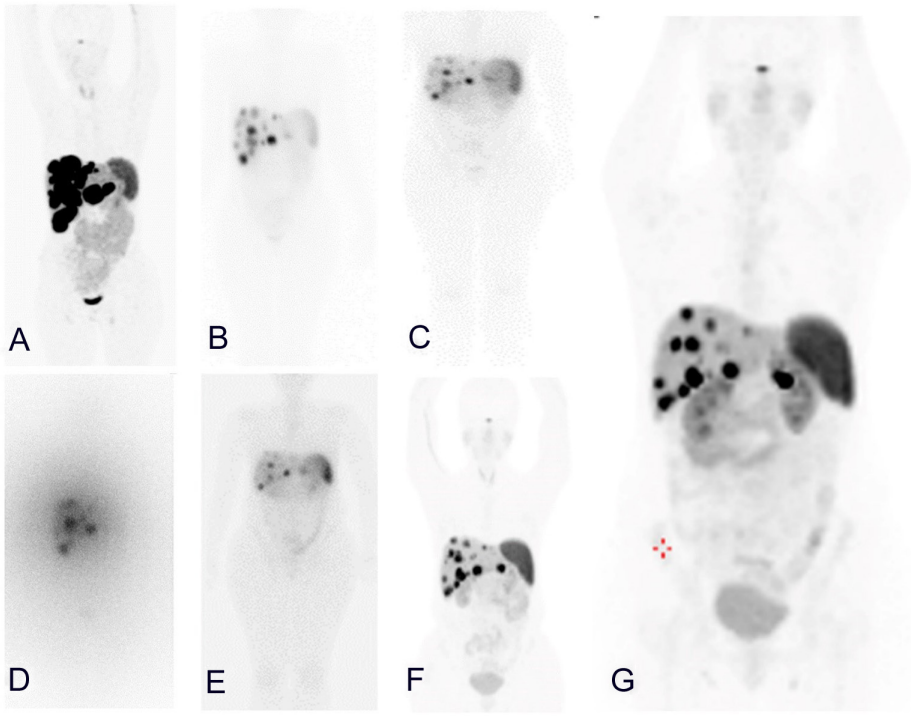

Figure 2. Positron emission tomography/CT scans. A. Baseline whole-body Ga-68 DOTATATE PET/CT showing intense Ga-68 DOTATATE uptake in the pancreatic tail and the liver. B. Whole-body the first Y-90 DOTATATE therapy Bremsstrahlung imaging showing radiotracer uptake in the pancreas and the liver. C. Whole-body Lu-177 DOTATATE second cycle therapy imaging showing pathological radiotracer uptake in the pancreas and the liver. D. Whole-body the third cycle Lu-177 DOTATATE therapy PET/CT imaging showing radiotracer uptake in the pancreas and the liver. E. Whole-body the fourth cycle Lu-177 DOTATATE therapy PET/CT imaging showing radiotracer uptake in the pancreas and the liver. F. Interim Ga-68 DOTATATE PET imaging showing relatively decreased tracer uptake, suggesting partial therapy response. G. End-therapy Ga-68 DOTATATE PET imaging showing stable disease.

used Ga-68 PET/CT imaging to confirm the diagnosis and identify metastatic sites.

Somatostatin analogs, particularly octreotide and lanreotide, are essential for reducing serum glucagon levels and inhibiting tumor growth, significantly alleviating NME.[5] Surgical removal is the definitive treatment for pancreatic glucagonoma and NME. However, metastases are present in 50% to 90% of cases at diagnosis.[6] Advanced metastatic disease requires a combination of anti-tumor therapies and cytoreductive surgery. Treatments such as chemotherapy, peptide receptor radionuclide therapy (PRRT), hepatic transarterial (chemo)embolization, selective internal radiation therapy, and percutaneous local tumor ablation (MWA) can alleviate symptoms or reduce tumor burden.[7,8] A study showed that neo-adjuvant PRRT, with 4 induction cycles followed by 2 maintenance cycles, is effective for recurrent advanced glucagonoma.[9]

For our patient, we employed a multimodal approach: PRRT as a neo-adjuvant strategy, followed by surgical intervention, chemotherapy, and MWA. Despite these efforts, metastases have recurred, and the patient is currently awaiting liver transplantation.

In conclusion, since NME can be the sole early indicator of glucagonoma, prompt and accurate diagnosis of NME is crucial. A collaborative effort involving dermatology, endocrinology, pathology, radiology, general surgery, nuclear medicine, medical oncology, and interventional radiology is essential for comprehensive treatment. This patient's management underscores the importance of a multidisciplinary approach in treating glucagonoma, highlighting the need for disease awareness at every stage of patient care.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

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