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Case Report

Necrolytic Migratory Erythema Impact on Prognosis and Diagnosis of Glucagonoma: A Case Report

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Abstract

Glucagonoma is a well-differentiated slowly proliferating pancreatic neuroendocrine tumor, characterized by variable manifestations related to glucagon excess. Glucagonoma syndrome is a rare neuroendocrine tumor-related syndrome, characterized by a frequent and early cutaneous manifestation, the necrolytic migratory erythema, along with variable systemic involvement. We present a case of a 51-year-old female diagnosed with glucagonoma, highlighting the clinical features, diagnostic approach, and management strategies. Early recognition of the necrolytic migratory erythema and multidisciplinary care of the syndrome are crucial for optimizing outcomes in affected patients.

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Introduction

Glucagonoma syndrome is a rare condition, which can develop in patients with *pancreatic neuroendocrine tumors* (pNET), with an estimated global incidence of one in 20 million people [1]. It is caused by uncontrolled secretion of glucagon by a NET originating from the alpha cells, usually located in the tail or body of the pancreas. Glucagonoma syndrome is characterized by a variable spectrum of symptoms such as *Necrolytic migratory erythema* (NME), *diabetes mellitus* (DM), weight loss, normochromic normocytic anemia, diarrhea/steatorrhea, venous thrombosis and neuropsychiatric disturbances [2-3]. Since NME is a rare paraneoplastic manifestation and most of its symptoms are unspecific, it is often discovered late at an advanced stage, already with the presence of metastases: there is a median time of 39 months from the onset of symptoms to diagnosis [4]. However, the NME is a peculiar manifestation, pathognomonic of Glucagonoma syndrome. The NME may precede systemic symptoms such as weight loss, diarrhea, DM, deep vein thromboses, anemia and neuropsychiatric disorders.

In order to emphasize the importance of an early recognition of this sign that lead a prompt diagnosis of the tumor and thus a better prognosis, we present a case of a 51-years-old patient whose glucagonoma was discovered through the recognition of NME.

Case presentation

In July 2015, a 51-years-old woman, with a history of papilliferous carcinoma treated with total thyroidectomy in 2003, post-surgical hypothyroidism and familiarity with type 2 DM, was admitted to the Digestive Disease Unit (Sant'Andrea ENETS Center of Excellence) due to the presence of weight loss (9 kg in 6 months), asthenia, and the evidence of multiple liver lesions (the largest measuring 7 cm) as seen on abdominal ultrasonography and contrast-enhanced computed tomography, along with a 7 cm hyper vascular lesion in the pancreatic tail. Additionally, she presented with erythematous, scaly, pruritic lesions in areas of the body subjected to greater pressure, such as the plantar and dorsal areas of the feet, in the intergluteal sulcus, and on the face; these lesions were in various stages of healing. At first, she had been treated for a chronic dermatitis with topic steroids that did not lead to an improvement of the lesions. Therefore, an endocrinology examination had been requested for the suspicious of not compensated hypothyroidism and the diagnosis of NME was considered. After being admitted to the Center, a total contrast-enhanced computed tomography (CT) showed an expansive-infiltrative lesion measuring 7.5 x 6.0 x 5.7 cm in dissociable from the tail of the pancreas with exophytic growth and multiple bilateral focal liver lesions (between 1.5 and 7.0 cm). ^{68}Ga-PET/CT showed an intense increase in radiopharmaceutical uptake of the primary pancreatic lesion (SUVmax 34) and multiple repetitive liver lesions (SUVmax 49 for the larger lesion) (Figure 1). ^{18}FDG-PET/CT documented intense uptake

(SUVmax 6.8) in the pancreatic tail and moderate glycometabolic activity of multiple hepatic secondaries (SUVmax 3.2). Liver biopsy established the diagnosis of NET G1 with Ki67 index 1% and positive immunostaining for glucagon. Screening for MEN (Multiple Endocrine Neoplasia)-1 was negative, while the biochemical assessment revealed the following serum values: chromogranin A 1.4 nmol/L (<3 nmol/L); gastrin 0.5 pmol/L (1-10 pmol/L); PTH 27.2 pg/ml (10-70 pg/mL); ionized calcium 1.2 mmol/L (1.17-1.30 mmol/L). Glycemic profile and glycated hemoglobin assay were within the normality range. A therapy with somatostatin analogues was started (lanreotide 120mg/28d) together with the administration of zinc and amino acids, resulting in rapid symptoms improvement. In April 2016, the primary tumor was removed with a distal splenopancreatectomy; pathology reported pancreatic NET of intermediate grade (G2) with a Ki67 of 5-10%. In the months following surgery, the patient showed a slight weight gain and the dermatological manifestations of the disease disappeared. The medical therapy with lanreotide 120mg/28d was maintained even after surgery. Since liver progression at the subsequent control occurred, the patient was treated with peptide receptor radionuclide therapy (PRRT) with ^{177}LuDOTATOC and ^{90}Yttrium since November 2016 until September 2017; the patient has been monitored periodically by CT scans and clinical examinations showing normal blood count and high level of HbA1c (64 mmol/mol in November 2016) (Figure 2). To control DM, occurred during PRRT, a low-glucose diet and metformin were started.

For further liver progression, in August 2019 the patient started Sunitinib 37.5 mg a day, subsequently reduced to 25 mg a day due to neutropenia. A loco regional treatment was then started in March 2020 and in June 2020 when *trans-arterial chemoembolization* (TACE) was used to for liver metastases. Tumor stability was observed until February 2022, when the patient reported weight loss, further tumor progression. Therefore, Sunitinib was discontinued, and chemotherapy with capecitabin and temozolomide (CAPTEM) was initiated, achieving stable disease for 18 months, as confirmed by the latest CT scan and ^{18}FDG-PET/CT. For post-prandial glycemia above the target (150-200mg/dL), the patient started linagliptin in addiction to metformin, resulting in improved glucose homeostasis.

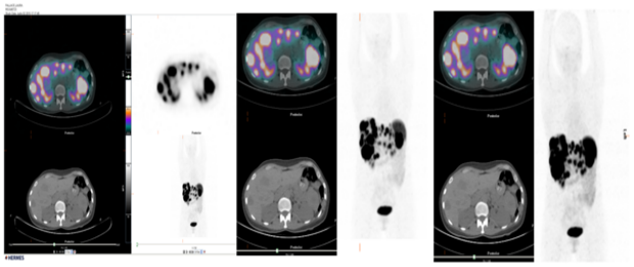

Figure 1: Radiological finding (July 2015): 68Ga-PET/CT showing an intense increase in radiopharmaceutical uptake of the primary pancreatic lesion (SUV max 34) and multiple repetitive liver lesions (SUV max 49 for the larger lesion).

Discussion

Glucagonoma is a rare NET originating from the alpha cells of the pancreas. Most glucagonomas are sporadic, rarely they can be inherited: around 3% of inherited glucagonomas can be associated with other tumors in the context of MEN1. The glucagonoma syndrome is characterized by NME (67%), weight loss (71%), DM (38%), cheilitis (29%), diarrhea (29%), steatorrhea, anemia, glossitis, venous thrombosis and neuropsychiatric disturbances occurring with different frequency as reported in a review by Wermers et al. of 21 patients with the glucagonoma syndrome evaluated at the Mayo Clinic from 1975 to 1991 in (Figure 3).

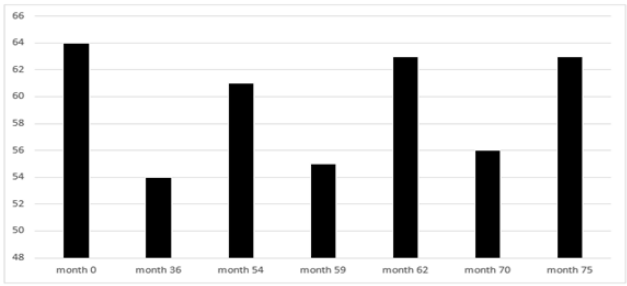

Figure 2: HbA1c patient's values (mmol/mol).

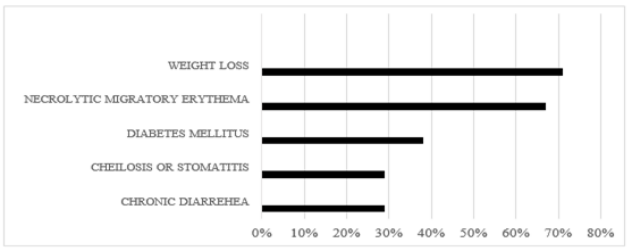

Figure 3: Frequency of glucagonoma syndrome symptoms.

The NME and the significant weight loss were the first symptoms occurred in our patient and they lead to the suspicion of glucagonoma. The delay between skin symptoms and glucagonoma diagnosis was 7 months, while a median of 39 months after the development of NME alone has been reported.

NME is a characteristic skin rash extremely erythematous that may precede systemic symptoms, as in this case. It shows superficial epidermal necrosis and often spreads in a centrifugal pattern. Individual lesions are pruritic and painful, initially appearing as erythematous vesicles and bullae that evolve into patches or plaques with irregular borders, crusting, ulcerations and scaling. In the pathogenesis of NME, hyperglucagonemia plays a central role inducing a catabolic state resulting in the depletion of one or more of zinc, amino acids and essential fatty acids; thus, NME can be classified as a deficiency dermatosis and it can improve up to 50% with somatostatin analogues, amino acid infusion, and antibiotics [5].

DM in glucagonoma syndrome is a typical consequence of the gluconeogenic and glycogenolytic actions of glucagon; in the development of DM are also implicated somatostatin analogues that may cause aberrations in glucose tolerance inhibiting pancreatic endocrine secretion. In oncologic patients, DM and glucose intolerance are associated with increased long-term, all-cause mortality [6]; on the other hand, metformin, the most widely used drug in the treatment of type 2 DM, has recently emerged as a potentially active agent in cancer chemoprevention and treatment [7]. Therefore, it is mandatory to control DM and the use of metformin should be considered as first choice together with a low-glucose diet.

Among the techniques used to identify the tumor, there are contrast-enhanced CT scan, magnetic resonance imaging (MRI), Gallium-DOTA *positron emission tomography* (PET); the diagnosis can

be confirmed by needle biopsy of the primary tumor or metastatic lesions.

The major diagnostic criteria of glucagonoma syndrome are: 1) Imaging study confirming presence of pancreatic tumor; 2) Elevated glucagon levels (>1000 pg/dL); 3) NME; 4) Personal history of MEN1 [8].

The definitive treatment for the tumor and NME is surgical removal. Although surgery in the presence of metastases cannot be definitive, it can still be recommended to confer a survival and quality of life benefit [9-10]. In patients with contraindications to surgery, chemotherapy or sunitinib should be considered [11]. In the present case, after surgery, the patient gained 2 kg and skin lesions disappeared. Furthermore, the therapy with somatostatin analogues was successful in resolving NME and other symptoms as well as in controlling tumor growth for long-time. Recently, in patients with advanced and progressive NET, *peptide receptor radionuclide therapy* (PRRT) achieved promising results [12]. The effectiveness and safety of therapy with Lu-177 DOTATE was recently evaluated in patients with well differentiated, functional PNETs of grade 1-2. In the study by Zandee et al., eight patients with glucagonoma were included. Partial or complete responses to PRRT were found in 59% of patients, disease control in 78% of patients with improvement of symptoms in 71% and decrease in hormone levels in 80% of patients [13]. To control liver metastases the first choice is surgery, but only if at least 30% of the liver will remain and if there is no evidence of non-resectable extrahepatic metastases. In non-resectable cases, hepatic artery embolization, radiofrequency ablation and cryoablation should be evaluated [14]. In a non-randomized study by Osborne et al., cytoreduction for metastatic NET resulted in improved symptoms and survival when compared with embolic therapy [15]. In selected patients with non-resectable metastatic NET should be considered liver transplantation; Coppa et al. proposed a selection based on the Milan criteria: young patients (less than 50 years) with carcinoids confirmed by histology, with less than 50% of the liver replaced by metastases, with a primary tumor (originating from the gastrointestinal tract) drained by the portal venous system, an absence of extrahepatic disease and stable disease during the pretransplantation period [16-17]. The present case is an example demonstrating the value of a multidisciplinary approach in a patient with a glucagonoma, who achieved good disease control after sequential treatment with somatostatin analogs, primary tumor surgery, PRRT, liver embolization, sunitinib, and lastly chemotherapy with CAPTEM.

Conclusion

NME is a common symptom of glucagonoma syndrome. Its early recognition is crucial in order to improve the prognosis, which varies greatly according to the stage at diagnosis, in terms of both survival and quality of life. In fact, being glucagonoma a rare pathology, skin lesions are often mistakenly treated as a dermatitis thus delaying the correct diagnosis of NME, the hallmark of glucagonoma syndrome. It is a key issue to raise suspicion of NME if skin lesions with the characteristics of NME (erythematous, pruritic, painful, epidermal lesions in areas of pressure and friction) do not improve with treatment especially if they are associated with other frequent nonspecific symptoms of glucagonoma syndrome (DM, weight loss, diarrhea, anemia etc.). In order to achieve an early diagnosis of glucagonoma starting from NME, a multidisciplinary advice is suggested. If a NME suspicion is confirmed, the patient should be addressed to a NET center for diagnosis and treatment.

References

1. Al-Faouri A, Ajarma K, Alghazawi S, Al-Rawabdeh S, Zayadeen A (2016) Glucagonoma and Glucagonoma Syndrome: A Case Report with Review of Recent Advances in Management. Case Rep Surg. 2016: 1484089.
2. Wermers RA, Fatourechi V, Wynne AG, Kvols LK, Lloyd RV (1996) The glucagonoma syndrome. Clinical and pathologic features in 21 patients. Medicine (Baltimore). 75: 53-63.
3. Magi L, Marasco M, Rinzivillo M, Faggiano A, Panzuto F (2023) Management of Functional Pancreatic Neuroendocrine Neoplasms. Curr Treat Options Oncol. 24: 725-741.
4. Wei J, Song X, Liu X, Ji Z, Ranasinha N, et al. (2018) Glucagonoma and Glucagonoma Syndrome: One Center's Experience of Six Cases. J Pancreat Cancer. 4: 11-16.
5. Foss MG, Hashmi MF, Ferrer-Bruker SJ (2023) Necrolytic Migratory Erythema. StatPearls Publishing. Available in online.
6. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, et al. (2008) Long-term allcause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 300: 2754-2764.
7. Pusceddu S, Buzzoni R, Vernieri C, Concas L, Marceglia S, et al. (2016) Metformin with everolimus and octreotide in pancreatic neuroendocrine tumor patients with diabetes. Future Oncol. 12: 1251-1260.
8. Stacpoole PW (1981) The glucagonoma syndrome: clinical features, diagnosis, and treatment. Endocr Rev. 2: 347-361.
9. Norton JA, Harris EJ, Chen Y, Visser BC, Poultsides GA, et al. (2011) Pancreatic endocrine tumors with major vascular abutment, involvement, or encasement and indication for resection. Arch Surg. 146: 724-732.
10. Hofland J, Falconi M, Christ E, Castaño JP, Faggiano A, et al. (2023) European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. J Neuroendocrinol. 35: e13318.
11. Yalcin S, Oyan B, Bayraktar Y (2007) Current medical treatment of pancreatic neuroendocrine tumors. Hepatogastroenterology. 54: 278-284.
12. Bergsma H, van Vliet EI, Teunissen JJ, Kam BL, de Herder WW, et al. (2012) Peptide receptor radionuclide therapy (PRRT) for GEP-NETs. Best Pract Res Clin Gastroenterol. 26: 867-881.
13. Zandee WT, Brabander T, Blažević A, Kam BLR, Teunissen JJM, et al. (2019) Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors. J Clin Endocrinol Metab. 104: 1336-1344.
14. Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A, et al. (2009) Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg. 96: 175-184.
15. Osborne DA, Zervos EE, Strosberg J, Boe BA, Malafa M, et al. (2006) Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol. 13: 572-81.
16. Coppa J, Pulvirenti A, Schiavo M, Romito R, Collini P, et al. (2001) Resection versus transplantation for liver metastases from neuroendocrine tumors. Transplant Proc. 33: 1537-1539.
17. Castro PG, de León AM, Trancón JG, Martínez PA, Alvarez Pérez JA, et al. (2011) Glucagonoma syndrome: a case report. J Med Case Rep. 5: 402.

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