Clinical Case Report

Medicine®

OPEN

Malignant transformation of glucagonoma with SPECT/CT In-111 OctreoScan features

A case report

Giuseppe Corrias, MD[a,b], Natally Horvat, MD[a,c,d], Serena Monti, PhD[e], Olca Basturk, MD[f], Oscar Lin, MD, PhD[f], Luca Saba, MD[b], Lisa Bodei, MD[a], Diane L. Reidy, MD[g], Lorenzo Mannelli, MD, PhD[a,*]

Abstract

Rationale: Glucagonoma is an uncommon disease but it has been associated with a pattern of symptoms defined as glucagonoma syndrome. These symptoms, if promptly recognized, could help to speed up the diagnosing process.

Patient concerns: We report a case of a 68-year-old woman with a pancreatic glucagonoma. Her symptoms at the onset were typical of the glucagonoma syndrome.

Diagnoses: After a significant weight loss, she underwent a computer tomography scan of the abdomen, which showed a hypervascular lesion of the tail of the pancreas and hypervascular lesions of the liver. An ultrasound guided biopsy was performed and pathology was consistent with glucagonoma. Her blood glucagon levels were elevated.

Outcomes: She was treated with chemotherapy and somatostatin analogs. After 4 years, the disease had a malignant transformation, and metastases suddenly started to grow up. She stopped being responsive to treatment and eventually passed away.

Lessons: Due to its rarity, clinical diagnosis is challenging and generally it comes after a long interval since the onset of symptoms. Awareness of physicians and dermatologists of the characteristic necrolytic migratory erythema, and of the other symptoms, often leads to early diagnosis.

Abbreviations: 5FU = 5-fluorouracil, ALT = alanine transaminase, AST = aspartate transaminase, CK 20 = cytokeratin 20, CK AE1/AE3 = cytokeratin AE1/AE3, CT = computed tomography, MEN 1 = multiple endocrine neoplasia type 1, MRI = magnetic resonance imaging, NGS = next-generation sequencing, PNET = pancreatic neuroendocrine tumor, PRRT = with peptide receptor radionuclide therapy, SPECT = single photon emission computed tomography, SRS = somatostatin receptor scintigraphy, SSA = stomato-statin analogs, WHO = World Health Organization.

Keywords: glucagonoma, multidetector computed tomography, neuroendocrine tumors, OctreoScan, somatostatin receptor imaging

1. Introduction

In this article, we report a case of a 68-year-old woman presenting with a glucagonoma syndrome.

She had a recent history of abdominal pain, cutaneous rash, and weight loss. She had a history of diabetes mellitus and hyperlipidemia. Her laboratory exams demonstrated elevation of liver function tests. She underwent abdominal contrast-enhanced computed tomography (CT), which showed multiple hypervascular liver masses with central necrosis and a nodule in the pancreatic tail.[1–3] An ultrasound-guided liver core-biopsy was performed and consistent with well-differentiated neuroendocrine tumor (glucagonoma). Her blood glucagon levels were elevated.[4] Thereafter, the patient underwent SPECT/CT with OctreoScan (^{111}In-pentetreotide), which demonstrated elevated uptake in both pancreatic and liver masses indicating that the lesions express high densities of somatostatin receptors.[5,6] The patient was initially treated with long-acting somatostatin analogs.

2. Case presentation

Written informed consent for this case report was not required, as established by our institutional review board polices. A 68-year-old woman presented with a recent history of abdominal pain,

Editor: Hongming Zhuang.

Authorship: The authors were equally involved in acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, technical, and material support of this study.

Funding: Grant support was provided by MSK Cancer Center Support Grant/ Core Grant P30 CA008748. Work by Giuseppe Corrias was partially supported by two scholarships awarded by ISSNAF Imaging Science Chapter and by European Union's Globusdoc Program.

The authors have no conflicts of interest to disclose.

[a] Department of Radiology, Memorial Sloan Kettering Cancer Center, NY, [b] Department of Radiology, University of Cagliari, Cagliari, Italy, [c] Department of Radiology, Hospital Sírio-Libanês, São Paulo, [d] Department of Radiology, Universidade de São Paulo, São Paulo, SP, Brazil, [e] IRCCS SDN, Naples, Italy, [f] Department of Pathology, [g] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY.

[*] Correspondence: Lorenzo Mannelli, 300 East 66th Street, New York, NY, USA (e-mail: mannellilorenzo@yahoo.it).

Medicine (2017) 96:50(e9252)

Received: 29 August 2017 / Received in final form: 25 October 2017 / Accepted: 21 November 2017

http://dx.doi.org/10.1097/MD.0000000000009252

cutaneous rash, chronic fatigue, and weight loss. She had a past medical history of diabetes mellitus, hyperlipidemia, gastro-esophageal reflux disease, irritable bowel syndrome, and arthritis. In the previous months, she referred some dyspnea on exertion and diarrhea. Her laboratory exams demonstrated elevation of liver function tests: Alkaline Phosphatase 289 (reference range 45–129 Units/L); AST 94 (reference range 10–37 Units/L) ALT 178 (reference range 5–37 Units/L). Her diabetes was uncontrolled for the previous months. On physical examination, she had dry mucous membranes, tachycardia, hepatomegaly and skin erythema localized to the lower abdomen, buttocks, and distal extremities. Given these abnormalities, she underwent a contrast-enhanced computed tomography (CT) of the abdomen which showed multiple hyper-vascular liver masses with central necrosis, measuring up to 14.5 cm (Fig. 1, white arrow) and a 4.0 cm nodule in the pancreatic tail (Fig. 1, dashed white arrow).[1] The liver was enlarged to 26 cm. There was no intrahepatic or extrahepatic dilatation. An ultrasound-guided liver core-biopsy was performed and demonstrated relatively uniform, round tumor cells with stippled chromatin and inconspicuous nucleoli arranged in diffuse sheets or nests, with a low mitotic activity (<1 mitosis/10 high-power fields) (Fig. 2A). Immunohistochemical stains demonstrated that the tumor cells were positive for CK AE1/AE3, CK20, chromogranin, synaptophysin, and glucagon (Fig. 2B). These findings were consistent with metastatic well-differentiated neuroendocrine tumor (glucagonoma). Her plasma glucagon was tested and was highly elevated to 1154 (reference range < 134). Thereafter, the patient underwent SPECT/CT with OctreoScan, which demonstrated uptake in the pancreatic tail lesion consistent with primary neuroendocrine tumor (Fig. 3 white arrow) and extensive octreotide avid masses in the liver corresponding to metastases (Fig. 3 asterisks), indicating that the lesions over-expressed somatostatin receptors.[3] The patient started treatment with dacarbazine, with an excellent clinical response. After 6 cycles, dacarbazine was stopped and she was treated with long-acting somatostatin analogs. Four years after the disease onset symptoms started worsening, with development of confusion, weakness, upper quadrant pain, and constipation. Blood tests showed elevated ammonia, bilirubin, and leukocytosis. A magnetic resonance imaging (MRI) scan showed the increased size of hepatic metastases compared to previous studies (Fig. 4A, T2 weighted image and Fig. 4B arterial subtraction image). Patient management was changed and several lines of treatment

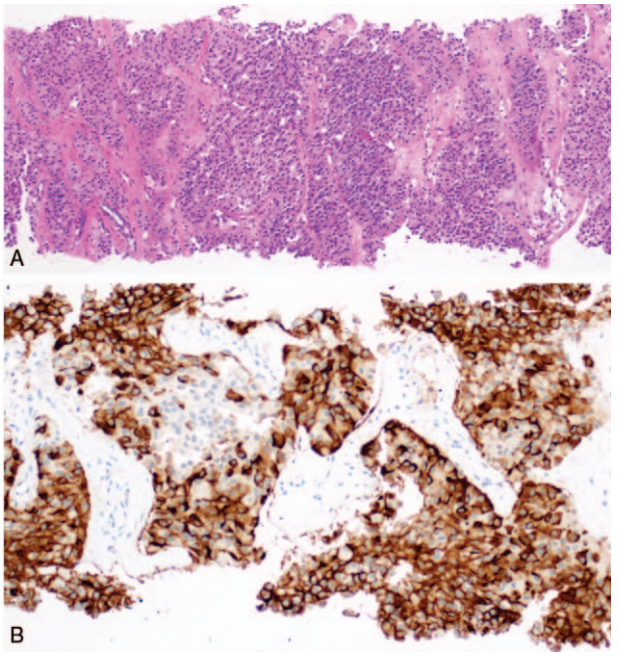

Figure 2. Hematoxylin and eosin (A): Liver core-biopsy, demonstrating relatively uniform, round tumor cells with stippled chromatin and inconspicuous nucleoli arranged in diffuse sheets or nests, with a low mitotic activity (<1 mitosis/10 high-power fields). (B) Immunohistochemical stains for glucagon: immunohistochemical stains demonstrated that the tumor cells were positive for CK AE1/AE3, CK20, chromogranin, synaptophysin (not shown), and glucagon. CK 20 = cytokeratin 20, CK AE1/AE3 = cytokeratin AE1/AE3.

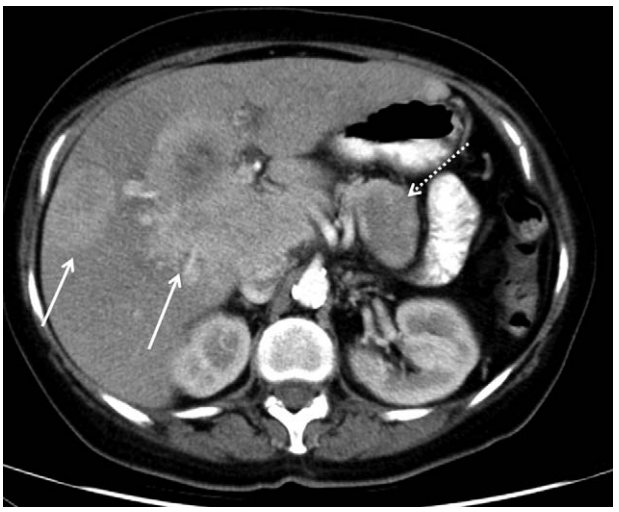

Figure 1. Contrast-enhanced computed tomography (CT) of the abdomen, axial images, post-contrast arterial phase. Multiple hyper-vascular liver masses with central necrosis, measuring up to 14.5 cm (white arrow) and a 4.0 cm nodule in the pancreatic tail (dashed white arrow). Liver enlarged (up to 26 cm). No intrahepatic or extrahepatic dilatation. CT = computed tomography.

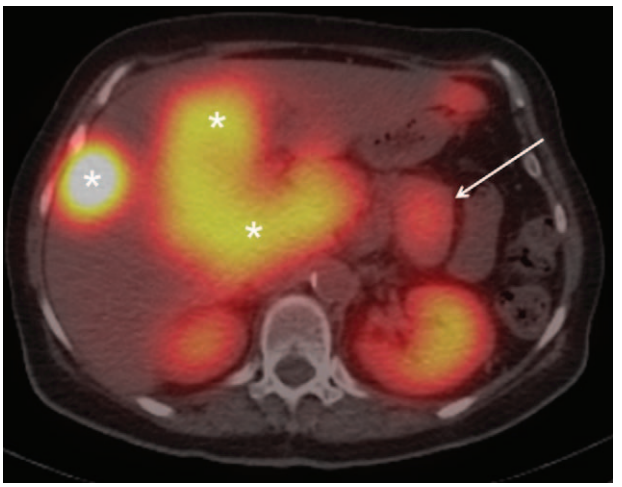

Figure 3. SPECT/CT with OctreoScan. Uptake in the pancreatic tail lesion consistent with primary neuroendocrine tumor (white arrow) and extensive octreotide avid masses in the liver corresponding to metastases (asterisks), indicating that the lesions over-expressed somatostatin receptors. CT = computed tomography, SPECT = Single Photon Emission Computed Tomography.

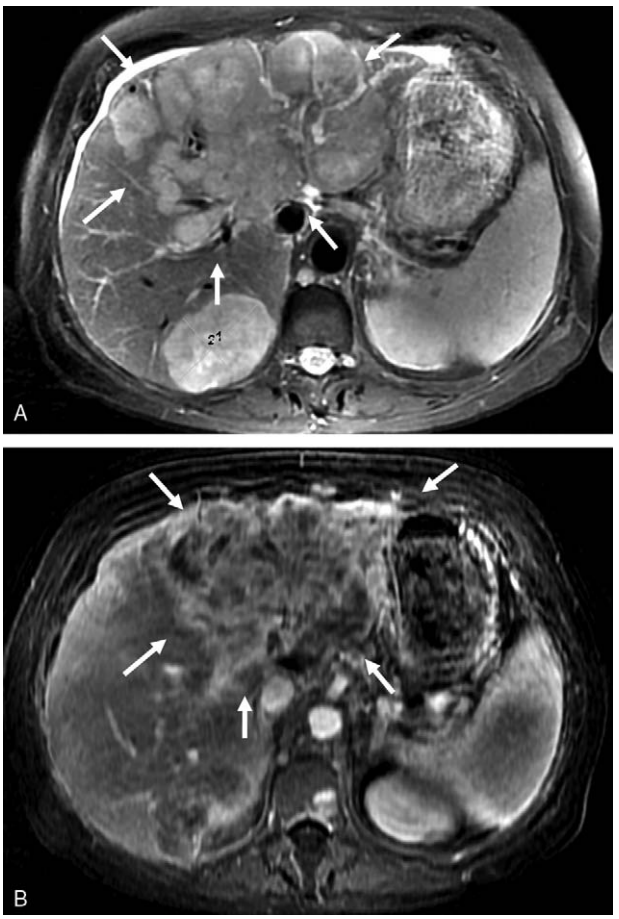

Figure 4. MRI axial T1-weighted post-contrast, arterial phase (A) and axial T1-weighted contrast subtraction (B). Increased size of hepatic metastases compared to previous studies (white arrows). MRI = magnetic resonance imaging.

including hepatic arterial embolization, 5-fluorouracil (5FU), and platinum based treatment were tried. Unfortunately, none of these was successful and the patient passed away in a couple of months. This aggressive "malignant transformation" was predicted by her DNA next-generation sequencing (NGS), which showed mutations in ERBB2, KRAS, NRAS, and TP53.

3. Discussion

The first description of glucagonoma is attributable to Becker et al.[7] Glucagonoma is a rare pancreatic neuroendocrine tumor (PNET) of the alpha cells of the pancreas. As recently defined by World Health Organization (WHO), only functioning tumors can be defined as glucagonomas, differentiating them from nonfunctioning pancreatic alpha-cell tumors.[8,9] Glucagonoma are associated with characteristic symptoms which can help making a prompt diagnosis: weight loss (10–15 kg), necrolytic migratory erythema (a characteristic but not pathognomonic red, blistering rash), diabetes mellitus,[10] anemia, venous thromboembolism, depression, and diarrhea.[4,11,12] This cluster of symptoms it is often referred to as glucagonoma syndrome. The literature reported incidence of glucagonoma is 2.4/100,000,000, even if many studies do not differentiate between functioning and not functioning alpha cell tumors.[2] It affects the 6th decade of life, but the age range is wide, from 15 to 90 years, with no predilection for sex.[13] The etiology is not yet fully understood, genetic factors may play a role. There is a strong association with a familiar history of multiple endocrine neoplasia type 1 (MEN 1).[14] This tumor is usually aggressive, with the cancer spreading and getting worse, but even if metastatic, the overall survival has been reported to be long, with a mean life expectancy reported ranging from 3 to 8 years.[15] Most of the cases reported in literature were already metastatic at the time of the diagnosis, with a long period between the onset of symptoms and the final diagnosis. An early diagnosis would allow for curative resection treatment. For this reason, it is important to highlight the classic symptoms associated with glucagonoma.[11] The imaging role is to localize disease, once clinically suspected.[16,17] Ultrasonography is not specific nor sensitive and has a low negative predictive value.[18] The most frequent anatomical site is distal part of the pancreas (90% body and tail) making the US identification even more difficult.[9,19] Tumor presence and localization is invariably documented by CT scan.[19] Secreting islet tumors and their metastasis are most commonly hyper-vascular with a definite enhancement during the contrast arterial phase.[20] Confirmation and staging of diseases can be performed in all patients by SPECT/CT OctreoScan with ^{111}In-pentreotide (Somatostatin Receptor Scintigraphy - SRS),[21–24] and more recently with ^{68}Ga-DOTATATE PET\CT.[6] Another useful purpose of performing SRS is the evaluation of the functional state of the tumor and of the secondary localization, thus providing suitability for therapy with peptide receptor radionuclide therapy (PRRT).[22,25]

Treatment may vary on stage of disease. If possible surgical resection and debulking procedures are performed.[26] Control of symptoms is almost always possible at the early stages of disease with stomato-statin analogs (SSA).[15] PRRT with ^{177}Lu DOTATATE has been proposed as a first-line therapy in patients with glucagonoma and secreting metastasis.[5,27,28] However, since the number of people affected by glucagonoma is too small, it has not yet been possible to draw results on the actual benefit of this therapy, especially in terms of long-time survival.[29]

References

[1] Belousova E, Karmazanovsky G, Kriger A, et al. Contrast-enhanced MDCT in patients with pancreatic neuroendocrine tumours: correlation with histological findings and diagnostic performance in differentiation between tumour grades. Clinical Radiol 2017;72:150–8.
[2] Lévy-Bohbot N, Merle C, Goudet P, et al. Prevalence, characteristics and prognosis of MEN 1-associated glucagonomas, VIPomas, and somatostatinomas: study from the GTE (Groupe des Tumeurs Endocrines) registry. Gastroentérol Clin Biol 2004;28:1075–81.
[3] Bhosale PR, Menias CO, Balachandran A, et al. Vascular pancreatic lesions: spectrum of imaging findings of malignant masses and mimics with pathologic correlation. Abdom Imaging 2013;38:802–17.
[4] Leichter SB. Clinical and metabolic aspects of glucagonoma. Medicine 1980;59:100–13.
[5] Makis W, McCann K, Riauka TA, et al. Glucagonoma pancreatic neuroendocrine tumor treated with 177Lu DOTATATE induction and maintenance peptide receptor radionuclide therapy. Clin Nucl Med 2015;40:877–9.
[6] Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with 68Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F-DOPA. Eur J Nucl Med Mol Imaging 2017;44:1588–601.
[7] Becker SW, Kahn D, Rothman S. Cutaneous manifestations of internal malignant tumors. Arch Dermatol Syphilol 1942;45:1069–80.
[8] DeLellis RA. Pathology and Genetics of Tumours of Endocrine Organs: IARC. 2004;World Health Organization, New York:320.
[9] Wermers RA, Fatourechi V, Wynne AG, et al. The glucagonoma syndrome clinical and pathologic features in 21 patients. Medicine 1996;75:53–63.

[10] Mannelli L, Yeh MM, Wang CL. A pregnant patient with hypoglycemia. Gastroenterology 2012;143:e3–4.
[11] Al-Faouri A, Ajarma K, Alghazawi S, et al. Glucagonoma and glucagonoma syndrome: a case report with review of recent advances in management. Case Rep Surg 2016;2016:1484089.
[12] Yao JC, Eisner MP, Leary C, et al. Population-based study of islet cell carcinoma. Ann Surg Oncol 2007;14:3492–500.
[13] Castro PG, de León AM, Trancón JG, et al. Glucagonoma syndrome: a case report. J Med Case Rep 2011;5:402.
[14] Johnson DS, Coel MN, Bornemann M. Current imaging and possible therapeutic management of glucagonoma tumors: a case report. Clin Nucl Med 2000;25:120.
[15] John A, Schwartz R. Glucagonoma syndrome: a review and update on treatment. J Eur Acad Dermatol Venereol 2016;30:2016–22.
[16] Lalwani N, Mannelli L, Ganeshan DM, et al. Uncommon pancreatic tumors and pseudotumors. Abdom Imaging 2015;40:167–80.
[17] Lewis RB, Lattin MJr, Grant E, et al. Pancreatic endocrine tumors: radiologic-clinicopathologic correlation. Radiographics 2010;30: 1445–64.
[18] Lv W-F, Han J-K, Liu X, et al. Imaging features of glucagonoma syndrome: a case report and review of the literature. Oncol Lett 2015;9:1579–82.
[19] Eldor R, Glaser B, Fraenkel M, et al. Glucagonoma and the glucagonoma syndrome—cumulative experience with an elusive endocrine tumour. Clin Endocrinol 2011;74:593–8.
[20] ElGuindy YM, Javadi S, Menias CO, et al. Imaging of secretory tumors of the gastrointestinal tract. Abdom Radiol 2017;42:1113–31.
[21] Fuccio C, Spinapolice EG, Chondrogiannis S, et al. Evolving role of SPECT/CT in neuroendocrine tumors management: staging, treatment response, and follow-up. Clin Nucl Med 2013;38:e384–9.
[22] Ito T, Jensen RT. Molecular imaging in neuroendocrine tumors: recent advances, controversies, unresolved issues, and roles in management. Curr Opin Endocrinol Diabetes Obes 2017;24:15–24.
[23] Wong KK, Wynn EA, Myles J, et al. Comparison of single time-point [111-In] pentetreotide SPECT/CT with dual time-point imaging of neuroendocrine tumors. Clin Nucl Med 2011;36:25–31.
[24] Patel N, Chiang P, Krasnow AZ, et al. Skeletal metastasis of malignant glucagonoma mimicking avascular necrosis of the hip: scintigraphic and MRI correlation. Clin Nucl Med 1993;18:70–2.
[25] Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40:800–16.
[26] Chu QD, Al-kasspooles MF, Smith JL, et al. Is glucagonoma of the pancreas a curable disease? Int J Pancreatol 2001;29:155–62.
[27] Sansovini M, Severi S, Ianniello A, et al. Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with 177Lu-D OTATATE. Eur J Nucl Med Mol Imaging 2017;44:490–9.
[28] Severi S, Nanni O, Bodei L, et al. Role of 18FDG PET/CT in patients treated with 177Lu-DOTATATE for advanced differentiated neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40:881–8.
[29] Kwekkeboom DJ, Kam BL, Van Essen M, et al. Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Rel Cancer 2010;17:R53–73.