Glucagonoma Syndrome: A Rare Paraneoplastic Disorder due to Neuroendocrine Tumor of the Pancreas

Muhammed Aasim Yusuf[1], Shafqat Mehmood[1], Jhanzeb Iftikhar[2], Muhammad Saqib[1], Muhammad Zeeshan Siddique[1] and Wania Imtiaz[1]

[1]*Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan*
[2]*Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan*

ABSTRACT

Glucagonoma syndrome is an extremely rare paraneoplastic disorder. The key presenting feature is a rash (necrolytic migratory erythema) which can easily be misdiagnosed as a primary skin disorder. Moreover, 50 to 80 % of patients already have metastatic disease at diagnosis. We report a case of a 38-year female presenting with epigastric pain and a skin rash all over the body. Workup revealed a neuroendocrine tumor (NET) of the pancreas, for which she underwent resection, resulting in a complete cure. A follow-up MRI after 8 months showed a hyperintense and arterially enhancing nodular liver lesion which did not show any uptake on the octreotide scan. However, a subsequent biopsy revealed a recurrence of the tumor. This was a unique finding in our case where a highly sensitive octreotide scan failed to identify metastasis, emphasising the importance of biopsy in such cases.

Key Words: *Glucagonoma, Necrolytic migratory erythema, Alpha-cell adenom.*

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INTRODUCTION

Glucagonomas are rare glucagon secreting neuroendocrine tumors (NETs), originating from alpha cells of the pancreas and have an annual incidence of 0.01 to 0.1 new cases per 100,000 population.[1] Majority of patients have metastatic disease at presentation. The glucagonoma syndrome is the paraneoplastic manifestation with various clinical features and elevated glucagon levels in the setting of solitary or multi-focal pancreatic NET. The clinical presentation includes a characteristic skin rash, called necrolytic migratory erythema (NME) in 70% of cases.[2] Other clinical features include diabetes mellitus (DM), anemia, weight loss, glossitis, cheilitis, steatorrhea, and diarrhea. The clinical course can be complicated by venous thrombosis, pulmonary embolism (30 to 50%), and neuropsychiatric disturbances, which include depression, psychosis, agitation, dementia, paranoid delusions, ataxia, hyperreflexia, and optic atrophy.[2,3] There is a high risk of recurrence, therefore, follow-up is necessary.

Correspondence to: Dr. Wania Imtiaz, Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan
E-mail: yesravian@hotmail.com

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The aim of reporting this case is to emphasise the importance of early diagnosis where curative resection is possible and obtaining a tissue diagnosis of any suspected lesion, on imaging.

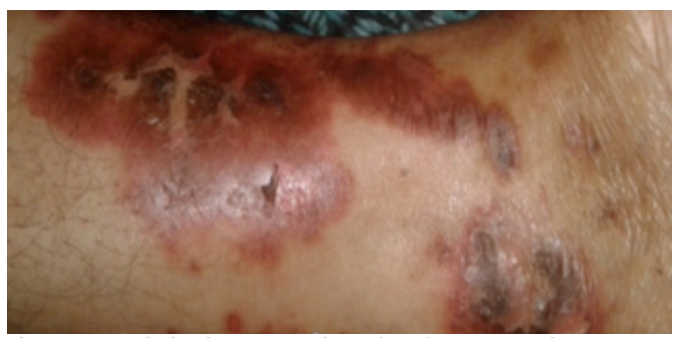

Figure 1: Necrolytic migratory erythema (NME) at presentation

CASE REPORT

A 38-year female was referred to a gastroenterology clinic for evaluation of epigastric pain for one and a half years. This was associated with a weight loss of 5 kg, oral ulcers, and excoriating skin rash with itching all over the body for the last two and half months. Before presenting to us, she was treated for eczema by a dermatologist with minimal benefit. Her past medical history revealed that she was diagnosed with diabetes mellitus eight months ago and was started on insulin. Family history was unremarkable. Physical examination showed the rash extending from below the neck to the feet. It appeared

erythematous and pigmented with a few ruptured blisters along with crusting (Figure 1). There was a firm and tender epigastric mass palpable on abdominal examination. Laboratory investigations showed hemoglobin of 11 g/dl, random blood sugar of 250 mg/dl, and cancer antigen (CA)-19.9 levels of 10.7 U/ml. The facility to check glucagon levels was not available. Computed Tomography (CT) abdomen showed a large arterially enhancing pancreatic body tumor of 10 cm, sparing its head. This was abutting the inferior surface of the stomach, portal vein, and superior mesenteric vein. An octreotide scan was performed, which showed intense uptake within the pancreatic body tumor and regional lymph nodes and no metastasis. An endoscopic ultrasound (EUS) for staging as well as for fine-needle aspiration (EUS-FNA) was done. This showed a T2N0 multi-lobulated pancreatic tumor. The FNA cytology was consistent with neuroendocrine tumor (NET), WHO grade-II (Chromogranin: Positive in tumor cells; Ki-67: 4%). The case was discussed in the multidisciplinary team (MDT) meeting. A presumptive diagnosis of glucagonoma syndrome was suggested, based upon clinical features, radiological and cytopathological findings. MDT recommended surgical resection. Multifocal pancreatic NET was found during operation, involving the right hepatic artery, left gastric artery, and short gastric vessels. She underwent total pancreatectomy, subtotal gastrectomy, and splenectomy. The histopathology of the surgical specimen confirmed the diagnosis of NET. The spleen and distal stomach were uninvolved by the tumor. There was a significant improvement in her skin lesions on 5th post-operative day. Four weeks after surgery, her rash was completely healed with only residual pigmentation. Our patient remained in remission for 8 months, after which a follow-up multiparametric MRI liver showed a suspicious liver lesion and abdominal nodes. Octreotide scan did not show any uptake in the liver lesion. However, a trucut biopsy of the liver lesion showed metastatic NET, WHO grade-III (Immunostaining positive for synaptophysin and Cam 5.2; Ki-67: 28%). The case was discussed in the MDT and she was given long-acting octreotide therapy; however, follow-up scans showed disease progression, so she was planned for four cycles of palliative chemotherapy (Cisplatin/Etoposide), followed by reassessment. Unfortunately, after two cycles of chemotherapy, the patient died of sepsis.

DISCUSSION

Becker first described a patient with typical skin lesions and pancreatic tumors in 1942. Twenty years later, glucagonoma syndrome was described by Mc Gavran.[4,5] The clinical presentation is variable. In our patient, the presentation was typical with necrolytic rash, abdominal pain, weight loss, and new-onset diabetes. However, the rash was initially treated as eczema and the underlying diagnosis was delayed for a few months. There were no thromboembolic or neuropsychiatric complications observed in this patient. The laboratory investigations in this patient, revealing mild anaemia and hyperglycemia, were consistent with the literature; however, glucagon levels were not available.[2,3] The majority of glucagonomas occur sporadically (80%), as in the present case; however, they can be associated with MEN-I syndrome.[6] Moreover, they are almost always located in the pancreas, either as a single or multiple lesions. However, a case of primary hepatic glucagonoma has also been reported in the literature, diagnosed on autopsy.[7] Contrast-enhanced CT is usually the initial imaging modality of choice. It has a sensitivity of more than 80% for pancreatic NETs.[8] A sequential approach of CT followed by EUS increases sensitivity from 84 % to 91% in a study of 56 patients.[8] In this patient, CT was used to diagnose the pancreatic tumor, while subsequent EUS-FNAC with immunohistochemistry helped to stage it and confirmed the diagnosis of NET. Due to the non-availability of glucagon levels, the presumed diagnosis of glucagonoma was made clinically.

If diagnosed early, the most effective treatment is surgery. Distal pancreatectomy and pancreaticoduodenectomy are often chosen depending upon the location of the tumor.[9] This patient underwent total pancreatectomy, subtotal gastrectomy, and splenectomy.

There was a significant improvement in her skin lesions following surgery, which confirmed our diagnosis of glucagonoma. After eight months of surgery, MRI in our patient showed a suspicious liver lesion and enlarged abdominal nodes; however, the octreotide scan did not show uptake in the liver. Recurrence of NET was found on a biopsy of the liver lesion. Thus, the octreotide scan, which is considered highly sensitive (up to 90 %) to identify the primary disease as well as metastasis, may miss the diagnosis, and therefore, tissue diagnosis should be considered, whenever a new lesion is detected, particularly in the liver.[10]

The clinicians should have a high index of suspicion for this disease when the presentation is with characteristic skin rash, as curative resection is possible at an early stage. Moreover, obtaining a tissue diagnosis of any suspected lesion, found on imaging during follow-up is of paramount importance.

PATIENT'S CONSENT:

A waiver for consent was granted by the institutional review board (EX-05-08-19-08).

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

SM: Conceived the concept.
WI, MZS, MS, JI: Reviewed literature and co-wrote the report.
SM, MAY: Reviewed, critically analysed, corrected and approved the final document.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, *et al*. *Neuroendocrinol* 2012; **95(2)**:98-119. doi: 10.1159/000335591.
2. Eldor R, Glaser B, Fraenkel M, Doviner V, Salmon A, Gross

DJ. Glucagonoma and the glucagonoma syndrome - cumulative experience with an elusive endocrine tumor. *Clin Endocrinol (Oxf)* 2011; **74(5)**:593-8. doi: 10.1111/j.1365-2265.2011.03967.x.

3. Vinik A, Pacak K, Feliberti E, Perry RR. Endotext De Groot LJ. Glucagonoma syndrome. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000.
4. Eriksson B, Annibale B, Bajetta E, Mitry E, Pavel M, Platania M, *et al*. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Chemotherapy in patients with neuroendocrine tumors. *Neuroendocrinol* 2009; **90(2)**:214-9. doi: 10.1159/000225950.
5. McGavran MH, Unger RH, Recant L, Polk HC, Kilo C, Levin ME. A glucagon-secreting alpha-cell carcinoma of the pancreas. *N Engl J Med* 1966; **274(25)**:1408-13. doi: 10.1056/NEJM196606232742503.
6. Ro C, Chai W, Yu VE, Yu R. Pancreatic neuroendocrine tumors: Biology, diagnosis, and treatment. *Chin J Cancer* 2013; **32(6)**:312-24. doi: 10.5732/cjc.012.10295.
7. Poggi G, Villani L, Bernardo G. Multimodality treatment of unresectable hepatic metastases from pancreatic glucagonoma. *Rare Tumors* 2009; **1(1)**:e6. doi: 10.4081/rt.2009.e6.
8. Khashab MA, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, *et al*. EUS is still superior to multidetector computerised tomography for detection of pancreatic neuroendocrine tumors. *Gastrointest Endosc* 2011; **73(4)**:691. doi: 10.1016/j.gie.2010.08.030
9. Rodriguez G, Vargas E, Abaunza C, Caceres S. Necrolytic migratory erythema and pancreatic glucagonoma. *Biomedica* 2016; **36(2)**:176-81. doi: 10.7705/biomedica.v36i3.2723.
10. Tamm EP, Bhosale P, Lee JH, Rohren EM. State-of-the-art imaging of pancreatic neuroendocrine tumors. *Surg Oncol Clin N Am* 2016; **25(2)**:375-400. doi: 10.1016/j.soc.2015.11.007.