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Case Reports

Refractory Hyperglycemia in Metastatic Adenocarcinoma: A Case of Suspected Paraneoplastic Hyperglucagonemia

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Abstract

Paraneoplastic syndromes are uncommon manifestations of malignancy that can produce significant metabolic derangements. Paraneoplastic hyperglucagonemia due to non-pancreatic malignancy is particularly rare and may present with refractory hyperglycemia. An 84-year-old female admitted following a fall from standing height was found to have a pathological fracture of cervical spine. Imaging demonstrated a destructive mass involving C5 vertebral body with widespread metastatic disease involving the lungs and liver. Biopsy of the cervical lesion revealed metastatic adenocarcinoma of suspected pancreaticobiliary, upper gastrointestinal, or pulmonary origin. Throughout her hospital course, the patient developed persistent hyperglycemia despite escalating insulin therapy and required intensive insulin management. Further evaluation demonstrated markedly elevated serum glucagon levels of 1,116 pg./mL, while adrenocorticotropic hormone (ACTH) levels remained within normal range. Following surgical debulking of the cervical lesion, the patient's insulin requirements substantially decreased, with subsequent improvement in glycemic control. The combination of refractory hyperglycemia, markedly elevated glucagon levels, widespread metastatic disease, and decreased insulin requirements following tumor debulking raised suspicion for a paraneoplastic endocrine process involving glucagon excess. However, tumor immunohistochemical staining for glucagon was not performed; serial glucagon measurements were unavailable, and other uncommon causes of insulin resistance, including anti-insulin receptor antibodies, were not evaluated. Therefore, ectopic glucagon secretion could not be definitively established. This case highlights the importance of considering paraneoplastic endocrine syndromes in patients with malignancy and otherwise unexplained worsening hyperglycemia despite insulin therapy.

BACKGROUND

Paraneoplastic syndromes are clinical manifestations caused by malignancy that occur independently of direct tumor invasion or metastatic burden. These syndromes are uncommon and are estimated to occur in approximately 8% of patients with cancer.[1] They may involve endocrine, neurologic, dermatologic, hematologic, or rheumatologic systems. Endocrine paraneoplastic syndromes are most commonly associated with ectopic production of adrenocorticotropic hormone (ACTH), parathyroid hormone related protein (PTHrP), and antidiuretic hormone (ADH).[1] However, the ectopic production of less commonly secreted hormones can be diagnostically challenging. We present a case of suspected paraneoplastic hyperglucagonemia in a patient with metastatic adenocarcinoma who developed refractory hyperglycemia during hospitalization that improved following surgical debulking.

CASE PRESENTATION

An 84-year-old woman residing in an extended care facility (ECF) presented to the emergency department following a mechanical fall from standing height after tripping over her feet. Her past medical history was significant for diabetes mellitus (DM), chronic kidney disease (CKD), liver cirrhosis secondary to non-alcoholic steatohepatitis (NASH) complicated by esophageal varices, inferior vena cava (IVC) filter placement, permanent pacemaker im-

plantation for bradycardia. On presentation, the patient reported severe right leg pain, progressive right- upper extremity weakness and right shoulder pain that had developed over the preceding four weeks. Physical examination demonstrated deformity and tenderness of the right lower extremity with decreased strength in the right upper extremity. Vital signs were stable. Initial laboratory evaluation was notable for a glucose of 250 mg/dL, creatinine of 2.0 mg/dL, lipase of 928 U/L, and pro-BNP of 1,100 pg/mL. Imaging demonstrated a severely comminuted displaced right femoral fracture. Computed tomography (CT) of the cervical spine additionally revealed a pathologic fracture involving the C5 vertebral body with near-complete destruction of the vertebra. Neurosurgery was consulted because of concern for malignant spinal involvement and progressive neurologic symptoms.

Magnetic resonance imaging (MRI) of the cervical spine revealed a mass replacing the entire C5 vertebral body, invading the C5-6 neural foramen, concerning for a malignant mass involving C5 vertebral body. The biopsy of the mass revealed metastatic adenocarcinoma of suspected upper gastrointestinal, pancreaticobiliary, or pulmonary origin. Further imaging demonstrated widespread disease, including scattered pulmonary nodules, consistent with metastatic disease, a hypodense region within the cirrhotic liver, and a calcific cystic mass in the right lower quadrant, concerning for malignancy versus an appendiceal mucocele. MRI of the abdomen additionally revealed a hyperintense mass encasing the intrahepatic IVC with retroperitoneal adenopathy, raising concern for hepatic malignancy. Notably, alpha-fetoprotein (AFP) was normal at 2.4.

The patient underwent an open reduction internal fixation of the right femoral fracture. Prior to admission, her diabetes was managed with 100 units of insulin glargine daily, with an additional 0-8 units of sliding-scale insulin per day. Her weight at that time was 66.2 kg, corresponding to approximately 1.5 units/kg/day of basal insulin. Her recent hemoglobin A1c was 6.8%, suggesting relatively adequate glycemic control before hospitalization. During hospitalization, blood glucose levels progressively worsened despite escalating insulin therapy.

The patient initially required an intravenous insulin infusion in the intensive care unit and was later transitioned to subcutaneous insulin therapy with insulin glargine 40 units twice daily and correctional insulin lispro. Despite escalation to 50 units of insulin glargine twice daily, glucose levels remained persistently elevated in the 300–400 mg/dL range. Given the refractory nature of her hyperglycemia, additional endocrine evaluation was pursued. A serum ACTH level was obtained and subsequently found to be within normal range. Serum glucagon was markedly elevated at 1,116 pg./mL (reference range 50-150 pg./mL). The specimen was diluted, and the result was confirmed. The glucagon assay was performed by ARUP Laboratories using quantitative radioimmunoassay (RIA). The glucagon result became available only after the patient had been discharged and after surgical removal of cervical lesion. Therefore, serial glucagon measurements could not be obtained to assess changes in glucagon concentration following surgery. The patient did not exhibit several classic clinical manifestations of glucagonoma syndrome, including necrolytic migratory erythema, diarrhea, significant weight loss, or venous thrombosis. No clinical evidence of Cushing syndrome was identified. Biopsy of the cervical lesion demonstrated metastatic adenocarcinoma of suspected upper gastrointestinal, pancreaticobiliary, or pulmonary origin. Immunohistochemical staining specific to glucagon was not performed on the tissue specimen.

The patient subsequently underwent surgical debulking of the cervical lesion. Following the intervention, insulin requirements decreased significantly, and glycemic control improved with insulin glargine reduced to 20 units daily with sliding-scale insulin coverage. Although postoperative glucagon measurements were unavailable, the temporal association between tumor debulking and improvement in insulin requirements raised suspicion for a tumor-mediated endocrine process. The patient was ultimately discharged with outpatient oncology, gastroenterology, and endocrinology follow-up as well as plans for positron emission tomography/computed tomography for further staging and evaluation.

DISCUSSION

Glucagon is a peptide hormone primarily secreted by pancreatic islet alpha cells and, to a lesser extent, intestinal enteroendocrine L cells.[2] Its principal metabolic function is to increase blood glucose by promoting hepatic glucose production, thereby acting in opposition to insulin. Glucagon also contributes to satiety, lipolysis, amino acid metabolism, and regulation of heart contractility.[2] Hyperglucagonemia is a rare metabolic disorder characterized by excessive circulating glucagon concentration. It classically presents with a triad of diabetes mellitus, necrolytic migratory erythema, and weight loss. It is most commonly associated with glucagonoma, a pancreatic neuroendocrine tumor (pNET). Glucagonomas are typically slow-growing tumors and are frequently metastatic at the time of diagnosis, most commonly to the liver.[3] Evaluation includes measurement of serum glucose, serum glucagon, amino acids, zinc levels, multiple endocrine neoplasia type 1 (MEN1) syndrome panel and cross-sectional imaging.[3] Diagnosis can be supported by clinical findings, laboratory abnormalities, imaging, and tumor histopathology. Immunohistochemical staining for glucagon, synaptophysin, and chromogranin A may assist in confirming a pancreatic neuroendocrine neoplasm.[4] However, other pNETs, including insulinomas, may demonstrate multihormonal secretion and can also stain positively for glucagon.[4] Diagnosis can be further

complicated by pre-existing diabetes and stress-related hyperglycemia. Management of glucagonoma may include surgical resection, as well as octreotide and supportive therapy, including insulin.[5] In contrast to glucagonoma, ectopic glucagon production from a non-neuroendocrine source is uncommon with only a few cases reported in literature.

This case describes suspected paraneoplastic hyperglucagonemia in a patient with metastatic adenocarcinoma who developed refractory hyperglycemia requiring escalating insulin therapy. Although hyperglycemia is common among hospitalized and critically ill patients, the degree and persistence of hyperglycemia in this patient prompted evaluation for an alternative endocrine process. Stress hyperglycemia is a well-recognized physiologic response to trauma, surgery, and critical illness. Activation of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system leads to increased secretion of catecholamines, cortisol, glucagon, and inflammatory cytokines, resulting in increased hepatic glucose production and peripheral insulin resistance.[6] In patients with underlying diabetes mellitus, this response may become exaggerated. However, in our patient, hyperglycemia persisted despite substantial escalation of insulin therapy, prompting further investigation.

Glucagonoma is a rare neuroendocrine tumor arising from pancreatic alpha cells.[7] Although glucagon excess is most commonly associated with pancreatic neuroendocrine tumors, ectopic glucagon secretion can rarely occur in non-pancreatic malignancy, leading to a paraneoplastic hyperglycemic state.[8] Ectopic hormone secretion is a recognized but uncommon feature of malignancy and may significantly complicate inpatient management.[9] Most reported cases of nonpancreatic ectopic glucagon secretion in the literature are associated with renal cell carcinoma (RCC). In one reported case, a patient with renal cell carcinoma and diabetes mellitus experienced normalization of glucose levels following nephrectomy, and tumor tissue stained positive for glucagon on immunohistochemistry.[8] This suggests that some non-pancreatic malignancies may acquire neuroendocrine secretory properties capable of producing clinically significant hyperglucagonemia. Our patient's presentation shared some features with these reported cases, particularly the marked elevation in measured serum glucagon and the reduction in insulin requirements following surgical debulking

The patient's pre-admission insulin requirements also provide important context. She was receiving insulin glargine 100 units with 0-8 additional sliding-scale insulin at a weight of 66.2 kg, corresponding to approximately 1.5-1.6 units/kg/day. During hospitalization, insulin glargine was increased to 50 units twice daily, with additional correctional insulin. Although this represented a substantial increase from her pre-admission regimen, the available documentation does not establish that her total daily insulin requirement consistently exceeded the commonly cited threshold of 2-3 units/kg/day used to define severe insulin resistance. Therefore, we describe her condition as refractory hyperglycemia rather than definitively classifying it as severe insulin resistance.

This case has several important limitations. Definitive ectopic glucagon production by the tumor could not be established because glucagon immunohistochemical staining was not performed on the tumor tissue. The serum glucagon assay was performed using quantitative RIA, but the available information does not establish that the assay specifically measured only biologically active mature glucagon. Serial postoperative glucagon measurements were not obtained because the initial result became available after discharge and after tumor removal. In addition, anti-insulin receptor antibody testing was not performed, and therefore autoimmune insulin resistance could not be excluded. Furthermore, chronic kidney disease, physiologic stress associated with trauma and surgery, and advanced malignancy may have contributed to the patient's hyperglycemia and elevated glucagon concentration. Although insulin requirements decreased following tumor debulking, this temporal association does not establish causality. Taken together, these limitations support describing the patient's presentation as suspected paraneoplastic hyperglucagonemia rather than definitively confirmed ectopic glucagon secretion. Despite the limitations, the combination of a markedly elevated glucagon concentration, persistent hyperglycemia requiring substantially increased insulin therapy, extensive metastatic malignancy and improvement insulin requirements following tumor debulking raises the possibility of a paraneoplastic endocrine process in patients with malignancy and unexplained or refractory metabolic abnormalities.

CONCLUSION

This case highlights the importance of early consideration of paraneoplastic endocrine syndromes in patients with malignancy and unexplained refractory hyperglycemia. Markedly elevated glucagon levels in the setting of increasing insulin requirements may raise suspicion for paraneoplastic hyperglucagonemia. The temporal improvement in insulin requirements following tumor debulking raises the possibility that a tumor-mediated endocrine process contributed to the patient's refractory hyperglycemia. When hyperglycemia is disproportionate to the expected response to acute illness and requires escalating insulin therapy, evaluation for endocrine drivers may be appropriate. Early recognition may facilitate more targeted diagnostic evaluation and management.

Disclosures/Conflicts of interest

The authors declare no conflicts of interest related to this manuscript.

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