Grand Rounds

Hypoglycemia in Renal Cell Carcinoma: A Rare Paraneoplastic Syndrome

Nicole DiIenno, Esther Han, Conrad Maitland, and Velji Kansara

CASE PRESENTATION

A 65-year-old male adult foster care patient presented to the emergency room with altered mental status and respiratory depression which required intubation. The patient was also found to be hypoglycemic and hypertensive. He was admitted to the medical intensive care unit where a chronic type B aortic dissection and an exophytic superior pole right renal mass measuring 4.5×5.5 cm were discovered on computed tomography scan (Fig. 1). He continued experiencing recurrent episodes of hypoglycemia during his admission and was placed on double portion meals and intravenous glucose with dextrose 10% (D10) in water. Following a hyponatremic episode, the patient was switched to dextrose 5% in normal saline (D5NS) with dextrose 50% (D50) and glucagon provided as needed for persistent hypoglycemia, all of which hindered his discharge. The work-up completed by his primary team concluded that the patient's hypoglycemia was likely due to a paraneoplastic syndrome due to the right renal mass. Biopsy of the renal mass showed low-grade clear cell papillary type renal cell carcinoma (RCC). Urology was subsequently consulted for possible right radical nephrectomy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for new onset hypoglycemia is broad. The most common cause of hypoglycemia in the nondiabetic adult is drug induced. Sepsis, organ failure, gastric bypass, and alcoholism, however, are also common etiologies. Less common etiologies include endogenous hyperinsulinemia (insulinoma, noninsulinoma pancreatogenous hypoglycemia, or autoimmune hypoglycemia) and hormonal deficiencies; these should still be ruled out in work-up. Finally, nonislet cell tumors, particularly those of mesenchymal origin, can be responsible for paraneoplastic hypoglycemia and should be considered in those with hypoglycemia and a known or newly diagnosed mass. In the case of our patient, a newly discovered renal mass accompanied by hypoglycemia increased our suspicion of nonislet cell tumor induced hypoglycemia.

DIAGNOSTIC ASSESSMENT

In addition to obtaining the computed tomography as mentioned, the patient's primary medical team tracked the trend of glucose, blood urea nitrogen (BUN), creatinine, and aldosterone until surgery on February 25, 2017. Glucose levels ranged between 60 and 148 while on double portioned meals and supplemental dextrose. BUN, creatinine, C-peptide, aldosterone, thyroid stimulating hormone (TSH), and cortisol were within normal limits. Imaging identified a renal mass and did not demonstrate an insulinoma or other masses. In the absence of sepsis, organ failure, exogenous drugs, and other more common etiologies, further laboratory testing was deferred and surgical intervention was expedited.

MANAGEMENT AND OUTCOMES

Once cleared by vascular and cardiology, the patient underwent right radical nephrectomy. During the procedure, the patient was found to have persistently elevated systolic blood pressure (180-190 mmHg) and his blood glucose level ranged between 90-160 mg/dL while being maintained on continuous dextrose drip. Vascular surgery was on standby due to the patient's known aortic dissection, but the nephrectomy was completed without complications. The patient was sent to the surgical intensive care unit (SICU) postoperatively for closer monitoring of his blood glucose level.

In the SICU, a nicardipine drip was started with a goal systolic blood pressure of < 140 mmHg for persistently elevated blood pressures, especially with his history of chronic aortic dissection. The dextrose drip was discontinued and blood glucose levels held steady at 140-160 mg/dL. He was eventually discharged from the SICU. His hypoglycemic episodes completely resolved following the procedure, and he remained stable from a blood

Figure 1. Computed tomography scan of chest, abdomen, and pelvis in axial (**A**) and coronal (**B**) views demonstrating renal mass and chronic aortic dissection.

glucose standpoint for discharge. The final pathology report showed pT1bNx clear cell papillary RCC, Fuhrman nuclear grade 2. Portions of the specimen contained papillary, tubular, and cystic architecture, and the cells demonstrated a low nuclear grade.

DISCUSSION

Written by Dr. Velji Kansara

Paraneoplastic syndromes are defined as clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease. RCC induced paraneoplastic syndromes have been reported to occur in 10%-40% of patients, while the classic triad of flank pain, hematuria, and palpable mass is described in only 15% of patients.[1] Some of the more commonly publicized paraneoplastic syndromes seen in RCC include hypercalcemia, ectopic production of parathyroid hormone-related protein or erythropoietin, anemia, fever, cachexia, amyloidosis, and hepatic dysfunction.[2] Hypoglycemia, however, is rarely listed in the literature as a possible paraneoplastic syndrome in RCC, and is more commonly reported to occur in relation to other neoplastic processes.

Among the many etiologies of discrete neoplasms that can cause hypoglycemia, insulinomas of the pancreatic islet cells are the most recognized. Insulinomas comprise 1%-2% of pancreatic neoplasms and have a reported incidence of 1-4 new cases per 1 million people.[3] Hypoglycemia as a result of a discrete tumor that originates outside of islet cells is referred to as nonislet cell tumor hypoglycemia (NICTH).[4] The incidence of NICTH is only 25% as common as an insulinoma, though its true incidence is likely underestimated.[5] While the pathophysiology of NICTH was historically attributed to glucose utilization by the tumor itself, as well as malnutrition associated with advanced disease, it is now thought to be due to tumor production of the proprotein of insulin-like growth factor-II (IGF-2), which mimics the effects of insulin due to its structure.[6,7] Those with tumors producing IGF-2 can have symptoms of hypoglycemia (diaphoresis, altered mental status, tremors, etc.) that is most often observed with fasting.[8] Patients may also demonstrate acromegaloid features in the absence of elevated growth hormone (GH) due to a negative feedback system.[8] These symptoms can begin weeks to months prior to diagnosis, and may be either the presenting symptom or a symptom occurring later in the disease course.[9]

NICTH can be classified under 2 broad categories from which the tumor originates; those of mesenchymal origin or those of epithelial origin. The most common mesenchymal causes of NICTH include fibromas and fibrosarcomas, which are the most common etiologies of NICTH overall. Those of epithelial origin in descending order of incidence include hepatocellular carcinoma, adrenocortical carcinoma, and lung carcinoma.[5,8,10] Other, much less common causes of

tumor induced hypoglycemia include myeloma, lymphoma, leukemia, tumors of the breast and stomach, and Wilms tumor.[5,8] The tumors of NICTH tend to be large at the time of presentation, but slow growing and typically asymptomatic, especially when located in the retroperitoneum.[8] Importantly, the degree of hypoglycemia caused by this syndrome is not used to estimate size, aggressiveness, or malignant potential of the tumor, and its presence is not an indication of poor prognosis.[11]

Only 4 cases, to our knowledge, have described paraneoplastic hypoglycemia associated with RCC specifically, although various other cases have been described under the broad category of NICTH.[12-15] A case by Berman and Harland described the complicated course of a patient with metastatic RCC and hypoglycemia refractory to all treatments, which ultimately lead to the patient's death in 1997.[14] Fernando et al presented a case of hypoglycemia due to a sarcomatoid variant of RCC that was treated symptomatically in 2006, as the patient was a poor surgical candidate.[15] In 2014, Kimura et al presented a case where a man with a history of nephrectomy presented with hypoglycemia as the presenting symptom of recurrence of his disease, for which excision was performed.[12] Finally, Bientinesi et al described a patient who presented with hypoglycemia, which quickly resolved after nephrectomy in 2016.[13] While each case contained unique qualities in terms of disease course and outcomes, every case highlighted the high index of suspicion necessary to identify this rare cause of hypoglycemia.

As with other, more well-known paraneoplastic syndromes, hypoglycemia can be the presenting symptom of neoplastic disease or a sign of recurrence.[1] In those with confirmed hypoglycemia, but of unknown etiology, the work-up should initially include identifying possible medication-induced hypoglycemia, critical illness, organ failure, and/or hormone deficiencies.[16] Causes of endogenous hyperinsulinism, such as insulinoma, history of gastric bypass surgery, and autoimmune hypoglycemia should also be assessed.[16] Laboratory work-up should include measurement of insulin, proinsulin, C-peptide, and beta-hydroxybutyrate. In the event that all of the aforementioned tests are low, IGF-1, IGF-2, and the IGF 2:1 ratio should be measured.[17] If the IGF 2:1 ratio is >10:1, glucose is <55 mg/dL, and insulin <75 pmol/L, then the diagnosis of NICTH is very likely.[18] It is important to note that the IGF 2:1 ratio may also be abnormally high in the setting of sepsis or severe cachexia, but this is due to both IGF-1 and IGF-2 being lower than normal.[19] If NICTH is diagnosed without the presence of a known neoplasm, which occurs in half of the reported cases, further exploration should be sought after, as it will influence treatment.[20]

The diagnosis of NICTH by laboratory confirmation in the setting of a mass should prompt the decision for mass excision.[20] This is the mainstay of treatment and, as demonstrated in prior cases, can lead to immediate and long-lasting resolution of hypoglycemia.[20] If complete excision cannot be accomplished, palliative tumor debulking is recommended.[20] When excision or debulking is impossible, or limitations of surgery have been met and the patient is still symptomatic, blood glucose optimization has been proven to be beneficial.[20] In the immediate and short-term, supplemental glucose can provide symptomatic relief and can be life-saving, but the benefit of its continued use is dependent on overall patient prognosis.[8] Long-term control can be accomplished by initiating and maintaining therapeutic levels of glucocorticoids with the goal of suppressing tumor IGF-2 production and increasing glucose production.[21] Subcutaneous recombinant human GH has also been described to help relieve symptoms of hypoglycemia primarily by stimulating gluconeogenesis and glycogenolysis, among other mechanisms.[21,22] Long-term recombinant human GH use, however, may lead to increased plasma IGF-1 and insulin, causing the opposite of the desired effect; this could potentially, albeit theoretically, promote growth of the tumor.[21,22]

References

1. Palapattu GS, Kristo B, Rajfer J. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. *Rev Urol*. 2002;4:163–170.
2. Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. *Semin Urol Oncol*. 1996;14:216.
3. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc*. 1991;66:711.
4. Fukuda I, Hizuka N, Ishikawa Y, et al. Clinical features of insulin-like growth factor-II producing non-islet cell tumor hypoglycemia. *Growth Horm IGF Res*. 2006;16:211–216.
5. Marks V, Teale JD. Tumours producing hypoglycaemia. *Endocrine-related Cancer*. 1998;5:111–129.
6. Phillips LS, Robertson DG. Insulin-like growth factors and non-islet cell tumor hypoglycemia. *Metabolism*. 1993;42:1093–1101.
7. Maki RG. Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer. *J Clin Oncol*. 2010;28:4985–4995.
8. Dynkevich Y, Rother KI, Whitford I, et al. Tumors, IGF-2 and hypoglycemia: insights from the clinic, the laboratory and the historical archive. *Endocr Rev*. 2013;34:798–826.
9. de Groot JW, Rikhof B, van Doorn J, et al. Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. *Endocr Relat Cancer*. 2007;14:979–993.
10. Koch CA, Rother KI, Roth J. Tumor hypoglycemia linked to IGF-II. In: Rosenfeld RG, Roberts CT, eds. *The IGF System: Molecular Biology, Physiology, and Clinical Applications*. Totowa, NJ: Humana Press; 1999:675–698.
11. Briselli M, Mark EJ, Dickersin GR. Solitary fibrous tumors of the pleura: eight new cases and review of 360 cases in the literature. *Cancer*. 1981;47:2678–2689.
12. Kimura S, Mitsuzuka K, Yamada S, et al. Hypoglycemia caused by recurrent renal cell carcinoma as result of production of high molecular weight insulin-like growth factor 2. *J Clin Oncol*. 2014;34:120–122.
13. Bientinesi R, Foschi N, Gandi C, et al. Paraneoplastic hyperinsulinism due to renal cell carcinoma treated with robotic nephrectomy. *Clin Genitourin Cancer*. 2016;14:107–109.
14. Berman J, Harland S. Hypoglycaemia caused by secretion of insulin-like growth factor 2 in a primary renal cell carcinoma. *Clin Oncol (R Coll Radiol)*. 2001;13:367–369.
15. Fernando HS, Hawkyard SJ, Poon P, et al. Renal cell carcinoma with non-islet cell tumor hypoglycemia. *Int J Urol*. 2006;13:985–986.
16. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. *J Clin Endocrinol Metab*. 2014;99:713–722.
17. Livingstone C. Insulin-like growth factor-II and cancer. *Endocr Relat Cancer*. 2013;20:R321–R339.

18. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:709–728.

19. Clark MA, Hentzen BT, Plank LD, Hill GI. Sequential changes in insulin-like growth factor 1, plasma proteins, and total body protein in severe sepsis and multiple injury. *JPEN J Parenter Enteral Nutr*. 1996;20:363–370.

20. Teale JD, Wark G. The effectiveness of different treatment options for non-islet cell tumour hypoglycemia. *Clin Endocrinol*. 2004;60:457–460.

21. Teale JD, Marks V. Glucocorticoid therapy suppresses abnormal secretion of big IGF-II by non-islet cell tumours inducing hypoglycaemia (NICTH). *Clin Endocrinol*. 1998;49:491–498.

22. Drake WM, Miraki F, Siddiqi A, et al. Dose-related effects of growth hormone on IGF-I and IGF-binding protein-3 levels in non-islet cell tumour hypoglycaemia. *Eur J Endocrinol*. 1998;139:532–536.