Primary Functioning Neuroendocrine Tumor of the Appendix with Hypoglycemia Syndrome: A Case Report and Review of Neuroendocrine Tumors

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ABSTRACT

Introduction: Primary neuroendocrine tumors (NETs) of the appendix are uncommon, but when present are usually not hyperfunctioning. This case represents an extraordinarily rare primary hyperfunctioning NET of the appendix with a clinical presentation of symptomatic hypoglycemia in an otherwise healthy man.

Case Presentation: A previously healthy 34-year-old male was found to be symptomatically hypoglycemic in early 2018. After the workup, the apparent explanation was a tumor in his midappendix, for which he was referred to our surgical oncology service for resection. The patient’s clinical course is described in detail, including imaging, as well as surgical and pathologic descriptions of the appendiceal NET.

Discussion: A literature review demonstrates no other case series or reports of a primary hyperfunctioning NET of the appendix presenting with hypoglycemic crisis. The symptoms of tumor-induced hypoglycemia more typically arise with islet cell tumors, such as pancreatic NETs or insulinomas. We believe this case represents a nonislet cell tumor-induced hypoglycemia. This patient’s elevated serum proinsulin level preoperatively implies secretion of proinsulin by the tumor. However, tumor-induced hypoglycemia caused by proinsulin has been described previously only in pancreatic tumors. This unique case adds knowledge to the possible glycemic endocrine effects of nonpancreatic NETs, specifically those that arise primarily in the appendix.

CASE PRESENTATION

A previously healthy 34-year-old male teacher presented with what probably was symptomatic hypoglycemia in early 2018. He arrived at an urgent care facility with systemic symptoms of hypoglycemia crisis. To our knowledge, there are no reports of primary appendiceal NETs that produce hypoglycemic symptoms, typically described with insulinomas.

This case provides detailed reports of the clinical course of our patient for whom a pathophysiologic explanation for hypoglycemia was his appendiceal NET. This analysis provides what appears to be one possible mechanism for tumor-induced hypoglycemia, the increased secretion of proinsulin. This is an addition to our fund of knowledge of the endocrine effects of NETs and illustrates one possible mechanism for tumor-induced hypoglycemia, secretion of proinsulin.

INTRODUCTION

Tumors of the appendix are a well-known phenomenon but are overall an uncommon disease. One study reports an incidence rate of 0.12 cases per 1,000,000 people per year.1 Neuroendocrine tumors (NETs), classically described as “carcinoid” tumors, represent up to 80% of all appendiceal neoplasms, but there are other histologic subtypes that make up a small minority.2 Usually, NETs of the appendix are found serendipitously on pathologic examination and often do not require further intervention.3 Symptoms associated with these tumors are typically related to obstruction, clinically consistent with appendicitis. Systemic symptoms of carcinoid syndrome have been described with an appendiceal primary tumor, but this constellation is rare and does not historically include symptoms of hypoglycemia crisis. To our knowledge, there are no reports of primary appendiceal NETs that produce hypoglycemic symptoms, typically described with insulinomas. This case represents an extraordinarily rare primary hyperfunctioning NET of the appendix with a clinical presentation of symptomatic hypoglycemia in an otherwise healthy man.

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A gallium dotatate Ga 68-enhanced scan of abdomen in transverse view demonstrating hyperactive, 1.3-cm nodule in midappendix.

Figure 2. Gallium dotatate Ga 68-enhanced scan of abdomen in transverse view demonstrating hyperactive, 1.3-cm nodule in midappendix.

A gallium dotatate 68 Ga-enhanced scan of body in coronal view. Hyperactive, 1.3-cm nodule in midappendix shows no evidence of metastatic disease or mass in pancreas or duodenum.

Figure 3. Gallium dotatate 68 Ga-enhanced scan of body in coronal view. Hyperactive, 1.3-cm nodule in midappendix shows no evidence of metastatic disease or mass in pancreas or duodenum.

The time of measured low serum glucose levels, and immediate relief of symptoms after the IV administration of glucose. The primary concern would be to rule out any cause of iatrogenic hypoglycemia, such as surreptitious use of insulin or sulfonylurea. With an iatrogenic cause already ruled out, a workup for tumor-induced hypoglycemia proceeded. The most common cause of this presentation is an insulinoma. Insulinomas are NETs derived of pancreatic beta cells and are found almost exclusively in the pancreas and duodenum. The resected specimen was found to be normal, it was decided to intervene on the appendiceal mass as the most likely cause of his hypoglycemia.

Therapeutic Intervention and Treatment

Initial treatment of this patient consisted of IV administration of 50% dextrose with continued infusion while he remained an inpatient for his diagnostic workup. Once discharged, he was maintained on a regimen of diazoxide (Proglycem, 50 mg/mL oral suspension taken as 1.2 mL every 12 hours. He was also given rescue glucagon 1-mg intramuscular injections for treatment of hypoglycemic crisis. His response to glucagon was not measured. He was maintained on this treatment until he was seen by our surgical oncology service the following month and was evaluated for surgical resection. Given the small size and the location of the tumor, he was advised that a laparoscopic appendectomy was likely sufficient but that an ileocecectomy might be required depending on operative findings.

At the time of laparoscopic exploration, a clear mass was seen in the midappendix more than 2 cm away from the appendiceal base, with no involvement of adjacent structures or evidence of metastatic disease or other masses. The appendix was removed, and a single line of surgical staples (Endo GIA stapler, Covidien Medtronic, North Haven, CT) was applied across the base of the appendix and another across the appendiceal mesentery. The specimen was evaluated intraoperatively by the surgical team and the pathologist; with clear margins, no involvement of the base, and a tumor diameter of less than 2 cm, the decision was made to conclude the operation.

The patient was observed overnight in the hospital. Serum glucose levels were checked every 6 hours, and he remained normoglycemic with no intervention. He was discharged on postoperative day 1. Pathologic evaluation confirmed a well-differentiated NET with negative margins (Figure 4). Microscopically, the tumor had a mitotic rate of less than 2 mitoses/mm² and a Ki-67 labeling index of 1% (reference range < 3%). There was no lymphovascular or perineural invasion and no necrosis. The round, uniform cells arranged in clusters with a prominent rosette formation and “salt and pepper type” chromatin were characteristic of a NET (Figure 5).

Follow-up and Outcomes

One month after resection, the patient followed-up in our clinic. He had recovered well from surgery and had no further symptoms of hypoglycemia. His measured fasting blood glucose level was between 80 mg/dL and 90 mg/dL without any requirements for dextrose or intramuscular glucagon injections. Results of a repeated laboratory evaluation postoperatively showed the following normal values: Insulin, 2.9 μIU/mL (reference range = 2.0-19.6 μIU/mL); C-peptide, 0.7 ng/mL (reference range = 0.8-3.8 ng/mL); and proinsulin, below 4.0 pmol/L (reference range = 0-6.0 pmol/L). The fasting proinsulin level was significantly elevated, which was consistent with a functioning NET.

The decision was made to continue with follow-up visits every 3 months and undergo follow-up imaging studies every 6 months.

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Ectopic insulin secretion from pancreatic beta cell tumors (insulinomas) is rare, with an incidence of 0.4/100,000 person years. This tumor is the most common functioning pancreatic NET. They are usually small and almost always located in the pancreas but have been known to reside in the duodenum or gastrohepatic ligament.7,4,10 Our patient’s presentation with symptomatic hypoglycemia that resolved with IV glucose administration ultimately spurred an investigation for a possible pancreatic NET; however, none could be seen on imaging studies. Given the rarity of other types of tumor-induced hypoglycemia, a pancreatic biopsy was performed that yielded normal tissue. With this in mind, other forms of tumor-induced hypoglycemia were considered.

A small number of nonislet cell tumors have been associated with ectopic insulin secretion from pancreatic NETs.6,7 These gastroenteropancreatic tumors are subdivided into 2 basic types: 1) those that occur in the pancreas, or pancreatic NETs; and 2) those occurring in the luminal gastrointestinal tract, or nonpancreatic NETs. Pancreatic NETs are tumors that are capable of producing systemic syndromes related to endocrine function of the tumor given its cell origins. These tumors are classically described as insulinomas, gastrinomas, pancreatic polypeptide-secreting tumors, VIPomas (secreting vasoactive intestinal polypeptide), glucagonomas, and somatostatinomas.6,8,9 Even rarer, however, are proinsulinomas, which are described later in this article.1 Nonpancreatic NETs such as those that occur in the stomach, small bowel, colon, appendix, and rectum can be hyperfunctioning, resulting in the carcinoid syndrome because of the hypersecretion of vasoactive amines and peptides from the tumor. The symptoms of this classic syndrome—watery diarrhea, flushing, bronchospasm, hypotension, and right-sided heart failure—do not include hypoglycemia.9

Tumor-induced hypoglycemia is a phenomenon that can be explained by 2 distinct pathophysiologic processes. The first and most common is the result of insulin secretion by tumors of pancreatic islet cell derivation (insulinomas), and referred to as islet cell tumor hypoglycemia. However, tumor-induced hypoglycemia can also develop in nonpancreatic tumors known as nonislet cell tumor hypoglycemia (NICTH). This case illustrates a previously undescribed phenomenon of NICTH derived from a primary appendiceal NET.

Figure 6. Timeline of the case.

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range ≤ 18 pmol/L). Our plan for continued follow-up is to repeat the gallium dotatate scan in 6 months. Figure 6 shows a timeline of the case.

DISCUSSION

It is important to consider the definitions of tumors considered in this case because the topic of NETs and the specific terms have changed over time and are frequently confused. NETs are a heterogeneous group of malignancies with varied histologic findings and nomenclature.6,7 The tumors are classified on the basis of both the “neuro” and “endocrine” histologic factors found in them. A consistent finding of dense core granules with a salt and pepper appearance that are similar to those found in serotonergic neurons makes up the descriptor of “neuro.” The “endocrine” refers to these core granules’ ability to secrete monoamines. Historically, these well-differentiated tumors were referred to as carcinoids, but this term led to errors in communication. In 2010, changes by the World Health Organization deemed that all tumors with histologic findings consistent with immunoexpression of neuroendocrine markers such as chromogranin A and synaptophysin in an organoid or neuroendocrine shape would be defined as neuroendocrine neoplasms or NET, scuttling the previous term carcinoid tumors.6,7

NETs can occur in a variety of tissues, but those that occur in the gastroenteropancreatic system are the most common (62%-67%).6 These gastroenteropancreatic tumors are subdivided into 2 basic types: 1) those that occur in the pancreas, or pancreatic NETs; and 2) those occurring in the luminal gastrointestinal tract, or nonpancreatic NETs. Pancreatic NETs are tumors that are capable of producing systemic syndromes related to endocrine function of the tumor given its cell origins. These tumors are classically described as insulinomas, gastrinomas, pancreatic polypeptide-secreting tumors, VIPomas (secreting vasoactive intestinal polypeptide), glucagonomas, and somatostatinomas.6,8,9 Even rarer, however, are proinsulinomas, which are described later in this article.1
secretion. Among these are bronchial carcinoid tumors, squamous cell carcinoma of the cervix, neurofibrosarcoma, schwannoma, paraganglioma, small-cell carcinoma of the cervix, and gastrointestinal stromal tumors. Some of these reports do not entirely explain the pathophysiologic mechanism for hypoglycemia because a pancreatic insulinoma was not specifically excluded. However, case reports of paragangliomas and small-cell carcinomas of the cervix have shown that the nonislet cell tumors were the source of the hyperinsulinemia given the detection of proinsulin mRNA and insulin protein in the tumor cells. The common factor among most of these tumors is that they are derived from mesenchyme or epithelium. Reporting on the percentages of nonislet cell tumors associated with hypoglycemia, de Groot et al concluded that NICTH can arise in virtually every benign and malignant tumor but mainly occurs with solid tumors of mesenchymal or epithelial origin, with 41% and 43% of these respective tumor classes having associated hypoglycemia. Interestingly, in their review, only 1% of nonpancreatic NETs were found to be associated with hypoglycemia, and of these cases, none was of primary origin of the appendix.

A PubMed literature review found few reports of nonpancreatic NETs with associated hypoglycemia. One recent publication did describe a NET of the kidney that produced ectopic insulin, requiring IV dextrose fluid resuscitation and curative resection. Another nonpancreatic NET found was of gastric origin that also required blood glucose intervention and resection. Curiously, these 2 tumors acted via different mechanisms in producing systemic hypoglycemia. The tumor found on the kidney produced ectopic insulin confirmed by elevated serum insulin and C-peptide levels. The gastric NET did not produce ectopic insulin, and the authors proposed that the tumor's pathophysiologic mechanism of action was via insulinlike growth factor 2 (IGF-2).

The pathophysiology of NICTH can be explained by several mechanisms. The first and most coherent is ectopic production of insulin by the tumor itself. Although this is typically described in islet cell tumors, it can also occur in NICTH but, again, is extremely rare. The clinical picture of this constellation would consist of elevated C-peptide levels as well as elevated serum insulin levels. Because our patient did not fit this clinical picture, we will not elaborate on this mechanism. Another mechanism commonly described is tumor production of IGF-2. Produced in the liver, IGF-2 binds to the same high-affinity tyrosine kinase receptors on cells as insulin. When a tumor secretes IGF-2, which is sometimes referred to as "big IGF-2" prohormone, it inhibits the secretion of insulin and growth hormone. The IGF-2 molecules interact poorly with the tyrosine kinase receptors, and this leads to high levels of free IGF-2 molecules, which cause hypoglycemia by inhibiting hepatic glucose uptake and enhancing the disposal of glucose into muscle. Several tumors and tumor syndromes have been associated with excess IGF-2 secretion, such as Doege-Potter syndrome. These tumors are almost always epithelial in origin, and this mechanism has not been described in great detail with an associated NET. Other described mechanisms include tumor consumption of glucose, but this has been attributed to large NETs of the mesenchyme and would not fit logically with our case. Also described are a combination of cachexia and renal and hepatic dysfunction, which, again, our patient did not manifest.

In reflection of the specifics of our case, it does not appear convincing that the tumor primarily produced insulin because this was not reflective in the preoperative findings (normal C-peptide and serum insulin levels). A reasonable explanation could be that the tumor did produce IGF-2, functioning to symptomatically lower serum glucose levels. Unfortunately, there was never a preoperative serum evaluation for IGF-2, and pathologic examination at our facility could not stain for IFG-2 to prove this definitively. The only abnormal laboratory test result in the patient was an elevated proinsulin level, which has been described as a mechanism for tumor-induced hypoglycemia in previous cases, often termed proinsulinoma. Proinsulin is a biological precursor to insulin and has approximately 10% of the biologic activity of insulin. In a review of proinsulin-secreting tumors, Murtha et al described the specific diagnostic criteria for this symptomatic syndrome, including low levels of serum glucose, normal serum insulin concentrations, and C-peptide with elevated proinsulin levels, which would fit our patient. The authors point out, however, that all these identified tumors resided in the pancreas. Although a biopsy of the pancreas was performed in the present case, this was not the ideal evaluation to rule out a functional tumor of the pancreas because pancreatic vein sampling has been shown to be superior. If our patient's tumor acted through proinsulin, it would be the first, to our knowledge, of a nonpancreatic NET to produce proinsulin causing systemic hypoglycemic syndrome. Unfortunately, proinsulin staining is not available at our institution, so this theory was impossible to confirm. Given the lack of symptoms after resection, it is still reasonable to infer that the cause of the patient's hypoglycemia was his appendiceal tumor. The exact mechanism of the patient's NET remains uncertain.

CONCLUSION

This case adds to the literature of the possible endocrine effects of a nonpancreatic NET that, to our knowledge, has not been previously described. Surgery with curative intent appears to be an effective therapy for these localized tumors that can be resected completely.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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