CASE REPORT

Non-islet cell tumor hypoglycemia associated with Gastrointestinal Stromal Tumor: Case report and review of the literature

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How to cite this article: Kumar V, Gala D, Wonders C, et al. Non-islet cell tumor hypoglycemia associated with Gastrointestinal Stromal Tumor: Case report and review of the literature. Arch Clin Cases. 2023;10(1):50-54. doi: 10.22551/2023.38.1001.10240

ABSTRACT

Non-islet cell tumor hypoglycemia is an uncommon paraneoplastic phenomenon commonly associated with tumors of mesenchymal origin like gastrointestinal stromal tumors (GIST). It causes the release of insulin-like growth factor type II. GIST are frequently asymptomatic but can present with vague symptoms such as gastrointestinal bleeding, gastric pain, anorexia, nausea, and vomiting. We present an interesting case of A 62-year-old male with GIST tumor admitted for refractory hypoglycemia found to have non-islet cell tumor hypoglycemia which is a relatively uncommon cause of hypoglycemia.

KEYWORDS: Non-islet cell tumor hypoglycemia; GIST; insulin-like growth factor-II

INTRODUCTION

Non-islet cell tumor hypoglycemia (NICTH) is an uncommon paraneoplastic phenomenon that causes the release of insulin-like growth factor-II (IGF-2). It is commonly associated with tumors of mesenchymal origin such as gastrointestinal stromal tumors (GIST). The incidence of NICTH has been estimated to be one case per one million people per year [1]. The average annual incidence of GIST has been reported to be between 5-15 cases per one million people per year [2]. These tumors can be asymptomatic, but when they do produce symptoms the most common presentation of GIST includes gastrointestinal bleeding, abdominal pain, anorexia, nausea, and vomiting [3]. The most reliable method of diagnosis involves the use of endoscopic ultrasound evaluation (EUS), along with immunohistological staining. Treatment of GIST is primarily reliant on surgical or endoscopic intervention, with pharmacological therapy being used as an adjuvant or neoadjuvant [4]. Patient symptoms typically resolve following treatment, with long-term morbidity being decreased due to a combination of surgical resection and pharmacological adjuvant therapy [5].

CASE REPORT

A 62-year-old male initially presented with symptoms of vague intermittent abdominal pain and weight loss. The physical examination was unremarkable and labs were significant for anemia. Computerized tomography (CT) scan of chest/abdomen/pelvis showed gastric mass measuring 25x19.6x11.4 cm with no evidence of metastatic disease in the abdomen or pelvis (Figure 1). Esophagogastroduodenoscopy (EGD) demonstrated large, bilobed subepithelial mass measuring 10-15 cm with an area of ulceration within the mass (Figure 2) followed up with Endoscopic ultrasound (EUS) demonstrating subepithelial lesion was found likely arising from the fundus, lesser curve and body of the stomach, layer of origin could not be determined on due to the large size of the mass (Figure 3). Biopsy revealed spindle shaped cells which stained positive for c-Kit (CD117) confirming the diagnosis of GIST.

He was started on imatinib but stopped taking it prior to presentation pending surgical evaluation for tumor, presenting with confusion, tiredness, increased sweating and irritability for one day. He also reports unintentional weight loss of 10 pounds in the past two months. Vitals on presentation showed temperature 98.2 F, Heart rate 105 beats/min, BP 123/93 mm of hg, RR 18 breaths/min with oxygen sat 98% on room air. Physical examination was significant for lethargy and tiredness, otherwise unremarkable with no signs of any focal neurological deficits. The patient had no prior history of diabetes or adrenal insufficiency. He denied use of any medications or alcohol consumption.

The patient's repetitive finger sticks glucose remained persistently low, less than < 55 mg/dl even after good oral intake and two D50 pushes Hypoglycemia workup included

Received: February 2023; **Accepted after review:** March 2023; **Published:** March 2023.

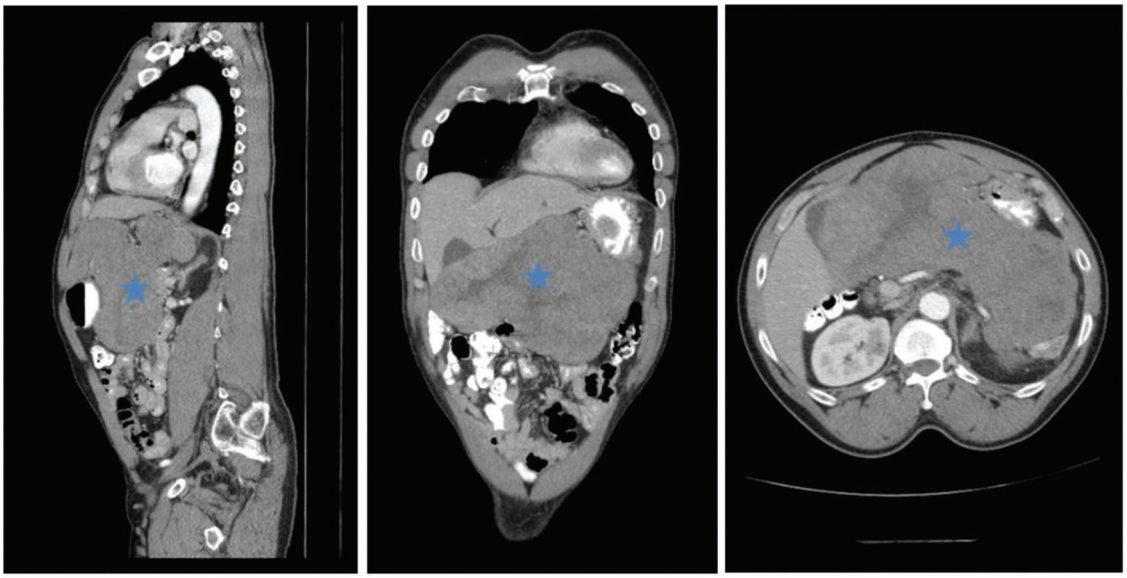

Fig. 1. CT scan abdomen/pelvis with contrast showing large soft tissue density mass inseparable from the lesser curvature of the stomach marked with asterisk.

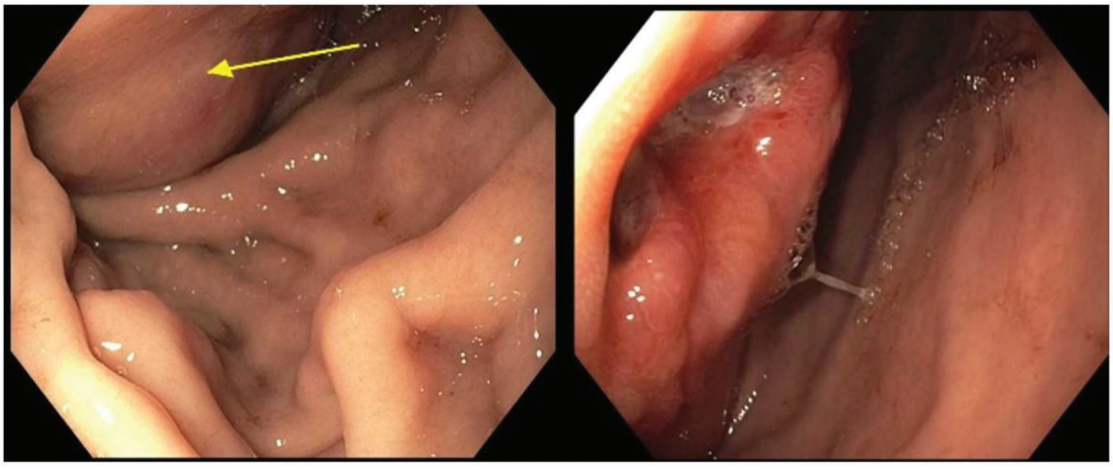

Fig. 2. EGD findings consistent with a large, bilobed subepithelial mass measuring 10-15 cm with an area of ulceration within the mass (seen best on retroflexion) was found on the lesser curvature of the stomach along the anterior wall of the stomach.

beta-hydroxybutyrate (BHOB), cortisol, and ACTH which were all within normal limits. Urine toxicology and drug screen for sulfonylureas were negative. Laboratory investigations showed reduced levels of insulin, C-peptide, and insulin-like growth factor-1 (IGF-1), but his IGF-2 was increased. Endocrinology was consulted for refractory hypoglycemia; recommended to start D10 fluids in the setting of resistant low blood glucose and start octreotide and steroids. Patient was noted to have transient improvement in glucose levels and mentation. CT scan of chest/abdomen/pelvis shows grossly unchanged gastric GIST, measuring 25x19.6x11.4 cm with no evidence of metastatic disease in the abdomen or pelvis. Oncology was consulted for further management of malignancy; imatinib was resumed and referred for surgical evaluation for tumor removal. Patient underwent laparoscopic surgical debulking of the GIST and was discharged on post-operative day four. Four weeks post-operative follow up, the patient denied any further similar episodes and continued to follow with oncology as outpatient.

DISCUSSION

The most frequently occurring mesenchymal tumor of the gastrointestinal tract is known as a GIST. These tumors are most often found in the stomach, but can also occur in the duodenum, small intestine, colon, rectum, and esophagus [6]. It has been suggested that GIST arises from the interstitial cells of Cajal, which are the cells that function as the pacemakers of the gastrointestinal tract [7]. The annual incidence of these tumors has been reported to be between 5-15 cases per one million people, making up around 2% of all gastrointestinal neoplasms [2]. NICTH is a rarely occurring paraneoplastic syndrome that has an estimated

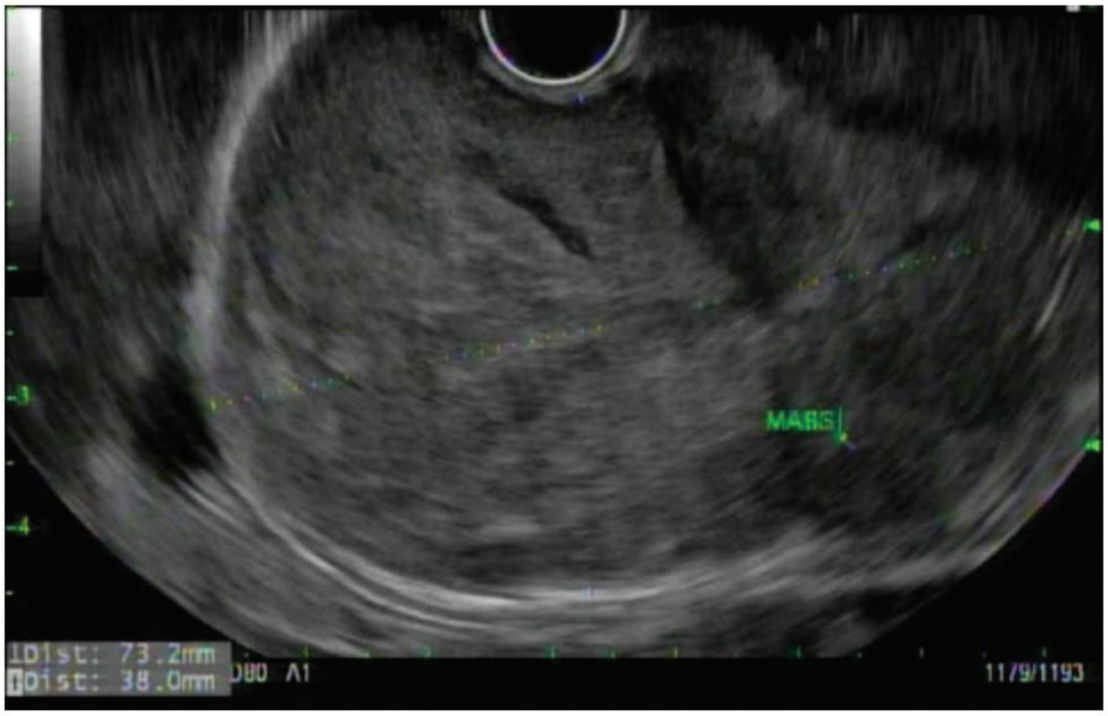

Fig. 3. Endoscopic US findings showed a 43.0x77.8 mm subepithelial lesion found likely arising from the fundus, lesser curve and body of the stomach s/p FNB x 4. The lesion was hypoechoic and had some cystic spaces within it in some areas. Sonographically, the lesion appeared to originate from the stomach, but the wall layers could not be determined due to the large size of the mass.

incidence of one case per one million people, per year [1]. This condition is associated with several types of tumors, including GIST, which can secrete IGF-2 that can both act as an autocrine growth factor for the tumor itself and cause hypoglycemic symptoms [8].

The cancerous cells secrete an abnormal form of IGF-2, which causes the hypoglycemia. Due to its larger molecular weight—11–18 kDa as opposed to the conventional IGF-2 molecular weight of 7.5kDa—this modified version of IGF-2 is known as "big" IGF-2. Normally, IGF-2 binds to IGFBP-3 and a labile acid component to create a ternary complex; however, "big" IGF-2 is unable to generate this ternary complex. As a result, the liver releases less glucose into the bloodstream, and skeletal muscle consumes more glucose, which causes hypoglycemia [9]. Additionally, "big" IGF-2 inhibits the production of growth hormone, glucagon, IGFBP-3 and other hormones. Therefore, the sustained hypoglycemia observed in NICTH is thought to be caused by "big" IGF-2.

The most common clinical presentation of GIST is gastrointestinal bleeding, but these tumors can also present with gastric pain and other ulcer-like signs and symptoms including nausea, vomiting, bloating, and unintentional weight loss [3]. Those associated with NICTH typically present with symptoms of hypoglycemia which can be confirmed by observation of Whipple's triad, which is defined as signs of hypoglycemia, a low plasma glucose concentration, and resolution of symptoms upon increasing blood glucose levels [10]. There are many etiologies for hypoglycemia with the most common being insulin or insulin secretagogues. NICTH is a rare etiology of low blood glucose levels caused secondary to IGF-2 secretion by either mesenchymal or epithelial tumors. The most common malignancy causing NICTH is hepatocellular carcinoma [11]. In patients with IGF-2-induced hypoglycemia, insulin and IGF-1 levels are typically low. Tumors of any size can potentially cause NICTH, however, previous study showed larger tumors are more likely to cause hypoglycemia with one study reporting an average tumor size of 20 cm [12].

Unless the symptoms previously described are noticeably present, the discovery of a GIST is often incidental, and there has been a recent increase in the number of these tumors found due to the increased use of endoscopy in the clinical setting. Most of these incidental findings are small tumors, with many of them being around 2 cm or less in size. The small size of some of these tumors is one of the main reasons that they are not often easily visualized during MRI or CT. Because tumors of this nature can often present asymptomatically, a confirmed diagnosis relies on both immunohistological staining and endoscopic ultrasound evaluation (EUS) [4].

Several methods exist for the diagnosis of GIST, with one of the most reliable being endoscopic ultrasound (EUS) which reveals a hypoechoic and homogenous lesion with well-defined margins [4]. The preferred histological method involves ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB). Upon examination of a biopsy specimen, the pattern most often observed is of a spindle-cell tumor with a fascicular or storiform growth pattern [13]. During the histological evaluation, the use of immunohistochemical methods that can detect several different mutations that are strongly associated with GIST are frequently used. One of which can distinguish the presence of the c-KIT proto-oncogene (CD-117), which was found to be positive in approximately 95% of GIST [14]. Another histological finding commonly associated with these tumors is a cell surface

protein, DOG1, which can be strongly upregulated in GIST, while rarely being expressed in other tumors that arise from soft tissues [4].

The treatment of these tumors includes both surgical and pharmacological intervention, with the first-line treatment being surgical or endoscopic resection [4]. The primary pharmacological intervention involves the use of imatinib (Gleevec), which is a tyrosine kinase inhibitor that targets c-KIT (CD-117) [15]. This has been found to significantly improve patient outcomes when used as adjuvant or neoadjuvant therapy [5]. Additionally, hypoglycemia related to NICTH can be managed with surgical tumor removal or medical management [11]. Medical treatment includes agents to increase glucose such as glucocorticoids, recombinant HCG (rHCG) and glucagon [14]. However, the role of octreotide and growth hormone is controversial [11,16]. Growth hormone leads to insulin resistance reducing peripheral uptake of glucose raising blood glucose levels. However, growth hormone use is controversial because it is not always successful and use is limited because of the need for high doses leading to increased risk of side effects such as fluid retention and orthostatic hypotension [17,18].

To prevent long-term morbidity in patients with GIST, the most important step is to resect as little gastrointestinal tissue as possible while also leaving the pseudocapsule of the tumor intact [4]. In GIST that are associated with NICTH, the levels of IGF-2 rapidly decrease following surgical intervention which also resolves the hypoglycemic symptoms [2]. In the case of most GIST, symptoms will consistently be resolved following successful resection of the tumor.

CONCLUSION

In summary, NICTH is a relatively uncommon cause of hypoglycemia, but it is also one that is probably underdiagnosed. NICTH secreting IGF-2 should be considered in addition to insulinoma as a differential for hypoglycemia particularly in patients with diagnosed GIST. One important mechanism is the hypersecretion of IGF-2, which functions as an autocrine growth factor. This is especially important to consider in cases of high tumor mass as this puts patients at risk of developing NICTH. Given that glucocorticoid therapy is beneficial regardless of tumor operability, physicians should be cautious of the development of hypoglycemia in patients with large or metastatic GIST. It has been demonstrated to reliably reverse biochemical abnormalities originating from high levels of IGF-2. Commonly used agents to reverse hypoglycemia include glucocorticoids, recombinant HCG (rHCG) and glucagon. However, further studies need to be done to understand the role of octreotide and growth hormone in the management of NICTH.

Ethics declarations

This case report was presented as an abstract at the 2023 American College of Gastroenterology Conference on 25th October 2022 and abstract was published in the Am J Gastroenterol 2022.

Conflict of interest

We declare that we have no known competing financial interests, personal relationships, or competing interests that could have influenced the work reported in this study.

Informed consent

Informed consent for this case report was obtained from the patient. This study does not contain identifying information about the patient.

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