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A Case of Non-Islet Cell Tumor Hypoglycemia (NICTH) Associated with Gastrointestinal Stromal Tumor (GIST)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1 John M. Wilson
AEF 1 Jessica Ginsberg
E 2 Karen Cutts
E 2 Steve Urban

1 Texas Tech University Health Sciences Center School of Medicine, Amarillo, TX, U.S.A.
2 Department of Internal Medicine, Texas Tech University Health Sciences Center School of Medicine, Amarillo, TX, U.S.A.

Corresponding Author: John Wilson, e-mail: JohnWilson1220@gmail.com
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Patient: Male, 60
Final Diagnosis: Non-islet cell tumor hypoglycemia (NICTH) associated with gastrointestinal stromal tumor (GIST)
Symptoms: Hypoglycemia
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Rare disease

Background: Non-islet cell tumor hypoglycemia (NICTH) is a newly recognized, but uncommon, paraneoplastic syndrome that is associated with tumors of mesenchymal origin. We report a case of NICTH associated with a gastrointestinal stromal tumor (GIST).

Case Report: A 60-year-old man presented to the emergency department of our hospital after being found unconscious in his home. His serum blood glucose on hospital admission was 40 mg/dL. He reported a three-month history of diffuse abdominal pain, fatigue, and blurred vision. Laboratory medicine investigations showed reduced levels of insulin, C-peptide, insulin-like growth factor binding protein (IGFBP)-3, and insulin-like growth factor (IGF)-1, but his IGFBP-2 was increased. Computed tomography (CT) scan of the chest and abdomen showed an abdominal mass that involved the small bowel, mesentery, and omentum, with lesions in the right lung and the left rib. Histopathology of a CT-guided biopsy of the abdominal mass showed a low-grade sarcomatous spindle cell neoplasm that was positive for CD117 using immunohistochemistry and with an exon 11 c-*KIT* mutation. These findings were consistent with a diagnosis of GIST and treatment with imatinib commenced.

Conclusions: This case report has shown that hypoglycemia in the setting of low levels of insulin, C-peptide, IGF-1, and IGFBP-3 is suggestive of a diagnosis of NICTH, which should be investigated for an underlying source, which in this case, was confirmed to be a malignant GIST.

MeSH Keywords: Gastrointestinal Stromal Tumors • Hypoglycemia • Paraneoplastic Syndromes • Proto-Oncogene Proteins c-kit

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/904753

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Background

Tumor-associated hypoglycemia can be caused by islet cell tumors or non-islet cell tumors. Insulinomas are tumors of the pancreatic islet cells that cause hypersecretion of insulin, resulting in hypoglycemia. Non-islet cell tumor hypoglycemia (NICTH) is a paraneoplastic syndrome that leads to release of insulin-like growth factor-2 (IGF-2) and can be caused by different types of tumor [1–3]. NICTH is a rare paraneoplastic syndrome with an estimated incidence of approximately one per one million person-years [4]. Tumors that are associated with NICTH produce peptides, cytokines, and growth factors, including IGF-2, which can lead to hypoglycemia. Tumors associated with NICTH range from benign, to low-grade malignant, to high-grade malignant tumors and include hepatocellular carcinoma, lymphoma, and mesenchymal tumors, including nerve sheath tumors, hemangiopericytoma, and fibrosarcoma [1–4].

Gastrointestinal stromal tumors (GISTs) are mesenchymal, or sarcomatous tumors of the gastrointestinal and are found most often in the stomach, small intestine, and large intestine [1,2 5]. The incidence of GIST in the United States is 6.8 out of one million [2]. GISTs are thought to arise from the interstitial cells of Cajal, which are the pacemaker cells of the GI tract, involved in gut motility [5]. Histologically, GISTs show features of both smooth muscle cells and nerve sheath cells. NICTH associated with GIST is very rare [3].

We report a rare case of NICTH in a patient with a GIST of low-grade malignancy with multiple abdominal, lung, and bone metastases and an initial presentation with hypoglycemia.

Case Report

A 60-year-old Caucasian man with a past medical history of hypertension, hypercholesterolemia, hepatitis C, and recurrent episodes of hypoglycemia was brought to the emergency department after being found unconscious in his home. His serum blood glucose was 40 mg/dL on arrival. He reported a three-month history of cramping diffuse abdominal pain that was not associated with food consumption or bowel movements. He had an undetermined amount of weight loss despite increased food intake. On review of his systems, he had noted fatigue, blurred vision, confusion, and shortness of breath on exertion. His family history was negative for cancer. He had a 40-pack year smoking history but denied alcohol and drug use. On physical examination, he had abdominal distention and tenderness with a palpable mass in the right upper quadrant.

On hospital admission, his initial laboratory findings (Table 1) showed decreased levels of insulin (1.19 IU/mL), C-peptide (<0.1 ng/mL), insulin-like growth factor-binding protein (IGFBP)-3 (1,069 mcg/L), and insulin-like growth factor (IGF)-1 (22 ng/mL), but his IGFBP-2 was increased (1,412 ng/mL).

Table 1. The laboratory findings of the patient on hospital admission (with normal ranges).

	Patient	Normal range
Insulin level	1.19 IU/mL	1.9–23 IU/mL
C-Peptide	<0.1 ng/mL	1.1–4.4 ng/mL
IGF-I	22 ng/mL	54–194 ng/mL
IGFBP-2	1412 ng/mL	140–727 ng/mL
IGFBP-3	1069 mcg/L	2133–5711 mcg/L

IGF-1 – insulin-like growth factor-1; IGFBP-2 – insulin-like growth factor binding protein-2; IGFBP-3 – insulin-like growth factor binding protein-3.

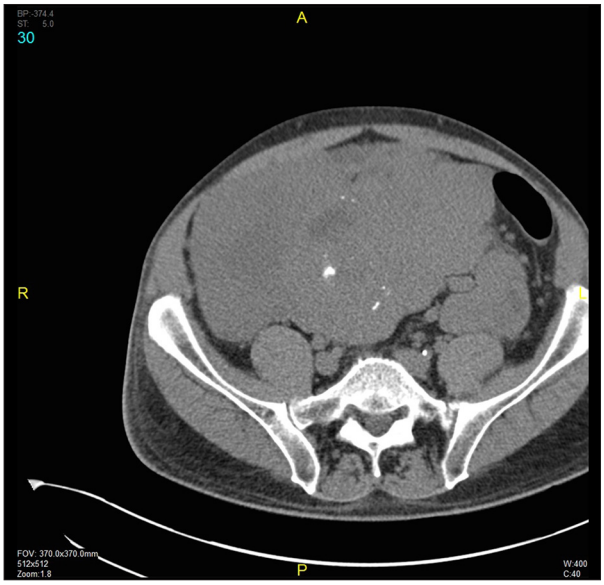

Figure 1. Diagnostic abdominal computed tomography (CT) imaging. A CT scan image shows an abdominal mass measuring 18×24 cm.

A computed tomography (CT) scan (Figure 1) of the abdomen showed an abdominal mass measuring approximately 18×24 cm originating from the pelvic cul-de-sac that was displacing his viscera toward the upper abdomen. The mass involved a few loops of small bowel, with multiple intra-peritoneal and retroperitoneal masses and lesions involving the omentum and mesentery, but there was no bowel obstruction. There were also multiple satellite lesions measuring from several millimeters in diameter to 10 cm in diameter that were visualized in the abdomen. A CT scan of the thorax showed a 1.5×1.5 cm mildly speculated, round, non-calcified soft tissue nodule consistent with a lung metastasis. There were also sclerotic foci

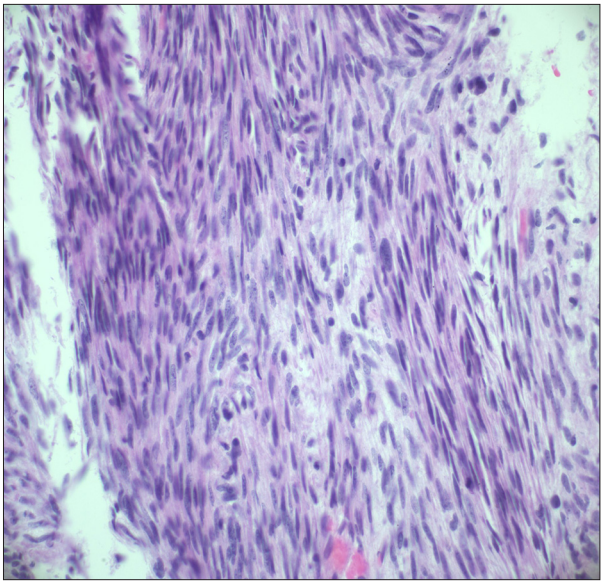

Figure 2. Photomicrograph of the histology of the tumor mass. A sarcomatous spindle cell tumor is shown, consistent with a diagnosis of gastrointestinal stromal tumor (GIST). (Magnification ×40).

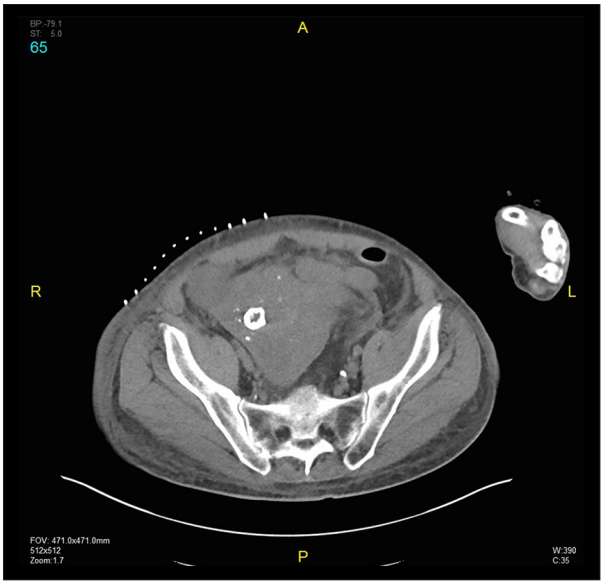

Figure 3. Abdominal computed tomography (CT) imaging at two months following treatment. A CT scan image shows that the abdominal mass was reduced in size after two months of treatment.

within the third and fourth ribs on the left side that were also likely to be metastases. Magnetic resonance imaging (MRI) of the brain was negative for metastasis or acute infarction.

A CT-guided core biopsy of one of the abdominal masses was obtained. Histopathology of the biopsy (Figure 2) showed a low-grade sarcomatous spindle cell neoplasm consisting of interlacing bundles of spindle cells with a moderate nuclear to cytoplasmic ratio and occasional prominent nucleoli. Immunohistochemistry was performed using a panel of tumor markers, which showed that the tumor cells were positively stained with antibodies to CD99, CD117, and smooth muscle actin (SMA), which was consistent with a diagnosis of gastrointestinal stromal tumor (GIST), with 20% of the tumor cells being positive for the proliferation marker Ki67. Molecular sequencing analysis showed an exon 11 *c-KIT* mutation. The GIST was staged as a T4, NX, M1.

Specialist surgical oncology review advised against surgical excision of the primary and metastatic tumors because of the high surgical risk of attempting to remove multiple tumors. Based on the initial pathology results, including the presence of CD117 positivity and an exon 11 c-*KIT* mutation, treatment with the tyrosine kinase inhibitor imatinib was begun.

One month later a repeat abdominal CT scan showed that the main abdominal tumor had decreased in size to 14.0×9.5 cm. Two months after beginning treatment, a second follow-up abdominal CT scan (Figure 3) showed that the tumor size had stabilized and there was no further reduction in size. Also, an intra-abdominal abscess had formed that required CT-guided drainage.

Although the patient had a good initial response to imatinib therapy, there has been no further improvement. The patient became non-compliant with therapy due to the side-effects of imatinib. The extensive metastatic spread of the GIST and lack of treatment compliance mean that the patient's prognosis is poor.

Discussion

As this case report has shown, hypoglycemia in the setting of decreased insulin levels is suggestive of a diagnosis of non-islet cell tumor hypoglycemia (NICTH) [3]. When NICTH is a paraneoplastic syndrome associated with gastrointestinal stromal tumor (GIST), the tumor produces an altered form of insulin-like growth factor (IGF)-2, which results in hypoglycemia. This altered form of IGF-2 is referred to as "big" IGF-2, because it has a molecular weight of 11-18 kDa, compared with the molecular weight of standard IGF-2, which is 7.5kDa [6,7].

Normally, IGF-2 binds to insulin-like growth factor-binding protein (IGFBP)-3 and a labile acid subunit, which together form a ternary complex; however, "big" IGF-2 is unable to form this ternary complex. This results in decreased release of glucose from the liver, and an increase in glucose consumption by skeletal muscle leading to hypoglycemia [10]. "Big" IGF-2 also suppresses growth hormone, glucagon release, and the production

of IGFBP-3 [8]. Therefore, it is believed that "big" IGF-2 is responsible for the sustained hypoglycemia seen in NICTH [9]. Also, low levels of insulin, proinsulin, C-peptide, growth hormone, and β-hydroxybutyrate, a ketone body, are also found in NICTH [4,9–12].

As this case report has shown, when a patient presents with unexplained hypoglycemia it is important to analyze serum glucose, insulin level, proinsulin level, C-peptide level, β-hydroxybutyrate level, and to perform an oral hypoglycemic agent screen. Other laboratory tests that are important to request include IGF-1, IGF-2, and growth hormone (GH) levels. The current Endocrine Society Clinical Practice Guideline advises the following cut off fasting plasma levels for laboratory testing in patients with hypoglycemia without diabetes: insulin level <3.0 mmol/L, proinsulin level >5.0 pmol/L, C-peptide level >0.2 nmol/L, and a β-hydroxybutyrate level <2.7 mmol/L [11]. Unfortunately, there is no commercially available assay to measure "big" IGF-2, an important diagnostic marker for NICTH. If the laboratory tests still indicate NICTH as a possible diagnosis, the next step is to order cross-sectional imaging of the chest, abdomen, and pelvis [11,13].

The diagnosis of GIST is confirmed by tumor sampling and histology supported by immunohistochemical staining for CD117 (c-KIT), which and is positive in approximately 95% of cases of GIST [3,5]. Aberrant activity of the mutated *KIT* gene is now believed to lead to unregulated cell proliferation and the development of GIST [14,15]. IGF-1receptor and IGF-2 are also highly expressed in GIST and can be evaluated using immunohistochemistry [14–17].

Ki-67 is a nuclear protein that is expressed in the G1, S, G2 and M phases of the cell cycle in proliferating cells and is absent in non-proliferating cells [18–20]. It has been shown that high percentage of Ki-67-positive cells, detected using immunohistochemistry, is significantly correlated with an increased risk of recurrence and worse patients prognosis in GIST [21]. There is ongoing debate in the literature regarding whether Ki-67 expression is a better prognostic indicator than mitotic rate in tumor tissue [18]. Further studies are needed to determine the role of Ki-67 and other prognostic markers in GIST [18,21].

Treatment of GIST is usually accomplished by surgical debulking of the tumor mass or tumor embolization [1–3,5]. Surgical removal cures the hypoglycemia when the tumor is completely removed. However, resection is not always a treatment option because of the large tumor burden, extensive metastatic disease, patient preference, and the relationship of the tumor to surrounding structures [13]. While waiting for surgical removal, the hypoglycemia is treated with an increase in food intake and sometimes with intravenous glucose or dextrose. The most effective treatment for NICTH is glucocorticoids, which suppress IGF-2 production and the hypoglycemia caused by "big" IGF-2 [1,2]. Glucocorticoid therapy should begin with the smallest possible dose. Tyrosine kinase inhibitors that target *KIT*, such as imatinib, can be used as neo-adjuvant therapy and have been shown to increase survival in unresectable or malignant tumors [1,2,14,16].

The patient we have discussed in this case report presented with hypoglycemia of unknown origin. A recognized limitation of the case report is that IGF-2 was not measured because the patient was transferred to another facility to receive further treatment. However, before the patient was transferred, imaging and laboratory investigations, including tumor biopsy and immunohistochemistry and molecular tumor analysis confirmed a diagnosis of NICTH. The patient had low plasma levels of insulin, C-peptide, and IGFBP-3, histology was consistent with GIST, immunohistochemistry was positive for CD117, and an exon 11 *KIT* mutation was identified, confirming the diagnosis of GIST.

Conclusions

This case report has described a rare case of non-islet cell tumor hypoglycemia (NICTH) associated with a gastrointestinal stromal tumor (GIST). As this case has shown, it is important to recognize that unexplained hypoglycemia can be a paraneoplastic phenomenon associated with an underlying malignancy. Currently, there is limited knowledge regarding this rare paraneoplastic syndrome caused by GIST, and further research is recommended.

References:

1. Saeed Z, Taleb S, Evans-Molina C: A case of extragastrointestinal stromal tumor complicated by severe hypoglycemia: A unique presentation of a rare tumor. BMC Cancer, 2016; 16(1): 930
2. Hirai H, Ogata E, Ohki S et al: Hypoglycemia associated with a gastrointestinal stromal tumor producing high-molecular-weight insulin growth factor II: A case report and literature review. Intern Med, 2016; 55(10): 1309–14
3. Guiteau J, Fanucchi M, Folpe A et al: Hypoglycemia in the setting of advanced gastrointestinal stromal tumor. Am Surg, 2006; 72(12): 1225–30
4. Marks V, Teale JD: Tumours producing hypoglycaemia. Diabetes Metab Rev, 1991; 7(2): 79–91
5. Escobar GA, Robinson WA, Nydam TL et al: Severe paraneoplastic hypoglycemia in a patient with a gastrointestinal stromal tumor with an exon 9 mutation: A case report. BMC Cancer, 2007; 7(1): 13
6. Baxter RC: The role of insulin-like growth factors and their binding proteins in tumor hypoglycemia. Horm Res, 1996; 46(4–5): 195–201
7. Hizuka N, Fukuda I, Takano K et al: Serum insulin-like growth factor II in 44 patients with non-islet cell tumor hypoglycemia. Endocr J, 1998; 45(Suppl.): S61–65

8. Davda R, Seddon BM: Mechanisms and management of non-islet cell tumour hypoglycaemia in gastrointestinal stromal tumour: Case report and a review of published studies. Clin Oncol (R Coll Radiol), 2007; 19(4): 265–68
9. Zapf J, Futo E, Peter M, Froesch ER: Can "big" insulin-like growth factor II in serum of tumor patients account for the development of extrapancreatic tumor hypoglycemia? J Clin Invest, 1992; 90(6): 2574–84
10. Shapiro ET, Bell GI, Polonsky KS et al: Tumor hypoglycemia: Relationship to high molecular weight insulin-like growth factor-II. J Clin Invest, 1990; 85(5): 1672–79
11. Cryer PE, Axelrod L, Grossman AB et al: Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2009; 94: 709–28
12. Daughaday WH, Kapadia M: Significance of abnormal serum binding of insulin-like growth factor II in the development of hypoglycemia in patients with non-islet-cell tumors. Proc Natl Acad Sci USA, 1989; 86(17): 6778–82
13. Bodnar TW, Acevedo MJ, Pietropaolo M: Management of non-islet-cell tumor hypoglycemia: A clinical review. J Clin Endocrinol Metab, 2014; 99(3): 713–22
14. Nielsen TO, West RB, Linn SC et al: Molecular characterisation of soft tissue tumours: A gene expression study. Lancet, 2002; 359(9314): 1301–7
15. Segal NH, Pavlidis P, Antonescu CR et al: Classification and subtype prediction of adult soft tissue sarcoma by functional genomics. Am J Pathol, 2003; 163(2): 691–700
16. Baird K: Gene expression profiling of human sarcomas: Insights into sarcoma biology. Cancer Res, 2005; 65(20): 9226–35
17. Hernando E, Charytonowicz E, Dudas ME et al: The AKT-mTOR pathway plays a critical role in the development of leiomyosarcomas. Nat Med, 2007; 13(6): 748–53
18. Wang H, Chen P, Liu XX et al: Prognostic impact of gastrointestinal bleeding and expression of PTEN and Li-67 on primary gastrointestinal stromal tumors. World J Surg Oncol, 2014; 12: 89
19. Brown DC, Gatter KC: Ki67 protein: the immaculate deception? Histopathology, 2002; 40(1): 2–11
20. Yerushalmi R, Woods R, Ravdin PM et al: Ki67 in breast cancer: Prognostic and predictive potential. Lancet Oncol, 2010; 11(2): 174–83
21. Pyo JS, Kang G, Sohn JH: Ki-67 labeling index can be used as a prognostic marker in gastrointestinal stromal tumor: A systematic review and meta-analysis. Int J Biol Markers, 2016; 31(2): e204–10