Hypoglycemia mediated by paraneoplastic production of Insulin like growth factor–2 from a malignant renal solitary fibrous tumor – clinical case and literature review

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Abstract

Background: Hypoglycemic episodes are infrequent in individuals without a history of diabetes mellitus or bariatric surgery. When hypoglycemia does occur in such individuals, an uncommon but important diagnosis to consider is non-islet cell tumor hypoglycemia (NICTH). We report a case of NICTH associated with paraneoplastic insulin-like growth factor-2 (IGF-2) production and review current relevant medical literature.

Case presentation: A 60 year old male with no relevant past medical history was referred to the endocrinology clinic with 18 month history of episodic hypoglycemic symptoms and, on one occasion was noted to have a fingerstick glucose of 36 mg/dL while having symptoms of hypoglycemia. Basic laboratory evaluation was unrevealing. Further evaluation however showed an elevated serum IGF-2 level at 2215 ng/mL (reference range 411–1248 ng/mL). Imaging demonstrated a large right suprarenal mass. A right nephrectomy with resection of the mass demonstrated a malignant solitary fibrous tumor. Post resection, the patient’s IGF-2 levels normalized and hypoglycemic symptoms resolved.

Conclusion: Due to the structural and biochemical homology between IGF-2 and insulin, elevated levels of IGF-2 can result in hypoglycemia. A posttranslational precursor to IGF-2 known as “big IGF” also possesses biologic activity. Review of recent reported cases of NICTH identified widespread anatomic locations and varied pathologic diagnoses of tumors associated with paraneoplastic production of IGF-2 causing hypoglycemia. Definitive management of hypoglycemia associated with paraneoplastic production of IGF-2 consists of resection of the tumor responsible for IGF-2 production. Accumulating literature provides a firm basis for routine IGF-2 laboratory evaluation in patients presenting with spontaneous hypoglycemia with no readily apparent cause.

Keywords: Non islet cell tumor hypoglycemia (NICTH), Insulin like Growth Factor–2 (IGF-2), Big IGF-2, Hypoglycemia, Paraneoplastic production, Insulinoma, Solitary fibrous tumor

Background

Hypoglycemia is a common medical problem in patients with diabetes mellitus treated with insulin or insulin se-cretagogues. Hypoglycemia is also associated with gastric bypass weight loss surgery [1].

Although rare, hypoglycemia is occasionally encountered in non-diabetic, non-gastric bypass patients. In such patients, hypoglycemia is usually a manifestation of pancreatic islet cell tumors producing insulin, primary or secondary adrenal insufficiency, advanced liver disease, pheochromocytoma, IGF-1 secreting tumors, hypothyroidism, substances interfering with insulin and insulin receptor mediated metabolism [non-islet cell tumor hypoglycemia (NICTH)] or antibodies interfering with insulin receptors [2].

In subjects with recurrent hypoglycemia and no history of diabetes or weight loss surgery, NICTH is an important disorder to consider in the differential diagnosis. Tumors
that have been reported to cause NICHT include malignancies associated with insulin receptor antibodies, tumor necrosis factor (TNF), interleukin (IL) -1 or −6; pheochromocytoma associated with excess catecholamine production; and paraneoplastic production of IGF-1 or IGF-2 [2].

In this article, we report a case of NICHT associated with paraneoplastic IGF-2 production. We have also reviewed the current literature on the subject and describe pathophysiology, diagnostic methods and treatment options.

Case presentation
A 60 year old male was referred to the Endocrinology clinic at the University of Minnesota for the evaluation of worsening symptoms that included diaphoresis, anxiety, inability to concentrate and episodic visual changes for the prior 18 months. Patient reported waking from sleep during the night with symptoms. He had discovered that carbohydrate rich snacks every 30–60 min prevented his symptoms. As a result of frequent snacking on carbohydrate containing foods, he had gained 30 pounds in the prior 12 months. He did not experience symptoms post-prandially. During one of his episodes, he obtained a finger stick glucose value of 36 mg/dL. His past medical history included hypertension, dyslipidemia and obstructive sleep apnea. He did not have history of diabetes mellitus or bariatric surgery. His medications included metoprolol extended release, hydrochlorothiazide, irbesartan, amlodipine, aspirin, terazosin, simvastatin and omeprazole. He occasionally consumed alcohol and had a remote history of smoking. Physical examination was within normal limits except for body mass index (BMI) of 33.2 kg/m².

Serial finger stick blood glucose monitoring during symptomatic episodes demonstrated recurrent hypoglycemia with blood glucose values of 41, 35 and 41 mg/dL. Diagnoses considered included medication induced hypoglycemia, insulinoma, chronic liver disease, pheochromocytoma, and adrenal insufficiency. These diagnoses were excluded based on laboratory evaluation (Table 1).

Subsequently, IGF-2 was measured and found to be 2215 ng/mL (reference range: 414–1248 ng/mL). Computed Tomography (CT) without contrast of chest, abdomen and pelvis showed a large right suprarenal mass measuring 14 × 17 × 16 cm, which was lobular in shape with central necrosis and calcifications (Figure 1). Technetium radionuclide bone scan did not show any metastatic disease.

The patient underwent right nephrectomy and resection of the mass. Surgical pathology showed a malignant solitary fibrous tumor with spindled to epithelioid cells and focal high-grade nuclear atypia (Figure 2). The tumor cell proliferation marker Ki67 index was elevated. The tumor was positive for CD34, CD99 and Bcl-2 consistent with a diagnosis of malignant solitary fibrous tumor.

The patient’s follow-up IGF-2 levels were within the normal range (Table 2). He did not experience further episodes of hypoglycemia and was able to lose 10 lbs over the next six months. A three year follow-up CT scan of the abdomen did not demonstrate any evidence of recurrence.

Discussion
The IGF-2 gene is located on short arm of chromosome 11 (11p15) adjacent to the insulin (INS) gene [3]. IGF-2 is a 67 amino acid polypeptide with 47% sequence homology with insulin. Post translational prepro IGF-2 contains 180 amino acids with a carboxy terminal peptide of 89 amino acids and a signal peptide of 24 amino acids. Prepro IGF-2 is cleaved to form mature IGF-2 [4]. Prepro IGF-2 molecules (known as “big IGF-2”) have also been shown to have biologic activity and can produce hypoglycemia in the setting of a normal IGF-2 level [5]. It is due to the structural and biochemical homology between IGF-2 and insulin that an unregulated and elevated level of IGF-2 stimulates glucose metabolism pathways thus leading to hypoglycemia [6].

Table 1 Laboratory evaluation of current case

| Test                              | Results  | Reference range |
|-----------------------------------|----------|-----------------|
| Insulin (after overnight fast)    | < 2 μU/mL| 0 – 20 μU/mL    |
| C-Peptide (after overnight fast)  | < 0.1 ng/mL| 0.9 – 6.9 ng/mL |
| Plasma glucose (after overnight fast) | 35 mg/dL| 60 – 99 mg/dL  |
| ALT                               | 19 U/L   | 0 – 70 U/L      |
| AST                               | 27 U/L   | 0 – 55 U/L      |
| Alkaline Phosphatase              | 75 U/L   | 40 – 150 U/L    |
| Total Bilirubin                   | Undetectable| 0.0 – 0.3 mg/dL |
| Albumin                           | 4.4 g/dL | 3.3 – 4.9 g/dL  |
| Total Protein                     | 5.2 g/dL | 6.8 – 8.8 g/dL  |
| Hemoglobin A1c                    | 49%      | 40 – 60%        |
| α-Fetoprotein                     | 5.5 ug/L | 0 – 8 ug/L      |
| IGF-1                             | < 0.1 ug/L| 0 – 5 ug/L      |
| TSH                               | 1.45 mU/L| 0.4 – 5.0 mU/L  |
| Free T4                           | 0.98 ng/dL| 0.70 – 1.85 ng/dL |
| Plasma Norepinephrine             | 549 pg/mL| 80 – 520 pg/mL  |
| Plasma free Normetanephrine       | 0.65 mmol/L| < 0.9 mmol/L    |
| Plasma Epinephrine                | 117 pg/mL| 10 – 200 pg/mL  |
| Plasma free Metanephrine          | 0.23 mmol/L| < 0.5 mmol/L    |
| Cortisol                          | 11 ug/dL | 4 – 22 ug/dL    |
| Adrenocorticoid Hormone           | 23 pg/mL | < 47 pg/mL      |
| IGF-2 (at diagnosis)              | 2215 ng/mL| 414 – 1248 ng/mL |
Under physiologic conditions, IGF-2 is mainly produced by the liver. However, other tissues may also produce IGF-2, allowing it to exert effects through endocrine, autocrine and paracrine pathways [7]. Physiologically, IGF-2 plays an important role in human fetal and post-natal development but whether it has significant physiological function in adults remain unknown [8]. As opposed to IGF-1, IGF-2 regulation is independent of growth hormone [9]. IGF-1 and IGF-2 both have glucose lowering potency that is approximately 5% of insulin’s potency. However, plasma concentrations of IGF-1 and IGF-2 can be 1000 times greater than insulin in NICHT allowing them to cause hypoglycemia [10]. More than 95% of IGF-2 in the circulation is bound to insulin like growth factor binding proteins (IGFBP) that have high affinity for both IGF-1 and IGF-2 [11]. In spite of structural homology with insulin, normal levels of IGF-2 do not cause hypoglycemia. At the cellular level, IGF-2 binds with IGF2R which is responsible for endocytosis, intracellular hormone transport and degradation of circulating IGF-2 [12].

Tumors producing elevated levels of circulating IGF-2 with resulting hypoglycemia are categorized as NICHT. NICHT has also been reported in conjunction with paraneoplastic production of insulin receptor antibodies, tumor necrosis factor (TNF), interleukin (IL) -1 and –6, catecholamine (pheochromocytoma) and IGF-1 [2]. For reasons not clear, there are several neoplasms noted to have high levels of IGF-2 mRNA without exhibiting elevated hormone activity [13].

The IGF-2 gene is an imprinted gene; normally only one parental allele is expressed [14]. Loss of imprinting leads to over expression of IGF-2 and has been demonstrated in multiple tumors including solitary fibrous tumors (independent of anatomical location), Wilm’s tumors, metastatic hemangiopericytomas, mesotheliomas, hepatocellular carcinomas, gastrointestinal stromal tumors (GIST), colorectal adenomas, osteosarcomas, rhabdomyosarcomas, leiomyosarcomas, paragangliomas, prostate cancers, breast cancers and bladder cancers [2,15]. Although these neoplasms often have elevated levels of IGF-2 mRNA, they do not always produce elevated circulating levels of IGF-2 or big IGF-2. Genetic and epigenetic mechanisms that determine isolated transcription of mRNA and the production of IGF-2 and big IGF-2 are not well understood; however, these mechanisms are thought to play an important role in carcinogenesis and tumor growth [13,16].

In a previous extensive review of this topic by de Groot and coauthors in 2007, authors noted that 41% of
the IGF-2 producing tumors causing hypoglycemia were of mesenchymal origin, 43% of epithelial origin, 1% of neuroendocrine and hematopoietic origin and 14% of unknown origin [2]. Although symptoms of hypoglycemia were predominant, other symptoms included skin tags, acne and rhinophyma.

We reviewed case reports of NICTH associated with paraneoplastic production of IGF-2 from 2008 to 2012 (Table 3) [17-38]. On our review of literature, we identified 22 published reports of NICTH with elevated IGF-2 levels causing hypoglycemia. Age range of the patients was 27 – 83 years (mean age 58 years), with 14 males and 8 females. Predominant symptoms included those of hypoglycemia (diaphoresis, tremor, anxiety, loss of consciousness) and mechanical symptoms depending on site of the tumor. Some tumors were associated with acromegaly. The anatomic location of tumors in these case reports included liver (n = 9), pleural cavities (n = 5), lungs (n = 3), retroperitoneum (n = 3), bones (n = 2), pelvis (n = 2), breasts (n = 2), cranium (n = 1), kidney (n = 1), uterus

| Reference | Age/sex | Tumor site | Tumor pathology | Hormone elevated | Management |
|-----------|---------|------------|-----------------|-----------------|------------|
| [17]      | 28, male | Retroperitoneal pelvic region | Malignant solitary fibrous tumor | IGF-2 | Surgical resection of tumor |
| [18]      | 68, male | Liver | Solitary fibrous tumor | Big IGF-2 | Partial hepatic resection |
| [19]      | 59, male | Lungs and bones | Meningeal hemangiopericytoma | IGF-II (elevated IGF-2/IGF-1 levels) | Interferon alpha |
| [20]      | 75, male | Left pleural cavity | Pleural solitary fibrous tumor | Big IGF-2 | Surgical resection |
| [21]      | 65, male | Retroperitoneal tumor | Retroperitoneal solitary fibrous tumor | IGF-2, Big IGF-2 | Surgical resection |
| [22]      | 66, female | Right inferior thorax | Solitary fibrous tumor | IGF-2 | Surgical resection |
| [23]      | 53, male | Liver | Metastatic hemangiopericytoma | Elevated IGF 2/IGF-1 ratio | Right hepatectomy |
| [24]      | 64, female | Right lower thorax | Malignant solitary fibrous tumor | Elevated IGFBP | Surgical resection, radiation post operatively |
| [25]      | 83, male | Retroperitoneum | Malignant solitary fibrous tumor | Big IGF-2 | Surgical resection |
| [26]      | 43, male | Right posterior cranial fossa, metastatic lesions in bilateral kidney, right iliopsoas muscle, right iliac body, thoracic vertebra 10 body and segment IV of the liver | Meningeal hemangiopericytoma | Elevated IGF-2/IGF-1 ratio | Adriamycin |
| [27]      | 59, female | Right hemithorax | Solitary fibrous tumor | Elevated IGF-2/IGF-1 ratio | Surgical resection |
| [28]      | 67, male | Pelvis | Solitary fibrous tumor | Elevated IGF-2/IGF-1 ratio | Tumor embolization and radiotherapy |
| [29]      | 49, female | Right breast | Benign Phyllodes tumor | Big IGF-2 | Mastectomy |
| [30]      | 49, female | Left breast | High grade Phyllodes sarcoma | Big IGF-2 | Mastectomy |
| [31]      | 80, female | Uterus | Uterine leiomyoma | IGF-II, elevated IGF-2/IGF-1 ratio | Exploratory laparotomy |
| [32]      | 69, male | Spleen, lungs, liver | Hepatocellular carcinoma | Elevated IGF-2 mRNA expression | Gastroctomy |
| [33]      | 61, male | Liver | Poorly differentiated gastric adenocarcinoma | Big IGF-2, elevated IGF-2/IGF-1 ratio | Gastroctomy |
| [34]      | 27, female | Lung and liver | Ovarian germ cell tumor | Big IGF-2 | Dexamethasone, recombinant Growth hormone |
| [35]      | 53, female | Right adrenal gland, liver | Elevated IGF-2/IGF-1 ratio | Phenoxybenzamine |
| [36]      | 45, male | Pelvis and peritoneum | Desmoplastic small round cell tumor | Elevated IGF-2 and IGF-2/IGF-1 ratio | Chemotherapy |
| [37]      | 77, male | Liver and lungs | Hepatocellular carcinoma | Big IGF-2 | Chemotherapy |
| [38]      | 41, male | Pleura and posterior mediastinum | Solitary fibrous tumor | Big IGF-2 | Chemotherapy |
High molecular weight IGF-2 (big-IGF-2) or an increased population. It is associated with elevated levels of IGF-2, NICTH is a rare cause of hypoglycemia in the general population. It is associated with elevated levels of IGF-2 (big-IGF-2) or an increased IGF-2 to IGF-1 ratio. Diagnosis of paraneoplastic IGF-2 induced hypoglycemia is an important and time sensitive consideration since earlier detection of tumors provides a better opportunity for complete resection and subsequent resolution of hypoglycemia. Whether IGF-2 level should be routinely measured in the evaluation of hypoglycemia depends on the prevalence of the condition. Accumulating literature supports screening for IGF-2 in non-diabetic individuals who present with hypoglycemia along with suppressed insulin and c-peptide levels.

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review.

Abbreviations
IGF-1: Insulin like growth factor–1; IGF-2: Insulin like growth factor–2; NICTH: Non-islet cell tumor hypoglycemia; TNF: Tumor necrosis factor; IL: Interleukin; BMI: Body mass index; CT: Computed tomography; LC-MS: Liquid chromatography–mass spectrometry.

Competing interest
The authors declare that they have no competing interests.

Authors' contribution
AK reviewed the literature and wrote the manuscript. BJR edited the manuscript, wrote the abstract and participated in the literature review. JB was involved in clinical management and reviewed and edited the manuscript. AM was involved in clinical management and reviewed and edited the manuscript. All authors read and approved the final manuscript.

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