



TUMOR INDUCED HYPOGLYCEMIA – A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Non-Islet cell tumor hypoglycemia (NICTH) is a rare syndrome caused by a wide range of tumors arising from both mesenchymal and epithelial tissue. Retroperitoneal sarcoma has rarely been reported to secrete insulin growth factor -2(IGF-2), causing Tumor Induced Hypoglycemia. We are reporting a case report of recurrent sarcoma arising from mesentery of rectum which had reached large dimensions causing incisional hernia and TIH.

KEYWORDS: NICTH, Retroperitoneal Sarcoma, IGF-2-oma, Refractory hypoglycemia.

CASE REPORT

51-year-old male patient with no history of diabetes mellitus was diagnosed with abdominal sarcoma in 2018. He had undergone resection of tumor with no adjuvant treatment. HPE was reported neurofibrosarcoma. A year later, he had pelvic recurrence and recurrent episodes of severe hypoglycemia, resulting in poor quality of life and loss of job. He was re-explored and tumor was found to be unresectable. He was presented to us with a history of abdominal distension, constipation, loss of appetite, multiple episodes of sweating, loss of consciousness, since November 2019. He did not give any history of indigenous medication. On examination, he was thin built, anemic, hypoproteinemia. There was a midline incision scar with presence of incisional hernia and prolapsed colostomy. A large lump was palpable in lower abdomen occupying pelvis and lower abdomen. On rectal examination, rectum was free up to 4 cms from anal verge. During hospitalization patient had multiple episodes of hypoglycemia needing 5% dextrose infusion, glucocorticoids and octreotide, and multiple blood transfusions. Contrast enhanced MRI of abdomen showed multiple large solid enhancing lesions in the abdominal cavity, predominantly involving small bowel mesentery and rectum. The largest one was approximately 22x18 cms. There were multiple small lesions in perihepatic space (Fig 1, 2). Serum C-peptide was 0.327ng/ml, Serum Insulin 0.24IU/ml, IGF-2 levels could not be done as the assay is not available locally. Cytoreductive surgery was done necessitating resection of small bowel, anterior resection of rectum and covering ileostomy. Post operatively patient was managed in ICU. Recovery was uneventful.

HPE revealed multiple tumors with segments of small intestine and recto sigmoid attached. Sections showed tumor cells in sheets and fascicles showing a whirling pattern. The cells were spindle shaped, fairly uniform with scanty cytoplasm and ovoid bland hyper chromatic nuclei. EMA, CD 99, CD56, CK was strongly positive in lesional cells. Tumor was negative for CD 117, DOG-1, SMA, S-100 protein, TLE-1, Calretinin, TTF-1, Ki -67 was 12%. Overall picture was suggestive of spindle cell synovial sarcoma.

Tumor Induced Hypoglycemia

The initial recognition of this syndrome dates to 1929 in patients with hepatocellular carcinoma.^[1,2] NICTH (Non –Insulin cell Tumor hypoglycemia) is a well-recognized etiology of TIH (Tumor induced Hypoglycemia). Non-islet-cell tumor hypoglycemia (NICTH), denotes the syndrome of hypoglycemia produced by or associated with any neoplasm, other than an insulinoma. Tumor induced hypoglycemia (TIH) is a rare clinical entity that may occur in patients with diverse kinds of tumor lineage. The tumors reported to cause TIH are Hepatocellular carcinoma, Hepatoma, Fibroma, Fibro sarcoma, Mesothelioma, Leiomyosarcoma and Hemangiopericytoma. The pathogenesis of TIH may be variable like the ectopic insulin secretion by non-islet cell tumors, such as bronchial carcinoids and gastrointestinal stromal tumors. The main etiology of hypoglycemia in NICTH is the release of insulin-like growth factor (IGF2) or its high-molecular-weight precursor (big IGF2),^[3,4] IGF1 and production of autoantibodies to insulin or its receptor and more rarely, the secretion of glucagon-like peptide (IGP1), while at times the tumor burden. Lastly, ectopic insulin secretion by a non-islet-cell tumor has also been reported.^[5,6] Since

then, many other types of neoplasms have been associated with the IGF-2oma syndrome. Frequently, these tumors are quite large at the time of diagnoses, weighing 3kg or more to the extent of 20 kg tumor has been reported in literature.^[7] The mass effect of the tumor depends on size and location. Tumors that arise in the thorax, retro peritoneum or pelvis are usually clinically silent and tend to reach to a significant size before diagnosis. On the other hand, lesion that are located in the extremities, e.g., in the thigh or knee, are detected much earlier due to signs and symptoms related to mass.

In about half of patients with IGF-2- linked hypoglycemia, the neoplasm is diagnosed often long before the onset of hypoglycemia.^[8] In these patients, the most common presenting features are weight loss, abdominal mass, pain, or detection on routine radiologic examination.

Although both neuroglycopenic and autonomic symptoms of hypoglycemia may occur, cerebral dysfunction dominates, repeated bouts of hypoglycemia or hypoglycemia that comes on slowly over a period of hours. An early sign of neuroglycopenia is the loss of good judgment. The patient may present with confusion, amnesia, or frank psychosis.^[9] Hypoglycemia, when severe or protracted, can cause seizures, coma, and death. Hypoglycemia may produce focal neurological signs and symptoms, mimicking a stroke or metastases. It is likely that IGF-2 linked tumor hypoglycemia remains unrecognized in many cancer patients who are receiving palliative care, where neuroglycopenic symptoms could be erroneously attributed to effects of narcotics or other medications.

Mechanism of Hypoglycemia

The underlying mechanism of hypoglycemia in nearly all patients with this syndrome is overproductions of IGF-2 by the tumor, which includes mature IGF-2 and incompletely processed forms of IGF-2. IGF-2 stimulates increased peripheral uptake of glucose by skeletal muscles, free fatty acid levels are decreased by IR (Insulin Receptor), mediated inhibition of Lipolysis, glycogenolysis, gluconeogenesis and ketogenesis in liver.^[10,11] Increased uptake of glucose by tumor contributes little to hypoglycemia. Circulating glucagon is suppressed by action of IGF-2 on IGF-1R and IR of pancreatic islet cells. Rarely, markedly elevated IGF-2 levels produce somatic changes suggestive of acromegaly. Due to suppression of growth hormone (GH) secretion, synthesis and secretion of IGF1 and IGF, binding protein 3 are also decreased. The ratio of pro IGF2:IGF2 and IGF2: IGF1, plasma levels of insulin, IGF-1, and GH (Growth Hormone). Complicating the pathophysiology are the IGF binding proteins (IGFBPs) that can bind IGF-2 and IGF-1, modifying hormone metabolism and action. IGFBP concentrations are often altered in the presences of these tumors. At the cellular level, the 3 hormone-related ligands, IGF-2, IGF-1, and

insulin, all bind to 4 (or more) types of IGF-1 receptor (IGF-1r) and insulin receptor (IR).

With hypoglycemia brought about by activation of insulin-related receptors, the rise in ketones is blunted, magnifying the brain's energy shortage. The continuing activation of insulin receptors (IRs) by IGF-2 leads to 1) continued glucose utilization, especially by skeletal muscle, 2) suppression of free fatty acid release by adipocytes and 3) inhibition of glucose release (glycogenolysis, gluconeogenesis, and ketogenesis in the liver). In addition to effects on glucose metabolism, IGF-2omas in rare instances can produce acromegaly. Trivedi et al.^[13] reported a woman with pelvic clear cell sarcoma and acromegaloid features including skin tags and coarse facial appearance which disappeared after removal of tumor. Skin lesions such as seborrheic keratosis, skin tags, and rhinophyma have all been described in patients with IGF-2 producing tumors. Although hypoglycemia is ascribed largely to IGF-2 activation of the IR, the acromegaloid features are thought to arise largely from IGF-2 mediated stimulation of multiple subclasses of insulin-related and IGF-2-related receptors.

Diagnosis

The evaluation should be initiated with the documentation of hypoglycemia and all components of Whipple's triad, 1) symptoms and/or signs of hypoglycemia, 2) low plasma glucose, and 3) resolution of signs and symptoms upon reversal of hypoglycemia.

In people without diabetes, the diagnosis of hypoglycemia is usually established when venous plasma glucose is <55 mg/dl (3 mmol/l) and supported by the presence of Whipple's triad. After confirmation of hypoglycemia, the next step is to evaluate carefully the patient's history and physical findings to identify any systemic conditions that may be causing or contributing to hypoglycemia.

Lab Investigations;

- 1) Cortisol deficiency induced hypoglycemia in Addison's disease.
- 2) Hypopituitarism as well as critical illnesses with liver failure, and/or kidney failure, sepsis, GH deficiency, and severe starvation.
- 3) Ethanol is known to inhibit gluconeogenesis in the liver, contributing to hypoglycemia.
- 4) Drug-induced hypoglycemia must be seriously considered in the differential diagnosis.
- 5) Measure plasma insulin and C peptide, along with the corresponding glucose level during an episode of hypoglycemia, either spontaneous or provoked by a supervised fast.

IGF-2- linked tumor hypoglycemia is suspected when hypoglycemia without hyperinsulinemia is present and the other etiologies mentioned above have been ruled out. Typically, insulin, proinsulin, C- peptide, and b hydroxybutyrate levels are low along with low plasma

levels of total IGF-1. Levels of total IGF-2 precursors are often elevated. An elevated ratio of IGF-2 to IGF-1 may be helpful in the diagnosis. In a patient with recurrent hypoglycemia, ratio of 10:1 are virtually diagnostic for IGF-2 linked hypoglycemia. Fukuda et al found IGF-2 to IGF-1 ration as high as 64:1.^[14]

Treatment

The mainstay of treatment of hypoglycemia with IGF-2 oma remains surgical resection of the tumor. Recurrence of hypoglycemia after surgical resection commonly signals tumor recurrence. When complete resection is not possible, palliative tumor debulking is recommended, as with other hormone secreting tumors. Debulking in conjunction with tumor embolization has been used with some success. Neo-adjuvant therapies such as radiation and chemotherapy have also been reported to abate instances of hypoglycemia, albeit temporarily.

When hypoglycemia persists after surgical interventions have reached their limits, multiple medical modalities have been employed. The most effective agents have been the glucocorticoids. They act to prevent hypoglycemia through several mechanisms: stimulation of hepatic gluconeogenesis, inhibition of peripheral glucose uptake, mobilization of amino acids from extra hepatic sites, and promotion of lipolysis with fatty acid release from adipose tissue. In these cases, long-term management with glucocorticoid therapy has been demonstrated to consistently reverse the biochemical abnormalities caused by tumor-derived big IGF2 and it has been suggested that this therapy alone or in combination with human growth hormone, with or without the addition of long-acting glucagon, is the most effective therapy in alleviating intractable hypoglycemia.^[15]

NICTH due to overproduction and secretion of IGF1 (IGF1oma) is an exceptional event.

Teale et al reported on 8 cases of hypoglycemia due to IGF-II secreting tumors. They concluded that chronic steroid therapy may successfully treat hypoglycemia in some patients and complete surgical resection is recommended when possible.^[15] De Groot et al reported on two adult patients with IGF-II secreting tumors: one with a solid fibrous tumor of the kidney and another with a metastatic hemangiopericytoma. The first patient hypoglycemia immediately resolved after resection of the kindly mass. The second patient harbored several unrespectable masses. With chronic corticosteroid therapy and chemotherapy, this patient remained free of hypoglycemia events for more than a year.^[16] Bourcigaux et al. reported resolution of hypoglycemia with combined chronic steroids and recombinant human growth hormone.^[17] Chan et al. reported resolution of hypoglycemia after steroids and complete resection.^[18] Dutta et al. reported 5 IGF-II secreting tumors including a retroperitoneal sarcoma, hemangiopericytoma, adrenocortical carcinoma pleural mesothelioma and a

retroperitoneal leiomyosarcoma. Four patients underwent complete resection and all remained free from hypoglycemia events at follow up (6 months – 6 years).^[19] Treatment such as chemotherapy, radiotherapy tumor embolization and alcohol injections into the tumor have been used with little effect on TIH.^[20]

CONCLUSION

Hypoglycemia is a rare but potentially life-threatening presentation of soft tissue tumors. The etiology of hypoglycemia may be difficult to diagnose. Retroperitoneal sarcomas have rarely been reported to secrete insulin-growth factor II (IGF II) which can lead to low blood glucose levels. IGF II secreting sarcomas represent an extremely rare subset of soft tissue tumors. Therefore, tumor-induced hypoglycemia should be considered in a patient with low blood glucose, low C-peptide, low fasting insulin levels and weight loss.

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