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CASE REPORT
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Late-Onset Non-islet Cell Tumor Hypoglycemia Associated with a Pleural Solitary Fibrous Tumor

ABSTRACT

A 53-year-old, non-diabetic lady was evaluated for worsening breathlessness over the past 1 year. She was diagnosed with a lung lesion a year ago, but the prevailing COVID-19 situation prevented her from seeking further evaluation. She began to have early morning episodes of symptomatic hypoglycemia over the previous 4 months, which were relieved with dextrose infusions. The evaluation showed low insulin, low C-peptide, and high insulin-like growth factor-2 to insulin-like growth factor-1 ratio. High-resolution computed tomography scan of the thorax showed a 19.5 cm × 16.6 cm × 23.8 cm mass in the left hemithorax, and a microscopic examination of a biopsy specimen of which was consistent with the diagnosis of solitary fibrous tumor. The patient underwent sternotomy with left anterior thoracotomy with successful excision of the fibrous tumor. Post-operatively, histopathological diagnosis of solitary fibrous tumor was confirmed. There were no further episodes of hypoglycemia, and the patient was completely recovered.

Keywords: Hypoglycemia, non-islet cell tumor hypoglycemia, solitary fibrous tumor, thoracotomy, tumor-induced hypoglycemia

Introduction

In a non-diabetic person, hypoglycemia is said to be present when venous plasma glucose level is less than 55 mg/dL, along with autonomic and/or neuroglycopenic symptoms suggestive of hypoglycemia and improvement in the symptoms after administration of glucose.[1] Non-islet cell tumor hypoglycemia (NICTH), previously known as Doege–Potter syndrome, is a rare paraneoplastic syndrome characterized by recurrent fasting hypoglycemia. Non-islet cell tumor hypoglycemia primarily occurs in patients with solid tumors originating from mesenchymal, epithelial, or hepatic tissues,[2,3] which secrete incompletely processed, high-molecular-weight insulin-like growth factor 2 (pro-IGF-2 or big IGF-2).[4,5] As total resection of the tumor is potentially curative, it is critical to diagnose NICTH and the source of IGF-2 secretion. In this study, we describe one such case of a large solitary fibrous tumor (SFT), arising from the lung pleura and causing recurrent hypoglycemic episodes.

Case Presentation

A 53-year-old, non-diabetic lady presented to our hospital with progressive breathlessness over the past 1 year. She was diagnosed with a left lung lesion on x-ray a year ago. The patient refrained from further evaluation and treatment till such a time the COVID-19 situation improved. Her husband further reported that she had a few episodes of confusion early in the mornings for the past 4 months, for which she needed hospitalization at another medical establishment, and was found to have low plasma glucose which was relieved with dextrose infusion. At that time, the patient was advised mid-night and early morning snacking. However, a carbohydrate-rich diet could hardly prevent hypoglycemia, as the patient used to experience palpitations and hunger during delayed meals and early mornings. During the first 2 days of hospitalization at our center, she developed altered sensorium in the early morning time, and capillary blood glucose by finger-stick at those times was found to be 42 and 44 mg/dL. Both times patient responded promptly to intravenous 25% dextrose therapy.

There was no history of diabetes mellitus, alcohol, and/or illegal drug abuse. She was neither on any medical therapy nor was there a history of diabetes in her family.

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On examination, her vital parameters were stable, and general examination was unremarkable. She did not show any acromegalic phenotype. Inspection of the respiratory system demonstrated abdomino-thoracic respiration with reduced chest movements on the left side and deviation of the trachea to the right. The air entry on the left side of the chest was noted to be markedly decreased as compared to the right side.

Renal and hepatic causes of hypoglycemia were ruled out as the metabolic panel workup was normal. During the episode of hypoglycemia, corresponding paired plasma glucose, serum insulin concentration, serum C-peptide, serum cortisol, and serum growth hormone (GH) were 32 mg/dL, undetectable, 0.17 ng/mL, 17.1 µg/dL, and 0.32 ng/ml respectively (Table 1). Thyroid function tests were normal and serum IGF-1 concentration was low (37.9 ng/mL). Although IGF-2 concentration was normal (508 ng/mL), the ratio of IGF-2 to IGF-1 was more than 10 (13.4).

High-resolution computed tomography (CT) scan of the chest revealed a mass of heterogeneous density of size 19.5 cm × 16.6 cm in axial dimension and 23.8 cm in superior-inferior extension, near totally occupying the left hemithorax with nodular and chunky calcifications and causing compression collapse of the left lung (Figure 1).

Computed tomography-guided biopsy of the mass demonstrated spindled cells, arranged around dilated vessels, within abundant stromal collagenization. Immunohistochemically, the tumor cells expressed vimentin, B-cell lymphoma 2, signal transducer, and activator of transcription 6 (STAT6), CD34, and desmin, suggestive of fibrous tumor.

The patient was initiated on hydrocortisone injections, 100 mg thrice a day, as there were frequent hypoglycemic episodes even with a high carbohydrate diet. A week later, after written informed consent, she underwent sternotomy with left anterior thoracotomy and excision of the fibrous tumor (Figure 2A).

Gross pathological examination demonstrated a mass of 3990 g measuring 27 cm × 21 cm × 15 cm, with the cut surface of serial sectioning showing pale white fibrous glistening areas, few yellow pale infarcted areas, and firm calcified/ossified areas (Figure 2B).

Table 1. Laboratory Assessment of Hypoglycemia

Lab Parameter	Value (Normal Range)	Lab Method
Glucose (mg/dL)	32 (70-100)	GOD-POD
Insulin (mIU/mL)	<2 (6-27)	CLIA
C-peptide (ng/mL)	0.17 (0.9-71)	CLIA
Growth hormone (ng/mL)	0.32 (0-7)	CLIA
IGF-1 (ng/mL)	37.9 (44.7-210)	CLIA
IGF-2 (ng/mL)	508 (333-967)	RIA
T_4 (µg/dL)	12.1 (4.5-12.5)	CLIA
TSH (mIU/mL)	1.54 (0.3-5)	CLIA
Cortisol (µg/dL)	17.1 (5-25)	CLIA

CLIA, chemiluminescence immunoassay; GOD-POD, glucose oxidase-peroxidase; IGF, insulin-like growth factor; RIA, radioimmunoassay; TSH, thyroid-stimulating hormone.

Histopathological examination showed moderate cellularity with varying amounts of stromal collagen, without nuclear atypia or pleomorphism. Mitotic activity was 2 per 10 high power fields. Immun ohistochemically, the tumor cells expressed vimentin, STAT6, CD99, and CD34 and were negative for smooth muscle actin, cytokeratin, and epithelial membrane antigen, with a Ki67 index of 8% (Figure 3). Thus, a diagnosis of SFT was confirmed.

Post-operatively, there were no further episodes of hypoglycemia. On the fifth day post-surgery, corresponding paired fasting plasma glucose, serum insulin concentration, serum C- peptide, and serum IGF-1 were 86 mg/dL, 7 mIU/mL, 5.9 ng/mL, and 64.3 ng/mL, respectively. The patient recovered swiftly without any complications and was discharged after 15 days.

At 3 months follow-up, there was no residual or recurrent disease on repeat imaging, and the patient was free from hypoglycemic episodes.

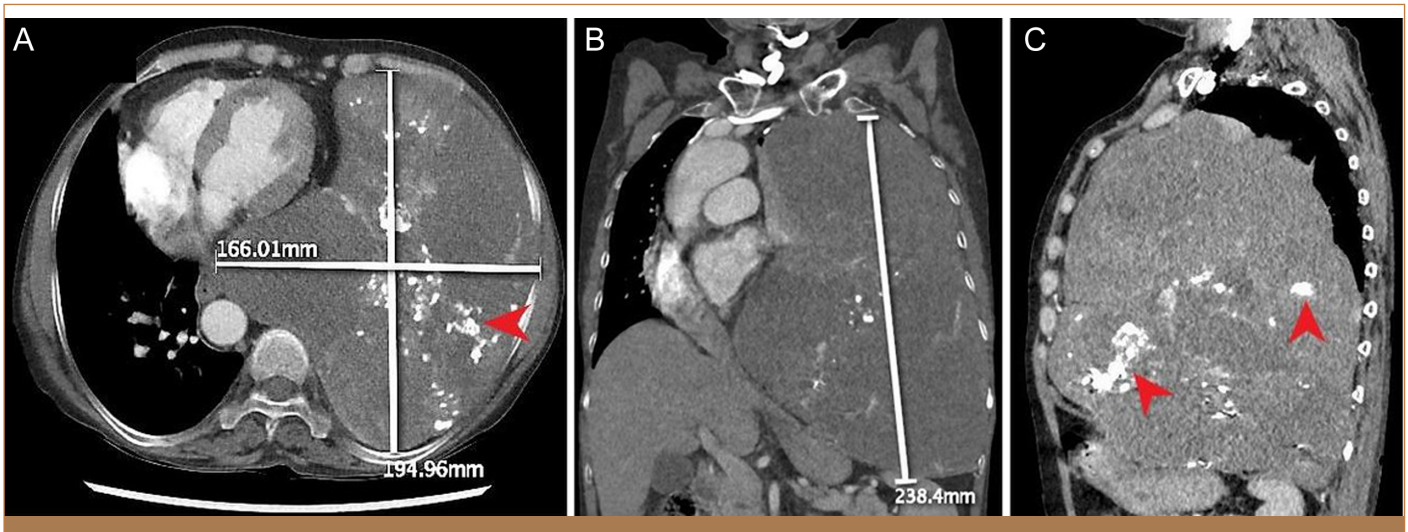

Figure 1. High-resolution CT scan showing a large, well-defined, isodense mass in left hemithorax of size 19.5 cm × 16.6 cm × 23.8 cm, with nodular-chunky calcifications (red arrowheads). CT, computed tomography.

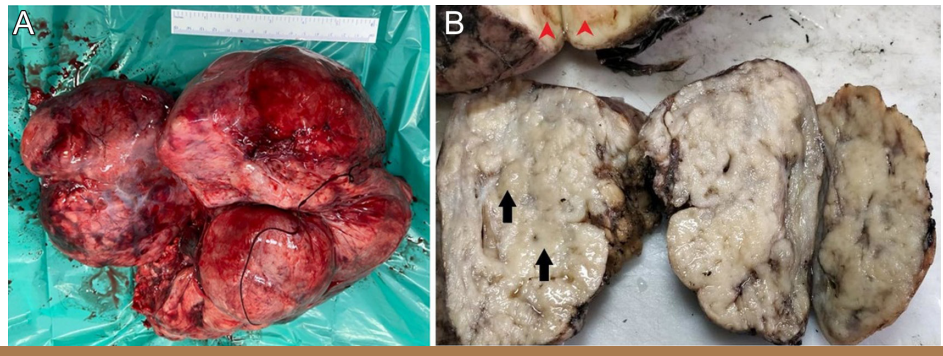

Figure 2. Intra-op photograph (A) after removal of multilobulated tumor and cut surface (B) showing the areas of infarction (black arrows) and calcifications (red arrowheads).

Discussion

Non-islet-cell tumor hypoglycemia is a rare paraneoplastic syndrome. It was first reported in 1929 in a patient suffering from hepatocellular carcinoma.[6] Since then, more than a hundred cases have been described worldwide, and it is now thought to be the next most prevalent cause of hypoglycemia after insulinoma, in non-diabetic seemingly well individuals.[7]

The tumors most commonly associated with NICTH are mesenchymal, epithelial, or hepatic in origin, and it is more likely to develop in those with a substantial tumor burden.[2] Solitary fibrous tumors are uncommon mesenchymal tumors, and 4%-6% of SFT patients develop NICTH.[3] Solitary fibrous tumors are reported to have an indolent course, with moderate malignant potential and a low risk of metastases.[8]

Non-islet-cell tumor hypoglycemia is often triggered due to the overutilization of glucose or the overexpression of IGF-2 gene by the tumor cells.[9,10] The loss of maternal allele imprinting of IGF-2 gene in the tumor cells results in an increased expression of IGF-2 gene within these cells. The translation product of IGF-2 mRNA is a 180-amino acid pre-pro-IGF-2, which is sequentially modified post-translation to pro-IGF-2 and then to the IGF-2 protein. Altered post-translational processing happens in these tumors, likely due to the synthesis of high levels of pro-IGF-2, resulting in increased production and secretion of pro-IGF-2 (or big IGF-2 or high-molecular-weight IGF-2).

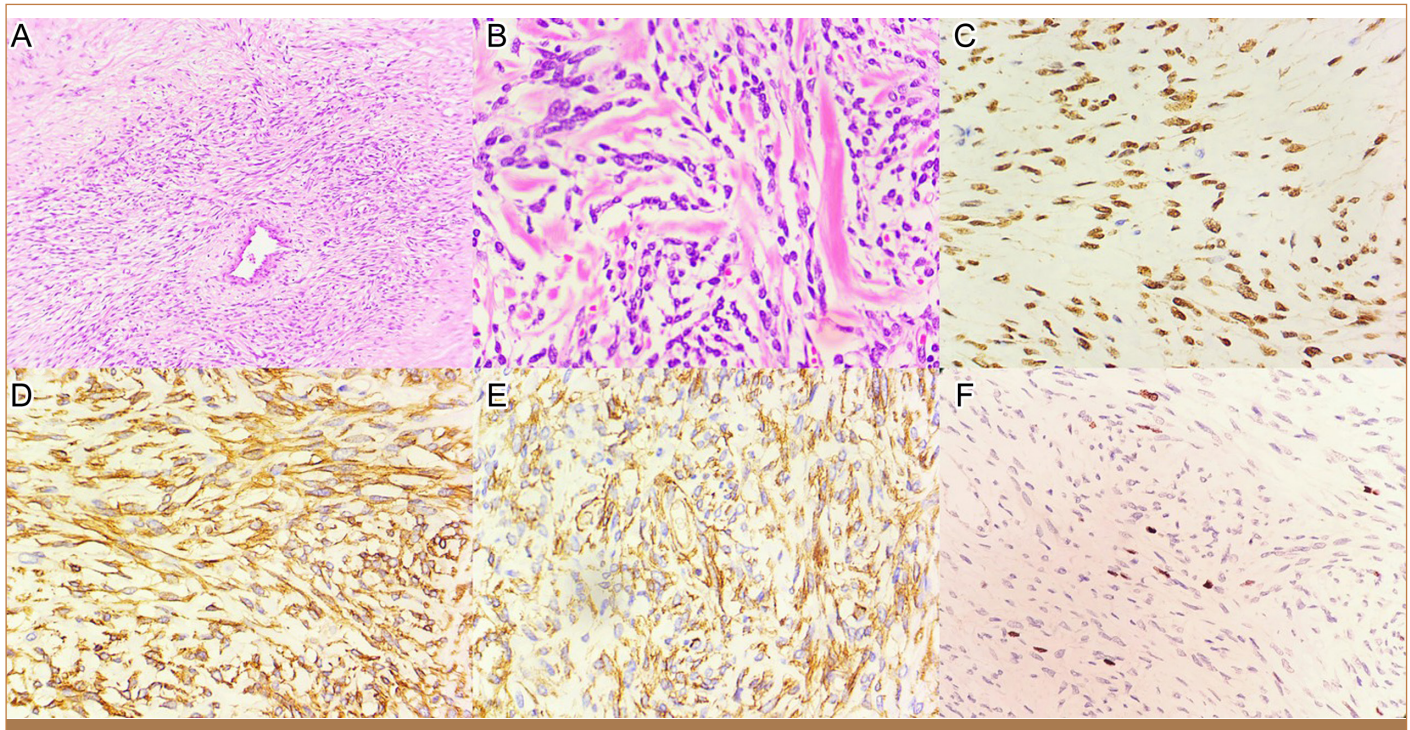

Figure 3. Hematoxylin and eosin (H&E) staining showing spindled cells clustering around a blood-vessel within the stromal collagen on low power (10×) photomicrograph (A); Typical SFT-like features with ovoid nuclei and a thick collagenous stroma seen on high power (40×, H&E) on photomicrograph (B). Immunoreactivity for STAT6 (C), hallmark of SFT; CD99 (D) and CD34 (E) was also present. Ki67 index was 8% (F). SFT, solitary fibrous tumor.

Normally, the IGF-2 protein, in combination with IGF-binding protein-3 (IGFBP-3) and acid-labile subunit (ALS), forms a 150-kDa ternary complex, which cannot cross the capillary membrane. However, in NICTH, the pro-IGF-2 combines with IGFBP-3 to form a 50-kDa binary complex but is unable to form a ternary complex with ALS. This smaller binary complex can cross the capillary membrane and interact with insulin receptors, thereby causing hypoglycemia.[11,12]

Similarly, the binary complex can also interact with IGF receptor 1 and can cause tissue overgrowth and skin changes, leading to features of acromegaly, seborrheic keratosis, skin tags, rhinophyma, etc.[13]

Biochemical investigations during hypoglycemia in patients with NICTH illustrate low serum insulin, C-peptide, IGF-1, and GH. High levels of pro-IGF-2 suppress the secretion of insulin, GH, and IGF-1. The secretion of normal IGF-2 is also suppressed but not to the degree of IGF-1, leading to an increased IGF-2 : IGF-1 ratio.[2] Normally, the ratio of IGF-2 to IGF-1 is about 3 : 1, and a ratio exceeding 10 : 1 suggests the secretion of IGF-2 precursors.[3,5,11] Therefore, in hypoinsulinemic hypoglycemia, an inappropriately normal IGF-2 level should not exclude the diagnosis of NICTH. The assays for high-molecular weight IGF-2 precursors are carried out only in a few research laboratories and are not freely available. Low IGFBP-3 level can additionally be used as an indirect clue to corroborate the diagnosis of NICTH.

Total excision of the offending tumor is curative in patients with NICTH. However, complete resection could be difficult due to location or size of the tumor, presence of metastases, and patient factors like associated co-morbidities or unwillingness of the patient to undergo surgery.[3,9] In cases where complete resection of the tumor is not possible, reduction in the tumor size by surgery, radiotherapy, chemotherapy, embolization, etc. can reduce tumor burden and relieve hypoglycemic episodes.[2,3] In circumstances where the underlying malignancy cannot be treated, primary management of hypoglycemia involves a frequent calorie and carbohydrate intake. Hypoglycemic episodes can be managed acutely by administering oral carbohydrates (specifically glucose) or subcutaneous or intramuscular injection of glucagon (0.5-1.0 mg). In the hospital setting, it can be treated by giving dextrose intravenously. When long-term management of NICTH with oral carbohydrate feeding fails, medical therapy with glucocorticoids (individual dose titration), glucagon (0.06-0.30 mg/hour infusion), and high-dose recombinant GH (3-12 mg daily) are effective options.[2,3,14] The effect of continuous glucagon therapy may be limited because of exhaustion of glycogen reserve, especially in critically ill patients where the tumor burden is high. The use of recombinant human GH (hGH) in patients with NICTH is limited as the high doses lead to peripheral edema, orthostatic hypotension, arthralgias, and paresthesias, especially in the elderly. Additionally, for long-term hGH therapy, the cost is a major limiting factor in resource-constrained settings. Diazoxide and octreotide have no role in NICTH, though there is a recent case report of successful treatment of NICTH with pasireotide.[3,15] Glucocorticoid therapy is considered a practicable initial medical therapy as it has an immediate beneficial effect on symptomatic hypoglycemia, and it has also demonstrated improvement in the underlying biochemical dysfunction by decreasing the production of pro-IGF-2.[14]

Our reported patient had a massive SFT, with progressive worsening of breathlessness for over a year. In all likelihood, the SFT might have been enlarging over many years prior to onset of symptoms, as significant unilateral pulmonary compromise is needed before dyspnea sets about. The patient had near complete collapse of the left lung during presentation to our center. However, the hypoglycemic episodes had been reported to occur only 4 months prior to presentation. There is no publication demonstrating that an increase in the tumor size results in hypoglycemia; although, 1 report showed that the tumor size may relate to the occurrence of hypoglycemia.[7] This hypothesis of hypoglycemia occurring as a function of tumor size is also supported by the fact that reduction in size of the tumor by partial surgical resection, radiotherapy, chemotherapy, or embolization reduces the incidence of hypoglycemic episodes.[2,3] The patient was treated with intravenous hydrocortisone in the interim period to which she had an excellent response. Following complete removal of the tumor, she did not develop any further hypoglycemic episodes.

Conclusion

Non-islet-cell tumor hypoglycemia must be considered in patients presenting with hypoglycemic episodes in the context of a known tumor. The acute onset of hypoglycemic episodes, in a person with long-standing tumor, suggests that NICTH could occur with the increase in size of the tumor leading to pro-IGF-2 levels rising above a certain threshold. Complete excision of the tumor is the primary treatment of NICTH and is curative. When the tumor is inoperable, glucocorticoid therapy is useful in alleviating the symptoms.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflict of interest to declare.

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