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Recurrent Hypoglycemia Due to a Massive Abdominal Tumor in a Nonagenarian: A Case Report and Review of the Literature

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

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Conflict of interest: None declared

Patient: Male, 94-year-old
Final Diagnosis: Doege Potter syndrome • solitary fibrous tumor
Symptoms: Falls • hypoglycemia
Medication: —
Clinical Procedure: —
Specialty: Geriatrics • Medicine, General and Internal

Objective: Unusual clinical course

Background: Whipple's triad is a rare condition that prompts urgent investigation. A rare cause of such a clinical presentation is excess production of insulin-like growth factor 2 (IGF-2) from a solitary fibrous tumor.

Case Report: A 94-year-old man presented to the hospital following episodes of confusion, gait disturbance, and multiple falls secondary to hypoglycemia. His initial blood glucose was 45 mg/dL, with normalization to 144 mg/dL after administration of 1 ampule of glucose in the field. By the time the patient arrived at our facility, his blood glucose had fallen to 75 mg/dL, and then fell further to 38 mg/dL. He had no preceding history of hypoglycemia and led an active lifestyle. His medical history was relatively unremarkable with the exception of a large but asymptomatic solitary fibrous tumor previously diagnosed, being managed conservatively. A physical examination demonstrated a large, left-sided, nontender abdominal tumor. Computed tomography demonstrated a very large well-defined, complex mass in the left upper quadrant of the abdomen. Hypoglycemic episodes occurred frequently, and reliably ensued with fasting. Hypoglycemia proved refractory to conservative strategies, and surgical intervention was recommended. Despite challenges due to the tumor's characteristics, the mass was successfully resected and normoglycemia was achieved within 24 hours.

Conclusions: Solitary fibrous tumors may rarely present with hypoglycemia refractory to medical therapy. We present the first reported case of a nonagenarian patient with hypoglycemia secondary to ectopic production of IGF-2 from a solitary fibrous tumor managed with surgical resection.

Keywords: Hypoglycemia • Insulin-Like Growth Factor II • Receptor, IGF Type 2 • Solitary Fibrous Tumors

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Background

Whipple's triad, or symptomatic hypoglycemia with a serum glucose <50 mg/dL and immediate relief of symptoms with intravenous glucose, is a rare condition that prompts urgent investigation. Clinical manifestations of hypoglycemia include adrenergic symptoms such as diaphoresis and tachycardia, and neuroglycopenic symptoms such as cognitive impairment, syncope, coma, and even death [1]. The etiology of hypoglycemia outside of the setting of diabetes mellitus is one with multiple life-threatening diagnoses including malnutrition, critical illness, and insulin-producing tumors classically associated with Whipple's triad. A rare cause of Whipple's triad is non-islet cell tumor hypoglycemia (NICTH) associated with a solitary fibrous tumor (SFT), commonly referred to as Doege-Potter syndrome [2].

Solitary fibrous tumors are rare tumors of primarily mesenchymal origin with isolated instances of epithelial origin [3]. Mesenchymal tumors most commonly derive from the pleura [3]. Extrapleural sites mainly include the upper respiratory tract and adjacent structures, but these tumors have also been reported in the abdominopelvic region in 34% of cases [4]. Most SFTs tend to develop between the sixth to seventh decades of life and affect men and women equally [5]. The majority are benign, with only 10-20% of the tumors found to be malignant; however, the incidence of malignancy increases to 66% when found outside of the thoracic cavity [2,5]. Histologically, they are identified by a patternless architecture consistent with a spindle cell tumor [2]. Immunohistochemistry positive reactivity for CD34 is a characteristic finding in addition to Bcl-2 and CD99 positivity, which are commonly encountered but not characteristic of an SFT [3]. Negative reactivity for cytokeratin, alpha-SMA, S-100, CD31, and c-kit help differentiate SFTs from other spindle cell tumors [2]. Patients typically present with symptoms of tumor compression such as cough, chest pain, and dyspnea [3]. Symptomatic hypoglycemia is the primary presenting symptom in only 4% of SFT cases [3]. Treatment of both benign and malignant SFTs has previously involved steroid therapy, feeding vessel embolization, radiotherapy, and surgical resection [6]. Surgical resection of abdominopelvic SFTs can be daunting given the size and hypervascularity of the tumor at time of diagnosis; however, surgery is the definitive treatment of this condition.

Hypoglycemia is thought to be induced by SFTs through the ectopic secretion of aberrant or "big" insulin-like growth factor 2 (IGF-2), which due to a lack of post-translational processing has different physiological effects than normal IGF-2, causing increased glucose utilization (most pronounced on the skeletal muscles) and inhibition of gluconeogenesis and glycogenolysis from the liver [1,7-9]. With an affinity to insulin receptors 35-40% greater than that of insulin, large amounts of ectopic IGF-2 can have profound hypoglycemic effects, similar to that of excess insulin [7]. Hypoglycemia therefore develops directly via increased glucose utilization peripherally and indirectly by inhibition of counterregulatory responses to hypoglycemia as a result of ectopic IGF-2 production by SFTs [1,7-9]. Here, we present the case of a 94-year-old man who presented to our institution with symptomatic, uncontrollable hypoglycemia secondary to a massive solitary fibrous tumor.

Case Report

A 94-year-old man presented to the Emergency Department for evaluation after multiple falls in the 24 h leading up to presentation. He denied fever, chills, malaise, cough, abdominal pain, or recent medication changes. The patient had no preceding history of falls, and was generally physically active, playing golf regularly. His past medical history was significant for atrial fibrillation, on metoprolol for rate control and rivaroxaban for anticoagulation, as well as a large solitary fibrous tumor being conservatively managed by his primary care physician with serial imaging. He had no known history of diabetes mellitus and was not taking any medications that would cause hypoglycemia. The tumor had been previously diagnosed via core-needle biopsy in January 2019 at an outside facility, and at the time measured 9.1×13.5×11.4 cm on abdominal computed tomography. Surgical resection was not pursued at the time, in part because of the patient's advanced age, the nature of the tumor, and largely because he was asymptomatic. A physical examination revealed a 175-cm tall, 72.5 kg, hypertensive, mildly anxious male. Examination of the abdomen was remarkable for a nontender, large, palpable, left-sided abdominal mass. En route to the hospital, blood glucose testing demonstrated a value of 45 mg/dL with normalization to 144 mg/dL after administration of 1 ampule of glucose intravenously in the field. By the time the patient arrived in the Emergency Department, his blood glucose had again fallen to 75 mg/dL, subsequently falling to 38 mg/dL shortly after admission. The hypoglycemic episodes were accompanied by confusion and gait disturbances. A computed tomography of the abdomen demonstrated a well-defined, large, complex mass in the left upper quadrant measuring 19.7×20.2×14.7 cm, revealing significant growth of the tumor since the initial diagnosis 1 year prior. Over the course of his hospitalization, the patient suffered multiple episodes of hypoglycemic events, particularly at night, during sleep, and when oral feeding was stopped (**Figure 1**). The patient was maintained on a complex carbohydrate diet with supplementary oral and intravenous dextrose as needed for symptom control.

An extensive laboratory workup was performed to assess the cause of the patient's hypoglycemia. Fasting insulin and C-peptide were both low at <1.0 uIU/mL and 0.23 ng/mL,

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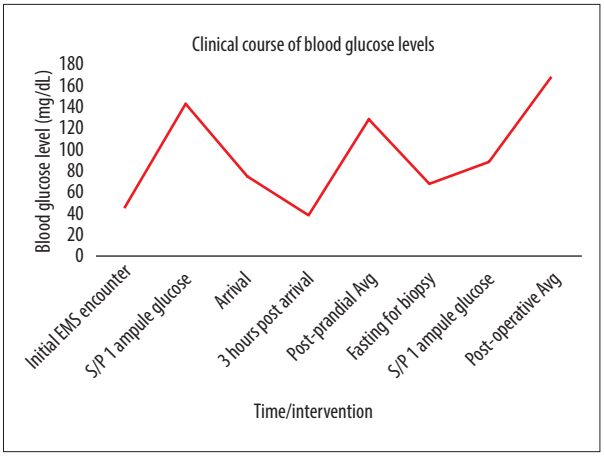

Figure 1. A timeline of blood glucose levels through the patient's clinical course from initial Emergency Medical Services (EMS) encounter to discharge. The patient was able to maintain a normal average blood glucose level of 128 mg/dL with regular feedings and continued to experience dramatic, recurrent hypoglycemic events with cessation of feedings (3 h post-prandial and fasting for biopsy) that corrected with supplemental glucose administration (status-post (S/P) 1 ampule glucose). Note the significant stabilization of blood glucose levels to an average of 167 mg/dL following resection of the tumor.

respectively, during a period of hypoglycemia to 59 mg/dL, effectively ruling out insulinoma and medication-induced hypoglycemia. Additionally, a serum hypoglycemic panel was negative for the presence of hypoglycemic medications. Other metabolic causes were ruled out with normal serum levels of growth hormone of 0.2 ng/mL, morning cortisol of 13.8 mcg/dL, and thyroid-stimulating hormone of 3.03 mIU/L. Serum IGF-1 was within normal limits at 67 ng/mL (normal reference range of 34-246 ng/mL) and IGF-2 was low at 67 ng/mL (normal reference range of 267-616 ng/mL) with an IGF-2: IGF-1 ratio of 2.78, consistent with NICTH. The level of IGF-2 was not found to be elevated, likely because the laboratory's chromatography/mass spectrometry was not sensitive enough to measure aberrant IGF-2. Contrast-enhanced computed tomography (**Figure 2**) and magnetic resonance imaging (**Figure 3**) studies were obtained, which were consistent with the initial diagnosis of a solitary fibrous tumor. No radiographic evidence of local invasion was noted.

As the patient's hypoglycemic symptoms could not be controlled by conservative means, the patient decided to pursue a course of surgical resection. His preoperative functional status was evaluated as excellent. His blood pressure had normalized, and his renal and hepatic functions were within normal limits (blood urea nitrogen 19 mg/dL, creatinine 0.9 mg/dL, creatinine clearance 42.1 mL/min, glomerular filtration rate calculated 84 mL/min, alanine transaminase 38 IU/L, aspartate transaminase 39 IU/L), making him an appropriate candidate for surgery. An open laparotomy incision was utilized due to the size of the mass. The mass was resected *en bloc* without resection of adjacent organs (**Figure 4**). Due to the hypervascularity nature of the tumor, resection proved challenging and required meticulous attention to control bleeding from the numerous, fragile, parasitic blood vessels emanating from the tumor, and

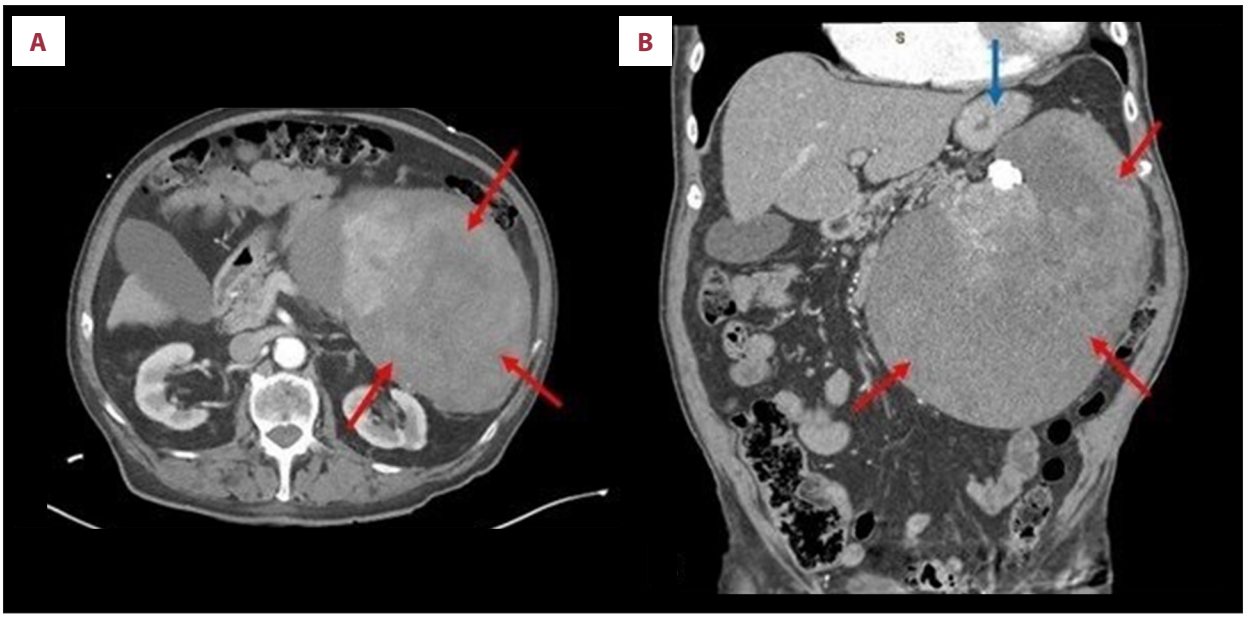

Figure 2. Abdominal CT scan of the benign solitary fibrous tumor. Axial scan (**A**) and coronal scan (**B**) demonstrate a 19.7×20.2×14.7 cm large complex mass (red arrows) in the left upper quadrant of the abdomen containing calcifications and hypodensities that does not seem to be arising from the stomach, spleen (blue arrow), pancreas, adrenal, or left kidney.

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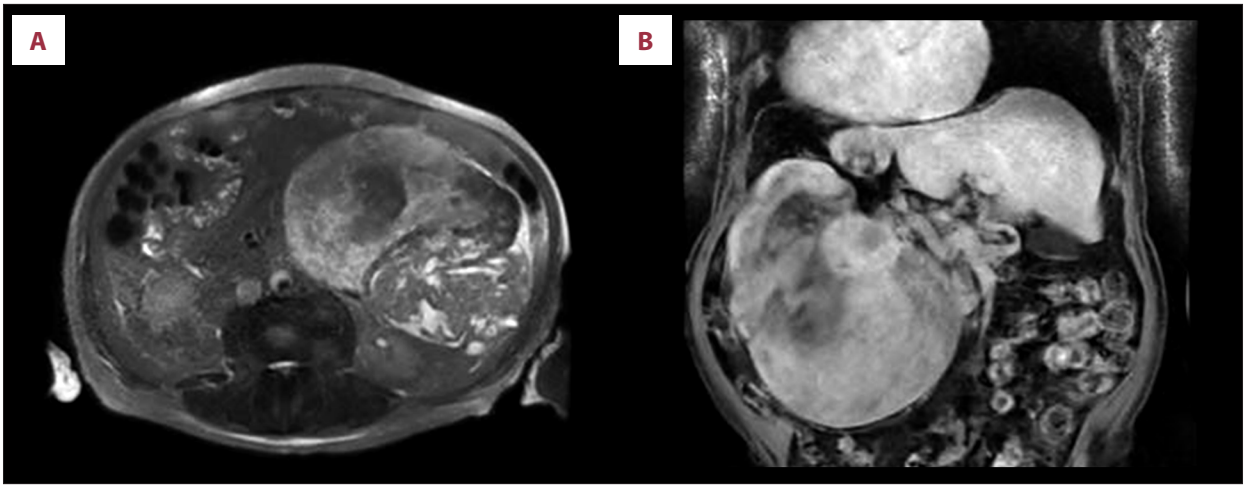

Figure 3. An axial T2 MRI demonstrating left-sided giant abdominal soft-tissue tumor (**A**). A coronal gradient echo MRI images demonstrating large left-sided abdominal soft-tissue tumor (**B**).

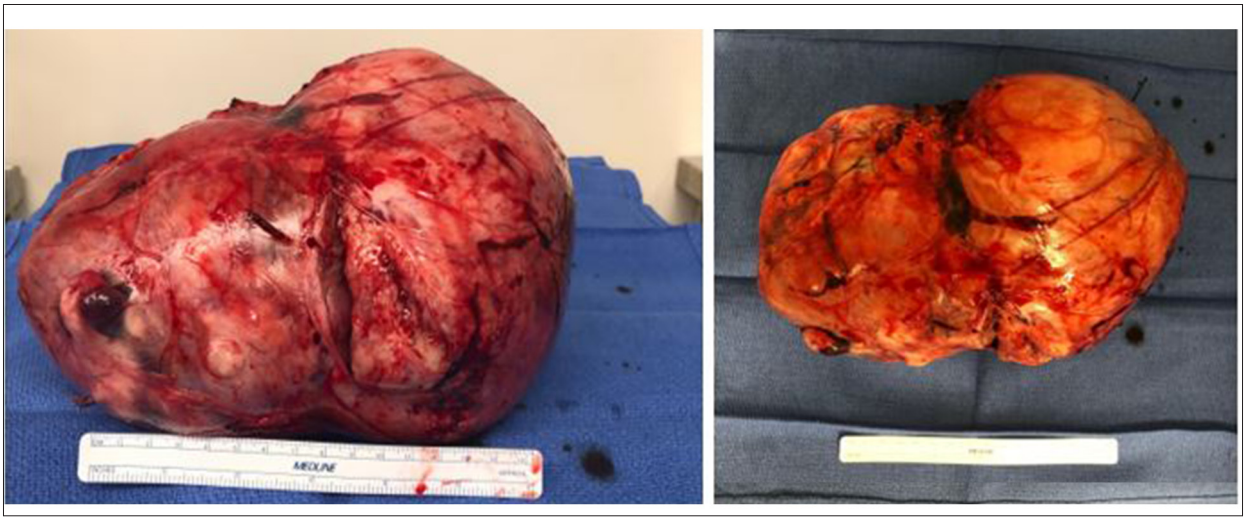

Figure 4. Gross examination of the abdominal mass resection demonstrated a 2860 g, 20×16.3×15 cm, well-circumscribed, unencapsulated mass. Sectioning showed a pale tan-to-yellow, whirled, lobulated appearance with areas of cystic degeneration and hemorrhage. Microscopic examination showed a characteristic patternless pattern of spindle cells with alternating hyper- and hypocellular areas, dense collagenous bands, staghorn vessels, and focal (<10%) tumor necrosis, consistent with a solitary fibrous tumor.

ultimately requiring 5 h to complete. Immunohistochemistry of the tumor revealed expression of CD34 and was negative for the presence of S100 protein, consistent with an SFT (**Figure 5**). The sample was not stained for the presence of other markers supportive of an SFT, including CD99, IGF2, cytokeratin, alpha-SMA, CD31, and c-kit. The patient's postoperative course was complicated by prerenal azotemia, likely due to intraoperative insensible fluid loss. In addition, there was an episode of narcotic-induced delirium and respiratory depression requiring reintubation for 24 h. He achieved normoglycemia within 24 h of surgical resection and was discharged to inpatient rehabilitation and subsequently to home without further hypoglycemic episodes to our knowledge.

Discussion

Solitary fibrous tumors were first described in the pleura and were thought to be primarily a tumor of the thoracic cavity but have since been reported to occur throughout the body, with 34% occurring in the abdominopelvic region [4]. Findings of abdominopelvic SFTs are often incidental or secondary to mass effect [10]. Our patient presented with recurrent hypoglycemia as his primary symptom and reported no other problems. A review of literature revealed the rarity of such a presentation, occurring in only 4% of cases [3]. To our knowledge, this is the first case report of hypoglycemia as a paraneoplastic syndrome in a nonagenarian patient with subsequent successful surgical resection.

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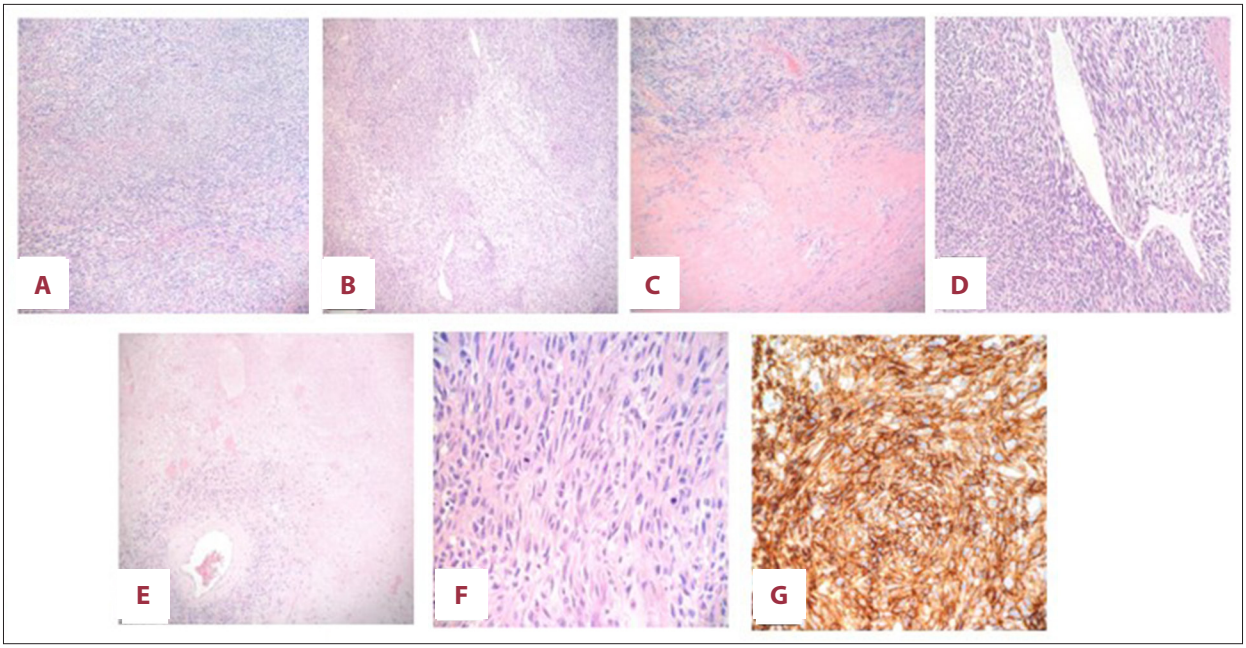

Figure 5. Microscopic examination showed a characteristic patternless pattern of spindle cells (**A**) with alternating hyper- and hypocellular areas (**B**), dense collagenous bands (**C**), staghorn vessels (**D**), and focal (<10%) tumor necrosis (**E**). On higher magnification (**F**), the cells exhibited bland, uniform, elongated nuclei with indistinct nucleoli, minimal atypia, and occasional (>4/10 HPF) mitotic figures. Immunohistochemical stains showed the tumor cells to be positive for CD34 (**G**), STAT6, TLE1, Desmin, AE1/AE3 (focal), CAM5.2 (focal), Beta-catenin and BCL-2, and negative for CD117, S100, Melan-A, SOX10, and ER. Ki-67 was positive in less than 1% of cells.

Solitary fibrous tumors typically present with symptoms of mass effect with a relatively indolent disease course [10]. The majority are benign, with only 10-20% of thoracic tumors found to be malignant. However, the incidence of malignancy increases to 66% when found outside of the thoracic cavity [2]. Most case reports describe presenting symptoms of chest pain, dyspnea, and cough, likely reflective of the common pleural derivation [11]. Reports involving extrathoracic disease report symptoms due to mass effect specific to the organ system affected, such as hematuria and urinary retention in a case of SFT of the urinary bladder [11]. Unfortunately, the flexibility of the abdominal cavity lends itself to diagnosis late in the disease course, as the mass effect may only become apparent at much larger sizes than in other body cavities. Despite the impressive size of our patient's tumor, he was without abdominal discomfort, fullness, or laboratory findings suggestive of surrounding organ dysfunction. His symptoms stemmed from hypoglycemic episodes leading to confusion and imbalance, which all resolved with tumor resection. The lack of neurogenic symptoms (eg, tremulousness, tingling, sweating, hunger) can likely be attributed to his age as well as beta blockade for atrial fibrillation. A study by Meneilly et al demonstrated that patients over the age of 65 had reduced awareness of the neurogenic but not neuroglycopenic (weakness, confusion, drowsiness) symptoms of hypoglycemia [1]. Interestingly, our patient was being evaluated by his primary care physician for concerns of memory loss over the last year prior to presentation, which may have been due to occult hypoglycemic episodes. Revisiting the patient's memory in the next year may demonstrate improvement or partial resolution.

Our patient underwent an extensive workup similar to those described in our review of cases of SFTs, consistent with the fact that Doege-Potter syndrome is typically a diagnosis of exclusion. Despite the presumed association with IGF-2 as described, the IGF-2 level in patients with SFTs can be elevated or within normal limits by virtue of the laboratory test itself, which traditionally evaluates for the lighter molecule [12]. In SFT patients who present with normal or low IGF-2 levels, further assessment with western blot can reveal an elevated composition of heavier IGF-2, or the IGF-2: IGF-1 ratio can be used as a surrogate marker for tumor presence [12,13]. An IGF-2: IGF-1 ratio of greater than or equal to 3: 1 is suggestive of NICTH but must be complemented with clinical and radiographic data suggesting the presence of NICTH [13]. The patient's IGF-2 level was low (186 ng/mL) and his IGF-2: IGF-1 ratio was 2.78, suggestive of NICTH. Immunohistochemistry of the tumor revealed expression of CD34 and Bcl-2 and was negative for the presence of S100 protein, consistent with an SFT [2]. The sample was not stained for IGF2 by the Pathology Department, nor was the serum level of IGF-2 measured postoperatively, which would have provided useful data in support

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of our diagnosis if it was histologically present and circulating at lower levels postoperatively.

Our conclusion that aberrant IGF-2 secreted from the SFT was the cause of his recurrent hypoglycemia was a diagnosis of exclusion after exclusion of insulinoma and exogenous insulin as the underlying etiology and was further supported by laboratory and pathology results. Likewise, we did not proceed with a more detailed evaluation of IGF-2 with western blot studies for our patient to prevent a delay in treatment, and doing so is unlikely to have changed his treatment. However, we do recommend measuring specifically for high-molecular-weight IGF-2 if SFT is suspected and other diagnoses cannot confidently be ruled out.

As a non-islet tumor, SFTs can induce hypoglycemia especially in periods with low nutrient intake, particularly overnight during sleep, which can complicate patient disposition and direct therapy. Over the course of the patient's stay, hypoglycemic episodes occurred frequently, and reliably ensued with fasting (**Figure 1**). Our patient was unique in that he was a 94-year-old widower who lived independently, tended to all his activities of daily living with minimal limitations, and was determined to maintain his independence. We considered medical therapy using daily corticosteroids as a long-term, non-invasive management option. Corticosteroids not only increase blood glucose levels but also can increase the clearance of "big" IGF-2 [14]. A study of glucocorticoid therapy by Tsuro et al for management of an inoperable SFT causing hypoglycemia was significant for achievement of glycemic control with prednisolone in a dose-dependent fashion, requiring 15-30 mg daily over the course of 3 months [15]. Despite reassuring evidence, we were hesitant to proceed with this course for 2 reasons. First, the patient's social history made it especially difficult to place him under 24-h care since he lived alone and we feared there would be recurrent hypoglycemic episodes, especially overnight, if he forget to take his medication. The second reason is that chronic complications associated with long-term steroid use can be exacerbated in geriatric patients, including immunosuppression, osteoporosis, and delirium. Alternative treatments include chemotherapy, radiotherapy, and tumor vessel embolization, although the efficacy is variable across case reports [6].

The definitive treatment for localized SFT is complete surgical resection, with a 10-year survival rate of 54-89% [16]. Recurrence of extrapleural SFTs, both local and metastasis, is uncommon after surgical excision with curative intent [16]. It is important to note that the lack of known recurrence may be due to the patient population and life expectancy. For SFT patients with recurrent hypoglycemia who are unlikely to maintain or have contraindications to medical therapy, we believe that surgical intervention should be undertaken, as the benefits of stabilizing serum glucose level outweigh the risks of post-surgical recovery and complications.

Conclusions

Although it is a rare cause of hypoglycemia, non-islet cell tumor hypoglycemia associated with a solitary fibrous tumor was identified in our patient. Diagnosis can be challenging as serum IGF-2 is not always elevated, and NICTH associated with a SFT is a diagnosis of exclusion. Clinicians should further assess serum levels of growth hormone, IGF1, and IGF-2: IGF-1 ratio, in addition to immunohistochemistry for the expression of IGF-2, CD34, and S100 protein to exclude other diagnoses. If uncertainty remains, it would be beneficial to obtain immunoblotting for the "big" IGF-2 level. Treatment options include surgical resection in appropriate candidates, and corticosteroid therapy, chemotherapy, radiation, and tumor vessel embolization for patients deemed unfit to undergo surgery.

Conflicts of Interest

None.

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