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Evolution of Pleural Solitary Fibrous Tumors Causing Severe Hypoglycemia after Exceptionally Long Asymptomatic Periods: Report of Two Surgical Cases

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Non-islet cell tumor hypoglycemia (NICTH) is one of the paraneoplastic syndromes manifesting severe hypoglycemia caused by aberrant production of high-molecular-weight insulin-like growth factor 2 (big-IGF2). Two surgical cases of extremely large thoracic solitary fibrous tumors (SFT) with unusual history of NICTH are presented. One case manifested severe hypoglycemia after four years of the first complete surgical resection of the tumor with potential malignant transformation, and the other case showed severe hypoglycemia after ten years of the first detection of the tumor. Meticulous laboratory testing, including serum endocrinological tests and western immunoblotting before and after surgery was performed, and both cases were diagnosed as NICTH. Both patients underwent open thoracic surgery. The patients showed normal glucose and hormone levels immediately after the resection of responsible tumors with elevated blood insulin concentration. SFTs are generally considered benign; however, life-threatening hypoglycemia can happen regardless of treatment. Careful follow-up of the tumor growth is warranted.

Keywords: big-IGF2; malignant transformation; non-islet cell tumor hyperglycemia; solitary fibrous tumor
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Introduction

Solitary fibrous tumors (SFT) are less common mesenchymal tumors, and 22% of them originate from visceral pleura in the thoracic cavity (Salas et al. 2017). Because of its slow-growing nature, the tumors often expand stealthily and tend to be large when they cause symptoms such as dyspnea, atypical chest pain, hemoptysis, or obstructive pneumonitis (Solsi et al. 2020). A part of SFT patients may develop severe hypoglycemia as a paraneoplastic syndrome caused by the circulating high molecular weight insulin-like growth factor 2 (big-IGF2) secreted from the tumor, which accounts for approximately 5% of SFTs (Bodnar et al. 2014).

Surgical resection with a negative margin is a definitive treatment of SFTs regardless of accompanying symptoms (Sung et al. 2005). Being a rare disease, the appropriate timing of surgical intervention and post-operative follow-up for SFTs is yet to be elucidated. There are reports describing surgically resected thoracic SFT cases with preceding severe hypoglycemia, yet, in some cases, hypoglycemia can emerge long after the initial diagnosis of SFTs (Kameyama et al. 2007). Here, we report two surgically resected SFT cases presenting severe hypoglycemia after years of endocrinologically inactive states since the first detection of tumors.

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Case Presentation

Case 1

A 61-year-old man with fatigue and anorexia was admitted to the previous hospital. The patient showed severe hypoglycemia despite the comorbidity of diabetes mellitus. A Chest X-ray and screening chest computed tomography (CT) revealed an extensive mass occupying the left thoracic cavity, causing the mediastinal shift toward the right thoracic cavity (Fig. 1a, b). This patient previously underwent chest surgery for a large solitary fibrous tumor in the ipsilateral thoracic cavity four years before the current episode (Fig. 1c). The patient had been treated with metformin and glimepiride, but no hypoglycemic event was observed around the first surgery. Interestingly, periodic laboratory testing toward this hospital admission showed a significant drop in fasting blood glucose concentration from 123 mg/dL six months before the admission to 72 mg/dL four months before the admission, suggesting that the patient presumably had preceding asymptomatic hypoglycemia approximately for five months before the second surgery (Fig. 1d).

The patient was transferred to our department for the second surgery. The laboratory examination showed hypoglycemia along with low-level insulin and C-peptide reactivity, suggesting that the tumor was producing big-IGF2. The open surgery was performed with a clamshell incision, and the tumor was resected with the surrounding adhered tissues, such as the pericardiac membrane and the lung (Fig. 1e). The patient suffered from re-expansion pulmonary edema immediately after the surgery and required non-invasive positive pressure ventilation for three days in the intensive care unit. There was no hypoglycemic event after the surgery. Endogenous insulin production was normal on postoperative day 7 (Table 1). The patient was discharged on postoperative day 39 after intensive in-hospital rehabilitation. The histological observation of the tumor revealed spindle to oval cells with high cellular density (Fig. 1f) and necrosis (Fig. 1g). The immunohistochemical expression of CD34 showed highly heterogeneous cell morphology (Fig. 1h) along with high positivity of Ki67 (Fig. 1i). The tumor also showed STAT6 (signal transducer and activator

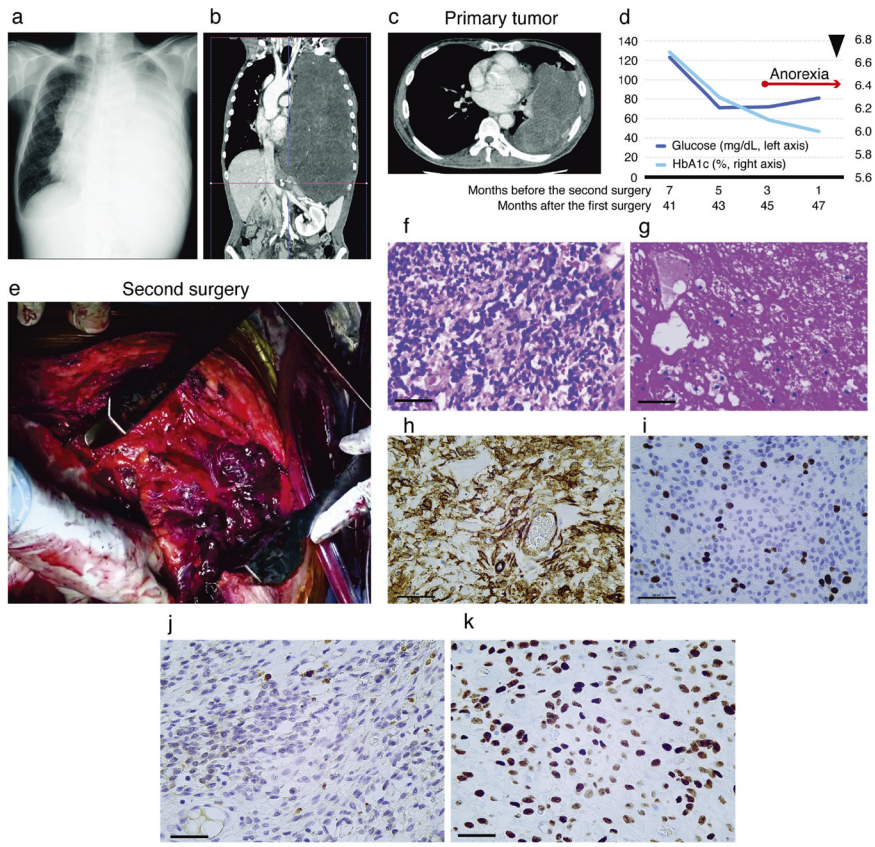

Fig. 1. Case 1: A recurrent large solitary fibrous tumor in the left thoracic cavity presenting with severe hypoglycemia. (a) Chest X-ray and (b) 3-dimensional reconstruction of enhanced CT scan on admission. (c) An enhanced chest CT scan showing the left thoracic tumor eventually resected four years prior to the second surgery. (d) The 6-month trend of plasma glucose and hemoglobin A1c immediately before the second surgery. The horizontal axis indicates the months before the second surgery (top) and the months after the first surgery (bottom). The arrowhead indicates the time point of the second surgery. Both plasma glucose (left axis) and HbA1c (right axis) dropped approximately five months before the second surgery. (e) An operative image of the tumor. (f and g) Hematoxylin-Eosin staining of the tumor. Immunohistochemistry of the tumor for (h) CD34, (i) Ki67, (j) IGF2, and (k) STAT6. Bars, 50 μm.

Table 1. Laboratory findings of Case 1.

Variable	Reference range (unit)	Pre-operation	Post-operative-day 7
Red blood cell	435-555 (10^4/μL)	452	348
Hemoglobin	13.7-16.8 (g/dL)	12.6	10.4
White blood cell	3.3-8.6 (10^3/μL)	16.6	10.5
Platelet	158-348 (10^3/μL)	345	502
Total bilirubin	0.4-1.5 (mg/dL)	0.79	0.6
Aspartrate aminotransferase	13-30 (U/L)	38	17
Alanine transaminase	10/42 (U/L)	46	52
Lactate dehydrogenase	124-222 (U/L)	265	244
Sodium	138-145 (mmol/L)	145	141
Potassium	3.6-4.8 (mmol/L)	2.6	3.6
Chloride	101-108 (mmol/L)	99	99
Glucose	73-109 (mg/dL)	56	100
Growth hormone	0.00-2.47 (ng/mL)	1.02	Not tested
Insulin-like growth factor-1	77-230 (ng/mL)*	120	Not tested
Insulin	< 18.7 (μU/mL)	< 0.2	4.4
C-peptide reactivity	0.8-2.5 (ng/mL)	< 0.2	1.85

*Reference, https://uwb01.bml.co.jp/kensa/search/detail/3803908

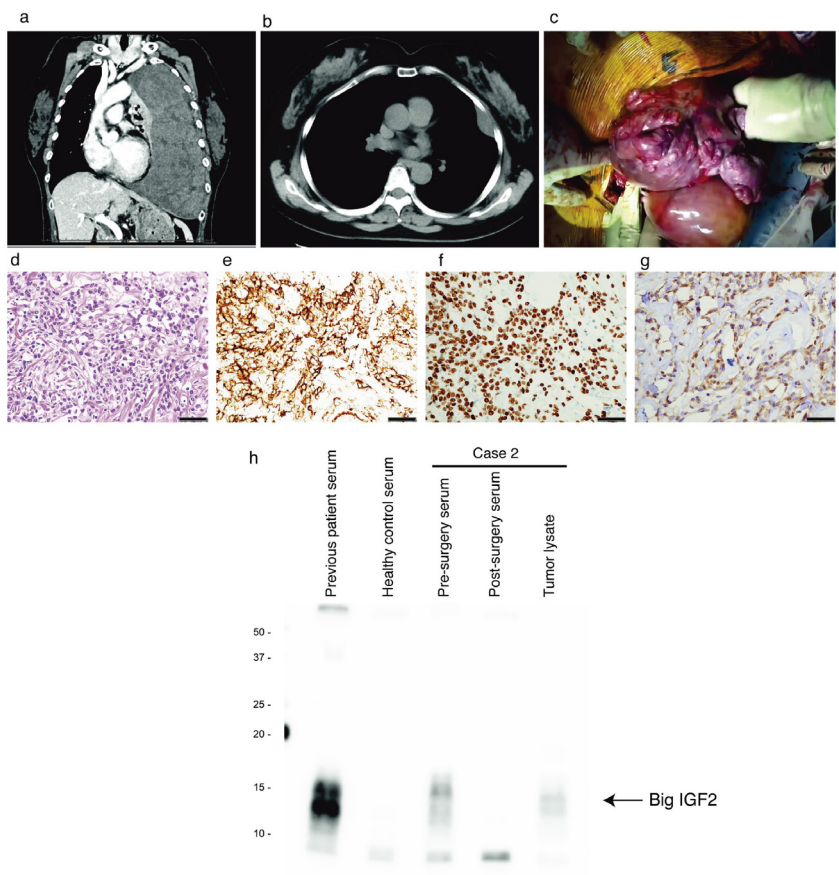

Fig. 2. Case 2: A long inactive left-sided solitary fibrous tumor diagnosed after the emergent admission due to severe hypoglycemia.
(a) Three-dimensional reconstruction of enhanced CT scan on admission. (b) A chest CT scan of the patient ten years before the primary surgery. A 5 cm tumor on the chest wall was detected. (c) Operative findings in the primary surgery. (d) Hematoxylin-Eosin image showed heterogeneously shaped tumor cells. Immunohistochemistry of (e) CD34, (f) STAT6, and (g) IGF2. (h) Western immunoblotting of big IGF2 using previously diagnosed patient serum, healthy control serum, and Case 2 patient pre- and post-surgery serum and tumor lysate. Bars, 50 μm.

of transcription 6) (Fig. 1j) and IGF2 (Fig. 1k) immunoexpression. Taken together, these findings were compatible with solitary fibrous tumors as well as England's criteria for the malignant solitary fibrous tumor (England et al. 1989).

The patient had been uneventful until two years after the second operation when the recurrent tumor was diagnosed. Again, he presented with hypoglycemia. The general condition was beyond operable; therefore, best supportive care was undertaken. He eventually died two years and ten months after the second surgery.

Case 2

A 67-year-old female presented with a sudden-onset paralytic episode and was admitted to the previous hospital. She had severe hypoglycemia on arrival, with a large tumor occupying the entire left thoracic cavity (Fig. 2a). The patient had been diagnosed with a left chest wall tumor ten years before the current illness at the same hospital (Fig. 2b); however, she discontinued periodic follow-ups of the tumor soon after the first diagnosis. She had virtually no symptoms until she had been hospitalized due to the current episode. After being hospitalized, the patient required continuous drop infusion of 10% glucose plus occasional injections of 20 mL of 20% glucose during the night to keep the plasma glucose level above 80 mg/dL. Despite the severe hypoglycemia, serum insulin and C-peptide reactivity was below the limit of detection, suggesting negative feedback from the potential production of big-IGF2 by the thoracic tumor (Table 2).

The patient was transferred to our department and underwent tumor resection surgery. The seventh rib was removed. The tumor was found to have originated from the chest wall around the fifth and sixth ribs, the location in which the chest wall tumor was detected in the CT scan ten years ago. The fifth and sixth ribs were also removed with the tumor (Fig. 2c), and the chest wall defect was reconstructed using a GORE® DUAL MESH® (W.L. Gore and Associates, Newark, DE, USA). The patient showed significant re-expansion edema in the left lung and required 24 hours of mechanical ventilation in the intensive care unit. The post-operative clinical course was uneventful after the extubation on postoperative day 1. The fasted blood glucose level became above 100 mg/dL immediately after the surgery, and the endogenous insulin level was also above a normal level on postoperative day 7 (Table 2).

Histological observation of the tumor revealed heterogeneous tumor cell morphology (Fig. 2d) with expressions of CD34, STAT6, and IGF2 (Fig. 2e-g). We also performed western blotting to demonstrate the production of big-IGF2 from the tumor. Big-IGF2 was detectable in the patient's serum as well as the tumor tissue and then became undetectable in the serum on postoperative day 7 (Fig. 2h).

Informed consent

The informed consent for the publication was obtained from the Case 2 patient. For the Case 1, informed consent for the research use of clinical information of the patient was obtained before the surgery.

Discussion

Hypoglycemia due to non-insulin-producing tumors is referred to as non-islet cell tumor hypoglycemia (NICTH) (Fukuda et al. 2006) or Doege-Potter syndrome when hypoglycemia is associated with solitary fibrous tumors (Solsi et al. 2020). Aberrant IGF2 production, which possesses insulin activity, is the major cause of NICTH (Fukuda et al. 2006). IGF2 is an abundantly expressed growth factor with insulin activity in the human body; however, its insulin

Table 2. Laboratory findings of Case 2.

Variable	Reference range (unit)	Pre-operation	Post-operative-day 7
Red blood cell	435-555 (10^4/μL)	414	399
Hemoglobin	13.7-16.8 (g/dL)	12.1	11.8
White blood cell	3.3-8.6 (10^3/μL)	5.2	6.9
Platelet	158-348 (10^3/μL)	234	316
Total bilirubin	0.4-1.5 (mg/dL)	1.0	1.7
Aspartrate aminotransferase	13-30 (U/L)	26	18
Alanine transaminase	7-23 (U/L)	32	26
Lactate dehydrogenase	124-222 (U/L)	173	193
Sodium	138-145 (mmol/L)	145	141
Potassium	3.6-4.8 (mmol/L)	3.9	4.2
Chloride	101-108 (mmol/L)	106	102
Glucose	73-109 (mg/dL)	111	125
Growth hormone	0.13-9.88 (ng/mL)	0.89	0.83
Insulin-like growth factor-1	61-183 (ng/mL)*	50	38
Insulin	< 18.7 (μU/L)	<0.2	9.6
C-peptide reactivity	0.61-2.09	<0.2	2.90

*Reference, https://uwb01.bml.co.jp/kensa/search/detail/3803908

activity is limited by a stringent regulation of free IGF2 concentration in serum (Livingstone and Borai 2014). IGF2 is also expressed in a wide range of tumors, particularly in mesenchymal tumors (Livingstone 2013). The mechanism behind the hypoglycemic syndrome is the production of high-molecular-weight IGF2 (big-IGF2) from non-islet cell tumors, resulting from incomplete post-translational processing of the *Igf2* gene (Livingstone and Borai 2014). At this time, the demonstration of big-IGF2 is only possible in a research laboratory setting, such as western immunoblotting after SDS-PAGE of serum or tumor samples (Bodnar et al. 2014), as performed in Case 2 (Fig. 2). Otherwise, NICTH can be suspected by low insulin and C-peptide and a high IGF2 to IGF-1 ratio (Bodnar et al. 2014), which were compatible with the present 2 cases (Tables 1 and 2).

Surgical resection of the tumor is the definitive treatment for SFTs (Salas et al. 2017). NICTH can also be treated by surgical resection of suspected tumors (Sung et al. 2005; Bodnar et al. 2014). Though most SFT is histologically benign, and the prognosis after the complete resection is favorable (Sung et al. 2005), sporadic local and metastatic recurrences were observed over a 20-year follow-up period after the initial diagnosis and subsequent surgery (Salas et al. 2017). Only a handful of reports were present about the recurrence of SFTs with newly developed NICTH (Deguchi et al. 2022; Keidai et al. 2023) or malignant transformation after surgical resection (Kanthan and Torkian 2004; Krishnadas et al. 2006; Tominaga et al. 2012; Inoue et al. 2016; Sakamoto et al. 2021). The laboratory findings of Case 1 are particularly interesting as a gradual decline of serum glucose and HbA1c before hypoglycemic symptom onset was detected over the bi-monthly follow-up of diabetes mellitus (Fig. 1d). This clinical course indicates that the recurrent SFT preceded well before the production of big-IGF2.

SFT is one of the most common tumor types developing NICTH; however, pleural SFTs do not typically result in NICTH (Fukuda et al. 2006; Bodnar et al. 2014). The predictive factor for NICTH in SFT patients has yet to be known. Also, the timing of when SFT patients develop hypoglycemia is yet inconclusive. In the series of 78 NICTH cases, including various tumor locations, 34 patients (52%) did not present hypoglycemia when the accompanying tumors were detected. The mean duration between the first detection of the tumor and the manifestation of hypoglycemia in those 34 patients was 8.5 ± 1.9 months (mean ± standard deviation) (Fukuda et al. 2006). However, several previous reports describe extremely long inactive periods (4 years and 30 years) after the first detection of SFTs until the development of NICTH (Kaneko et al. 2020; Matsumoto et al. 2021) . These observations indicate that, although rare, the evolution of SFTs toward big-IGF2-producing tumors, as described in Case 2, is possible.

Taken together with the previous literature and present cases, the clinical course of SFT can vary significantly depending on individual cases. Therefore, long and careful follow-up with radiological images after the detection of the tumor as well as after the resection of the tumor is warranted.

Conflict of Interest

The authors declare no conflict of interest

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