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Non-Islet Cell Tumor Hypoglycemia at the Second Recurrence of Malignant Solitary Fibrous Tumor in the Retroperitoneum and Pelvis: A Case Report

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Key Words
Non-islet cell tumor hypoglycemia · Solitary fibrous tumor · Insulin-like growth factor II

Abstract
An 83-year-old man underwent complete resection of a large malignant solitary fibrous tumor in the retroperitoneum in 2006 and of a local recurrent tumor in 2010. In 2011, he was admitted to our hospital because of hypoglycemia. His serum glucose level was very low, and his levels of insulin and C-peptide were low. Furthermore, he had a recurrent tumor in the retroperitoneum and pelvis. Immediately after the third surgery for complete resection, he had no hypoglycemic episodes and his serum glucose level was within the normal range. Immunoblotting analysis revealed a high-molecular-weight form of insulin-like growth factor II in the patient's serum and in the protein extract obtained from the resected specimen in 2011. To our knowledge, this is the first report of non-islet cell tumor hypoglycemia caused by a malignant solitary fibrous tumor secreting a high-molecular-weight form of insulin-like growth factor II at the second recurrence.

Introduction

Solitary fibrous tumors (SFTs) are soft tissue neoplasms that usually originate from the pleura, but occasionally they originate from other regions, including the retroperitoneum and pelvis [1–3]. Approximately 80% of all SFTs are located in the

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thoracic cavity, while the remaining 20% are found in various regions, including the retroperitoneum [4, 5]. Although SFTs are typically benign, they can be malignant, especially if they grow to a large size or in case of repeated recurrence [6–8].

Non-islet cell tumor hypoglycemia (NICTH) is rare but associated with various tumor types, including SFT [9, 10]. Approximately 4% of all SFTs are associated with hypoglycemia [11]. In most patients with NICTH, a high-molecular-weight form of insulin-like growth factor II (IGF-II) derived from the tumor causes hypoglycemia [12]. The structure of the normal-molecular-weight form of IGF-II is similar to that of pro-insulin and has a hypoglycemic effect. The incompletely processed precursor of IGF-II, the so-called high-molecular-weight form of IGF-II, has a strong insulin-like effect and more strongly induces hypoglycemia than normal IGF-II [9]. Therefore, elevated serum and tissue levels of the high-molecular-weight form of IGF-II are useful in the diagnosis of NICTH. Herein, we report a case of NICTH caused by recurrent malignant SFT in the retroperitoneum and pelvis that produced a high-molecular-weight form of IGF-II.

Case Report

An 83-year-old man had the first surgery for SFT in the retroperitoneum in 2006. The histological findings showed that the surgical margin of the tumor was intact. The tumor was 10 cm in diameter with macroscopic hemorrhagic and necrotic changes. Immunohistochemical analysis revealed that the tumor was composed of patternless cellular proliferation and was stained positive for CD34 and bcl-2 but negative for α-smooth muscle, desmin, S-100 protein, and c-kit (**fig. 1**). Three mitoses per 10 high power fields (HPF) were observed. Therefore, we diagnosed SFT with high malignant potential and a high risk of recurrence and metastasis. The tumor recurred in the retroperitoneum and pelvis in 2010, and we again performed complete resection. Since this tumor had similar histological and macroscopic findings, we diagnosed local recurrence of malignant SFT. In these 2 perioperative periods, hypoglycemic attacks did not occur.

In May 2011, the patient was admitted to our hospital because of frequent syncopal attacks. His serum glucose level was 44 mg/dl. The cause of these repeated syncopal attacks was thought to be hypoglycemia. On admission, serum insulin was undetectable (normal range 2.2–12.4 μU/ml), C-peptide was 0.1 ng/ml (normal range 0.8–2.5 ng/ml), and glucose was very low. Serum levels of thyroid hormones and cortisol were within normal ranges (free triiodothyronine 2.2 pg/ml, free tetraiodothyronine 1.3 pg/ml, thyroid-stimulating hormone 1.2 μIU/ml, cortisol 16.4 μg/dl). Furthermore, HbA1c (5.1%), growth hormone (0.15 ng/ml), and IGF binding protein-3 (0.6 μg/ml) were all within normal ranges. Abdominal computed tomography (CT) showed a sequentially lobulated tumor in the retroperitoneum from close to the left common iliac artery to the pelvis (**fig. 2**a, b). Colonoscopy showed that the lower rectum was compressed, but the mucosa appeared normal. Based on these findings, insulinoma, insulin autoimmune syndrome, and adrenal insufficiency were excluded. Finally, at the second recurrence, we diagnosed NICTH caused by malignant SFT in the retroperitoneum and pelvis.

We performed complete resection of the recurrent tumors in June 2011, combined with resection of portions of the rectum and bladder, which was necessary because of severe adhesion. To prevent bowel obstruction due to further recurrence in the pelvic cavity, we avoided anastomosis of the rectum and performed a colostomy at the sigmoid colon. The tumor was a solid, elastic, lobulated mass with hemorrhagic and necrotic changes (fig. 2c). Histological findings were similar to those of the previously excised tumors, which showed patternless proliferation of the cells (fig. 2d). These findings confirmed the diagnosis of recurrent malignant SFT. In this excised specimen, 25 mitoses per 10 HPF were observed, suggesting the presence of high-grade malignancy. Serum levels glucose, insulin, and C-peptide were 143 mg/dl, 11.4 μU/ml, and 2.5 ng/ml, respectively; therefore, all these levels recovered to their normal ranges.

Immunoblotting analysis was performed to investigate the heterogeneity of IGF-II in serum and the excised tumor. The normal-molecular-weight form of IGF-II (7.5 kDa) was not detected in serum

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from a normal healthy control or from the patient. In contrast, a high-molecular-weight form of IGF-II (13 kDa) was detected in the patient's serum before the surgery, and it disappeared after the surgery (**fig. 3**a). Furthermore, immunoblotting analysis of protein extracted from paraffin-embedded tumor specimens showed that the high-molecular-weight form of IGF-II was not detected in the first tumor removed in 2006 or the first recurrence removed in 2010, but it was detected in 2011, at the second recurrence (fig. 3b).

The patient had an uneventful postoperative course and did not suffer from any additional hypoglycemic attacks. However, 1 year after the last surgery, a small local recurrent tumor was detected in the pelvis. Although we planned and recommended further intensive examination and treatment, informed consent was not obtained because the patient was doing well and had no signs of hypoglycemia.

Discussion

Almost all SFTs have been reported in the pleura, but they have also been rarely reported in other sites, including the liver, kidney, retroperitoneum, and soft tissues [13]. Goodlad and Fletcher [1] reported that 6% of all SFTs originated from the pelvis. In our case, the large tumor removed during the first surgery in 2006 was not connected to the gastrointestinal tract or the peritoneum and was thought to have originated from the retroperitoneum.

Although nearly all SFTs have low malignant potential, malignancy can occur, especially if they grow to a large size or in case of repeated recurrence [6, 14]. England et al. [14] described high cellularity, high mitotic activity (more than 4 mitoses per 10 HPF), pleomorphism, necrosis, and hemorrhagic changes as the criteria for malignancy. Takizawa et al. [13] reported malignancy in 14.6% of all retroperitoneal SFTs. Based on these criteria, all three excised specimens in our case were considered histologically malignant SFTs. Interestingly, the number of mitoses per 10 HPF was 3 in 2006, 15 in 2010, and 25 in 2011. In other words, in the tumors removed from successive surgeries, more mitoses per 10 HPF were detected. This result suggests that the malignant potential of the tumors increased with repeated recurrence. In fact, malignant transformation in recurrence of previously benign SFT has been reported [7, 8].

NICTH is a cause of hypoglycemia; approximately 4% of all SFTs are associated with hypoglycemia, and NICTH develops because of the production of a high-molecular-weight form of IGF-II, which is an incompletely processed IGF-II that has greater bioavailability than normal IGF-II [11]. In our case, no hypoglycemic attacks occurred in the past two perioperative periods in 2006 and 2010. Because NICTH first occurred at the second recurrence, we suspect that the tumor had newly acquired the capability of producing a high-molecular-weight form of IGF-II. To clarify this hypothesis, immunoblotting analysis was performed. Because serum IGF-II is not always elevated in patients with IGF-II-producing NICTH, it is important to detect the high-molecular-weight form of IGF-II by immunoblotting [10]. Preoperative analysis of the patient's serum revealed the presence of a high-molecular-weight form of IGF-II (13 kDa), and postoperative analysis revealed the absence of it. Furthermore, the high-molecular-weight form of IGF-II was only present in the tumor excised in 2011 but not in those excised in 2006 and 2010. In all serum samples tested, including one healthy control, normal IGF-II (7.5 kDa) was not detected. We thought that the reason for this result

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was either the very low amount of endogenous normal IGF-II in this study or the loss of integrity of the protein during the extract purification process.

In summary, we reported a rare case of NICTH caused by a high-molecular-weight form of IGF-II produced by the second recurrent malignant SFT in the retroperitoneum and pelvis. Although several cases of NICTH with malignant SFT in the pelvis have been reported, to our knowledge, this is the first report of a NICTH at the second recurrence of malignant SFT. With repeated recurrence, the SFT obtained high malignant potential and a new phenotype of hypoglycemia caused by the production of a high-molecular-weight form of IGF-II as one type of acquired transformation. Symptoms of hypoglycemia should be carefully monitored during treatment and long-term follow-up for SFT.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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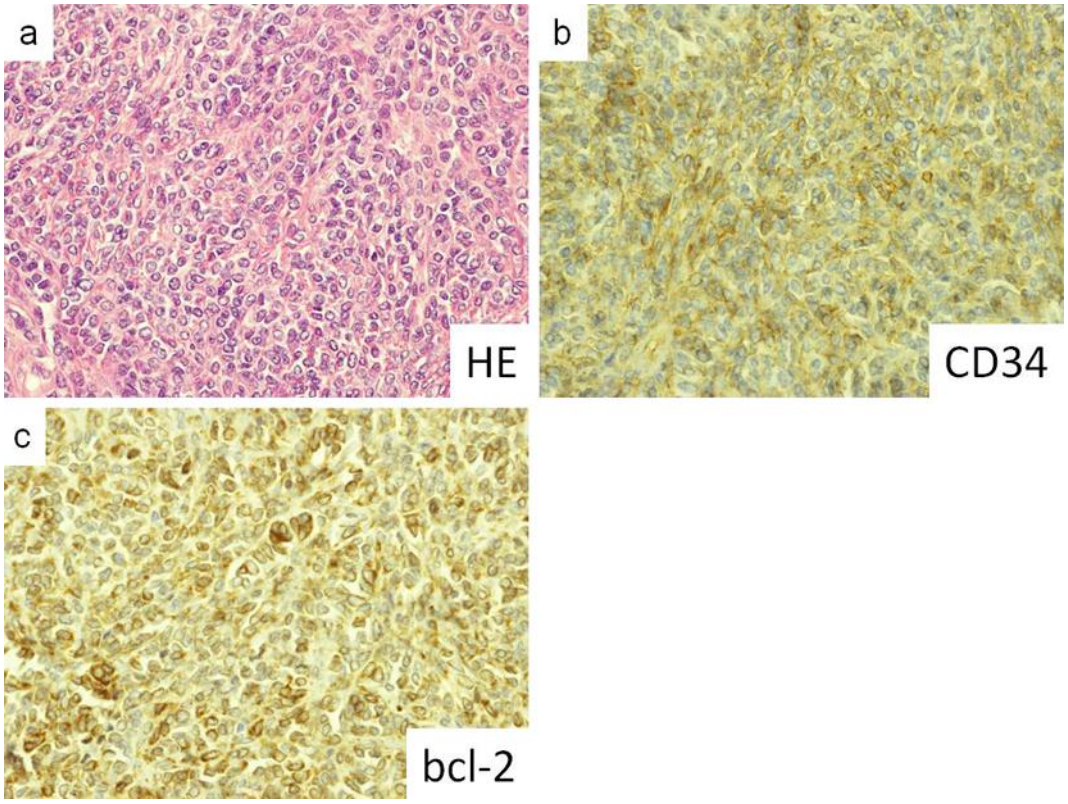

Fig. 1. Histopathological and immunohistochemical findings of the primary tumor excised in 2006. **a** Patternless pattern of tumor cells was seen (hematoxylin-eosin, ×40). **b**, **c** Tumor cells were positive for CD34 (**b**) and bcl-2 (**c**; immunohistochemistory, ×40), respectively.

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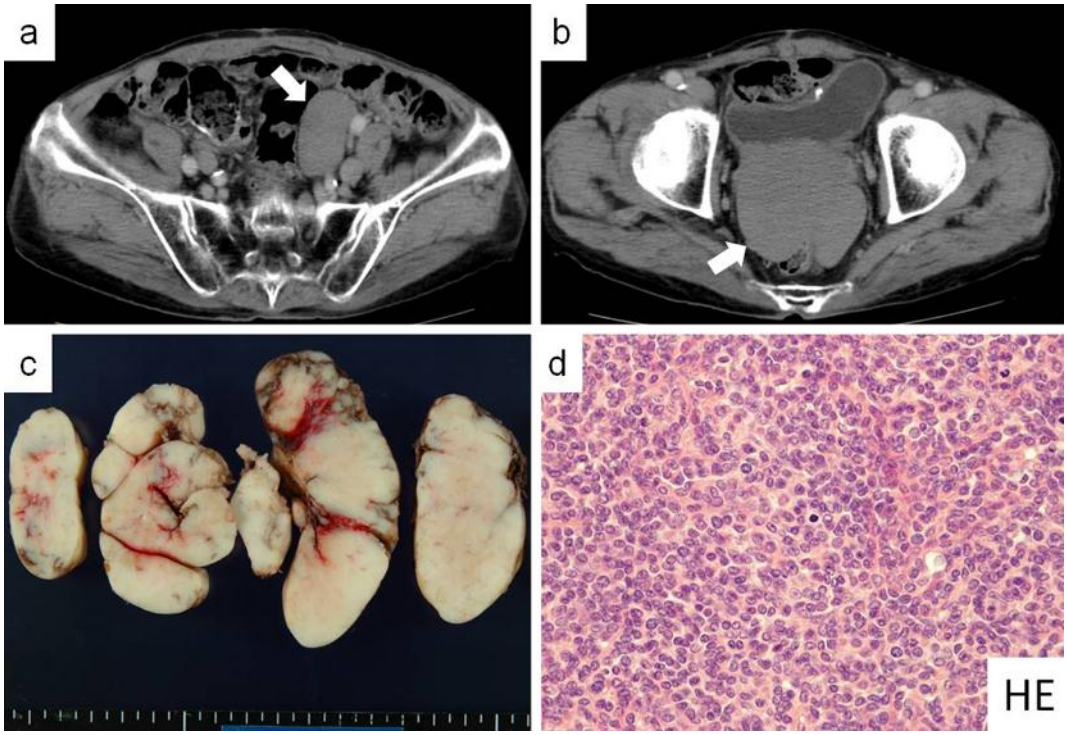

Fig. 2. **a**, **b** Enhanced CT findings of the tumor at the second recurrence in 2011. CT showed a sequentially lobulated mass in the retroperitoneum close to the left common iliac artery (**a**) and the pelvic cavity (**b**). **c**, **d** Macroscopic and microscopic findings of the tumor excised at the second recurrence in 2011. The excised tumor was an elastic mass with hemorrhagic and necrotic changes (**c**). The microscopic finding of a patternless pattern was similar to that of the specimen excised in 2006 (**d**; hematoxylin-eosin, ×40).

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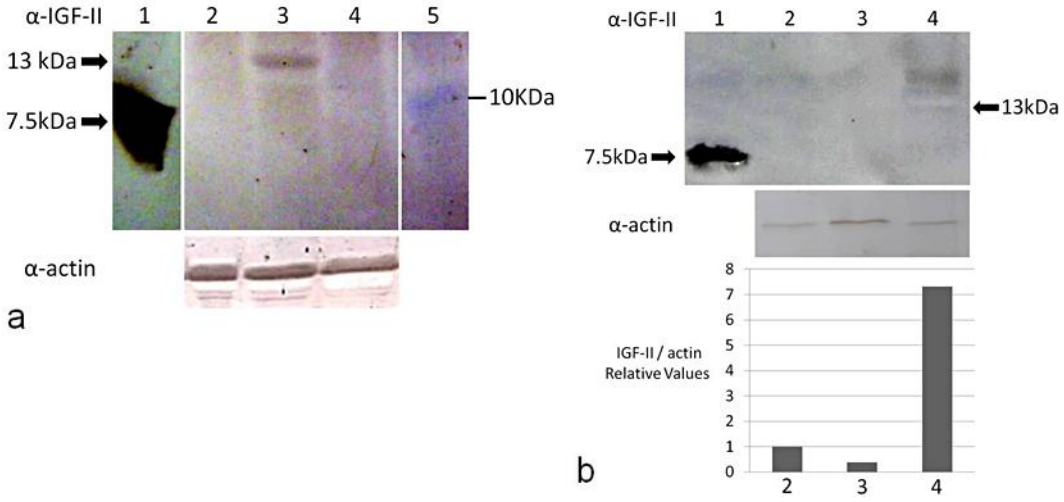

Fig. 3. **a** Immunoblotting analysis of serum IGF-II. Lane1 shows migration of the recombinant IGF-II protein (7.5 kDa). Lane 2 shows a blot of serum from the normal healthy control. Lanes 3 and 4 show the patient's pre- and postoperative blots, respectively. A high-molecular-weight form of IGF-II (13 kDa) was detected in the patient's preoperative serum but not in the postoperative serum. Lane 5 shows the protein marker. **b** Immunoblotting analysis of IGF-II in samples extracted from paraffin-embedded tumor specimens. Lane 1 contains recombinant IGF-II protein (7.5 kDa). Lanes 2, 3, and 4 show the blots of excised specimens from 2006, 2010, and 2011, respectively. The high-molecular-weight form of IGF-II was only detected in the sample from the second recurrence in 2011.

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References

1 Goodlad JR, Fletcher CD: Solitary fibrous tumour arising at unusual sites: analysis of a series. Histopathology 1991;19:515–522.

2 Kunieda K, Tanaka Y, Nagao N, Yamaguchi K, Sano J, Osada S, Saji S, Shimokawa K: Large solitary fibrous tumor of the retroperitoneum: report of a case. Surg Today 2004;34:90–93.

3 Katsuno H, Maeda K, Hanai T, Sato H, Masumori K, Koide Y, Matsuoka H, Noro T, Takakuwa Y, Hanaoka R: Trans-sacral resection of a solitary fibrous tumor in the pelvis: report of a case. Surg Today 2011;41:1548–1551.

4 Vallat-Decouvelaere AV, Dry SM, Fletcher CD: Atypical and malignant solitary fibrous tumors in extrathoracic locations: evidence of their comparability to intra-thoracic tumors. Am J Surg Pathol 1998;22:1501–1511.

5 Hasegawa T, Matsuno Y, Shimoda T, Hasegawa F, Sano T, Hirohashi S: Extrathoracic solitary fibrous tumors: their histological variability and potentially aggressive behavior. Hum Pathol 1999;30:1464–1473.

6 Gold JS, Antonescu CR, Hajdu C, Ferrone CR, Hussain M, Lewis JJ, Brennan MF, Coit DG: Clinicopathologic correlates of solitary fibrous tumors. Cancer 2002;94:1057–1068.

7 Kanthan R, Torkian B: Recurrent solitary fibrous tumor of the pleura with malignant transformation. Arch Pathol Lab Med 2004;128:460–462.

8 Krishnadas R, Froeschle PO, Berrisford RG: Recurrence and malignant transformation in solitary fibrous tumour of the pleura. Thorac Cardiovasc Surg 2006;54:65–67.

9 de Groot JW, Rikhof B, van Doorn J, Bilo HJ, Alleman MA, Honkoop AH, van der Graaf WT: Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. Endocr Relat Cancer 2007;14:979–993.

10 Hizuka N, Fukuda I, Takano K, Okubo Y, Asakawa-Yasumoto K, Demura H: Serum insulin-like growth factor II in 44 patients with non-islet cell tumor hypoglycemia. Endocr J 1998;45(suppl):S61–S65.

11 Briselli M, Mark EJ, Dickersin GR: Solitary fibrous tumors of the pleura: eight new cases and review of 360 cases in the literature. Cancer 1981;47:2678–2689.

12 Daughaday WH, Emanuele MA, Brooks MH, Barbato AL, Kapadia M, Rotwein P: Synthesis and secretion of insulin-like growth factor II by a leiomyosarcoma with associated hypoglycemia. N Engl J Med 1988;319:1434–1440.

13 Takizawa I, Saito T, Kitamura Y, Arai K, Kawaguchi M, Takahashi K, Hara N: Primary solitary fibrous tumor (SFT) in the retroperitoneum. Urol Oncol 2008;26:254–259.

14 England DM, Hochholzer L, McCarthy MJ: Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. Am J Surg Pathol 1989;13:640–658.