[Case Report]

Hypoglycemia Associated with Localized Fibrous Mesothelioma of the Pleura

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Abstract : Hypoglycemia is known to be a rare consequence of non-islet cell tumors. A patient having severe, episodic hypoglycemia was found to have a large mass occupying the right hemithorax. The hypoglycemia resolved immediately after surgical removal of the tumor. Histologic examination of the tumor revealed localized fibrous mesothelioma.

Key words: hypoglycemia, benign mesothelioma, IGF-II.

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Introduction

The association of hypoglycemia with non-islet cell tumors was among the earliest recognized endocrine paraneoplastic syndromes, and more than 250 cases of non-islet cell tumor induced hypoglycemia have been reported [1]. The majority of intra-thoracic tumors associated with hypoglycemia are either fibrosarcoma, rhabdomyosarcoma, neuroblastoma, or bronchogenic carcinoma [2]. To our knowledge, there have been 19 reported cases of hypoglycemia caused by benign fibrous mesothelioma.

Case Report

A 63-year-old woman was admitted to our hospital because of repeated episodes of loss of consciousness and was found to have a thoracic mass. She had noticed exertional dyspnea for 6 months prior to admission. One week before admission, she had two episodes of loss of consciousness and had urinary incontinence.

Her medical history revealed that a mass lesion had been noted on her

chest radiograph 20 years before, that a needle biopsy was non-diagnostic, and that an old inflammatory pleural lesion had been diagnosed. This mass lesion had been present on subsequent chest radiographs. There was no history of exposure to asbestos. Glucose intolerance had been diagnosed 10 years prior to admission, and was controlled by diet alone.

On examination, she was alert and oriented. Her pulse rate was 93/min

Fig. 1. Posteroanterior chest radiograph, showing a large right-sided thoracic mass.

Table 1. Daily profile of blood glucose with synchronous IRI and CPR

Time	Blood sugar (mg/dl)	IRI (IU/ml)	CPR (ng/ml)
7:30 am	18	<5.0	<0.3
9:30	143	9.6	1.0
11:30	87	5.4	0.3
2:00 pm	157	6.9	0.6
5:00	34	5.1	<0.3
8:00	137	5.3	0.3
11:00	15	6.3	<0.3
4:00	444	5.6	0.4

Glucose was administered according to the level of hypoglycemia

Fig. 2. a) Surgically removed tumor (lower segment). Encapsulated pleural tumor.
b) Histologic section of tumor showing interlacing bundles of elongated cells, consistent with localized fibrous mesothelioma. (haematoxylin and eosin stain; scale bar = 100 μ m).

and respiratory rate 28/min. Blood pressure was 142/78 mmHg. The arterial blood gas analysis while breathing room air showed: pH 7.45, PaO₂ 6.8 kPa, PaCO₂ 4.2 kPa. There was dullness and no respiratory sounds over the right hemithorax. The left lung was clear and her heart examination was normal. There was no mass or tenderness on abdominal examination, and no

peripheral edema or clubbing. Neurologic examination was non-focal. Peripheral white blood cell count was 7000/mm³ with a normal differential. Routine blood chemistry and urinalysis were normal. The blood glucose concentration had decreased to 48mg/dl. Insulin like growth factor-I (IGF-I) was normal, and insulin like growth factor-II (IGF-II) was also normal (590 ng/ml).

A chest radiograph revealed a large mass in the right thorax (Fig. 1). A computed tomograph (CT) of the chest showed a large soft tissue, non-homogeneous mass in the right thorax, associated with pleural effusion. The mediastinum was slightly displaced to the left by the mass. There was no enhancement of the mass by contrast medium. Gallium scintigram revealed a slightly increased accumulation in the right lung. The mass showed low vascularity on angiography and was perfused from the intra-thoracic, intercostal, inferior phrenic and common hepatic arteries.

During admission, episodes of mental confusion were observed each morning and found to be secondary to the hypoglycemia. These were quickly reversed by infusion of hypertonic glucose. A daily profile of the levels of blood glucose, synchronous immunoreactive insulin (IRI), and C-peptide reaction (CPR) are shown in Table 1. Neither IRI nor CPR were elevated during the hypoglycemic attacks.

A postero-lateral thoracotomy was performed. The tumor was segmented and encapsulated; the upper segment of the tumor measured 16×13

Fig. 3. Changes in blood glucose level after removal of the tumor. Prior to the surgery, there were frequent falls in the blood glucose level, causing hypoglycemic attacks, whereas after surgery the blood glucose level was elevated and insulin therapy was required.

$\times 8$ cm, the lower $21 \times 14 \times 9$ cm (Fig. 2a), and the total weight was 2500 g. The cut surface showed a yellowish white, firm, rubbery, fibrous tumor, with no necrosis. Microscopic examination disclosed interlacing fascicles of spindle cells, consistent with localized fibrous mesothelioma (Fig. 2b).

Immediately after the operation, the patient developed hyperglycemia, in contrast to the previous hypoglycemia, and required insulin injections (Fig. 3). The dose of insulin was gradually decreased and finally discontinued. There was no evidence of local recurrence or metastasis for at least 28 months after surgery.

Discussion

Tumor-induced hypoglycemia is categorized into two groups, islet cell tumor-induced hypoglycemia, and non-islet cell tumor-induced hypoglycemia. In contrast to islet cell tumors, non-islet cell tumors are of diverse origin, including mesoderm, epithelium and hematopoietic cells, and can be benign or malignant [1]. In 1929, two cases of hypoglycemia associated with hepatoma were described [3]. The next year, Doege reported a case of hypoglycemia associated with a mesenchymal tumor [4]. In most cases, non-islet cell tumors associated with hypoglycemia are large with symptoms of a space-occupying lesion. Hypoglycemia due to a mesenchymal tumor is referred to as Doege-Potter syndrome, which accounts for 45% of non-islet cell tumors associated with hypoglycemia [1]. In 115 cases of such mesenchymal tumors, 38 cases were intra-thoracic tumors [5]. However, there have been only 19 previously reported cases of tumor-induced hypoglycemia associated with benign pleural mesothelioma.

Serum IRI levels in patients with non-islet cell tumor-induced hypoglycemia are low or unmeasurable. However these patients have metabolic features of typical insulin action including inhibition of glycogenolysis and gluconeogenesis, and a block of lipolysis in the adipose tissue [6]. Therefore, molecules that have insulin-like action such as IGF-I and IGF-II have been suggested as the cause of the non-islet cell tumor-induced hypoglycemia. However, the measurement of serum IGF-I or IGF-II does not provide a clear solution, because in most of these patients the IGF-I level is decreased [7], and IGF-II is elevated in a few patients only [6, 7].

In 1988 Daughaday *et al.* found that 70% of IGF-II in the serum of a patient with non-islet cell tumor-induced hypoglycemia forms "big IGF-II" that has a higher molecular weight than normal IGF-II, when examined by gel filtration chromatography [8], and suggested that the big IGF-II corresponds to incompletely processed pro-IGF-II peptide. They also found that the tumor

contained a high level of IGF-II mRNA and that the big IGF-II in serum dropped nearly to zero after removal of the tumor. They therefore concluded that the tumor secreted big IGF II. Despite the production of big IGF-II from the tumor, it is unclear why the serum IGF-II remains normal in many patients with non-islet cell tumor-induced hypoglycemia. Zapf *et al.* [6, 9] determined the concentration of big IGF-II and normal IGF-II in serum samples from 30 patients by gel filtration chromatography. They discovered that normal IGF-II was decreased, but in contrast, big IGF-II increased. After removal of the tumors, the big IGF-II disappeared and normal IGF-II increased. They therefore suggested that an increase of big IGF-II and a concomitant decrease of normal IGF-II leads to a normal range of the total IGF-II in many of these patients. The elevated big IGF-II probably plays a key role in the hypoglycemia, because the big form is bioactive [9] and much more bioavailable than normal IGF-II due to an increased ability to cross the capillary barrier [6]. The big IGF-II forms a binary 50 kDa complex with insulin-like growth factor binding protein (IGFBP) in the serum and does not form a ternary 150 kDa complex like normal IGF-II.

In the present case, the dramatic improvement of hypoglycemia following the resection of the tumor strongly suggested that the benign mesothelioma was the cause of the hypoglycemia. The clinical features of hypoglycemia, and low serum IRI level coincide with non-islet cell tumor-induced hypoglycemia. In general, the activity of glycolysis in tumor cells is the dominant pathway to generate ATP instead of using the mitochondrial TCA cycle. It may be suggested that hypoglycemia was due to the active glucose consumption by 2.5 kg of tumor. Therefore, Doege-Potter syndrome due to localized fibrous mesothelioma is thought to be the case. It is important to recognize that a chronic lung mass may cause loss of consciousness due to a severe hypoglycemic attack.

The development and establishment of conventional methods for detection of serum big IGF-II is awaited.

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低血糖を伴った限局性線維性胸膜中皮腫の一例

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要 旨: 非腭島腫瘍に低血糖が合併することは稀である。高度の低血糖発作を繰り返す63歳女性の右胸郭内に大きな腫瘍が発見され、腫瘍の外科的切除により、低血糖発作は消失した。切除された腫瘍は限局性線維性胸膜中皮腫であった。低血糖発作中のIRIおよびCPR, IIRGF-I, IIRGF-IIはすべて正常範囲であった。

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