High-Molecular-Weight Insulin-Like Growth Factor II Secreting Phyllodes Tumor of the Breast Presenting as a Hypoglycemic Coma: A Case Report

Yuki Ichinose1, Shigeto Ueda2, Tomonori Kawasaki3, Takanori Hayashi4, Akihiro Fujimoto1, Asami Nukui1, Hiroko Shimada4, Aya Asano5, Kazuo Matsuura1, Takahiro Hasebe1, Akihiko Osaki1* and Toshiaki Saeki1

1Department of Breast Oncology, Saitama Medical University International Medical Center, Japan
2Department of Breast Surgery, JR Tokyo General Hospital, Japan
3Department of Pathology, Saitama Medical University International Medical Center, Japan
4Department of Biochemistry, Fujita Health University School of Medicine, Japan
5Department of Breast Oncology, Saitama Medical University Hospital, Japan

Abstract
We report the case of a patient who presented with a hypoglycemic attack associated with a Phyllodes tumor and the presence of high-molecular-weight Insulin-like Growth Factor II (IGF-II). A 42-year-old premenopausal woman, who had had a palpable mass in her left breast for several months, was found unconscious at her home by a family member early in the morning. She was emergently transported to our hospital. Her clinical examination revealed an approximately 15-cm mass in the entire left breast. Her blood glucose level was 33 mg/dL, resulting in hypoglycemia, and a 50% glucose injection immediately improved her awareness level. Thoracoabdominal computed tomography demonstrated a large, lobulated left breast tumor showing heterogeneous internal echotexture without enlargement of the lymph nodes (axillary, supraclavicular, cervical, and mediastinum) or distant metastasis. We performed a vacuum-assisted needle biopsy of the breast lesion that showed a Phyllodes tumor. We performed mastectomy, including the tumor, and the patient recovered from the hypoglycemic episode. The histological examination revealed a borderline Phyllodes tumor. Immunohistochemical examinations revealed neoplastic cells diffusely positive for IGF-II. Moreover, Western blot analysis demonstrated large amounts of high-molecular-weight IGF-II in the resected tumor. No relapse of a hypoglycemic attack and tumor recurrence has been reported post-surgery.

Keywords: Non-islet cell tumor hypoglycemia; Insulin-like growth factor type II; Hypoglycemic coma

Abbreviations
IGF: insulin-like growth factor; NICTH: non-islet cell tumor hypoglycemia

Introduction
Hypoglycemia is a common endocrine emergency, often associated with diabetes treatment or endocrine deficiency [1], although tumor-induced hypoglycemic coma occurs rarely. Non-Islet Cell Tumor Hypoglycemia (NICTH) is the possible cause for this condition, seemingly rarer than hyperinsulinism from insulinoma [2,3]. NICTH has been reported to be related to Insulin-like Growth Factor type II (IGF-II) production [4]. There have been a few reports of borderline Phyllodes tumors with NICTH due to high-molecular-weight IGF-II [5]. We herein report the case of a woman with a giant borderline Phyllodes tumor of the breast presenting with a hypoglycemic coma.

Case Presentation
A 42-year-old premenopausal Japanese woman, who had had a palpable mass in her left breast for several months, was found unconscious at home by a family member early in the morning. She was urgently transported to our hospital. She had no significant medical or family history.
The laboratory findings were as follows: Blood glucose level, 33 mg/dL; routine liver and renal function test results, normal.

Clinical examination revealed a mass of approximately 15 cm in diameter with a circulatory skin disorder (Figure 1). The blood sugar level was 33 mg/dL, resulting in hypoglycemia, and a 50% glucose injection immediately improved her awareness level.

Thoracoabdominal computed tomography demonstrated a massive, lobulated left breast tumor showing heterogeneous internal echotexture without enlargement of the lymph nodes (axillary, supraclavicular, cervical, and mediastinum) or distant metastasis (Figure 2). We performed a vacuum-assisted needle biopsy of the breast lesion after obtaining informed consent, and the histologic diagnosis was a Phyllodes tumor.

After hospitalization, she repeatedly lost consciousness due to hypoglycemia. On day 2 of hospitalization, she underwent left mastectomy to remove the Phyllodes tumor.

Pathological findings

The cut surface of the mastectomy specimen contained a relatively well-defined solid tumor, measuring 170 mm × 148 mm × 118 mm, partly with a typical Phyllodes pattern. Histologically, the lesion comprised proliferative epithelial and stromal components (Figure 3A-3C). We observed a focally permeative tumor border (Figure 3B), moderate stromal cellularity with mild to moderate stromal atypia, and a very focal stromal overgrowth (Figure 3C). Six mitotic figures were observed per 10 high-power fields (Figure 3D). There were no malignant heterologous elements found. Immunohistochemical examinations revealed neoplastic cells diffusely positive for IGF-II (Figure 4), appropriate positive and negative controls were included and negative for insulin and STAT6. The Ki-67 (MIB-1) labeling index of the mesenchymal cells was 13.7%.

Moreover, Western blot analysis demonstrated large amounts of high-molecular-weight IGF-II in the formalin-fixed-paraffin-embedded surgical sample. Briefly, samples for Western blot analysis were isolated from the formalin-fixed-paraffin-embedded sample using Protein Isolation Kit® (ITSI-Biosciences K-0017). After adding 5 × sodium dodecyl sulfate sample buffer to each of the samples, equal amounts (1 µg) of proteins from the serum and the Phyllodes tumor were used for the analysis. Protein extracts were separated by 15% polyacrylamide gel electrophoresis and transferred onto a 0.2 µm pore size polyvinylidene difluoride membrane (GE Healthcare, Chicago, USA). They were probed with rabbit polyclonal anti-IGF-II antibody (Atlas Antibodies, Bromma, Sweden). Then, it was detected with a Horseradish Peroxidase (HRP) -labeled secondary anti-rabbit IgG antibody (Bio-Rad Laboratories, Hercules, USA). As a result, Western blot detection images were observed only in IGF-II positive breast cancer tissue (Figure 5). Based on these pathological as well as biochemical findings, NICTH due to a borderline Phyllodes tumor of the breast was identified. Postoperatively, the patient’s hypoglycemia immediately disappeared, and her blood glucose level stabilized.
near 120 mg/dL. No relapse of a hypoglycemic attack and tumor recurrence has been reported post-surgery.

**Discussion**

The most common causes of hypoglycemia in adults are classically related to diabetes treatment and drugs, alcohol, critical illness, cortisol insufficiency, and insulinoma. Rarer etiologies may involve genetic, autoimmune, or paraneoplastic conditions (involving NICTH) [6]. Here, we report a rarer case of a patient with paraneoplastic hypoglycemic coma.

NICTH has been reported as one of the causes which induce hypoglycemia [3,7]. There are many reports involving overproduction of IGF-II from a tumor causing hypoglycemia, promptly corrected by surgical resection of the tumor. Although the incidence of NICTH is uncertain, hepatomas, fibromas, and fibrosarcomas are the most common types of NICTH. Phyllodes tumors of the breast account for 0.3% to 1% of breast tumors in females [8]. Phyllodes tumor of the breast with NICTH is a rare fibroepithelial tumor; moreover, borderline Phyllodes tumor—which occurs in 12% to 18% of Phyllodes tumor cases-accompanying NICTH, is still rarer [5].

Although NICTH diagnosis has been confirmed by identifying IGF-II protein by Western blotting method [3], the assay is not common practice. Therefore, surgical resection is considered a treatment after ruling out diabetes mellitus and other endocrine diseases. In our case, the patient had a giant Phyllodes tumor in her left breast, and hypoglycemic attack occurred several times after hospitalization. We suspected NICTH and performed an urgent surgical resection of the tumor. Although the incidence of NICTH is uncertain, hepatomas, fibromas, and fibrosarcomas are the most common types of NICTH. Phyllodes tumors of the breast account for 0.3% to 1% of breast tumors in females [8]. Phyllodes tumor of the breast with NICTH is a rare fibroepithelial tumor; moreover, borderline Phyllodes tumor—which occurs in 12% to 18% of Phyllodes tumor cases-accompanying NICTH, is still rarer [5].

In terms of IGF-II levels in serum, Daughaday et al. [9] reported high levels of large-molecular-weight-IGF-II in both the tumor and circulation of a patient with leiomyosarcoma-associated hypoglycemia. Fukuda et al. [10] evaluated serum levels of glucose-regulatory hormones in patients with high serum levels of large-molecular-weight-IGF-II and normal serum levels of IGF-II and concluded that differences in hormone profiles might help select patients who require analysis of IGF-II.

However, our study provides limited inferences since we did not measure serum IGF-II levels (due to lack of time) in this case, as we resected the tumor urgently.

In conclusion, we herein described a rarer case of borderline Phyllodes tumor secreting high-molecular-weight-IGF-II. This is the first report of detection of high-molecular-weight IGF-II by Western blotting from formalin-fixed-paraffin-embedded Phyllodes cancer sample.

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**References**