A Case of Giant Borderline Phyllodes Tumor of the Breast Associated with Hypoglycemia

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(Received May 26, 2016; Accepted June 11, 2016)

We report a patient with a giant phyllodes tumor of the right breast associated with a hypoglycemic attack. A 48-year-old woman experienced a loss of consciousness and was transferred via ambulance to our hospital emergency department. Upon arrival, her blood glucose level was 26 mg/dl, and a giant tumor (> 20 cm in diameter) with skin ulceration was observed on the right breast. Core needle biopsy led to a histological diagnosis of a phyllodes tumor of the breast. Ultrasonography and computed tomography detected neither distant metastasis nor a pancreatic endocrine tumor. Her preoperative serum insulin-like growth factor (IGF)-II and insulin levels were 1,330 ng/ml (normal range, 519–1067 ng/ml) and < 1.0 μU/ml, respectively. Following a simple mastectomy, the 24-h postoperative serum IGF-II and insulin levels were 496 ng/ml and 10.0 μU/ml, respectively. The IGF-II levels detected in the phyllodes tumor and normal breast tissue were 10,600 ng/Wg (wet weight in grams) and 855 ng/Wg. We conclude from these findings that the hypoglycemic attack was related to the elevated IGF-II level in the giant phyllodes tumor of the breast.

Key words: phyllodes tumor, IGF-II, hypoglycemic attack

INTRODUCTION

Phyllodes tumor of the breast is a rare, often benign (> 50%) type of fibroepithelial tumor that accounts for less than 1% of breast tumors [1]. Phyllodes tumors are generally first identified during routine breast medical examination and/or on mammography.

There have been a few reports of tumor-induced hypoglycemia, which is an infrequent condition occurring most often due to insulin secretion by pancreatic islet beta-cell tumors (insulinomas) or rarely due to excess secretion of insulin-like growth factor (IGF)-II from a tumor, leading to insulin receptor stimulation and increased glucose utilization. This latter condition is called non-islet cell tumor hypoglycemia (NICTH), which is a serious complication. In this report, we describe a rare case of a giant phyllodes tumor of the breast that induced NICTH consequent to excess IGF-II secretion.

CASE REPORT

In December 2004, a 48-year-old woman was brought to our emergency department after losing consciousness. Her past medical history and family history were unremarkable. Physical examination revealed a giant (> 20 cm in diameter), hard, elastic bleeding mass with skin ulceration in the right breast (Fig. 1). The axillary, supraclavicular, and cervical lymph nodes were not palpable. No neurological disorders were noted.

Blood studies indicated severe hypoglycemia (20 mg/dl), hypokalemia (2.4 mEq/L), hypernatremia (151 mEq/L), and hypoinsulinemia (1.0 μIU/ml) (Table 1). Imaging findings (X-ray of the chest and abdomen and computed tomography (CT) of the head) were unremarkable. The patient was administered 160 ml of a 40% glucose solution (6.4 g), which restored her serum blood sugar level and consciousness, and was discharged from the hospital the same day.

However, the next day after discharge, she again experienced a loss of consciousness and was brought to the emergency department. Because of hypoglycemia (29 mg/dl), she received another infusion of 40% glucose (40 ml, 1.6 g), which alleviated the hypoglycemic symptoms. However, her case was considered urgent with respect to examination and therapy because she had experienced continuous hypoglycemic attacks on 2 consecutive days. Consequently, she was administered continuous infusion of glucose (100 g/day) to alleviate the hypoglycemia.

Ultrasonographic evaluation of the breast mass indicated a heterogeneous internal echo and internal structures containing small cystic components, calcification, and hyperechoic separations. The mass had a nearly smooth margin with a somewhat irregular contour (Fig. 2). No axillary lymphadenopathy was observed. CT showed a giant mass in the right breast, with no tumor infiltration into the pectoral muscle fascia. Areas of high density observed within the tumor

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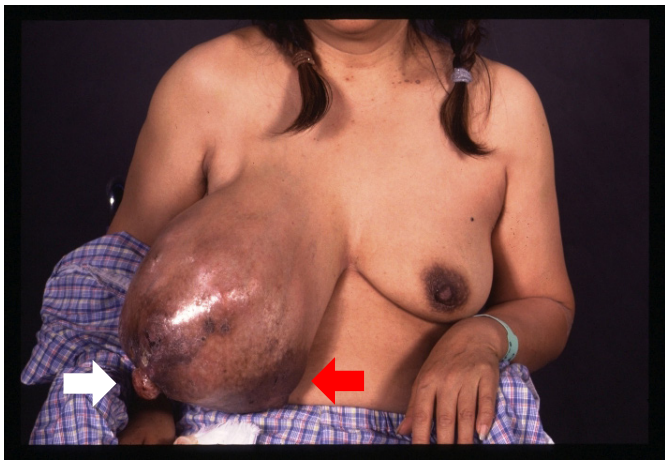

Fig. 1 Physical examination findings.
A giant right breast tumor, measuring approximately 20 cm in diameter with skin ulceration (white arrow), was observed. The red arrow indicates the right nipple. The tumor was hard and elastic, with good mobility, and bled easily from the skin ulcer. The axillary lymph node was not palpable.

Table 1 Blood analyses conducted upon arrival or before surgery

White blood cell	$10.1 \times 10^3/mm^3$ (4.0–8.0)
Red blood cell	$4.6 \times 10^6/mm^3$ (3.8–4.8)
Hemoglobin	13.8 g/dl (11.5–15.5)
Hematocrit	40.8% (34.0–42.0)
Platelet	$30.0 \times 10^4/mm^3$ (14.0–40.0)
Total protein	7.3 g/dl (6.5–8.0)
Albumin	4.1 g/dl (4.1–5.0)
AST	27 U/L (< 30)
ALT	14 U/L (< 35)
LDH	266 U/L (110–219)
ALP	252 U/L (100–300)
BUN	6 mg/ml (8–20)
Creatinine	0.4 mg/ml (0.5–0.8)
Sodium	151 mEq/L (136–145)
Potassium	2.4 mEq/L (3.5–4.8)
Chlorine	107 mEq/L (98–108)
Blood sugar	20 mg/dl (70–110)
Insulin	< 1.0 μIU/ml (1.5–13.3)
CEA	1.4 ng/ml (< 5)
CA15-3	27.7 U/ml (< 30)
IGF-I (serum)	210 ng/ml (46–282) (preoperatively)
IGF-II (serum)	1330 ng/ml (519–1067) (preoperatively)
IGFBP-3	3.57 μg/ml (2.17–4.05) (preoperatively) (normal ranges)

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP, alkaline phosphatase, BUN: blood urea nitrogen CEA: carcinoembryonic antigen, CA15-3: carbohydrate antigen 15-3, IGF: insulin-like growth factor, IGFBP-3: insulin-like growth factor binding protein-3

on plain CT images (Fig. 3A) were thought to be calcifications. Contrast-enhanced CT (Fig. 3B) indicated heterogeneous enhancement within the mass, with no cystic component. T1-weighted, fat-saturated magnetic resonance imaging (MRI) (Fig. 4A) indicated relative homogeneity within the tumor; an area of high signal intensity was thought to indicate a possible focal hemorrhage. Furthermore, contrast-enhanced T2-weighted, fat-saturated MRI (Fig. 4B) revealed a giant, lobulated mass with heterogeneous high signal intensity, as well as septa and well-circumscribed margins. These findings were typical of a phyllodes tumor.

A subsequent core needle biopsy (CNB) revealed that the tumor comprised both epithelial and stromal elements. Although high stromal cellularity was not observed, the stromal elements were abundant. These histological findings suggested a fibroepithelial lesion, including phyllodes tumor. The patient's baseline serum IGF-II level was high at 1330 ng/ml (normal range, 519–1067 ng/ml), whereas IGF-I and insulin growth factor binding protein-3 (IFGBP-3) levels were normal (210 ng/ml [normal, 46–282 ng/ml) and 3.57 mg/ml [normal, 2.17–4.05 mg/ml)]. The serum insulin level was low, at < 1.0 μU/ml (Table 1). The patient was

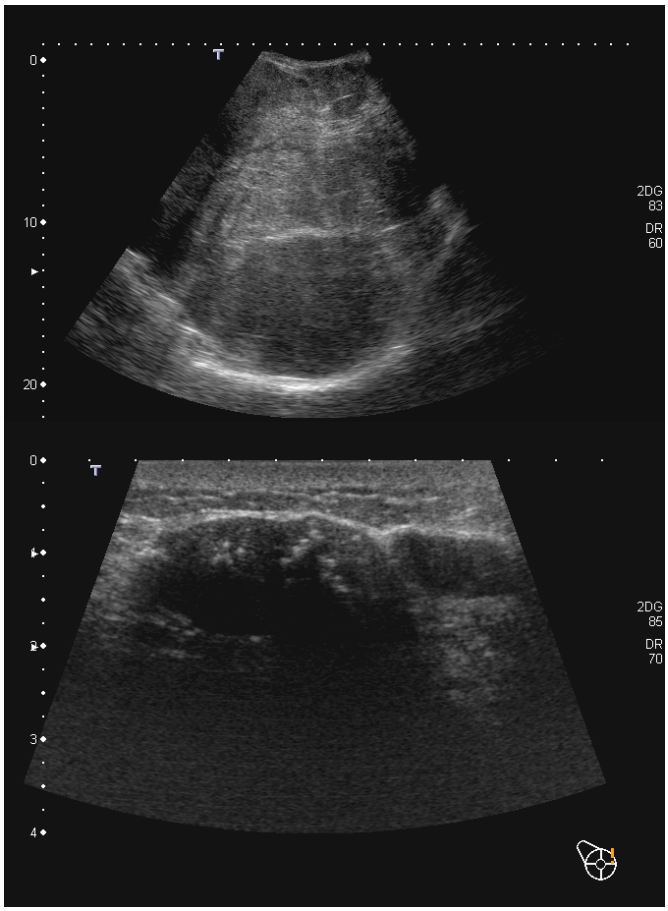

Fig. 2 Ultrasonography findings.
The right giant breast mass appeared as an area of heterogeneous internal echo, with had internal structures comprising small cystic parts, calcification and hyperechoic separations. The mass exhibited a nearly smooth, partially irregular contour.

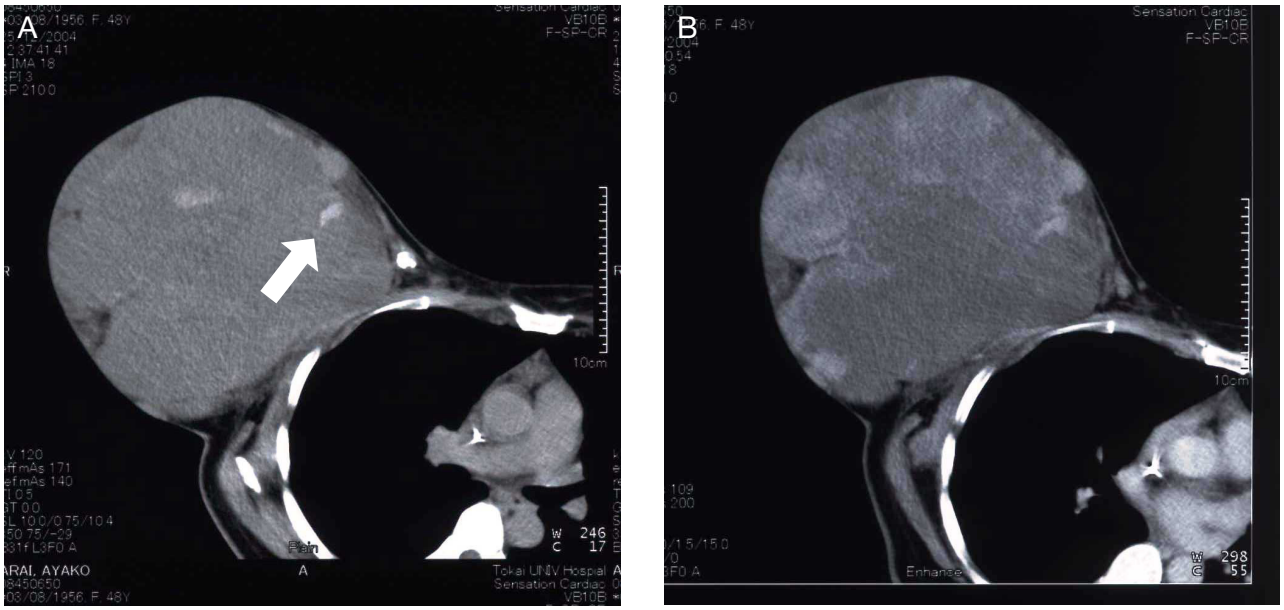

Fig. 3 CT findings.
Computed tomography (CT) revealed a giant mass in the right breast. (A) Areas of high density within the tumor on plain CT were thought to be calcifications (arrow). (B) Contrast-enhanced CT indicated heterogeneous enhancement within the mass.

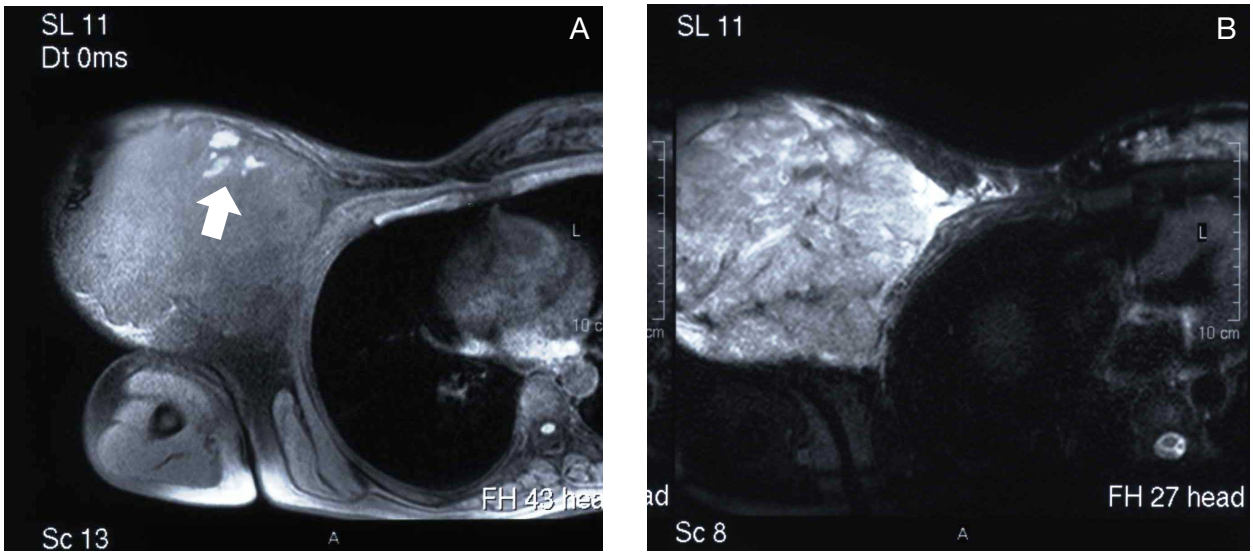

Fig. 4 MRI findings.
Magnetic resonance imaging (MRI) of the giant tumor in the right breast. (A) T1-weighted, fat-saturated MRI indicated relative homogeneity within the tumor, with an area of high signal intensity, possibly indicative of focal hemorrhage (arrow). (B) Contrast-enhanced, T2-weighted, fat-saturated MRI showed a lobulated giant mass with heterogeneous high signal intensity. The tumor contained some septa and well-circumscribed margins.

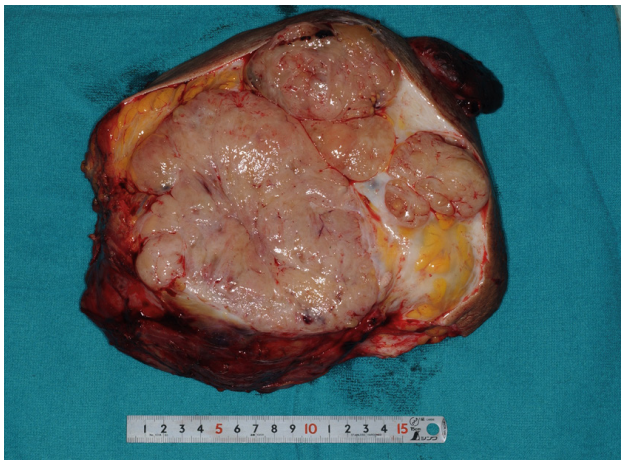

Fig. 5 Gross appearance of the cut surface of the tumor.
The cut surface of the tumor was white-to-gray with hemorrhagic foci.

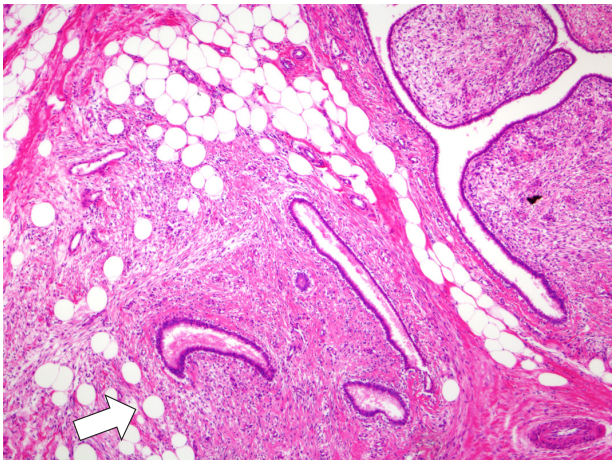

Fig. 6 Histopathological findings (Hematoxylin eosin stain; low magnification).
The stromal cells exhibited nuclear hyperchromasia and mild pleomorphism.
Invasive growth patterns were focally detected (arrow).

diagnosed with an IGF-II-secreting phyllodes tumor.

A simple mastectomy was performed to remove the tumor. The approximate size and weight of the removed tumor were 25 × 18 × 17 cm and > 5 kg, respectively. The cut surface of the tumor was white-to-gray with hemorrhagic foci (Fig. 5). The tumor was relatively well defined, and a phylloid pattern with cystic lumina was focally detected at the periphery of the tumor. As indicated by the CNB findings, the tumor comprised abundant stromal and epithelial elements. The stromal cells exhibited nuclear hyperchromasia and mild pleomorphism, with few mitotic figures (1–2/10 high-powered field), and a focal invasive growth pattern was identified. These histological features were consistent with a borderline phyllodes tumor (Fig. 6). Furthermore, the IGF-II concentration in the tumor was 10600 ng/Wg, compared with the normal tissue value of 855 ng/Wg (Table 2). Thus, this phyllodes tumor produced a large quantity of IGF-II to which the recurring hypoglycemic attacks were attributed.

The patient's post-operative serum IGF-II levels decreased to within the normal range over time—with values of 921 ng/ml at 1 h, 790 ng/ml at 3 h, 666 ng/ml at 6 h, 521 ng/ml at 12 h, and 496 ng/ml at 24 h (Table 3). Her blood sugar level accordingly increased after surgery without requiring an intravenous administration of high-concentration glucose, and her postoperative serum insulin level consistently exceeded 10.0 μU/ml. The borderline phyllodes tumor as well as the hypoglycemic attacks did not recur within a 10-year postoperative follow-up period.

Table 2 IGF-II concentration in the phyllodes tumor relative to the normal breast tissue.

IGF-II concentrations in tissue extracts	
Phyllodes tumor	10,600 ng/Wg
Normal breast tissue	855 ng/Wg

IGF: insulin-like growth factor

Table 3 Changes over time in serum IGF-II, glucose, and insulin levels and the concentration of administered glucose after tumor resection.

		Time after resection					
	Before surgery	1 h	3 h	6 h	12 h	24 h	72 h
Serum IGF-II (ng/ml)	1,330	921	790	666	521	496	680
Serum glucose (mg/ml)	122	145	202	159	-	144	145
Insulin (μU/ml)	<1.0	12.2	11.0	-	-	10.0	-
Administration glucose (%)	50	5	5	5	5	5	-

IGF: insulin-like growth factor

DISCUSSION

Breast phyllodes tumor was reported for the first time in 1838 by Johannes Muller, and was originally designated "cystosarcoma phyllodes" [2]. Histologically, these uncommon fibroepithelial tumors are classified as benign, borderline, or malignant according to the presence of stromal cellular atypia, cell density, mitotic activity, infiltrative vs. circumscribed tumor margins, and the presence of an interstitial one-sided increase [3]. In the present case, the tumor stromal cells exhibited nuclear hyperchromasia and mild atypia, along with mitotic activity and a circumscribed infiltrative tumor margin. These pathological features were consistent with a borderline phyllodes tumor.

NICTH, which was first reported in 1929 [4], is usually associated with large tumors of mesodermal or epithelial origin [5]. Notably, the first report of hypoglycemia associated with a phyllodes tumor was published in 1983 [6]. The most common cause of NICTH is tumoral overproduction of IGF-II, a single-chain peptide that shares approximately 50% sequence homology with proinsulin. Hypoglycemia appears to be consequent to increased glucose utilization and inhibited release of glucose from the liver consequent to the tumoral secretion of incompletely processed IGF-II. The laboratory evaluation for hypoglycemia includes episodic measurements of glucose, insulin, proinsulin, C-peptide, beta-hydroxybutyrate, and sulfonylurea/meglitinide levels [7]; in addition, measurements of serum IGF-I and IGF-II levels might be diagnostically useful. Accordingly, a diagnosis of NICTH is based upon both clinical and biochemical findings, and is not usually difficult. When a patient with a known tumor presents with hypoglycemia, the cause is typically apparent from the history and physical examination. Furthermore, a healthy person who experiences hypoglycemia is less likely to have NICTH, although in some cases, hypoglycemia is the initial event that leads to the diagnosis of a tumor. Although we were unable to measure the serum C-peptide, proinsulin, and beta-hydroxybutyrate levels, the current patient was a typical case in which the measured high serum IGF-II level led to a preoperative diagnosis.

Complete resection of the IGF-producing tumor is the most effective treatment for NICTH [8]. However, if surgery is delayed, ongoing management of hypoglycemia might include an increased caloric intake and intravenous glucose administration. In the present case, the patient received a continuous intravenous administration of 50% glucose before surgery to remove the tumor, which had a very high IGF-II concentration relative to that of the normal breast tissue. Following mastectomy, her serum IGF-II concentration decreased over time, resulting in an increase in her blood sugar level without intravenous glucose.

In summary, we have reported our experience with a rare case of a giant borderline phyllodes tumor with hypoglycemic attacks caused by tumor-secreted IGF-II. This is the first report in which the IGF-II concentration has been measured in the tumor and corresponding normal tissues.

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