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Malignant Phyllodes Tumor of the Breast with Hypoglycemia: Report of a Case

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A surgically resected case of giant malignant phyllodes tumor of the breast associated with a hypoglycemic attack is reported. A 54-year-old woman was referred to our hospital with loss of consciousness and a huge chest wall tumor. She was diagnosed as having a malignant phyllodes tumor by core needle biopsy and underwent palliative simple mastectomy because lung metastasis was detected on computed tomography and by other imaging modalities on admission. The preoperative laboratory data revealed a very low fasting blood sugar level of 37 mg/dl. After removal of the tumor, the blood sugar level gradually normalized (90–100 mg/dl) and the plasma insulin-like growth factor-II (IGF-II) level promptly decreased. The IGF-II level of tumor extracts was high (2500 ng/g wet weight) and the majority of atypical cells stained positively for IGF-II immunohistochemically. These findings suggested that the patient's hypoglycemia was associated with IGF-II produced by a giant malignant phyllodes tumor that consumed glucose.

Key words: breast – malignant phyllodes tumor – hypoglycemia – insulin-like growth factor

INTRODUCTION

Malignant phyllodes tumor of the breast is an uncommon neoplasm, reportedly accounting for no more than 1.0% of all malignant breast tumors (1,2). Moreover, there have been few reports of them causing hypoglycemic attacks (3–7). Recently, we experienced an extremely rare case of enormous breast tumor associated with severe hypoglycemia. We present this case below with a discussion of similar cases in the literature.

CASE REPORT

Clinical History

A 54-year-old woman with a huge tumor of the left breast was admitted following loss of consciousness. Her family history and past history were unremarkable. The patient's height was 157 cm and her weight was low, 55 kg (44 kg after removal of the tumor). Despite having been aware of the tumor for more than 20 years, she had not sought medical attention. The tumor started to grow rapidly in February 1996 and in May of the same year she was admitted in emergency by a local physician for treatment of unconsciousness associated with severe hypoglycemia (fasting blood sugar 18 mg/dl). The tumor was suspected of being a phyllodes tumor based on examination of a core needle biopsy specimen and the patient was referred to our hospital while receiving continuous intravenous glucose infusion.

Blood studies on admission revealed moderate anemia and a low fasting blood sugar level, 37 mg/dl. The serum insulin level was also low, 4.4 μU/ml and the IRI/BS ratio was 0.12. The plasma insulin-like growth factor-I (IGF-I) level was normal, 150.2 ng/ml, but the IGF-II level was low, 320 ng/ml. Based on these data , we ruled out insulinoma. Serum levels of the tumor markers CEA, CA15-3 and NCC-ST439 were all within the normal range (Table 1).

The breast tumor was extremely large, approximately 30 cm in diameter, and had an indistinct boundary. It was elastic hard, bled easily and necrotic changes were seen in some parts. Although computed tomography (CT) detected no tumor infiltration into the pectoral muscle fascia, lung metastasis was suspected based on a tumor shadow 1.2 cm in diameter in the S_3 region of the left lung on CT-scan and chest X-ray. Angiography revealed an arterial blood supply to the tumor from the hypervascular thoraco-acromial artery. Preoperative embolization with spongel was performed because of persistent bleeding. No other organs showed signs of metastases on magnetic resonance imaging from the neck to the abdomen and whole body bone-scintigraphy and gastrointestinal examination results were unremarkable.

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Abbreviations: IGF, insulin-like growth factor; IRI, immunoreactive insulin; FBS, fasting blood sugar; CT, computed tomography; RIA, radioimmunoassay; MPA, medroxyprogesterone acetate; PgR, progesterone receptor

Table 1. Laboratory findings on admission

Complete blood count	WBC	9700/mm^3	(4500–9000)
	RBC	391 × 10^4/mm^3	(389–484)
	Hb	9.2 g/dl	(11.9–15.0)
	Ht	28.5%	(34.6–43.0)
	Plt.	52.6 × 10^4/mm^3	(13.2–38.0)
Blood chemistry	T.Bil.	0.3 mg/dl	(0.5–1.0)
	GOT	29 IU/l	(8–40)
	GPT	24 IU/l	(0–40)
	LDH	972 IU/l	(240–530)
	ALP	294 IU/l	(90–340)
	T.P.	6.4 g/dl	(6.5–8.3)
	Alb.	2.3 g/dl	(3.3–4.7)
	T.Ch.	161 mg/dl	(120–240)
	Amylase	122 IU/l	(70–210)
	BUN	7.0 mg/dl	(8–15)
	Creat.	0.55 mg/dl	(0.46–0.67)
	Na	143 mEq/l	(137–149)
	K	3.8 mEq/l	(3.7–5.0)
	Cl	108 mEq/l	(98–109)
	Fe	6 μg/dl	(17–150)
	FBS	37 mg/dl	(70–120)
	Insulin	4.4 μU/ml	(12–30)
		(IRI/BS = 0.12)	
	IGF-I	150.2 ng/ml	(121–436)
	IGF-II	320 ng/ml	(374–804)
Tumor marker	CEA	2.5 ng/ml	(0.6–4.0)
	CA15-3	26 U/ml	(≤30)
	NCC-ST439	1.8 U/ml	(≤7.0)

Normal values in parentheses.

Based on the suspicion of pulmonary metastasis and the diagnosis of primary malignant phyllodes tumor of the breast, a palliative simple left mastectomy and sampling of ipsilateral axillary lymph nodes were performed. The plasma IGF-II level promptly decreased by nearly half after surgical resection. On the other hand, although the blood sugar value transiently rose to more than 200 mg/dl during the first few postoperative days, it later normalized to 90–100 mg/dl and remained within normal limits during the follow-up period. The IGF-II level of the tumor extracts was high (2500 ng per g wet weight of the tumor). The tissue IGF-II level was determined by radioimmunoassay (RIA) using an anti-IGF-II monoclonal antibody (Amersham, Chicago, IL). This RIA is specific for IGF-II and cross-reactivity with IGF-I is only 1%.

Because the tumor tissue was estrogen receptor-negative, but progesterone receptor (PgR)-positive, medroxyprogesterone acetate (MPA), 600 mg/day, was administered for 6 months postoperatively. There has been no evidence of relapse in the approximately 16 months since the operation and the lung metastatic lesion has disappeared from CT-scan and chest X-ray images. The patient has returned to her routine, active lifestyle (Fig. 1).

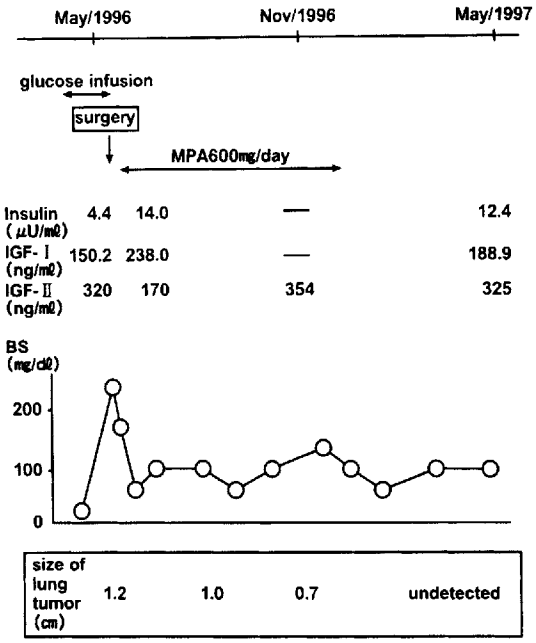

Figure 1. Clinical course of the case. MPA, medroxyprogesterone acetate; IGF, insulin-like growth factor; BS, blood sugar.

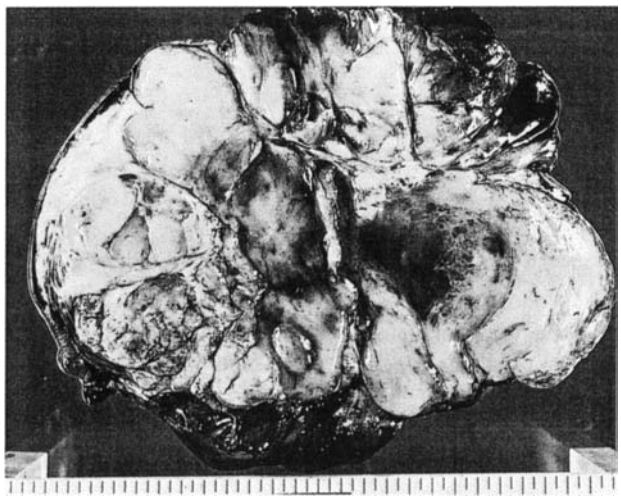

Figure 2. Gross appearance of cut surface of the resected tumor, containing several cystic and necrotic areas. Note the expanding margins.

Histopathological Findings

The resected tumor weighed approximately 9.0 kg and measured 35 × 28 × 27 cm. Gross examination of the cut surface showed a grayish-white, solid, elastic hard, multi-lobular tumor with recent multifocal hemorrhage and necrosis (Fig. 2).

Histologically, the tumor was composed of a large amount of hypercellular stroma which overwhelmed a small amount of irregular tubules as the epithelial components. The stromal cells showed pleomorphism, marked nuclear atypia and prominent

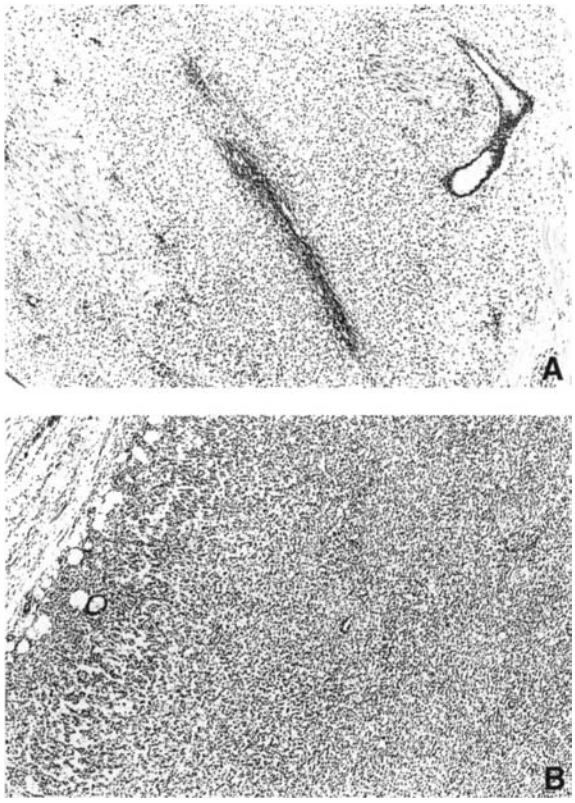

Figure 3. Photomicrographs of malignant phyllodes tumor. (**a**) Low-power view of the tumor, showing hypercellular growth of the stroma which overwhelmed the epithelial components (H&E; original magnification, ×10). (**b**) At the periphery of the tumor, the stromal cells show ill-defined invasion into the adjacent adipose tissue (H&E; original magnification, ×10).

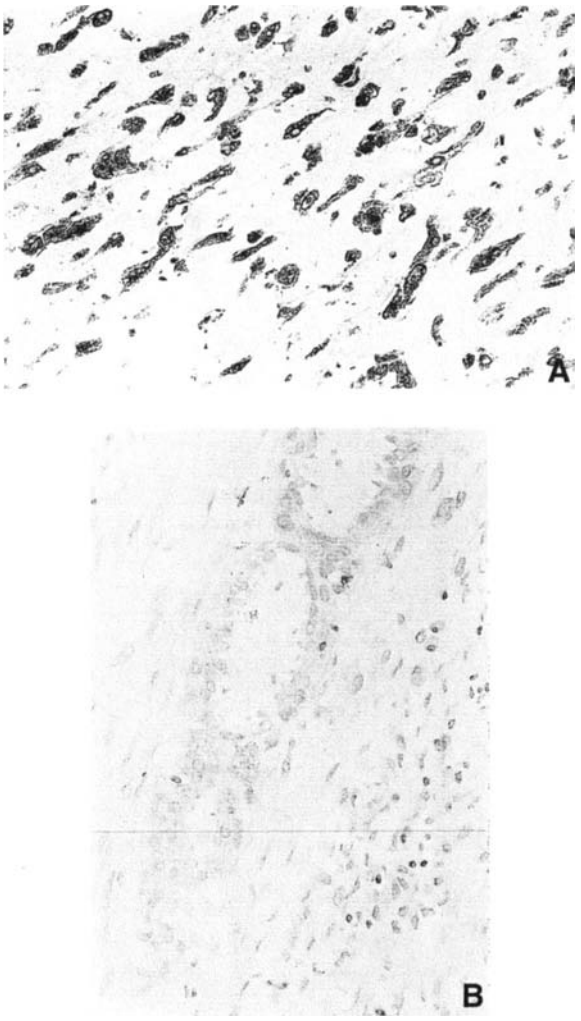

Figure 4. Immunohistochemical findings for expression of IGF-II. (**a**) The expression of IGF-II is noted in the cytoplasm of the pleomorphic stromal cells (immunohistochemical stain; original magnification, ×40). (**b**) The epithelial cells in the tumor showed no expression of IGF-II (immunohistochemical stain; original magnification, ×20).

focal mitotic activity, exceeding five mitoses per 10 high-power fields. At the periphery of the tumor, the stromal cells showed ill-defined invasion into the adjacent breast tissue (Fig. 3), the overlying skin and the pectoral fascia. Based on these findings, the diagnosis of malignant phyllodes tumor was made. There were no metastases to the axillary lymph nodes sampled.

IGF-II immunohistochemical examination was performed on frozen sections of the tumor by the avidin–biotin–peroxidase complex (ABC) method using a Histofine SAB-PO kit (Nichirei, Tokyo, Japan). The antibodies used were rabbit polyclonal antiserum for human IGF-II (Mediagnost, Tubingen, Germany) that had less than 0.05% cross-reactivity with IGF-I. Various degrees of expression of IGF-II were noted in the cytoplasm of most stromal cells, but no expression of it was seen in the epithelial cells (Fig. 4).

DISCUSSION

Some extrapancreatic neoplasms are known to cause hypoglycemic attacks, but the mechanism responsible for the hypoglycemia and the biological behavior of these tumors remain matters of controversy. Fasting hypoglycemia generally occurs in certain types of malignant tumors, usually in the extrapancreatic tumors except for insulinomas (1,2). It is noteworthy that more than 100 such cases, with leiomyosarcoma, fibrosarcoma, mesothelioma, etc., have been reported (8–11). Hypoglycemic attacks can also be produced by certain epithelial cell tumors, such as hepatocellular carcinoma, adrenocortical tumor and lung cancer (9). However, there have been few reports of malignant phyllodes tumor causing severe hypoglycemia, as in our case. To our knowledge, Li et al. (3) described the first case of hypoglycemia associated with phyllodes tumor in 1983 and the present case is the sixth and the largest tumor reported in the international literature (3–7) (Table 2).

The hypoglycemia induced by these tumors is thought to be due to excess secretion of an insulin-like growth factor, IGF-II (2,8–10). In general, these IGF-II producing extrapancreatic tumors are large, slow-growing, low-grade malignancies and fall into one of the following two categories: deficient glucose production and excess glucose utilization (8–10). Shapiro et al. (9) suggested that high molecular weight IGF-II readily binds to cell surface receptors because it has a low serum binding protein affinity and can circulate in its free form.

Table 2. Phyllodes tumor of the breast with hypoglycemia

Authors	Reported year	Characteristics of phyllodes tumor					
		Age (yrs)	Size (cm)	Weight (kg)	Histological subtype	IGF-II level*	
						Plasma	Tissue
Li et al. (3)	1983	43	28	4.2	Benign	High	N.D.
Tanaka et al. (4)	1986	65	25	4.0	Malignant	N.D.	N.D.
Bleau et al. (5)	1991	66	Unknown	6.0	Unknown	Normal	High
Ishido et al. (6)	1992	26	Unknown	3.0	Benign	High	N.D.
Miura et al. (7)	1992	66	26	3.1	Unknown	Normal	N.D.
Kataoka et al.	1997	54	35	9.0	Malignant	Low	High

*N.D. = not determined.

While the physiological role of IGF-II is also not fully understood, the observation of a nearly 50% decrease in IGF-II postoperatively suggests a possible etiological role in the hypoglycemic attack experienced by our patient. Teale and Marks (12) suggested that even when the plasma IGF-II level is not high, as in our case, hypoglycemia would be produced by plasma IGF-I suppression via a relative increase in IGF-II. In practice, in patients bearing the tumors mentioned above, circulating IGF-II levels detected by RIA are usually normal, because the majority of IGF-II binds to IGF binding proteins (IGFBP), especially IGFBP-3 (2,5,9). Moreover, increased expression of IGF-II mRNA by the tumor may be an oncogenic factor inducing tumor growth (8). The hypoglycemia in patients with malignant tumors that overproduce IGF-II could be interpreted as a consequence of inappropriate stimulation of insulin or of IGF-I receptors by IGF-II (8,9). In our case, however, the plasma IGF-II level was low preoperatively, while the tissue IGF-II level was high and the plasma IGF-II level promptly decreased upon removal of the tumor. Moreover, the expression of IGF-II was detected immunohistochemically in the cytoplasm of the majority of atypical cells, such that tumor production of IGF-II may have been a causative factor in our patient's severe hypoglycemia.

On the other hand, complete resection of the tumor, the treatment of choice, produced prompt normalization of the serum glucose level despite the presence of lung metastasis (1). However, many studies assessing whether to carry out postoperative adjuvant chemotherapy for malignant phyllodes tumor have yielded negative results. There have been many reports describing a very poor outcome, especially for tumors with diameters of 10 cm or more and in cases with confirmed distant metastasis, e.g. to the lung (1,2).

Although few reports recommend hormonal therapy for malignant phyllodes tumor (13), Rao et al. (14) reported that hormonal therapy is effective and that the receptor is a potential therapeutic target, because there are many PgR-positive cases (14,15). In our patient, MPA was administered because of the PgR positivity and the effect of this treatment was apparently adequate, since the tumor shrank and local recrudescence of metastatic lesions has not been seen for more than a year. In general, the growth of stromal cells and the development of lobuloalveolar components of the mammary gland are considered to be regulated by several endocrine hormones such as progesterone (2). Moreover, although there are few cases of concomitant phyllodes tumor and breast cancer, the many histological types of these associated breast cancers are described as intraductal carcinomas or lobular neoplasms (16). We therefore conclude that phyllodes tumors which are PgR positive are a good indication for MPA therapy, because MPA can be expected to suppress progression of the disease and the development of a second primary breast cancer. Unfortunately, definite guidelines for the treatment of malignant phyllodes tumor have not yet been established and further studies are needed to assess our results. Our hope is that new therapeutic approaches will be developed.

In conclusion, we have reported an extremely rare case of giant malignant phyllodes tumor of the breast associated with severe hypoglycemia. The hypoglycemic attack in this patient may have been caused by IGF-II produced by the huge tumor, which itself apparently consumed glucose.

References

1. Reinfuss M, Mitus J, Duda K, Stelmach A, Rys J, Smolak K. The treatment and prognosis of patients with phyllodes tumor of the breast—an analysis of 170 cases. *Cancer* 1996;77:910–16.
2. Petrek JA. Phyllodes tumor. In: Harris JR, Lippman ME, editors. Disease of the Breast. Philadelphia: Lippincott-Raven, 1996;863–9.
3. Li TCM, Reed CE, Stubenbord WT Jr, Ettinghausen S, Peterson CM, Jovanovic L, et al. Surgical cure of hypoglycemia associated with cystosarcoma phyllodes and elevated non-suppressible insulin-like protein. *Am J Med* 1983;74:1080–4.
4. Tanaka S, Muramoto Y, Sakae K, Sato E. Giant malignant phyllodes tumor of the breast with hypoglycemia and left hemiplegia; Report of a case. *Nippon Byori Gakkai Kaishi* 1986;75:481–2 (in Japanese).
5. Bleau B, Vlahos W, Guyga H. High molecular weight insulin-like growth factor-II (HMW IGF-II) associated with fasting hypoglycemia and a phyllodes tumor of the breast. *Clin Invest Med* 1991;14(Suppl.):36(abstr.).
6. Ishido H, Kitaoka M, Uchigata M, Kaji M, Maeda M, Nagayama T. A case of phyllodes tumor of the breast producing IGF-II. *Nippon Naibunpitsu Gakkai Zashi* 1992;68:825 (abstr.) (in Japanese).
7. Miura K, Noma M, Ishikawa K, Katayama S. Giant breast tumor (cystosarcoma phyllodes) associated with unconsciousness by persistent hypoglycemia; report of an autopsied case. *Iryou* 1992;46:179 (abstr.) (in Japanese).
8. LeRoith D, Clemmons D, Nissley P, Rechler MM (NIH Conference). Insulin-like growth factors in health and disease. *Ann Intern Med* 1992;116:854–62.

9. Shapiro ET, Bell GI, Polonsky KS, Rubenstein AH, Kew MC, Tager HS. Tumor hypoglycemia: relationship to high molecular weight insulin-like growth factor-II. *J Clin Invest* 1990;85:1672–9.
10. 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;12:1434–40.
11. Masson EA, MacFarlane IA, Graham D, Foy P. Spontaneous hypoglycaemia due to a pleural fibroma: role of insulin like growth factors. *Thorax* 1991;46:930–1.
12. Teale JD, Marks V. Inappropriately elevated plasma insulin-like growth factor II in relation to suppressed insulin-like growth factor I in the diagnosis of a non-islet cell tumor hypoglycaemia. *Clin Endocrinol Oxf* 1990;33:87–98.
13. Burton GY, Hart LL, Leight GS Jr, Iglehart JD, McCarty KS Jr, Cox EB. Cystosarcoma phyllodes. Effective therapy with cisplatin and etoposide chemotherapy. *Cancer* 1989;63:2088–92.
14. Rao BR, Meyer JS, Fry CG. Most cystosarcoma phyllodes and fibroadenomas have progesterone receptor but lack estrogen receptor: stromal localization of progesterone receptor. *Cancer* 1981;47:2016–21.
15. Mechtersheimer G, Kruger KH, Born IA, Moller P. Antigenic profile of mammary fibroadenoma and cystosarcoma phyllodes. A study using antibodies to estrogen and progesterone receptors and to a panel of cell surface molecules. *Pathol Res Pract* 1990;186:427–38.
16. Rosen PP, Urban JA. Coexistent mammary carcinoma and cystosarcoma phyllodes. *Breast* 1975;1:9–15.