CASE REPORT

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Recurrent Severe Hypoglycemia Secondary to Benign Phyllodes Tumor of the Breast: A Rare Case of Non-Islet Cell Tumor-induced Hypoglycemia (NICTH)

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Abstract

Non-islet cell tumor-induced hypoglycemia (NICTH) secondary to phyllodes tumor is extremely rare but potentially life threatening if not treated promptly. We report a case of a 46-year-old Indian female without underlying diabetes mellitus who presented with a large breast tumor and recurrent severe symptomatic hypoglycemia. Investigations supported the diagnosis of NICTH. The hypoglycemia only resolved after corticosteroids and mastectomy. This case highlights the importance of considering NICTH in the evaluation of patients with voluminous tumor and hypoglycemia.

Key words: hypoglycemia, insulin-like growth factor II, phyllodes tumor, mastectomy, corticosteroids

INTRODUCTION

Phyllodes tumor is an uncommon fibroepithelial tumor that accounts for less than 1% of all breast neoplasms, with 54 to 64% classified as benign, 12 to 18% borderline and 18 to 35% malignant.[1,2] Non-islet cell tumor-induced hypoglycemia (NICTH) is also a rare but serious paraneoplastic syndrome in which a tumor secretes insulin-like growth factor II (IGF-II), causing hypoglycemia. Although the true incidence of NICTH is unclear, it is generally believed to be much less frequent than hypoglycemia from insulinomas. In most cases, NICTH occurs in patients with solid tumors of mesenchymal and epithelial origin, such as hepatocellular carcinoma, fibrosarcoma or mesothelioma.[3] Only a few cases of NICTH secondary to breast tumors, especially phyllodes tumors, have been previously reported. We present an interesting case of a patient with benign phyllodes tumor presenting with recurrent severe hypoglycemia which only resolved after corticosteroid therapy and mastectomy.

CASE

A 46-year-old Indian female with a six-month history of a rapidly growing left breast mass presented with altered mental status for three days. She was observed to be less responsive and incoherent at times. There were no preceding autonomic symptoms or fever. She was on atenolol for underlying hypertension. She had no previous history of diabetes mellitus. There was no known use of any anti-diabetic medication, insulin or traditional medicine. There was no family history of malignancy.

Upon presentation, she was confused, afebrile and normotensive. She had a Glasgow Coma Scale (GCS) of E4V3M5 and a capillary glucose of 1.9 mmol/L. Her GCS improved after intravenous infusion of 50 mL 50% dextrose, with a capillary glucose of 5.2 mmol/L. Physical examination revealed a large, firm and mobile left breast mass measuring 20 cm x 20 cm, with three ulcerated lesions and *peau d'orange* skin changes (Figure 1). There was no lymphadenopathy or hepatosplenomegaly.

Initial laboratory data showed severe hypoglycemia (random blood glucose 1.7 mmol/L) and hypokalemia (serum potassium 2.8 mmol/L). Otherwise, her full blood count, venous blood gas, and function tests of the kidney, liver and thyroid were normal. Random serum cortisol taken before initiation of hydrocortisone was inappropriately low (166 nmol/L) when her random blood

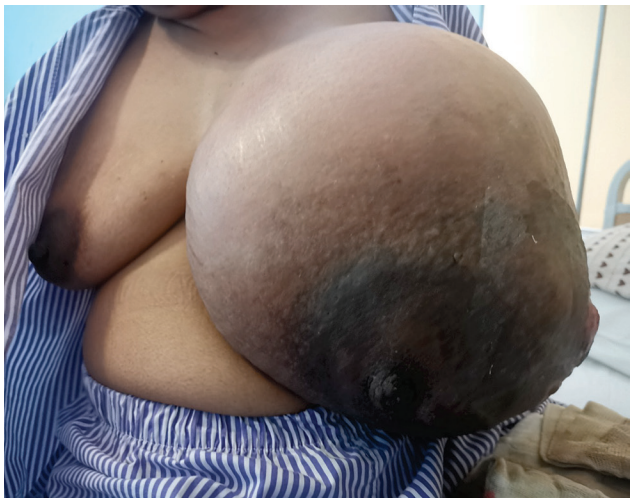

Figure 1. Physical findings showed a giant left breast mass measuring 20 cm × 20 cm in diameter with ulceration of the overlying skin.

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glucose was 1.7 mmol/L. During the same hypoglycemic episode, the serum levels of insulin (<0.5 mU/mL) and C-peptide (35 pmol/L) were suppressed, suggesting that the hypoglycemia was not linked to either endogenous or exogenous hyper-insulinism. Plasma insulin-like growth factor I (IGF-I) (67.4 ng/mL, reference range 53 to 192 ng/mL) and IGF-II (481 ng/mL, reference range 333 to 967 ng/mL) were within normal, but the elevated IGF-II/IGF-I ratio (7:1, normal <3:1) supported the diagnosis of NICTH. Computed tomography (CT) of the brain, chest, abdomen and pelvis showed a large, heterogenous left breast mass with no obvious infiltration of the chest wall and no evidence of lymphadenopathy or metastasis. Bone scan was not done as the patient did not have bone pain and alkaline phosphatase level was normal.

During hospitalization, she experienced recurrent daily hypoglycemia, ranging from 1.7 to 3.2 mmol/L. This resulted in recurring confusion and seizures despite multiple 50% dextrose injections and continuous 20% dextrose infusion at 62.5 mL/hour. She also required large amount of potassium supplementation of up to 150 mmol/day to maintain a normal serum level. Intravenous hydrocortisone at 100 mg three times daily was started on day 3 of admission. This was subsequently converted to oral prednisolone 40 mg daily on day 5. After steroid initiation, she was able to achieve euglycemia, ranging from 4.5 to 7.1 mmol/L within two days, with concurrent continuous 5% dextrose infusion at 62.5 mL/hour. There were also resolution of confusion, seizure and hypokalemia.

Core needle biopsy of the breast lesion showed spindle cell neoplasm. A simple mastectomy was then performed to remove the tumor. On cut section, the 6.3 kg mastectomy specimen showed a well-circumscribed tumor measuring 30 cm x 24 cm x 14 cm with a 2 cm clear resection margin. The tumor contained abundant stromal and epithelial components. The hypercellular stroma was composed of spindle-shaped cells with mild nuclear atypia. Mild epithelial hyperplasia and a few cystically dilated ducts were also seen. There was no evidence of malignancy. Hormone receptor tests were positive for both estrogen and progesterone. All these histological features were consistent with a benign phyllodes tumor (Figure 2).

Infusion with 5% dextrose was continued in the immediate postoperative period until the patient was able to tolerate oral intake. There were no more hypoglycemic episodes subsequently. Prednisolone was converted to hydrocortisone replacement dose in view of possible adrenal insufficiency. After one week, a short Synacthen® test showed adequate cortisol response (baseline, 197 nmol/L; after 30 minutes, 544 nmol/L; after 60 minutes, 587 nmol/L) prompting discontinuation of hydrocortisone. There has been no recurrence of hypoglycemia, confusion or seizure during the subsequent four-month follow-up.

DISCUSSION

Fourteen cases of phyllodes tumor of the breast with NICTH have been described in literature, with only

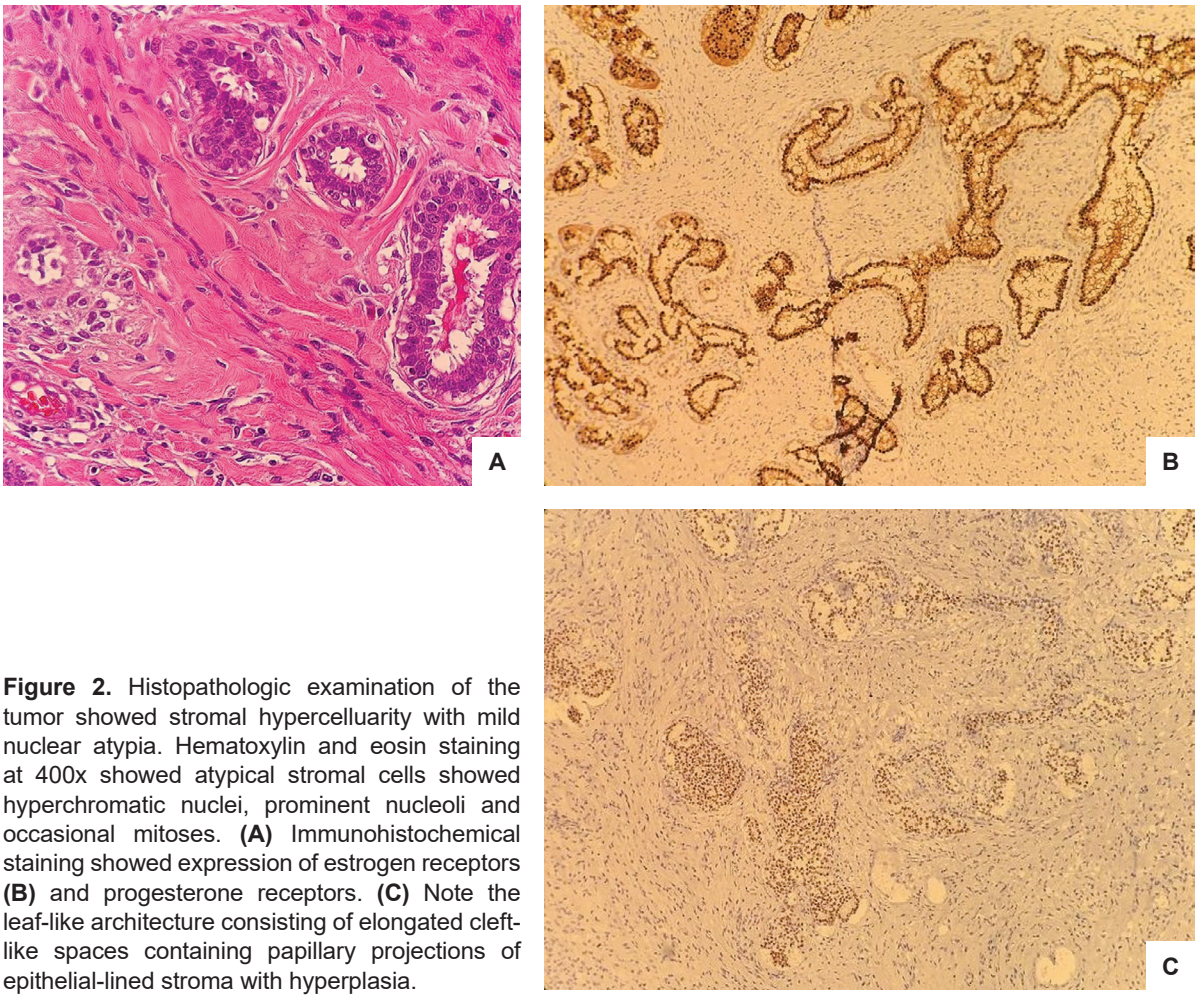

Figure 2. Histopathologic examination of the tumor showed stromal hypercelluarity with mild nuclear atypia. Hematoxylin and eosin staining at 400x showed atypical stromal cells showed hyperchromatic nuclei, prominent nucleoli and occasional mitoses. **(A)** Immunohistochemical staining showed expression of estrogen receptors **(B)** and progesterone receptors. **(C)** Note the leaf-like architecture consisting of elongated cleft-like spaces containing papillary projections of epithelial-lined stroma with hyperplasia.

Table 1. Summary of 14 cases of phyllodes tumor of the breast with NICTH reported from 1983 to 2021

Authors	Year	Tumor size (cm)	Tumor weight (kg)	Histological subtypes	Serum potassium	Serum IGF-II	Serum IGF-I	IGF-II: IGF-I ratio	Big IGF-II[a]	Tissue
Li et al[4]	1983	28	4.2	Benign	Low	High	NA	NA	NA	NA
Tanaka et al[5]	1986	25	4.0	Malignant	NA	NA	NA	NA	NA	NA
Bleau et al[6]	1991	NA	6.0	NA	NA	Normal	NA	NA	NA	Expression of IGF-II[b]
Ishido et al[7]	1992	NA	3.0	Benign	NA	High	NA	NA	NA	NA
Miura et al[8]	1992	26	3.1	NA	NA	Normal	NA	NA	NA	NA
Katoka et al[9]	1998	35	9.0	Malignant	Normal	Low	Normal	2.0	NA	Expression of IGF-II[b]
Bujanda et al[10]	2007	33	10.0	Malignant	NA	NA	Low	NA	High	NA
Hino et al[11]	2008	25	4.2	Benign	Low	Normal	Normal	5.7	High	NA
Renard et al[12]	2012	27	5.8	Malignant	Low	NA	Low	NA	High	High IGF-II mRNA
Argawal et al[13]	2012	34	NA	Benign	NA	NA	NA	NA	NA	NA
Pacioles et al[14]	2014	29	NA	Malignant	Low	Normal	Low	16.9	NA	NA
Saito et al[15]	2016	25	5.0	Borderline	Low	High	Normal	6.3	NA	High IGF-II in tissue extract
Hikichi et al[16]	2018	27	4.5	Borderline	Normal	NA	NA	NA	High	Expression of IGF-II[b] High big IGF-II in tissue extract
Zhao et al[17]	2021	20	NA	Borderline	NA	NA	NA	NA	NA	Expression of IGF-II[b]

[a] Big IGF-II measurement was done by western immunoblotting of the serum with identification of abnormal IGF-II peptide in excess in its precursor form, pro-IGF-II or big IGF-II (10-20 kDa)
[b] Expression of IGF-II was demonstrated by immunohistochemical examination of frozen sections of the tumor
IGF, insulin-like growth factor; NA, not available; mRNA, messenger ribonucleuc acid

four being benign (Table 1).[4-17] Our patient had a similar presentation of a large breast mass compared to previous case reports, describing sizes from 23 to 35 cm in maximal diameter. The median size at diagnosis of phyllodes tumors without NICTH seems considerably smaller (3 cm) compared to those with NICTH, supporting the idea that a large tumor size is necessary to reach a sufficient level of IGF-II secretion to promote hypoglycemia.[18] Similar to findings in insulinoma, hypoglycemia associated with an IGF-II-producing tumor typically presents in the fasting state. Neuroglycopenic symptoms are more commonly seen than autonomic symptoms as in our patient, due to repeated hypoglycemic events and insidious progression. Hypokalemia, frequently observed in NICTH, is attributed to the insulin-like activity of IGF-II, which acutely decreases serum potassium by moving extracellular potassium into cells.[19]

The cause of NICTH is the overproduction of IGF-II or incompletely processed IGF-II from tumor cells. This immature form of IGF-II precursor, also known as high-molecular-weight or big IGF-II (10 to 20 kDa fraction), has higher bioactivity than mature IGF-II (7.5 kDa fraction).[4,20] IGF-II binds to insulin receptor isoform (IR)-A with a higher affinity, about 35 to 40% that of insulin. In contrast, IGF-II binds with IR-B with an affinity of roughly 5% that of insulin.[4] With markedly elevated IGF-II levels and higher bioavailability of big IGF-II found in NICTH, hypoglycemia can occur via activation of insulin receptors. This results to inhibition of hepatic glycogenolysis and gluconeogenesis as well as lipolysis in adipose tissue.

IGF-II levels may or may not be elevated in NICTH. Even if IGF-II levels are normal, IGF-I levels are usually less than 100 ng/mL.[20] This is due to suppression of growth hormone at the level of the pituitary gland by negative feedback mechanisms, leading to suppressed IGF-I levels. While elevated big IGF-II is helpful in diagnosing NICTH, testing is not always readily available.

A clinical review by Bodnar et al., recommended that the diagnosis of NICTH can be established by fulfilling the following criteria: (1) hypoglycemia fulfilling Whipple's triad; (2) low insulin/pro-insulin/C-peptide levels; (3) rapid response to glucocorticoid therapy; (4) IGF-I level less than 100 ng/mL, normal/high IGF-II, IGF-II:IGF-I ratio more than 3 (if feasible, measurement of high molecular weight IGF-II); and (5) identification of culprit tumor.[20]

Our patient fulfilled all these criteria for the diagnosis of NICTH. While an IGF-II:IGF-I ratio more than 10 is frequently found in NICTH, the biggest series of NICTH patients (n=44) showed that 7 out of 13 patients with NICTH without big IGF-II had IGF-II:IGF-I ratios between 3 and 10. The IGF-II:IGF-I ratio is higher in patients with big IGF-II, ranging from 16.4 to 64.2, and lower in normal subjects (3.0 ± 0.2).[21]

Two cases of phyllodes tumor with NICTH reported normal IGF-II levels with elevated IGF-II:IGF-I ratios (5.7 and 16.9, respectively).[11,14] As phyllodes tumors arise principally from mammary fibroblast and epithelial cells known to produce high amounts of IGF, overexpression of IGF-II within the tumor cells had also been observed in four previous case reports of NICTH mainly related to borderline or malignant phyllodes tumor.[6,9,16,17]

Our patient's serum cortisol was inappropriately low during hypoglycemia. A subsequent short Synacthen® test excluded the possibility of hypocortisolism. Repeated hypoglycemia induces attenuation of counter-regulatory hormonal responses to hypoglycemia in patients with insulinomas or in patients with diabetes on intensive insulin therapy. Hence, low plasma cortisol during hypoglycemia is not sufficient evidence of cortisol deficiency.[22] There is a possibility that the same mechanism, specifically a shift in glycemic thresholds for cortisol release in response to lower plasma glucose concentrations, may occur in some patients with IGF-II-producing NICTH.

Complete resection of the IGF-producing tumor is the most effective treatment for NICTH. However, if surgery cannot be readily performed, management of hypoglycemia may include increasing caloric intake, infusion of intravenous glucose and administration of glucocorticoids. Glucocorticoids can prevent hypoglycemia

through several mechanisms, including augmentation of hepatic gluconeogenesis, inhibition of peripheral glucose uptake, mobilization of amino acids from extrahepatic sites, stimulation of lipolysis with fatty acid release from adipose tissue and reduction in IGF-II levels.[3] In our patient, the operation was put on hold while waiting for the CT scan and Tru-cut biopsy results. Systemic steroid was started in view of recurrent severe hypoglycemia despite intravenous glucose.

There are some limitations in our case report. We were not able to perform of serum pro-IGF-II measurement and immunohistochemical analysis to search for IGF-II in the tumor tissue as these tests are commercially unavailable. However, we showed that suppressed insulin and C-peptide levels with elevated IGF-II/IGF-I ratio are sufficient to support the diagnosis of NICTH. The excellent response with resolution of hypoglycemia from glucocorticoids and tumor removal further supports the diagnosis.

CONCLUSION

Despite its rarity, NICTH must be considered in any patient with a large phyllodes tumor and hypoglycemia. Early recognition of symptoms of hypoglycemia is essential in those patients to avoid irreversible neurological sequelae. Whenever possible, excision of the tumor must be attempted. Glucocorticoids can be given to aid hypoglycemia if surgery may not be done immediately.

Ethical Considerations
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

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