CASE REPORT

Non-Islet Cell Tumour Induced Hypoglycaemia (NITCH) in Patients with Giant Phyllodes Tumours: A Case Report

Asdi Wihandono[1,2], Desak Gede Agung Suprabawati[1,2], Budi Susetyo Pikir[1,3], and Yohana Azhar[4]

[1] Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, 60286 Surabaya, Indonesia
[2] Department of Surgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3] Department of Cardiology and Vascular Medicine, Universitas Airlangga, Surabaya, Indonesia
[4] Department of Surgery, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

ABSTRACT

Phyllodes tumours are rare breast neoplasms, with most being benign. Non-islet cell tumour hypoglycaemia (NICTH) is a rare condition caused by excessive insulin-like growth factor II (IGF-II) or its precursor, big IGF-II, often linked to large mesenchymal tumours. We report two cases of giant phyllodes tumours (~30 cm) of the left breast, presenting with hypoglycaemia symptoms such as lethargy and diaphoresis. Preoperative blood glucose levels were 73 mg/dL and 69 mg/dL, unresponsive to intravenous dextrose. Hypoglycaemia resolved immediately postoperative, without further intervention. Due to healthcare limitations, IGF-II and serum insulin receptor, and cortisol level testing were unavailable. However, thorough clinical assessments found no signs of adrenal insufficiency. NICTH likely resulted from impaired hepatic glucose production, increased tumour glucose consumption, and big IGF-II activating insulin receptors. The resolution after tumour removal supports a paraneoplastic mechanism. Early surgical intervention is essential for managing NICTH and restoring normoglycaemia.

Malaysian Journal of Medicine and Health Sciences (2025) 21(SUPP10):208-210. doi:10.47836/mjmhs.21.s10.39

Keywords: giant phyllodes tumor, non-islet cell tumour-induced hypoglycaemia, IGF-II, IGF-1, simple mastectomy

Corresponding Author:
Desak Gede Agung Suprabawati, PhD
Email: desak.gede@fk.unair.ac.id
Tel : +62 31 5501327

INTRODUCTION

Phyllodes tumour accounts for 0.2% to 0.5% of all breast tumours, occurring at a rate of two cases per one million individuals. Nearly all cases were observed in women, although male cases have also been documented. The median age upon diagnosis is between 42 and 45 years. The majority of cases are benign, typically manifesting as a large asymptomatic breast tumour. The median tumour size ranges from 4 to 7 cm and can lead to dyspnoea, tiredness, and bone pain if metastasised.

Non-islet cell tumour induced hypoglycaemia (NICTH) is a unique paraneoplastic syndrome associated with significant mesenchymal tumours, including phyllodes tumours. Several discoveries in the 1970s and early 1980s contributed to the elucidation of NICTH. In 1974, Megyesi et al. documented an increase of plasma NSILA-s levels in patients experiencing hypoglycaemia due to extrapancreatic tumours. In 1981, Zapf et al. reported for the first time the discovery of IGF-I and IGF-II in patients with growth disorders and extrapancreatic tumour hypoglycaemia (1). Throughout the 1980s and early 1990s, big IGF-II was then identified to be the cause of non-islet cell tumour hypoglycaemia.

CASE REPORT

This paper presents two cases of patients with giant phyllodes tumours and NICTH. The initial case study concerns a 39-year-old female patient who presented at the surgical clinic with a large tumour in her left breast. The patient had first observed the lump two months prior, noting that it had initially been small but had subsequently increased in size at a rapid pace. By the time she sought medical advice, the tumour had reached an approximate diameter of 30 cm and was of a similar volume to that of a watermelon (approximately 20 cm).

It had caused the overlying skin to become thin and shiny (See Fig. 1). An ulcer had formed on the lateral side of the breast, which had progressively enlarged, become infected, and emitted a foul odor.

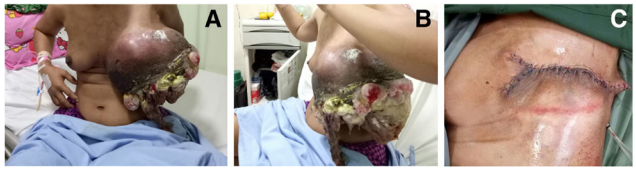

Figure 1: The clinical picture of patient 1: large mass on left breast with ulcer on the lateral side seen from anterior side (A), and lateral side (B). Post-op picture after simple mastectomy (C).

Notwithstanding the aforementioned symptoms, the patient did not experience any pain in the affected breast. Laboratory tests demonstrated low blood sugar levels (73 mg/dL), despite the administration of a 10% dextrose infusion, and the hypoglycaemia persisted. Although this value does not meet the strict definition of hypoglycaemia (<55 mg/dL in non-diabetic individuals), the presence of symptoms such as lethargy and diaphoresis suggests an abnormal glucose metabolism likely induced by the tumour's production of IGF-II or big IGF-II. An abdominal ultrasound demonstrated the absence of any pathological alterations within the liver or pancreas. Due to limitations in the healthcare system, specific laboratory tests for IGF-II, IGF-1, serum insulin, and cortisol levels were not available. However, the patient was clinically evaluated for adrenal insufficiency, including assessments for hypotension, hyperpigmentation, and electrolyte imbalances, none of which were observed.

A fine-needle aspiration biopsy (FNA) revealed the presence of mammary dysplasia. The patient subsequently underwent a simple mastectomy, which was successful. Postoperatively, blood glucose levels normalized immediately without further intervention, and the patient demonstrated a full and uncomplicated recovery. The pathological report diagnosed the condition as a malignant phyllodes tumour, and the patient was subsequently scheduled for adjuvant therapy.

The second case study concerns a 62-year-old female patient who presented with a sizable neoplasm in her left breast, which she had identified four years earlier. The initial size of the lump was approximately 1 cm, equivalent to that of a marble. Over the subsequent three-year period, it exhibited a gradual increase in size, reaching that of a tennis ball. Over the preceding six months, the tumour exhibited a rapid expansion, reaching a diameter of 30 cm, comparable to that of a football (See Fig. 2). In contrast to the initial case, the patient did not develop an ulcer.

Laboratory tests indicated that the patient's blood sugar level was 69 mg/dL, and despite intravenous dextrose administration (10%), hypoglycaemia persisted. As

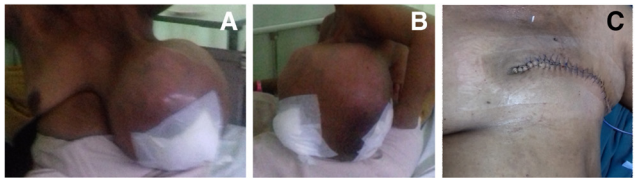

Figure 2: The clinical picture of patient 2: large mass on left breast seen from anterior side (A), and lateral side (B). Post-op picture after simple mastectomy (C).

in the first case, this value does not strictly define hypoglycaemia but was associated with significant symptoms. Abdominal ultrasound findings were normal, with no abnormalities detected in the liver or pancreas. Similar to the first case, testing for IGF-II, IGF-1, serum insulin, and cortisol was not conducted due to healthcare system constraints. However, no clinical signs of adrenal insufficiency were observed upon physical examination. The fine-needle aspiration biopsy suggested that the tumour was benign. The patient underwent a simple mastectomy, which was performed successfully. There were no complications in the postoperative period, and her blood sugar levels returned to normal immediately after surgery. The final pathology report confirmed that the tumour was benign.

DISCUSSION

In 1838, Johannes Mьller published the earliest known account of a phyllodes tumour (2). The tumour is most commonly referred to as cystosarcoma phylloides. It is of mixed solid-cystic consistency, displaying a leaf-like pathology, hence the name "phyllodes", derived from the Latin term phyllodium, meaning leaf-like. The categorisation of a phyllodes tumour as benign, borderline, or malignant is contingent upon a number of factors, including the margin (infiltrative or expansive), cellular atypia, mitotic activity, and stromal growth. Phyllodes tumours represent between 0.2% and 0.5% of all breast tumours, occurring at a rate of two cases per one million individuals. The overwhelming majority of cases have been observed in women, although there have been documented instances of males affected. Cases tend to be diagnosed between the ages of 42 and 45. The majority of cases are benign, manifesting as a large, asymptomatic tumour in the breast. Tumour sizes range from 4 to 7 cm on average and can cause fatigue, dyspnoea, and bone pain in the event of metastasis.

Non-islet cell tumour hypoglycaemia (NICTH) represents a hypoglycemic condition linked to the presence of tumours other than insulinomas. It has been established that the excessive production of insulin-like growth factor (IGF)-II by the tumour represents the underlying cause of this paraneoplastic syndrome. The identification of insulin-like growth factor (IGF) as the underlying cause of NICTH was first reported by Gorden et al. in 1981 (3). Subsequent studies by Fukuda et al. reported on 78 cases of NICTH associated with big-IGF-II, with the majority of cases arising from hepatomas (n

= 24) and gastric cancers (n = 10). Only two cases of breast tumours were reported.

The underlying pathophysiology of NICTH is the elevation of the pro-form of insulin-like growth factor II (pro-IGF-II), which subsequently releases the big form, pro-IGF-IIE, into the circulation. The release of big-IGF-II competes for binding to IGFBP with IGF-I and IGF-II. In contrast to IGF-II, big-IGF-II is unable to form a tertiary complex with acid-labile subunit (ALS), instead forming a binary complex with IGF-binding protein. As a consequence of the binding of big-IGF-II and IGF-binding protein, there was an increase in the concentrations of free-IGF-I and free-IGF-II (4). The considerable size of the ternary complex renders it unable to traverse the capillary membrane. The binary complex, however, is able to cross the capillary membrane, along with the free forms of IGF-I and IGF-II. Following the binding of this complex with the insulin B receptor in tissues, a reduction in the concentration of glucose is observed.
While IGF-II, IGF-1, serum insulin, and cortisol levels were not measured in our cases due to resource limitations, the clinical presentation, response to dextrose infusion, and immediate postoperative resolution of hypoglycaemia strongly support NICTH as the underlying mechanism. The absence of hepatic or pancreatic abnormalities on imaging further strengthens this hypothesis. The presence of symptomatic hypoglycaemia despite borderline glucose levels suggests a paraneoplastic alteration of glucose homeostasis. This phenomenon has been described in other reports of NICTH, where hypoglycaemia symptoms can occur even at glucose levels higher than the traditional hypoglycaemia threshold (5).

The elevation in free IGF-I and free IGF-II triggered a negative feedback mechanism within the pituitary GH/IGF-I axis, which culminated in a reduction in IGF-I levels. This could be utilised as a diagnostic tool for NICTH. It can be observed that the minimum value of IGF-I is 53 ng/mL, while the normal value of IGF-II is between 288 and 736 ng/mL. In addition, the normal ratio of IGF-II/IGF-I is below 10 ng/mL. For additional assessment, the predominant serum form of IGF-II is the "big-IGF-II", exhibiting a molecular weight of 20 kDa (the mature IGF-II weight is approximately 7.5 kDa).

The proposed diagnostic criteria for NICTH are as follows: (a) hypoglycaemia consistent with Whipple's triad; and (b) levels of proinsulin, insulin, C peptide and beta hydroxybutyrate below 5 pmol/L, 3 U/mL, 0.2 nmol/L and 2.7 mmol/L, respectively. (c) an IGF-I level below 100 ng/mL, a normal or elevated IGF-II level, and an IGF-II ratio above 3 (with a comprehensive IGF-II evaluation if possible); (d) identification of the tumour causing the condition; and (e) rapid improvement with glucocorticoid therapy. While plasma cortisol levels were not measured in our cases, neither patient exhibited clinical signs of adrenal insufficiency, making an alternative diagnosis unlikely.

CONCLUSION

NICTH can be life-threatening in patients with large mesenchymal tumours. While specific endocrine markers may not always be available, careful clinical evaluation and a high index of suspicion are essential for diagnosis. Timely surgical intervention is crucial to restore normal blood glucose levels and to prevent further complications.

ACKNOWLEDGEMENTS

The authors would like to thank the Director of dr Hasan Sadikin General Hospital Bandung for the permission to publish this case report.

REFERENCES

1. Zapf J, Walter H, Froesch ER. Radioimmunological determination of insulinlike growth factors I and II in normal subjects and in patients with growth disorders and extrapancreatic tumor hypoglycemia. Journal of Clinical Investigation. 1981;68(5). DOI: 10.1172/JCI110379
2. Fiks A. Cystosarcoma phyllodes of the mammary gland - mьller's tumor - For the 180th birthday of Johannes Mьller. Vol. 392, Virchows Archiv A Pathological Anatomy and Histology 1981. DOI: 10.1007/BF00430543
3. Gorden P, Hendricks CM, Kahn CR, Megyesi K, Roth J. Hypoglycemia Associated with Non-Islet-Cell Tumor and Insulin-like Growth Factors. New England Journal of Medicine. 1981;305(24). DOI: 10.1056/nejm198112103052405
4. Alvino CL, Ong SC, McNeil KA, Delaine C, Booker GW, Wallace JC, et al. Understanding the mechanism of insulin and insulin-like growth factor (IGF) receptor activation by IGF-II. PLoS One. 2011;6(11). DOI: 10.1371/journal.pone.0027488
5. Fukuda I, Hizuka N, Ishikawa Y, Yasumoto K, Murakami Y, Sata A, et al. Clinical features of insulin-like growth factor-II producing non-islet-cell tumor hypoglycemia. Growth Hormone and IGF Research. 2006;16(4). DOI: 10.1016/j.ghir.2006.05.003