Clinical case

Severe hypoglycemia with “Big”-IGF-2 oversecretion by a giant phyllode tumor of the breast: A rare case of non-islet cell tumor-induced hypoglycemia (NICTH)

Hypoglycémies sévères secondaires à une sécrétion de “Big”-IGF-2 par une tumeur phyllode mammaire géante : un cas rare d’hypoglycémies tumorales non insulaires (NICTH)

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Abstract

Objective. – We report an exceptional case of non-islet cell tumor-induced hypoglycemia (NICTH) secondary to “Big”-IGF-2 oversecretion due to a giant phyllode tumor of the breast. Clinical presentation. – A 49-year-old woman was admitted in emergency for brutal neurologic defect revealing severe hypoglycemia. Several similar episodes were observed throughout hospitalization, requiring continuous perfusion of hypertonic glucose solution. Beside these metabolic disorders, we observed a giant and hard tumor of the left breast (about 30 cm in diameter). Interpretation. – Supplementary blood analysis revealed serum levels of C-peptide and insulin suppressed during hypoglycemia, excluding the possibility of either endogenous or exogenous hyperinsulinism. Low plasma levels of GH and IGF-1 were found, suggesting a negative feedback loop on somatotroph axis function. Therefore, the hypothesis of an insulinomimetic compound released by tumor cells was evoked because of abnormal presence of high-weight and immature form of IGF-2 (called “Big”-IGF-2) in the serum identified by western immunoblot analysis. A left mastectomy was performed and completely restored glucose homeostasis and confirmed the paraneoplastic origin of hypoglycemia because of markedly elevated expression of IGF-2 mRNA (qPCR) within the tumor cells. Finally, the anatomicopathology analysis diagnosed a mesenchymatous tumor, namely a high-grade phyllode sarcoma of the breast. Conclusion. – Although NICTH due to “Big”-IGF-2 overproduction is a rare phenomenon, mainly observed in case of mesenchymatous tumor, it should be considered in presence of severe hypoglycemia with voluminous tumor and without hyperinsulinism.

Résumé


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Étude anatomopathologique définitive était en faveur d’une tumeur mésenchymateuse de type sarcome phyllode de haut grade.

Conclusion. — Bien que les hypoglycémies tumorales non-insulaires secondaires à une sécrétion de « Big »-IGF-2 soient rares et souvent le fait des tumeurs mésenchymateuses, elles doivent être évoquées devant l’association d’hypoglycémies sévères, d’une volumineuse masse tumorale, et en l’absence d’hyperinsulinisme.

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1. Introduction

Hypoglycemia is a common emergency, which can sometimes, by various mechanisms, be the first manifestation of tumor disease [1,2]. In majority of cases, it is the consequence of an excessive production of insulin by a pancreatic tumor (insulinoma) [2]. However, some other molecules synthesized in excess by tumor cells can also have an hypoglycemic effect, such as insulin-like growth factor 2 (IGF-2, 7kDa) or its high-weight precursor (“Big”-IGF-2, 10–20 kDa), a pathological condition known as non-islet cell tumor-induced hypoglycemia (NICTH). In 1988, Daughaday et al. reported the first description of NICTH due to aberrant expression of immature form of IGF-2 in a patient with leimyosarcoma [3]. Even if the biological effects of IGF-1 and IGF-2 in the organism are primarily mediated by IGF-1 receptor (IGF-1R) [4], both of these growth factors are structurally and functionally related to insulin, so they can stimulate the insulin receptor with its subsequent pleiotropic effect [5]. IGF-2 is a peptide of 67 aminoacids, arising for different steps of maturation from a primary IGF-2 translation product known as pre-pro-IGF-2 with a specific N-terminal signal peptide for subsequent cleavage [6]. The post-translational processing of pre-pro-IGF-2 involves removal of N-terminal signal sequence with glycosylation of threonine residues, leading to an intermediate form called pro-IGF-2 or “Big”-IGF-2 that may be secreted by the cell [7]. “Big”-IGF-2 brings also to insulin receptor and therefore inhibits hepatic glucose synthesis and stimulates the glucose intake by muscle. Most of the time, NICTH reveals a massive tumor of mesenchymal origin (fibrosarcomas, mesotheliomas, hemangiopericytomas...) or hepatocellular and gastric carcinoma [8]. Only few cases of NICTH secondary to breast tumors, especially phyllode tumors have been previously reported [9–11].

Here, we report the case of a woman who presented severe hypoglycemia secondary to “Big”-IGF-2 secretion by a giant phyllode tumor of the left breast.

2. Case report

In April 2009, a Caucasian 49-year-old woman was admitted in emergency for paralysis of the left superior and inferior members and right facial paralysis associated with sensation of weakness and peribuccal paresthesia. She also described since few months, a deterioration of her general status with tiredness, anorexia and loss of weight (less 7 kg). On physical examination, she presented a voluminous and hard mass in the left breast with purplish-blue skin without any lymph nodes palpable (Fig. 1A).

Although this mass was growing up since more than a year, the patient refused any medical attention. In order to rule out an acute ischemic stroke, a cerebral computed tomography was performed and did not show any ischemic or hemorrhagic process. The thoracic-abdomino-pelvic CT showed a large and heterogeneous tumor in the left breast, measured 25 × 19 × 24.5 cm. There were no distant metastases (particularly in the hepatic parenchyma) or lymph nodes (Fig. 1B).

Blood analysis on admission indicated an anemia (11.1 g/dL), a hypokalemia (3.4 mmol/L) without ECG signs, and a severe hypoglycemia (24 mg/dL, 1.33 mmol/L). She recovered quickly after administration of i.v. glucose. There was no history of diabetes mellitus in her family or notion of treatment that could interfere with glucose homeostasis.

During hypoglycemia, the serum levels of insulin and C-peptide were suppressed (< 1 mUI/L and 0.01 nmol/L respectively), suggesting that hypoglycemia were no linked to either endogenous or exogenous hyperinsulinism. Sulphonylurea derivatives or insulin antibodies were not detected.

Because of this massive tumor of the breast without evidence of hepatic tumor infiltration, we hypothesized that a paraneoplastic syndrome was responsible of these severe hypoglycemic episodes.

Fig. 1. Clinical aspect of the giant tumor of the left breast on physical examination (A) and on computed tomography (B).
Hypoglycemia and performed a complementary analysis (western immunoblot) of the serum with identification of abnormal IGF-2 peptide in excess in its precursor form, pro-IGF-2 or “Big”-IGF-2 (10–20 kDa) (Fig. 2). Moreover, in this patient, both GH (growth-hormone) and IGF-1 serum levels were low (0.04 mIU/L and 58.94 ng/mL [N: 92.7–244.6 ng/mL], respectively). The major blood binding protein, IGFBP-3, serum levels of ACTH, cortisol and TSH were within the normal range.

During hospitalization, symptoms associated with hypoglycemia occurred frequently, mostly at morning, and required continuous hypertonic glucose infusion.

A left mastectomy was rapidly performed with axillary lymph node dissection. The resected tumor weighed 5800 g and measured $27 \times 26 \times 20$ cm. In a macroscopic manner, this lesion was whitish, multinodular with central zones of necrotic altering with cystic evolution. The histological diagnosis was a high-grade sarcoma phyllode (grade III) of the breast without metastasis in the axillary lymph nodes sample (pT4N0M0).

After the mastectomy, serum levels of glucose, insulin and C-peptide normalized in a spectacular way. GH and IGF-1 returned to normal range (8.42 mIU/L and 123.6 ng/mL respectively).

The IGF-2 mRNA expression within the tumor tissue was studied by quantitative PCR (polymerase chain reaction) and was markedly elevated compared to normal tissue (more than 1000 times), or positive sample (colon tumor, more than 20 times). In the same time, a second analysis of the serum after tumor excision revealed strong decrease, although without complete disappearance, of “Big”-IGF-2 form, suggesting persistence of tumor cells.

The treatment was completed in July by external radiotherapy (60 grays, in 30 sessions during 45 days). During the follow-up, the evolution was marked by metastatic extension in the cerebral parenchyma without recurrence of hypoglycemia. Despite an intensive medical care, the patient died unfortunately one year later.

### 3. Discussion

Hypoglycemia due to NICTH is a rare disease, with an estimated prevalence that remains approximate, about four times less common than insulinoma [12]. In most of the cases, NICTH occurs in patients with solid tumors of mesenchymal and epithelial origins, such as hepatocellular carcinoma, gastric carcinoma or mesothelioma [8]. In a study of 78 patients, breast tumor was exceptional and found in only one case [8]. To our knowledge, only eight cases of phyllode tumor of the breast with NICTH have been currently described in the literature, probably due to low proportion of phyllode tumor among all breast tumors, estimated less than 1% [13], and the low prevalence of NICTH. The hypoglycemia induced by these tumors is secondary to excess secretion of IGF-2, in its immature and high-weight molecular forms, namely pro-IGF-2 or “Big”-IGF-2. Whereas incompletely processed pro-IGF-2 accounts for 10–20% of the total IGF-2 in the normal human serum, a much higher proportion is classically observed in serum of patients of NICTH [14].

Here, we report the case of a young patient with severe hypoglycemia due to paraneoplastic secretion of “Big”-IGF-2 by a phyllode tumor of the breast. The clinical course of our present case presents similar features compare to previous reports: there is a massive and hard tumor of the breast (27 cm of maximal diameter compared to mean size of 28.6 ± 4.3 cm in previous reports) with progressive evolution and acute and severe hypoglycemic attack. It is noteworthy that the median size at diagnosis of phyllode tumor without NICTH seems considerably smaller (3 cm) than their counterpart with NICTH [15], supporting the idea that a large size of tumor is necessary to reach a sufficient level of “Big”-IGF-2 secretion by stromal and mesenchymal cells, to promote hypoglycemia [16].

Our patient was diagnosed at perimenopausal period (49 years old), in agreement with the eight previous cases (median age at diagnosis: 52.7 ± 14.8 years), roughly similar to the median age of diagnosis of phyllode tumor, near 44 years [15]. Unlike breast carcinoma, where IGF-2 can activate estrogen receptor in a crosstalk manner [17], there is no established link between estrogen exposition and the growth of phyllode tumors [18,19]. Thus, only few cases have reported hormonal therapy in phyllode therapy, without significative effect.

As phyllode tumors arise principally from mammary fibroblast and epithelial cells, known to produce high amounts of IGFs [20], this is not surprising to observe overexpression of IGF-2 mRNA within the tumor cells like in our case and in previous report [16,21]. Bertherat et al. previously observed a dysregulation of IGF-2 gene expression on chromosome 11p15 region with lost of the maternal imprinting within tumor cells of NICTH [22].

Hypoglycemia due to “Big”-IGF-2 production by a voluminous phyllode tumor can be the consequence of various mechanisms. Unlike mature forms of IGFs, “Big”-IGF-2 displays low affinity for IGFBP-3 and induces an instable complex with the acid labil subunit (ALS) and therefore, primarily forms small binary complex with IGFBPs (IGF binding proteins) in the serum. These complexes have greater
capillary permeability than the usual ternary complex form by mature form of IGFs, and therefore increase IGF bioavailability to the tissues. As “Big”-IGF-2 is able to bind both Insuline- and IGF-1 receptor [5], it results in hypoglycemia and at a lesser degree to moderate hypokaliemia, like in our case. On the other hand, previous studies report a highly proportion of free (i.e. not link to IGFBPs) IGF-1 and -2 forms in serum of patients with NICTH [23], compared to normal population. As seen in our case before the surgical management, GH and IGF-1 plasma levels are classically low because of the negative feedback exerts by free IGF forms on GH/IGF-1 axis in the anterior pituitary gland. This could contribute also to hypoglycemia and lead to diminish levels of circulating IGFBP-3 and ALS (data not shown in our case). Finally, glucose consumption by the tumor itself might contribute to hypoglycemia [12].

Overexpression of IGF-2 within the tumor can be a useful tool to predict a potential relapse, as it was noted in gastrointestinal stromal tumors (GIST) [24]. Whether this finding can be applied in phyllode tumors where IGF-2 overexpression is frequently described remains unknown, but could be of great interest in case of malignant phenotype [25].

In conclusion, we have reported an exceptional case of giant phyllodes tumor of the breast with severe hypoglycemia due to paraneoplastic secretion of “Big”-IGF-2. This pathological entity belongs to the common NICTH syndrome, but represent one of the rarest presentations currently described in the literature.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

The authors wish to thank Laurence Perin, Patricia Leneuve and Annick Blaise from Pr Le Bouc’s laboratory for technical help in IGF-2 and its high weight forms analysis.

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