Special Issue manuscript "Neuroendorine Tumour" Case Report

Non-Islet Cell Tumour Hypoglycaemia in a Patient with Gastric Neuroendocrine Tumour

Versluis JM[1*], Valk GD[2], van Rossum H[3] and Tesselaar MET[1*]

[1]Department of Medical Oncology, Netherlands Cancer Institute, Netherlands

[2]Department of Endocrine Oncology, University Medical Center Utrecht, Netherlands

[3]Department of Clinical Chemistry, Netherlands Cancer Institute, Netherlands

ARTICLE INFO

Received Date: January 19, 2019
Accepted Date: March 11, 2019
Published Date: March 18, 2019

KEYWORDS

Neuroendocrine tumour
Insulin-like growth factor II
Non-islet cell tumour hypoglycaemia

Citation for this article: Versluis JM, Valk GD, van Rossum H and Tesselaar MET. Non-Islet Cell Tumour Hypoglycaemia in a Patient with Gastric Neuroendocrine Tumour. SL Clinical Medicine: Research. 2019; 2(1):115

Corresponding author:
Judith Versluis, Tesselaar MET
Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands,
Phone: 020-5122569; Fax: 020-5122572;
Email: j.versluis@nki.nl

ABSTRACT

Non-Islet Cell Tumour Hypoglycaemia (NICTH) is a very rare condition. It has been reported in several tumour types but has never been described as consequence of a neuroendocrine tumour.

A 61-year old male, without noteworthy medical history, presented himself initially with complaints of progressive fatigue and flushes. Diagnostic imaging revealed a large tumour in the stomach with liver metastases and histopathological examination showed a well differentiated gastric neuroendocrine tumour. After treatment with chemotherapy, upon progression everolimus was started. With further progression PD-1 inhibitor PDR001 was given. Two weeks after the first gift he was admitted with loss of consciousness and a blood level glucose of 1.6 mmol/L (28.8 mg/dL). Endocrinological tests revealed levels of plasma insulin below 0.5 mU/L, plasma C-peptide of 250 pmol/L, insulin-like growth factor-II (IGF-II) of 804 ng/mL and a pro-IGF-IIE level of 80 µg/L.

Based upon the clinical findings this patient was diagnosed with NICTH with an overproduction of pro-IGF-IIE and eventually IGF-II, due to a progressive metastatic well differentiated gastric NET.

INTRODUCTION

Tumour-Induced Hypoglycaemia (TIH) is a rare clinical type of hypoglycaemia and may be caused by different mechanisms.1 Usually it originates due to insulin hypersecretion by a pancreatic islet β-cell tumour, an insulinoma [1]. However, TIH can also be developed by non-pancreatic tumours, known as Non-Islet Cell Tumour Hypoglycaemia (NICTH). A NICTH is characterized by recurrent fasting hypoglycaemia and associated with secretion of incompletely processed precursors of insulin-Like Growth Factor II (IGF-II) by the tumour [2]. This 'big'-IGF-II induces secondary changes in the circulating levels of insulin, growth hormone, IGF-I and IGF-binding proteins, which results in an insulin-like hypoglycaemic activity [2].

Non-islet cell tumour hypoglycaemia is a rare paraneoplastic phenomena, but reported in many tumour types since the first description in 1929 in a patient with hepatocellular carcinoma [3]. It has never been reported to be associated with a well differentiated Neuroendocrine Tumour (NET), only once it has been described in a patient with a poorly differentiated gastric Neuroendocrine Carcinoma (NEC) [4].

We herein report a patient with a gastric well-differentiated NET with multiple liver metastases who presented with severe hypoglycaemia during the course of his disease, which appeared to be due to non-islet cell tumour-induced hypoglycaemia.

CASE PRESENTATION

A 61-year old male, without noteworthy medical history, had initially consulted his general practitioner because of complaints of progressive fatigue and flushes. Alongside he had weight loss, a dark stool and anaemia. An upper gastrointestinal endoscopy revealed a large tumour in the stomach, located at the large curvature with necrosis. The gastric biopsy showed a well differentiated NET, 100% positive for synaptophysin and chromogranin A. Abdominal Computed Tomography (CT) scan identified the mass in the stomach, four liver metastases and some lymphogenic metastases para-aortal (Figure 1).

Biopsy of the suspected liver metastases showed the same histopathological image as the primary tumour, a grade 3 well differentiated NET with a Ki67 index of 25%. The blood chromogranin-II-A level was 129,400 µg/L (normal <100 µg/L), the haemoglobin was 7.1 mmol/L (11.4g/dL, normal 8.5-11.0 mmol/L) and some slightly elevated liver function tests were seen. A ^{68}Ga-DOTATATE PET scan showed no uptake apart from a small part of the gastric primary tumour (Figure 2). An iodine meta-iodobenzylguanidine scan revealed intense uptake in one of the liver metastases but no uptake in the remaining metastases or primary tumour.

Treatment was first started with capecitabine (day 1-14; twice daily 1200mg) and temozolomide (day 10-14; daily 300mg), upon progression mTOR inhibitor everolimus (daily 10mg) was started. After 10 weeks of everolimus further progression was seen and patient was switched to PD-1 inhibitor PDR001 (400mg three weekly) in a clinical trial. Before the start of this new therapy the blood glucose level was found to be 3.0 mmol/L (54. 1 mg/dL).

Two weeks after the first gift of PDR001 the patient was admitted with loss of consciousness and a blood level glucose of 1.6 mmol/L (28.8 mg/dL). The low blood sugar levels responded well on intake, but lowered again and especially during the nights. Endocrinological tests revealed a reduced level of plasma insulin below 0.5 mU/L (normal <27mU/L) and a plasma C-peptide level of 250 pmol/L (normal 400-1500 pmol/L) at a blood glucose level of 3.4 mmol/L (61.3 mg/dL). The blood cortisol and ACTH levels were within their normal ranges, as was calcium. The serum level of insulin-Like Growth Factor-II (IGF-II) was elevated with 804 ng/mL (normal 280-610 ng/mL) and the pro-IGF-IIE was elevated as well, 80 µg/L (normal 9-27 µg/L).

Conservatively, tube-feeding was started during the night and hereby stable glucose levels were achieved. After three cycles of PDR001 patient was readmitted to the hospital with severe hypoglycaemia (1.9 mmol/L, 34.2 mg/dL) and progression of his disease. IGF-II and pro-IGF-IIE were 1310 ng/mL and 170 µg/L, respectively. Glucose and steroids were given with success, but due to progression of disease, the patient died.

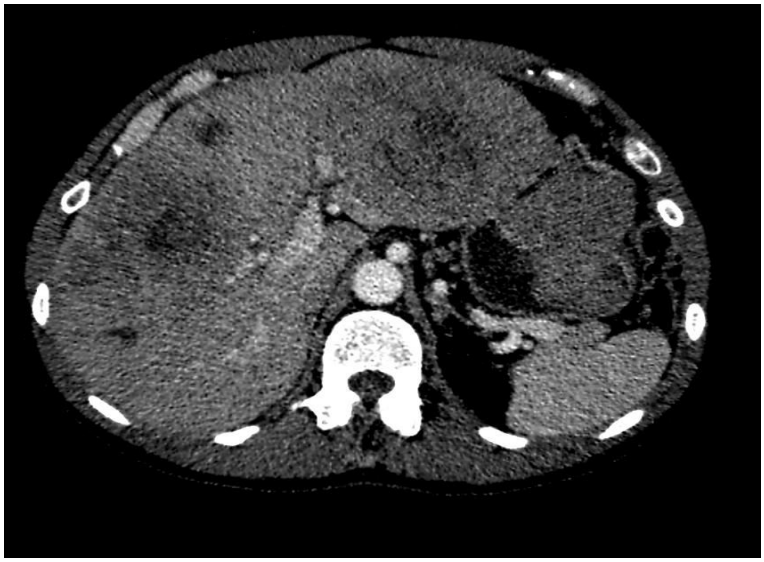

Figure 1: Abdominal computed tomography scan identified four liver metastases.

Non-Islet Cell Tumour Hypoglycaemia in a Patient with Gastric Neuroendocrine Tumour. SL Clinical Medicine: Research. 2019; 2(1):115.

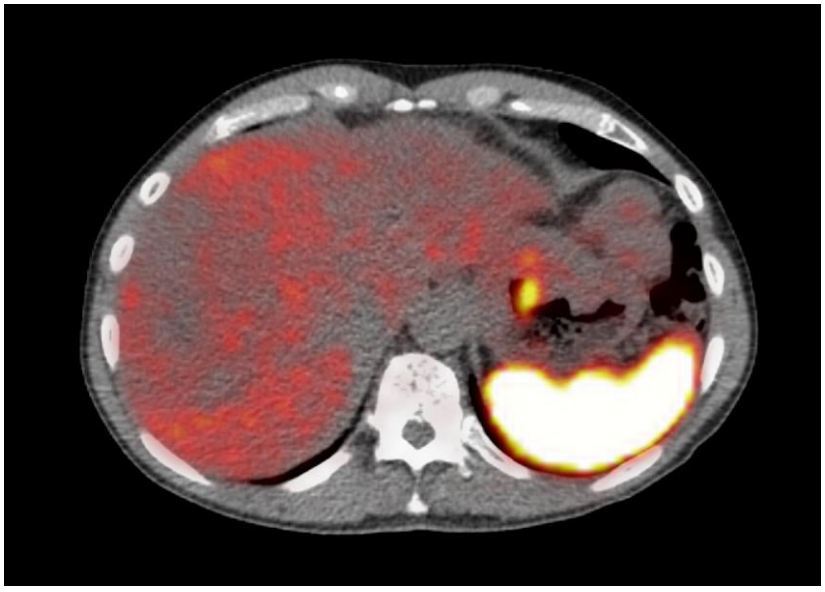

Figure 2: The 68Ga-DOTATATE PET scan showed no uptake apart from a small part of the gastric primary tumour.

DISCUSSION

Based upon the clinical findings this patient was diagnosed with non-islet cell tumour induced hypoglycaemia with an overproduction of pro-IGF-IIE and eventually IGF-II, due to a metastatic well differentiated gastric NET upon progression.

Non-islet cell tumour hypoglycaemia is a rare and complex biochemical syndrome; it is associated with aberrant production of pro-IGF-II, which results in a persistent insulin-like activity [5]. During the process of development of IGF-II a relatively stable intermediate is formed, pro-IGF-IIE, also known as 'big'-IGF-II [6,7].

The IGF system is formed by the two IGF ligands and the IGF receptors, IGF-I receptor (IGF1R) and IGF-II/mannose-6-phosphatereceptor (IGF2R) [8]. The IGF-I and IGF-II are both structurally and functionally related to insulin [2]. Though most of their biological actions are thought to be mediated via IGF1R, [9-13] the IGFs may also interact with the insulin receptor [2]. IGF-II binds with high affinity to the A-isoform of the insulin receptor, which leads to mitogenic effects [14-16] and with low affinity to the B-isoform, which results in insulin-like metabolic effects [2]. The IGFs have about 10 times less glucose-lowering effects than insulin. In contrast their serum concentration is about 1000 times higher than insulin in healthy persons and most (>90%) circulating IGFs are bound to IGF-bounding proteins [17,18]. It is believed that the unbound IGFs and the pool of circulating IGFs are exchanging relatively rapidly with the tissue compartments and are more readily available for binding to IGF and insulin receptors [19-21]. Hence they have an extended half-life in circulation [2]. Pro-IGF-IIE has an insulin-like activity and affinity towards IGF-binding proteins 2 and 3 which is similar as normal IGF-II, but two or threefold higher on a molar basis [22].

Non-islet cell tumour hypoglycaemia is a rare paraneoplastic phenomena. The exact incidence and prevalence data are not available, but it has been estimated to be four times less common than insulinoma. Although the incidence is probably higher since many cases go unrecognised, especially in patients with disseminated disease [23]. NET are a heterogeneous group of rare malignancies, most commonly found in the gastro-intestinal system [24]. Non-islet cell tumours associated with hypoglycaemia are 1% of all tumours of neuroendocrine origin [2].

Unique for this case is the presence of NICTH due to a well differentiated gastric neuroendocrine tumour, which developed during progression of the disease. Up to now, only one case report discussing a poorly differentiated gastric NEC with NICTH [4] is published but no other references in literature are

Non-Islet Cell Tumour Hypoglycaemia in a Patient with Gastric Neuroendocrine Tumour. SL Clinical Medicine: Research. 2019; 2(1):115.

made. With the change of the WHO classification for neuroendocrine neoplasia in to well differentiated grade 1 to 3 and poorly differentiated NEC [25] it would be interesting whether Ida et al. were dealing with a well differentiated grade 3 NET instead of a NEC.

For now this is the first case report discussing a patient with a well differentiated gastric neuroendocrine tumour, which progressed from a non-functional to a functional NET with the overproduction of pro-IGF-IIE and -IGF-II.

Conflict of Interests Disclosure

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

REFERENCES

1. Iglesias P, Díez J. (2014). Management of endocrine disease: a clinical update on tumor-induced hypoglycemia. Eur J Endocrinol. 170: R147-157.
2. de Groot J, Rikhof B, van Doorn J, Bilo HJ, Alleman MA, et al. (2007). Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. Endocrine-Related Cancer. 14: 979-993.
3. Nadler W, Wolfer J. (1929). Hepatogenic hypoglycemia associated with primary liver cell carcinoma. Archives of Internal Medicine. 44: 700-710.
4. Ida T, Morohashi T, Ohara H, Toru Goto, Masahiko Inamori, et al. (2013). Gastric neuroendocrine carcinoma with non-islet cell tumor hypoglycemia associated with enhanced production of insulin-like growth factor II. Intern Med. 52: 757-760.
5. Daughaday W, Emanuele M, Brooks M, Barbato AL, Kapadia M, et al. (1988). Synthesis and secretion of insulin-like growth factor II by a leiomyosarcoma with associated hypoglycemia. N Engl J Med. 319: 1434-1440.
6. Daughaday W, Trivedi B. (1992). Heterogeneity of serum peptides with immunoactivity detected by a radioimmunoassay for proinsulin-like growth factor-II E domain: description of a free E domain peptide in serum. J Clin Endocrinol Metab. 75: 641-645.
7. Duguay S, Jin Y, Stein J, Duguay AN, Gardner P, et al. (1998). Post-translational processing of the insulin-like growth factor-2 precursor. Analysis of O-glycosylation and endoproteolysis. J Biol Chem. 273: 18443-18451.
8. Pollak M, Schernhammer E, Hankinson S. (2004). Insulin-like growth factors and neoplasia. Nat Rev Cancer. 4: 505-518.
9. Le Roith D. (1997). Insulin-Like Growth Factors. N Engl J Med. 336: 633-640.
10. O'Dell S, Day I. (1998). Insulin-like growth factor II (IGF-II). Int J Biochem Cell Biol. 30: 767-771.
11. Dupont J, Pierre A, Froment P, Moreau C. (2003). The insulin-like growth factor axis in cell cycle progression. Horm Metab Res. 35: 740-750.
12. Denley A, Cosgrove LJ, Booker GW, Wallace JC, Forbes BE. (2005). Molecular interactions of the IGF system. Cytokine Growth Factorr Rev. 16: 421-439.
13. Hartog H, Wesseling J, Boezen H, van der Graaf WT. (2007). The insulin-like growth factor 1 receptor in cancer: old focus, new future. Eur J Cancer. 43: 1895-1904.
14. Frasca F, Pandini G, Scalia P, Sciacca L, Mineo R, et al. (1999). Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. Mol Cell Biol. 19: 3278-3288.
15. Sciacca L, Mineo R, Pandini G, Murabito A, Vigneri R, et al. (2002). In IGF-I receptor-deficient leiomyosarcoma cells autocrine IGF-II induces cell invasion and protection from apoptosis via the insulin receptor isoform A. Oncogene. 21: 8240-8250.
16. Belfiore A. (2007). The role of insuline receptor isoforms and hybrid insulin/IGF-I receptors in human cancer. Curr Pharm Des. 13: 671-686.
17. Rinderknecht E, Humbel RE. (1978). Primary structure of human insulin-like growth factor II. FEBS Lett 89: 283-286.
18. Rinderknecht E, Humbel R. (1978). The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J Biol Chem. 253: 2769-2776.
19. Guler H, Zapf J, Schmid C, Froesch ER. (1989). Insulin-like growth factors I and II in healthy man. Estimations of half-lives and production rates. Acta Endocrinol. 212: 753-758.
20. Møller N, Frystyk J, Skjaerbaek C, Pedersen HB, Christensen C, et al. Systemic and regional tumour metabolism in a patient with non-islet cell tumour

hypoglycaemia: role of increased levels of free insulin-like growth factor. Diabetologia. 39: 1534-1535.

21. Frystyk J, Skjaerbaek C, Zapf J, Orskov H. (1998). Increased levels of circulating free insulin-like growth factors in patients with non-islet cell tumour hypoglycaemia. Diabetologia. 41: 589-594.
22. Zapf J, Futo E, Peter M, Froesch ER. (1992). Can 'big' insulin-like growth factor II in serum of tumor patients account for the development of extrapancreatic tumor hypoglycemia. J Clin Invest. 90: 2574-2584.
23. Marks V, Teale J. (1991). Tumours producing hypoglycaemia. Diabets Metab Rev. 7: 79-91.
24. Hallet J, Law C, Cukier M, Saskin R, Liu N, et al. (2015). Exploring the Rising Incidence of Neuroendocrine Tumors: A Population-Based Analysis of Epidemiology, Metastatic Presentation, and Outcomes. Cancer. 121: 589-597.
25. Tang LH, Untch BR, Reidy DL, O'Reilly E, Dhall D, et al. (2016). Well differentiated neuroendocrine tumors with a morphologically apparent high grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. Clin Cancer Res. 22: 1011-1017.