Case report

Non-islet cell tumour hypoglycaemia in a patient with a well-differentiated gastric neuroendocrine tumour

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SUMMARY

A 61-year-old man, without noteworthy medical history, presented 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 (NET). After chemotherapy, everolimus was administered, and upon progression, PD-1 inhibitor PD001 was started. Two weeks after the first gift, he was admitted with loss of consciousness and a blood glucose level of 1.6 mmol/L. Plasma insulin was below 0.5 mU/L, C-peptide level was 250 pmol/L, insulin-like growth factor (IGF)-II was 804 ng/mL, and pro-IGF-II level was 80 µg/L. Based on the clinical findings, the patient was diagnosed with non-islet cell tumour hypoglycaemia (NICTH) with an overproduction of pro-IGF-II and eventually IGF-II due to progressive metastatic well-differentiated gastric NET. NICTH is a very rare condition. It has been reported in several tumour types but has never been described as a consequence of NET.

BACKGROUND

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). NICTH is characterised by recurrent fasting hypoglycaemia and associated with secretion of incompletely processed precursors of insulin-like growth

factor (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

NICTH 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 has it 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 TIH.

CASE PRESENTATION

A 61-year-old man, 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 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 level was 7.1 mmol/L (11.4 g/dL, normal 8.5–11.0 mmol/L); and some slightly elevated liver function tests were seen. A ⁶⁸Ga-DOTATATE positron emission tomography 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 started first with capecitabine (days 1–14, 1200 mg two times per day) and temozolomide (days 10–14, 300 mg daily); on progression, mammalian target of rapamycin (mTOR) inhibitor everolimus (daily 10 mg) was started. After 10 weeks of everolimus, further progression was seen and the patient was switched to PD-1

Figure 1 Abdominal CT scan identified four liver metastases.

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Figure 2 The ^{68}Ga -DOTATATE positron emission tomography scan showed no uptake apart from a small part of the gastric primary tumour.

inhibitor PDR001 (400 mg once every 4 week) in a clinical trial. Before the start of this new therapy, the blood glucose level was found to be 3 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 glucose level of 1.6 mmol/L (28.8 mg/dL).

INVESTIGATIONS

Endocrinological tests revealed a reduced level of plasma insulin of below 0.5 mU/L (normal <27 mU/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 adrenocorticotrophic hormone (ACTH) levels were within their normal ranges, as was calcium. The serum level of IGF-II was elevated with 804 ng/mL (normal 280–610 ng/mL), and the pro-IGF-IIIE was elevated as well with 80 µg/L (normal 9–27 µg/L).

TREATMENT

The low blood sugar levels responded well on intake but lowered again and especially during night-time.

Conservatively, tube feeding was started during the night, and hereby, stable glucose levels were achieved.

OUTCOME AND FOLLOW-UP

After three cycles of PDR001, the 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-IIIE were 1310 ng/mL and 170 µg/L, respectively. Glucose and steroids were given with success initially.

Due to progression of disease, the patient died within 3 months after the initial presentation with hypoglycaemia.

DISCUSSION

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

NICTH 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-IIIE, also known as big IGF-I.^{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.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 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-binding 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-IIIE has an insulin-like activity and affinity towards IGF-binding proteins 2 and 3, which is similar as normal IGF-II, but twofold or threefold higher on a molar basis.²²

NICTH is a rare paraneoplastic phenomenon. The exact incidence and prevalence data are not available, but it has been estimated to be four times less common than insulinoma. However, the incidence is probably higher since many cases go unrecognised, especially in patients with disseminated disease.²³ NET is a heterogeneous group of rare malignancies most commonly found in the gastrointestinal 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 NET, which developed during progression of the disease. Up to now, only one case report discussing a poorly differentiated gastric NEC with NICTH⁴ is published, but no other references in literature are made. With the change of the WHO classification for neuroendocrine neoplasia into well-differentiated grades 1–3 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.⁴

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

Learning points

- ▶ Non-islet cell tumour hypoglycaemia (NICTH) is a rare and complex biochemical syndrome.
- ▶ Although the patient presented with a non-functional metastatic neuroendocrine tumour (NET), a functional NET can develop.
- ▶ In a functional NET, NICTH, although rare, can be seen.

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