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CLINICAL

Insulin-mediated hypoglycaemia secondary to recurrent clear cell renal carcinoma

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ABSTRACT Renal cell carcinoma has previously been associated with hypoglycaemia in the setting of non-islet cell tumours, caused by a paraneoplastic phenomenon relating to the production of insulin-like growth factor type II. We present a case of recurrent clear cell renal cell carcinoma, leading to an insulin-mediated paraneoplastic phenomenon causing severe recurrent hypoglycaemia. Hypoglycaemina was managed successfully using diazoxide therapy, in conjunction with pazopanib and radiotherapy to reduce tumour burden.

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CASE REPORT

A 75-year-old male was diagnosed in 2011 with stage T3a renal cell carcinoma (RCC) of clear cell histology. Initial staging scans were clear, and he underwent right nephrectomy with curative intent. Background medical history included bronchiectasis, chronic obstructive pulmonary disease and ischaemic heart disease.

In May 2015 the patient presented with a one week history of haemoptysis, initially thought to be related to an exacerbation of bronchiectasis. However, a CT angiogram revealed a right upper lobe pulmonary embolus, together with a 2 x 2 cm left upper lobe mass lesion highly suspicious of malignancy. Histopathology obtained via bronchoscopic biopsy was consistent with metastatic clear cell RCC. Initial management consisted of localised radiotherapy to treat the haemoptysis followed by systemic pazopanib for treatment of the metastatic disease.

During the investigation of his haemoptysis and prior to initial management, the patient had a severe hypoglycaemic event with loss of consciousness and a blood glucose level of < 1 mmol/L. He responded to intravenous glucose but continued to have further recurrent severe hypoglycaemic episodes, with venous blood glucose levels ranging between 1.0–1.8 mmol/L. These episodes usually occurred while the patient was fasting for tests.

Further investigations revealed his insulin, proinsulin and c-peptide levels were elevated at the time of hypoglycaemia, with reduced beta hydroxybutyrate levels (Table 1).He was noted to have a mildly raised IGF-1 level, but this was thought to be a response to his recurrent hypoglycaemia rather than the cause. A sulphonylurea screen and measurement of insulin antibodies were both negative. Insulin-mediated hypoglycaemia was diagnosed, on the basis of a venous glucose of < 3 mmol/L, insulin > 3 mU/L, C-peptide > 0.2 nmol/L and proinsulin > 5 pmol/L.[1]

TABLE 1 Patient biochemistry consistent with insulin-mediated hypoglycaemia

Glucose (mmol/L)	1.8
IGF-1 (nmol/L)	36
Proinsulin (pmol/L)	84.7
Insulin (mU/L)	18
C-Peptide (nmol/L)	5.0
Beta-hydroxybutyrate (mmol/L)	< 0.1

Imaging of the pancreas with both ultrasound and MRI did not reveal any abnormality, and in particular did not reveal an insulinoma or other malignant mass lesion. The suspected cause was insulin secretion by his RCC pulmonary metastasis. A CT/PET scan revealed pulmonary metastatic lesions but no other distant sites of disease. His histopathology was reviewed again and did not reveal beta cell histology. Immunohistochemistry was performed to look specifically for insulin expression; this was inconclusive and thus was not able to confirm the clinical suspicion.

Twice daily prednisolone 10 mg was initially commenced to prevent hypoglycaemic events. However, due to concerns about side effects from ongoing high-dose glucocorticoid therapy, and the fact that his biochemistry was consistent with an insulin-driven process, a trial of diazoxide was undertaken. He demonstrated a good

response to this and has been able to maintain normoglycaemia with 100 mg diazoxide taken at night. He has since been able to stop taking prednisolone.

Repeat imaging after three months of systemic pazopanib therapy showed a reduction in size of his metastasis, although they remain non-resectable. He underwent a 72 hour fast in October 2015 during which he did not receive any diazoxide and did not develop any hypoglycaemia, consistent with the reduction in tumour mass noted on his staging scans.

DISCUSSION

Non-islet cell tumour hypoglycaemia (NICTH) is a rare paraneoplastic phenomenon seen in solid organ tumours, both benign and malignant.[2,3] On occasion, it may be the first manifestation of the tumour. Three cases have previously been reported with primary RCC, where resolution of hypoglycaemia occurred with resection of the primary mass.[4-6] There has previously been only one reported case of this phenomenon in recurrent disease.[7]

NICTH is usually caused by overproduction of insulin-like growth factor type II (IGF-II) by the tumour mass.[4,7] Tumour cells that over-express the IGF-II gene produce a high molecular weight protein, known as 'big'-IGF.[8,9] The molecule resembles insulin both structurally and functionally and interacts with the insulin receptor, leading to hypoglycaemia.[4,7] Thus, when investigations are undertaken at the time of hypoglycaemia, IGF-II levels are high and insulin, proinsulin and c-peptide levels are low. IGF-1 levels are usually low due to suppressed growth hormone secretion.[1]

The case described shows insulin-mediated hypoglycaemia, and the elevated c-peptide levels suggested endogenous insulin as the cause. As previously mentioned, the marginally elevated IGF-1 result could be a response to recurrent hypoglycaemia. This biochemistry raised the possibility of an insulinoma and prompted investigation for this. No insulinoma has been found in our patient to date, nor has any other malignant lesion (such as lymphoma, producing insulin antibodies) been detected, leading to the conclusion that this insulin-mediated hypoglycaemia is indeed from the metastatic deposit. The apparent improvement in hypoglycaemia during a period when the tumour mass was reduced by treatment, further supports this theory.

Previous case reports have described both hepatic and ileal carcinoid tumours causing insulin-mediated hypoglycaemia.[10-12] The hepatic carcinoid patient had transformation from extra-pituitary acromegaly to hyperinsulinaemic hypoglycaemia.[10,11] The ileal carcinoid patient had hepatic metastases that produced serotonin, calcitonin, gastrin and insulin, leading to hypoglycaemia.[11,12] Both these patients had aggressive disease progression and severe recurrent hypoglycaemia.[10] Otherwise, this particular mechanism of hypoglycaemic is not usually seen as a paraneoplastic syndrome, and has not been reported in the literature in the context of RCC.

Complete resection of the culprit tumour mass is the best management strategy for hypoglycaemia.[2,4] However, this is not always feasible, in which case antitumour therapies and targeted pharmacological agents to cytoreduce and control the culprit lesion/s are recommended.[4,13] While there are reports of radiation therapy helping control hypoglycaemia secondary to NICTH, systemic therapy traditionally has not been very successful, and without surgical resection the outcomes have generally been poor.[2]

Symptomatic measures are also important in dealing with hypoglycaemia. Glucocorticoids work in the setting of NICTH in two ways. First, by reducing the circulating IGF-II levels where this is the underlying mechanism of hypoglycaemia, and second, due to their well-established effects of gluconeogenesis and insulin inhibition.[2,14] For insulin-mediated hypoglycaemia, diazoxide (a thiazide diuretic used for treating malignant hypertension) is an established therapy for hypoglycaemia secondary to insulinoma.[8,15] By acting as a potassium ATP channel opener, diazoxide inhibits insulin secretion by pancreatic beta cells.[15] Diazoxide may therefore be a useful therapy if abnormal beta cell activity (either within or distant to the pancreas) is the cause of hypoglycaemia. An alternative option specifically for hypoglycaemic management is octreotide, a somatostatin analogue that works by inhibiting growth hormone, insulin and glucagon, but it is not an ideal long term management strategy.

We present this case to alert clinicians to the possibility that clear cell RCC (either as a primary tumour mass or in the metastatic setting) may, on occasion, present with recurrent episodes of hypoglycaemia. Our case shows that hypoglycaemia can be managed successfully by a combination of therapy to reduce tumour mass, plus diazoxide therapy to reduce insulin secretion. In patients presenting with repeat episodes of hypoglycaemia of unknown aetiology, concerted efforts should be made to exclude malignancy as a potential cause.

REFERENCES

1 Cryer P, Axelrod L, Grossman A et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; 94: 709-28. http://dx.doi.org/10.1210/jc.2008-1410

2 Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet cell tumour hypoglycemia: a clinical review. *J Clin Endocrinol Metab* 2013; 99: 713–22. http://dx.doi.org/10.1210/jc.2013-3382

3 Scott K. Non-islet cell tumour hypoglycaemia. *J Pain Symptom Manage* 2009; 37: e1–e3. http://dx.doi.org/10.1016/j.jpainsymman.2008.11.004

4 de Groot, JW, Rikhof B, van Doorn J et al. Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. *Endocr Relat Cancer* 2007; 14: 979-93. http://dx.doi.org/10.1677/ERC-07-0161

5 Herman SF, Hawkyard SJ, Poon P et al. Renal cell carcinoma with non-islet cell tumor hypoglycaemia. *Int J Urol* 2006; 13: 985–6. http://dx.doi.org/10.1111/j.1442-2042.2006.01452.x

6 Baldwin RS. Hypoglycemia with neoplasia (Doege-Potter Syndrome). *Wis Med J* 1965; 64: 185–9.

7 Kimura S, Mitsuzuka K, Yamada S et al. Hypoglycemia Caused by Recurrent Renal Cell Carcinoma As Result of Production of High Molecular Weight Insulin-Like Growth Factor 2. *J Clin Oncol* 2016; 34: e120–2. http://dx.doi.org/10.1200/JCO.2013.49.5374

8 Davda R, Seddon BM. Mechanisms and management of non-islet cell tumour hypoglycaemia in gastrointestinal stromal tumour: case report and a review of published studies. *Clin Oncol* 2007; 19: 265–8.

9 Marks V, Teale JD. Tumours producing hypoglycaemia. *Endocr Relat Cancer* 1998; 5: 111–29. http://dx.doi.org/10.1677/erc.0.0050111

10 Rehman R, Childress R, Solomon S et al. Neuroendocrine tumor presenting as metastatic carcinoid and later as insulinoma: a rare metamorphosis. *Endocrinology Studies* 2012; 2: e7. 29–31. http://dx.doi.org/10.4081/es.2012.e7

11 Furrer J, Hättenschwiler A, Komminoth P et al. Carcinoid syndrome, acromegaly, and hypoglycemia due to an insulin-secreting neuroendocrine tumor of the liver. *J Clin Endocrinol Metab* 2001; 86: 2227–30.

12 Pelletier G, Cortot A, Launay JM et al. Serotonin-secreting and insulin-secreting ileal carcinoid tumor and the use of in vitro culture of tumoral cells. *Cancer* 1984; 54: 319–22.

13 Teale JD, Wark G. The effectiveness of different treatment options for non-islet cell tumour hypoglycaemia. *Clin Endocrinol* 2004; 60: 457–60.

14 Perros P, Simpson J, Innes JA et al. Non-islet cell tumour-associated hypoglycaemia: 111In-octreotide imaging and efficacy of octreotide, growth hormone and glucocorticosteroids. *Clin Endocrinol* 1996; 44: 727–31.

15 George P, McCrimmon R. Diazoxide. *Practical Diabetes* 2012; 29: 36–7. http://dx.doi.org/10.1002/pdi.1655