Unusual site and presentation of a neuroendocrine tumour

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INTRODUCTION

Neuroendocrine tumours (NET) are rare and slow growing. They can occur in any part of the body, sporadically or in association with different syndromes such as multiple endocrine neoplasia. NET are usually named according to the predominant secreted peptide and they often cause symptoms as a result of excess hormone secretion, local growth or metastasis (Fauci et al, 1998). Diagnosis is established with standard histochemical, electron microscopy and immunohistochemical analysis (Polak, 1993). Insulin growth factor-II (IGF-II) production by NET is extremely rare and this article reports a novel site of an IGF-II producing NET.

CASE REPORT

A 44-year-old man presented with acute confusion, having collapsed at home. His medical history included mild asthma, for which he required inhaled salbutamol. He smoked 30 cigarettes/day and consumed 6 units of alcohol daily. His admitting capillary glucose was low at 2.2 mmol/litre and he was resuscitated with intravenous dextrose infusion. His collapse had resulted in a fracture to his right neck of femur, which was managed by closed reduction and internal fixation. Clinical examination was otherwise unremarkable.

Given the possibility of a pathological fracture he had a bone scan which revealed widespread bony metastasis. In a search for the primary source, an abdominal computed tomography scan revealed a lobulated calcified retroperitoneal mass arising from the medial aspect of the left kidney (*Figure 1*). A tentative diagnosis of metastatic renal cell carcinoma was made; however, this did not entirely account for his hypoglycaemia.

On the ward he had recurrent episodes of hypoglycaemia, which were unrelated to food or physical activity. On questioning, he gave a 2-month history of excess sweating and weight loss of 7 kg, and he denied any use of insulin, oral hypoglycaemic agents or unprescribed drugs; there was no suggestion of binge drinking. Biochemical and haematological parameters, including liver function tests, pituitary hormones, urinary sulphonylurea and toxicology screen were unremarkable; a short synacthen test excluded Addison's disease. During a hypoglycaemic episode, his insulin and C-peptide levels were <10 pmol/litre (normal range (NR) = 21.5–115.0 pmol/litre) and <94 pmol/litre (NR = 180–630 pmol/litre) respectively, excluding the diagnosis of an insulinoma. Assessment of insulin-like growth factors (IGF) revealed an inappropriately raised serum IGF-II level of 127.2 nmol/litre and low IGF-I level of 6.4 nmol/litre (NR = 9–40 nmol/litre), such that the IGF-II:IGF-I ratio was 19.9 (NR = <10), consistent with non-islet cell tumour hypoglycaemia (NICTH). An ultrasound-guided biopsy was performed and, based on electron microscopy (*Figure 2*) and immunohistochemistry study findings (*Figure 3*), a diagnosis of a malignant neuroendocrine tumour (NET) was reached. IGF-II staining was not performed as it is not done locally at the authors' hospital and it was not going to change the management plan. Levels of plasma chromogranin A and B, markers for NET, were elevated at 518 pmol/litre (NR <60 pmol/litre) and 273 pmol/litre (NR <150 pmol/litre) respectively. Fasting gut hormones, 24-hour urinary catecholamines and 5-hydroxyindole acetic acid levels were unremarkable. An octreotide scan demonstrated extensive uptake throughout the body (*Figure 4*). The diagnosis of IGF-II-secreting NET was based on the histology results and the exclusion of other common secreted neuroendocrine peptides.

For the hypoglycaemic episodes, he was commenced on oral diazoxide which had little effect. Following the diagnosis of NET and NICTH he was started on prednisolone (40 mg/day) and subcutaneous octreotide (300 μg/day); subsequently he required continuous 10% dextrose infusion. Following a multidisciplinary meeting, surgery was not considered appropriate and the patient rejected embolization treatment. Palliative radiotherapy was given for metastatic spread to the right orbit and thoracic spine, and adequate analgesia was maintained. Growth hormone treatment was considered, but his health deteriorated rapidly and he died 4 months after his first presentation. Post mortem examination confirmed a renal NET measuring 20 x 12 x 9 cm, with metastasis.

DISCUSSION

NET are rare causes of non-islet cell tumour hypoglycaemia (NICTH) and in a review of 68 tumours producing NICTH through production of IGF-II, only one case was a carcinoid (Marks and Teale, 1998). This case is the first reported renal NET causing hypoglycaemia through IGF-II overproduction.

IGF-II is an embryonic growth promoter and cell survival factor. Most

Figure 1. Abdominal computed tomography revealed a large lobulated retroperitoneal mass arising from the medial aspect of the left kidney with a rim of calcification.

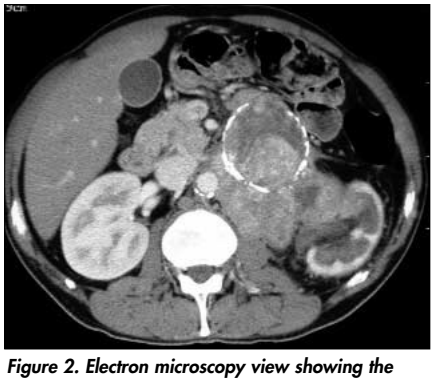
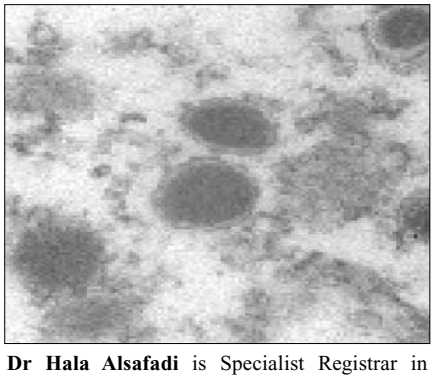


Figure 2. Electron microscopy view showing the dense core secretory granules in the cell cytoplasm.



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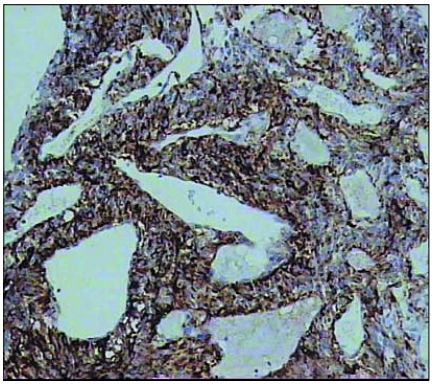

Figure 3. Chromogranin staining: the tumour is highly vascular and there is a strong expression of chromogranin (brown discolouration); chromogranins A, B and C are acid-soluble protein located in the dense core secretory granules.

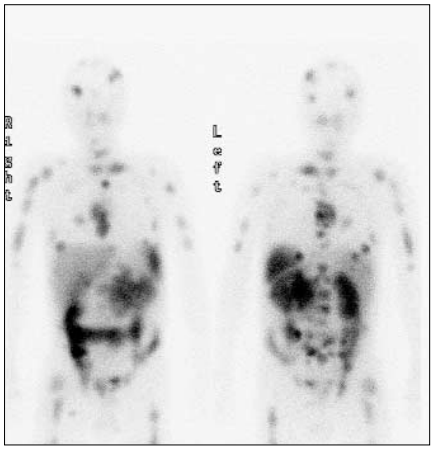

Figure 4. Octreotide scan showed increased uptake throughout the body including the bones and the tumour.

fetal growth depends on IGF-II production in the tissues independent of growth hormone (GH), while after birth growth becomes dependent on GH. IGF-II levels fall slowly throughout childhood while IGF-I levels rise.

IGF-II is similar in structure to proinsulin, but does not cause hypoglycaemia, as it circulates almost completely bound to specific IGF-binding proteins (IGFBPs) to form a ternary complex with an acid-labile subunit (ALS) (Marks and Teale, 1998). Therefore, any factor that may interfere with this complex will lead to increased bioavailability of free IGF-II, which binds to IGF and insulin receptors, causing hypoglycaemia.

Factors contributing to the defect are raised IGF-II levels, the production of high molecular weight IGF-II (big IGF-II) (Shapiro et al, 1990), or low levels of IGFBPs or ALS (Baxter, 1996). Improvement in glucose homeostasis and biochemical markers has been noted with high-dose corticosteroids and human growth hormone. Both therapeutic modalities improve ternary complex formation by increasing the levels of serum ALS and IGFBP-3; furthermore corticosteroid treatment suppresses tumour IGF-II (Baxter et al, 1995).

CONCLUSIONS

The precise aetiology of NET is still poorly understood, and this case serves to highlights the complexities encountered in the diagnosis and management of NET. Surgery remains the only curative treatment for localized NET; however, some of these tumours are malignant and have spread at the time of diagnosis. The principal therapeutic goals in malignant metastatic NET are to decrease the tumour growth and to relieve the symptoms of hormone overproduction. HM

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