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ARTICLES

Ectopic growth hormone-releasing hormone (GHRH) acromegaly secondary to adrenal phaeochromocytoma: A case report
Eswari Chinnasamy, Darshi Sivakumaran, Gideon Mlawa and Gul Bano
Case Report

Ectopic growth hormone-releasing hormone (GHRH) acromegaly secondary to adrenal phaeochromocytoma: A case report

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Ectopic growth hormone releasing hormone (GHRH) secretion is a rare cause of acromegaly and accounts for <1% of cases. It is most commonly secondary to gastropancreatic neuroendocrine tumours and bronchial carcinoid tumours. We report a case of 57 years old man with adrenal phaeochromocytoma and acromegaly due to ectopic GHRH secretion in a patient with neurofibromatosis type 1. He presented with headache, sweating and newly diagnosed diabetes. The diagnosis was of acromegaly and pheochromocytoma was confirmed on investigations and imaging. Surgical removal of the pheochromocytoma in this case resulted in resolution of his diabetes, normalisation of his IGF-1 with adequate GH suppression on oral glucose tolerance test (OGTT) and regression of enlarged pituitary on postoperative magnetic resonance imaging (MRI) scan. To our knowledge, this is the first case of acromegaly associated with pheochromocytoma due to ectopic GHRH in a patient of neurofibromatosis in literature.

Key words: Growth hormone releasing hormone (GHRH), pheochromocytoma, acromegaly, somatotrophs, neurofibromatosis.

INTRODUCTION

Ectopic growth hormone releasing hormone (GHRH) secretion is a rare cause of somatotroph hyperplasia and acromegaly. 74 of such cases have been reported over the last 30 years (Borson-Chazot et al., 2012). These cases account for <1% of acromegaly and are most commonly secondary to gastroenteropancreatic neuroendocrine tumors and bronchial carcinoid tumors. Dynamic pituitary tests are not helpful in distinguishing acromegalic patients with pituitary tumors from those due to extrapituitary tumors. Growth hormone (GH) and IGF-1 are invariably elevated and GH levels fail to suppress (<1 mL/L) after an oral glucose load in all forms of acromegaly regardless of the etiology. The distinction of pituitary versus extrapituitary acromegaly is extremely important in planning effective management. Surgical resection of the tumor secreting ectopic GHRH if possible is the treatment of choice in a patient with the ectopic GHRH syndrome. We report a case of adrenal

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Abbreviations: GHRH, Growth hormone releasing hormone; OGTT, oral glucose tolerance test.

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phaeochromocytoma with ectopic GHRH secretion in a patient with neurofibromatosis type 1 positive mutation and review literature for ectopic GHRH acromegaly in association with phaeochromocytoma. To our knowledge, this is the first case in the literature of GHRH induced acromegaly and phaeochromocytoma in context of neurofibromatosis type 1.

CASE REPORT

A 57 year old male presented with haematuria. His imaging revealed a 9×8 cm renal mass and a 5 cm left adrenal mass. He had a history of sweating and headaches and was diagnosed with Type 2 Diabetes a year ago. His HbA1C was 56 mmol/L on Gliclazide 80 mg twice a day. He was recently investigated for episodes of chest pain and his exercise tolerance test and echocardiogram were normal. His body mass index (BMI) was 25 kg/m^2 and his blood pressure was 130/80 mmHg. He had café-au-lait spots, axillary freckles and cutaneous neurofibromas on his back. The patient had genetically confirmed mutation in the NF1 gene. Apart from sweaty palms he had no other clinical features of acromegaly. Biochemical investigations of his adrenal mass ruled out cortisol and aldosterone hypersecretion. His 24 h urinary metanephrines were elevated; normetadrenaline 16.8 μmol/L (0 to 2.5) and met adrenaline 21.03 μmol/L (0 to 1.2). His IGF1 was high at 36.5 nmol/L (10.5 to 29.3). He had normal thyroid function and gonadotrophin levels and had normal serum levels of glucose. He had normal clinical features of acromegaly.

DISCUSSION

Hypothalamic GHRH is secreted into the portal system, binds to specific surface receptors of the somatotroph cell and modulates pituitary GH synthesis and/or secretion. GHRH is also synthesized and expressed in multiple extrapituitary tissues. Excessive peripheral production of GHRH by a tumor can cause somatotroph cell hyperstimulation, increased GH secretion and eventual pituitary acromegaly. Immunoreactive GHRH is present in several tumors, including carcinoid tumors, pancreatic cell tumors, small cell lung cancers, endometrial tumors, adrenal adenomas, and phaeochromocytomas which have been reported to secrete GHRH (Gola et al., 2006). Acromegaly in these patients is uncommon and the severity of the disease is variable. GHRH was first isolated and sequenced in 1982 from the pancreatic tumors of patients presenting with acromegaly and associated pancreatic tumor (Guillemin et al., 1982). Biological activity lies in the first 29 amino acids. GHRH is rapidly inactivated by dipeptidylaminopeptidase and has an estimated biological half life of only 10 min. From these tumors, three GH-releasing peptides were identified and the sequences of two were found to be similar to that of hypothalamic GHRH (Frohman et al., 1986).

Regardless of the cause, GH and IGF-1 are invariably elevated and GH levels fail to suppress (<1 μg/L) after an oral glucose load in all forms of acromegaly. Dynamic pituitary tests are not helpful in distinguishing acromegalic patients with pituitary tumors from those harboring extrapituitary tumors.

Despite the frequent immunoreactivity of nearly 48% for GHRH in phaeochromocytomas, only four cases of acromegaly associated with ectopic GHRH secretion by these tumors have been reported (Table 3).

The discrepancy between high frequency of positive GHRH immunostaining and overt clinical acromegaly in phaeochromocytoma has been explained by Faglia et al. (1992) and Baughan et al. (2001): insufficient amounts of circulating GHRH due to rapid degradation; production of immunoreactive GHRH with poor biologic activity; absent or inefficient secretion of the synthesized peptide; simultaneous production of inhibitory substances by the tumor; the tumor may be operated before clinical expression of acromegaly.

The pituitary may be normal or enlarged at MRI, which may be difficult to interpret. The plasma GHRH assay has proven a sensitive method to confirm an ectopic source.
Table 1. Pre Adrenalectomy OGTT: High glucose and failure of GH suppression

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (µg/L)</td>
<td>0.26</td>
<td>0.70</td>
<td>1.33</td>
<td>1.94</td>
<td>1.49</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>7</td>
<td>12.5</td>
<td>17.4</td>
<td>20.4</td>
<td>19.2</td>
</tr>
</tbody>
</table>

IGF-1: 36.5 nmol/L (10.5 – 29.3).

Table 2. Post Adrenalectomy OGTT: Normal glucose and adequate GH suppression

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (µg/L)</td>
<td>2.51</td>
<td>2.75</td>
<td>2.17</td>
<td>0.68</td>
<td>0.34</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.1</td>
<td>5.6</td>
<td>5.3</td>
<td>7.9</td>
<td>6.0</td>
</tr>
</tbody>
</table>

IGF-1: 22 nmol/L (10.5 – 29.3).

Figure 1. MRI pituitary showing diffuse pituitary enlargement.

of GHRH secretion. Plasma GHRH levels are usually elevated in patients with peripheral GHRH-secreting tumors and are normal or low in patients with pituitary acromegaly. Using a threshold of 250 to 300 ng/L appears to be a highly specific indicator of an ectopic GHRH secretion in acromegalic patients. It is a good tool for follow-up of patients after treatment. The significance of lower values remains largely unknown (Vieira Neto et al., 2001; Mumby et al., 2014). We were not able to measure GHRH in this patient due to lack of facility for the assay. His MRI pituitary revealed a diffusely enlarged pituitary gland. His CT thorax, abdomen and pelvis were normal. Patients with NF1 more frequently develop benign and malignant tumors during their life. Conditions in which GH excess occurs include neurofibromatosis type 1. The number of cases of pituitary adenomas reported in NF1 is very small. On the other hand, NF1 patients have a lifetime risk of 1 to 5% for the development of a pheochromocytoma. To our knowledge, this is the first case in the literature of GHRH induced acromegaly and pheochromocytoma in context of neurofibromatosis type 1 where there was biochemical
resolution of GH excess and regression of enlarged pituitary after adrenalectomy for pheochromocytoma. The distinction of pituitary versus extrapituitary acromegaly is extremely important in planning effective management. Surgical resection of the tumor secreting ectopic GHRH if possible is the most effective treatment in a patient with the ectopic GHRH syndrome. As in our patient removal of pheochromocytoma led to the resolution of his diabetes, normalization of his IGF-1 with adequate GH suppression on OGTT and regression of enlarged pituitary on postoperative MRI scan. 25-75% of phaeochromocytoma patients have diabetes or glucose intolerance. Resolution of diabetes occurs in 40% to 100% of patients with complete resection of phaeochromocytoma (Turnbull et al., 1980; Stenstro¨m et al., 1984).

Standard chemotherapy directed at GHRH-producing tumors are generally unsuccessful in controlling the activated GH axis. Somatostatin analogues provide an effective option for medical management of patients, especially those with recurrent disease. Long-acting somatostatin analogues may be able to control not only the ectopic hormonal secretion syndrome, but also, in some instances, tumor growth. Long-acting somatostatin analogues are preferred as a second-line therapy in patients with the ectopic GHRH-syndrome.

Conclusions

Ectopic GHRH acromegaly should be suspected in a patient with biochemical/clinical features of acromegaly in the presence of co-existing neuroendocrine tumors when there is diffuse pituitary enlargement on imaging or resolution of acromegaly after the surgical resection of the primary neuroendocrine tumour or persistent acromegaly after surgery if there is histological evidence of somatotroph hyperplasia.

Conflict of Interests

The authors have not declared any conflict of interests.

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Table 3. Case reports of pheochromocytoma associated with acromegaly.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Sex</td>
<td>42/M</td>
<td>43/M</td>
<td>23/M</td>
<td>25/F</td>
<td>57/M</td>
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<td>-Dyspnoea</td>
<td>-Abdominal pain</td>
<td>-Acromegaly</td>
<td>-Abdominal pain</td>
<td>-Chest pain</td>
</tr>
<tr>
<td></td>
<td>-Acromegalic</td>
<td>-Acromegalic</td>
<td>-Acromegaly</td>
<td>-Acromegalic</td>
<td>-Diabetes</td>
</tr>
<tr>
<td></td>
<td>-Features</td>
<td>-Features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Acromegaly</td>
<td>Pheochromocytoma</td>
<td>Acromegaly</td>
<td>Pheochromocytoma</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Pheochromocytoma size</td>
<td>19×17</td>
<td>20×20</td>
<td>9.5×9.8</td>
<td>5×4.5</td>
<td>10×16</td>
</tr>
<tr>
<td>Predominant Metanephrine/Catecholamine</td>
<td>Epinephrine</td>
<td>Metanephrine</td>
<td>Epinephrine</td>
<td>Normetanephrine</td>
<td>Metadrenaline</td>
</tr>
<tr>
<td>Clinical acromegaly</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>GHRH immunostaining</td>
<td>Positive</td>
<td>-Not done</td>
<td>Positive</td>
<td>Positive</td>
<td>-Not done</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Cured after surgery</td>
<td></td>
<td></td>
<td>-Cured after surgery</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>No</td>
<td>-Glucose</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Intolerance</td>
<td></td>
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</tbody>
</table>
Figure 2. $^{123}$IMIBG scan showing intense uptake in left adrenal gland.

interests.

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