Acromegaly caused by a GHRH-producing pancreatic neuroendocrine tumor: a rare manifestation of MEN1 syndrome

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Summary

Multiple endocrine neoplasia type 1 NM_001370259.2(MEN1):c.466G>C(p.Gly156Arg) is characterized by tumors of various endocrine organs. We report on a rare, growth hormone-releasing hormone (GHRH)-releasing pancreatic tumor in a MEN1 patient with a long-term follow-up after surgery. A 22-year-old male with MEN1 syndrome, primary hyperparathyroidism and an acromegalic habitus was observed to have a pancreatic tumor on abdominal CT scanning, growth hormone (GH) and insulin-like growth factor 1 (IGF1) were elevated and plasma GHRH was exceptionally high. GHRH and GH were measured before the treatment and were followed during the study. During octreotide treatment, IGF1 normalized and the GH curve was near normal. After surgical treatment of primary hyperparathyroidism, a pancreatic tail tumor was enucleated. The tumor cells were positive for GHRH antibody staining. After the operation, acromegaly was cured as judged by laboratory tests. No reactivation of acromegaly has been seen during a 20-year follow-up. In conclusion, an ectopic GHRH-producing, pancreatic endocrine neoplasia may represent a rare manifestation of MEN1 syndrome.

Learning points:

- Clinical suspicion is in a key position in detecting acromegaly.
- Remember genetic disorders with young individuals having primary hyperparathyroidism.
- Consider multiple endocrine neoplasia type 1 syndrome when a person has several endocrine neoplasia.
- Acromegaly may be of ectopic origin with patients showing no abnormalities in radiological imaging of the pituitary gland.

Background

Acromegaly is usually caused by a growth hormone (GH)-producing tumor of the pituitary gland. Multiple endocrine neoplasia type 1 (MEN1) is an autosomally inherited disease characterized by tumors and/or hyperplasia of endocrine organs, especially parathyroids, pituitary gland and endocrine pancreas. All patients are screened for primary hyperparathyroidism, pituitary adenomas and gastrointestinal neuroendocrine tumors. Here, we describe a patient with MEN1 manifesting as primary hyperparathyroidism, pancreatic endocrine neoplasm and clinical signs of acromegaly. Eventually, his acromegaly was found to be caused by the pancreatic endocrine neoplasm that was shown to produce growth hormone-releasing hormone (GHRH).
Case presentation

In May 1994, a 22-year-old male student was invited to the outpatient clinic of the Department of Clinical Genetics, Oulu University Hospital, for genetic counseling and evaluation of health status because he was a first-degree relative of two known MEN1 patients. His mother (proband of the family) had a pancreatic neuroendocrine tumor (pNET), primary hyperparathyroidism and a pituitary adenoma, and his maternal aunt had an insulinoma. Linkage analysis in the subject gave 98% probability for the MEN1 gene mutation. At that time, the presence of the mutation was not identified. The features of acromegaly were observed at the initial endocrinological visit. He had large hands, coarse acromegalic facial prominences, a protruding mandible with dental wear, increased shoe size and excessive sweating.

Investigation

Laboratory tests

Screening tests for acromegaly were taken after the initial visit. Insulin-like growth factor 1 (IGF1) was elevated (70.3 nmol/L; normal range 9.1–46) and a paradoxical GH rise in 3-h oral glucose loading test was observed (B-gluc 5.1–6.8–6.0–5.8 mmol/L, S-GH 8.5–4.3–16.0–8.2 µg/L). Repeated S-GH values showed abnormal values 9.5–6.2–26.1–14.8–22.5–13.2–15.7–27.8–8.3–17.2 (usually <7) µg/L. Additionally, serum GH levels in the GHRH stimulation test were 7.1–31.6–14.1–7.6 µg/L and in the octreotide suppression test, 8.0–1.3–0.7–2.0–2.1–2.7 µg/L, thus verifying clear suppression. Because ectopic production of GHRH by the pancreatic tumor was suspected, plasma (4 mL) was extracted by Sep-Pak cartridges and measured by GHRH (RIA) which was exceptionally high, with values of 10,250–9500 ng/L (reference range ≤10 ng/L). The laboratory analyses also revealed primary hyperparathyroidism (PHP) (S-Ca 2.90 mmol/L, S-parathyroid hormone 91.8 ng/L (normal range 10–55ng/L), dU-Ca 12.66 mmol (normal range 1.50–5.50 mmol), ionized calcium 1.62 mmol/L) and mild hyperprolactinemia (S-prolactin 872 mU/L). Serum gastrin and pancreatic polypeptide levels were normal.

Radiological and histological examinations

MRI showed a slightly hyperplastic pituitary gland and raised suspicion of a 5-mm microadenoma on the left margin of the gland. The adenoma was also detectable in an octreotide scan. Ultrasound (US) examination of the neck showed enlarged lower parathyroids. In abdominal US examination, a pancreatic tumor was discovered, confirmed by abdominal CT examination where a clearly defined tumor 4.0 × 3.4 cm in size and connected to the pancreatic tail was observed (Fig. 1). The octreotide scan of the pancreatic region was negative. Fine needle aspiration biopsy confirmed the diagnosis of the pNET.

Treatment

In December 1994, a trial with subcutaneous octreotide therapy (Sandostatin®, Novartis Finland Oy, Espoo, Finland,) with a dose of 100 µg three times daily was implemented; after a month, a clear response to the therapy was observed: serum IGF1 was in normal range (41.5 nmol/L) and the GH curve was close to normal: S-GH 4.1–1.5–0.5–2.7–2.2–3.8–5.5–17.6–4.6–4.3 µg/L. In contrast, octreotide therapy did not result in the normalization of GHRH values, which remained high (17 500–12 500 ng/L).

In May 1995, PHP was treated with removal of the parathyroids and autotransplantation of fragments of the parathyroid gland to the left arm.

In March 1996, enucleation of the tumor of the pancreatic tail was performed. Macroscopically, the tumor was 5 cm in diameter, soft and reddish. On light microscopy, the pancreatic tumor was encapsulated by a thin collagenous sheath and consisted of solid growth of cells with relatively scarce cytoplasm and round nuclei, occasionally forming glandular structures (Fig. 2). Immunohistochemical analysis was performed with antibodies against GHRH (Fig. 3) and various other peptide hormones. The results are presented in Table 1. Recently, the tumor histology was re-evaluated and graded using the World Health Organization classification of tumors of endocrine origin 2019. The proliferation rate was five mitoses
per ten high-power fields, and the Ki-67 proliferation index was 9%, classifying the tumor as NET G2.

**Outcome and follow-up**

In April 1996, Sandostatin® treatment was ceased. Two months later, the patient was asymptomatic and his acromegaly was clinically cured as judged by laboratory tests: IGF 1 level was 33.3 nmol/L and the GH curve was 0.7–4.7–<0.25–<0.25–<0.25–<0.25–0.4–<0.25–0.3–<0.25 µg/L. Hypophyseal MRI performed the following autumn showed neither hyperplasia nor other abnormalities.

One year later, signs of mild PHP recurred but reoperation was not needed. In 2006, a new, hormonally inactive pancreatic lesion was identified. The size of the tumor was 1.1 cm and no growth was observed during the follow-up. In 2009, hypogonadotropic hypogonadism caused by mild hyperprolactinemia (S-prolactin 1093 mU/L, normal upper limit 320 mU/L) was revealed and a dopamine agonist treatment was started. No hypophyseal adenoma was found on MRI scanning. Between 2015 and 2016, chromogranin A was doubled (5.9–13 nmol/L). Ga 68-DOTATOC PET/CT revealed three different foci in the pancreas including the one seen in body CT. Also, two suspected metastatic lymph nodes were observed. No hormonal activity was detected. Total pancreatectomy was performed in 2017 and insulin therapy was started (MDI). Nine different neuroendocrine tumor foci in the pancreas and two metastatic lymph nodes were found. The proliferation rate was two mitoses per ten HPF, and the Ki-67 was 2% classifying the tumor as NET G1. During the follow-up, body CT has not revealed any new tumors, IGF1 concentration has remained normal and no signs of activation of acromegaly have been seen.

Several years later, the MEN1 gene mutation of his mother was reanalyzed and a MEN1 c.466G>C, p.(Gly156Arg) mutation was found. This gene mutation was classified as likely pathogenic for MEN1.

**Discussion**

pNETs are rare, accounting for only 2–5% of all pancreatic tumors. Familial forms of pNETs are mostly encountered in MEN 1 syndrome and rarely in von Hippel Lindau disease, neurofibromatosis 1 and tuberous sclerosis (1). Manifestations of MEN 1 syndrome in the pancreas often include multiple small endocrine tumors, which are usually clinically silent, and large, mass-producing tumors with a clinical presentation related to tumor mass.

### Table 1  Results of immunohistochemical analysis.

| Antibody     | Reaction |
|--------------|----------|
| Chromogranin A | +        |
| Synaptophysin  | +++      |
| GHRH         | +++      |
| GH           | –        |
| Insulin      | +        |
| Gastrin      | –        |
| Calcitonin   | +        |
| Somatostatin | –        |
| ACTH         | –        |

--, negative; +, weak positivity or positivity <5% of cells; ++, moderate or non-uniform positivity; ++++, strong, uniform positivity.
or hormone production (2). PNETs are capable of secreting various hormones, for example, insulin, gastrin, VIP, glucagon, pancreatic polypeptide and somatostatin (1). Ectopic GHRH-producing tumors are rare; slightly more than 70 cases have been documented, and ectopic GHRH production comprises only 1% of cases of acromegaly (3). A few MEN1 cases with ectopic GHRH production originating from a pancreatic tumor have been published (3, 4, 5).

In normal circumstances, GHRH expression is not restricted to the hypothalamic region, but GHRH immunoreactivity has been observed in endocrine cells of the antrum of the stomach and in pancreatic islet cells (6). GHRH stimulates exocrine pancreatic cell secretory activity in vitro, and a role for GHRH in autocrine growth stimulation of tumor cells has also been suggested in in vitro experiments. Thus, it is not surprising that extrahypothalamic GHRH-producing tumors – although very rare – may arise from different organs.

Extrahypothalamic GHRH secretion by neoplastic cells has been described in various tumors. Bronchial carcinoid tumors account for most of the tumors associated with ectopic GHRH secretion (7). PNETs are the next most frequent neoplasm causing ectopic secretion of GHRH (7). Small cell lung cancers, adrenal adenoma, pheochromocytoma, medullary thyroid, endometrial and breast cancer are the rare causes of ectopic GHRH secretion (7).

Acromegaly resulting from extrahypothalamic GHRH expression is a rare manifestation of MEN 1 syndrome. The acromegaly in this patient was a result of ectopic GHRH production by his pNET. It was well differentiated based on chromogranin and synaptophysin stainings. The tumor immunohistochemistry, which included GHRH staining, was positive for various hormones. His pNET did not markedly overexpress somatostatin receptors 2 and 5 based on the negative octreoscan scintigraphy. The somatostatin receptor analog octreotide did not reduce GHRH levels but suppressed GH secretion. Before the pancreatic surgery, there was a small 5-mm pituitary lesion visible on the octreoscan, which disappeared after the surgery. It seems therefore that pituitary GH secretion was directly reduced by the somatostatin analog. The removal of pNET normalized serum GHRH levels, resulting in a reduction of GH-secreting cells and lowering of GH secretion.

This case adds to a rare manifestation of MEN 1 syndrome. Extracranial processes should be sought in patients with acromegaly showing little or no abnormalities in clinical and radiological examinations of the pituitary region. This case also illustrates the GH suppressing effect of octreotide in both pretreatment testing and in the clinical treatment of ectopic GHRH-mediated acromegaly, as has been shown in acromegaly due to pituitary somatotrophic tumors. In the literature, some isolated cases and one series of patients (3, 8, 9) with ectopic GHRH syndrome treated with somatostatin analogs and one case treated with a selective GHRH antagonist (10) have been published. In our case, octreotide reduced GH values while GHRH values were unchanged, which is in line with other publications, with the exception of a report by Moller where both values were reduced (8). Therapeutic cure by the removal of pancreatic tumor has been ascertained in a follow-up of more than 20 years.

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

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Patient consent
A written informed consent has been obtained from the patient for publication.

Author contribution statement
M L K and T M L E wrote the manuscript. M J M accounted for the histological analysis, table and figures. J L was responsible for the laboratory analyses. P S accounted for the diagnostics and treatment of the patient. P A updated the clinical data. All the authors read and approved the final version of the manuscript.

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