Ockham’s Razor for a Retinal Lesion and Acromegaly and Breaking the Vicious Circle

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Abstract
Acromegaly due to ectopic secretion of growth hormone-releasing hormone (GHRH) is rare. Treatment consists of surgical removal of the primary tumor, cytostatic therapy, “cold” or radioactive somatostatin analogue treatment, and medical therapy for acromegaly, if needed. A 53-year-old female had an ocular lesion noted on a routine optician visit, originally considered to be an ocular melanoma. She had a bronchial carcinoid successfully removed 22 years previously. She had acromegalic features with an enlarged pituitary gland on magnetic resonance imaging and, additionally, metastatic lesions in her bones, liver, and thyroid gland. Elevated GHRH levels (>250× upper limit of normal) suggested a metastatic lung neuroendocrine tumor secreting GHRH. Cold and radioactive somatostatin analogue therapy reduced both GHRH and insulin-like growth factor 1 (IGF-1) levels, but normalization of the biochemical markers of acromegaly was only achieved after pegvisomant was introduced. Complete control of IGF-1 was achieved, and this may have hindered the growth of the metastatic lesions as well, as the patient remains well 13 years after the diagnosis of metastatic disease and 35 years after the original lung operation. A gradual rise in prolactin levels over last 4 years was noted, which is likely due to the prolonged effect of GHRH on prolactin-secreting cells. The diagnosis of this case applied the law of parsimony from the Ockham’s razor principle. We consider that breaking the vicious circle of IGF-1 feeding the metastatic tumor was key for the long-term outcome of this case.

Key Words: acromegaly, GHRH, neuroendocrine tumor, bronchial carcinoid, pegvisomant

Growth hormone-releasing hormone (GHRH)-secreting tumors are rare causes of acromegaly/gigantism [1-3]. Neuroendocrine tumors (NETs), predominantly in the lung [4-10] and pancreas [4, 9, 11-14], represent the vast majority of the cases, but the gastrointestinal tract [15, 16], thymus [17, 18], phaeochromocytomas [19-21], mediastinal paragangliomas [22], teratomas [23], hypothalamic [24] or pituitary [25] gangliocytomas, diffuse B-cell lymphoma [26], and even a pituitary tumor [27] have been shown to be the source of GHRH. The majority of GHRH-secreting pancreatic NET patients have the MEN1 syndrome, some starting in childhood causing gigantism [3]. A germline MAX mutation has also been described with ectopic GHRH from a phaeochromocytoma [28]. GHRH can be coexpressed with other neuropeptides, such as calcitonin or adrenocorticotropic hormone, in the latter cases causing both acromegaly and Cushing’s syndrome [23, 29]. To date, over 90 GHRH-associated acromegaly cases have been reported in the English-language literature [22, 30].

We describe here a patient who presented with a metastatic bronchial carcinoid causing acromegaly. She has been successfully treated to date with a “cold” and radiolabeled somatostatin analogue and a growth hormone receptor antagonist over a period of 13 years and currently remains with a good quality of life and stable disease.

Case Presentation
A 53-year-old woman was referred to an ophthalmologist due to a suspicious retinal lesion in her left eye, identified at a routine visit to her optician (Fig. 1). The suspicion of amelanotic melanoma was raised, and radiotherapy was planned. However, the orbital magnetic resonance imaging (MRI) also revealed an enlarged pituitary gland (Fig. 1). Biochemical testing showed an increased elevated bilirubin (52 µmol/L; normal range 1.71-20.5 µmol/L) and borderline raised alkaline phosphatase (145 IU/L; normal range 20-140 IU/L). Abdominal ultrasound revealed multiple liver lesions suggesting metastases, but this finding was not thought to be consistent with metastases from such a small ocular primary tumor. In addition, plain chest radiology exhibited sclerotic changes in the fifth rib and volume loss in the right hemithorax.

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The patient was referred to Oncology, where further review of her history revealed that she had had a bronchial carcinoid removed from her right lung 22 years previously. Since that time she had been in good health. Computed tomography of the chest and the abdomen was performed, which exhibited multiple hypervascular lesions in liver, a right adrenal nodule (adenoma appearance), and sclerotic bone lesions, suggestive of metastases. Liver biopsy confirmed the presence of a highly vascular neuroendocrine neoplasm suggestive of a lung primary origin (Fig. 1) with low Ki-67 labeling index < 1% (not shown). The clinical picture was highly suggestive of a metastatic NET. At that time, however, there was clearly no evidence of neoplastic lung disease on plain chest X-ray and on chest computed tomography. No meta-iodobenzylguanidine–avid disease was observed on 123I-meta-iodobenzylguanidine single-photon emission computed tomography. In the light of the diagnosis of a metastatic lung carcinoid, she was initiated on chemotherapy in 2009 with lomustine and capecitabine, but this had to be discontinued due to thrombocytopenia.

She was at that point referred to Endocrinology, where she gave a history of increased sweating, snoring, and difficulty with ring tightness and fatigue as well as increased shoe size over the preceding 3 years. Physical examination revealed striking facial and acral acromegalic features: as neither she nor her partner had noticed any obvious facial changes, these were clearly long-standing. Visual fields were full to confrontation. Endocrine testing demonstrated an elevated serum insulin-like growth factor 1 (IGF-1) level of 768 µg/L (normal age-adjusted range, 81-225 µg/L) (Fig. 2), and a lack of GH suppression after a glucose load with a nadir GH level of 15 µg/L. Both chromogranin A and B levels were elevated (904 pmol/L, normal range < 60 pmol/L, and 171 pmol/L, normal range 150 pmol/L, respectively). Urinary 24-hour 5-hydroxyindoleacetic acid excretion was normal. Pituitary MRI showed an enlarged fossa with a homogeneous T2-hypointense content, 15.7 mm in transverse diameter (Fig. 3). Plasma GHRH was markedly elevated at 8315 ng/L (normal range < 30 ng/L, >300 ng/L indicates ectopic secretion) (Fig. 2).

An 111In-oradioctreotide single-photon emission computed tomography scan revealed somatostatin receptor–positive bone and liver metastatic disease with no clear signs of lung disease, while a technetium 99m-methyl diphosphonate bone scan revealed multiple metastatic bone lesions in the thorax, lumbar spine, ribs, and humerus. The patient was initiated on monthly pamidronate and 10 mg octreotide–long-acting release, the latter then being gradually increased to 30 mg/month. This reduced her IGF-1 initially from 3× upper limit of normal (ULN) to 1.2× ULN and GHRH from 277× ULN to 109× ULN. Her pituitary showed significance shrinkage.

**Outcome and Follow-up**

A year after the somatostatin analogue treatment was initiated her IGF-1 increased to 2× ULN (Fig. 2), and pegvisomant treatment (30 mg weekly) was started, which immediately normalized her IGF-1 level. However, to treat her underlying disease she received 3 cycles of peptide receptor radionuclide therapy with 90Y-octreotide: 90Y-edotreotide (Onalta, Molecular Insight Pharmaceuticals, Cambridge, MA, USA) was infused intravenously over 10 to 15 minutes in 3 individual doses of 4.4 GBq (120 mCi) administered in 6- to 9-week cycles to a total cumulative dose of 13.3 GBq (360 mCi) in 2011-2012. The first dose dramatically reduced GHRH levels from 182× ULN to 9× ULN before and after the first dose. In the subsequent years, GHRH has remained stable between 10× to 20× ULN levels, while her IGF-1 remained within or close to the normal range. Both the clinical picture and the pituitary MRI scans showed remission of her acromegaly. Chromogranin A and B levels also were reduced (chromogranin A from 904 to 220 pmol/L).

The combined somatostatin analogue and pegvisomant therapy allowed for good control of the secondary acromegaly (Fig. 2), with the pegvisomant dose increased to 50 mg twice weekly in 2018. Her bone and liver lesions have remained stable, while the ocular lesion shrank from the original 2.4 mm to 0.8 mm in height.
While previously in the normal range, her prolactin level has gradually increased and since 2018 became abnormally high (Fig. 2). She was not taking any medication that could increase prolactin levels and had normal thyroid function. The latest MRI scan shows a pituitary gland slightly enlarged compared to 2012 (still significantly smaller than at diagnosis) and still shows hypointensity on T2 imaging (Fig. 3).

**Additional Issues**

- Due to the slightly elevated bilirubin but otherwise normal liver function tests we suspected Gilbert syndrome, and a homozygous UGT1A variant was identified. She did not develop liver enzyme elevations at the start of her pegvisomant therapy. Moreover, she was diagnosed with gallstones, before administration of “cold” somatostatin analogue, which have not progressed during treatment.
- In 2011, she has developed diabetes and is currently controlled on metformin and linagliptin. Her dyslipidemia is controlled with atorvastatin therapy. Since 2017 she has needed medication to control her blood pressure.
- She had repeated rectal and colon polyps (2010, 2014, and 2021), and a 4 cm tubulovillous sigmoid adenoma with focal high-grade dysplasia was removed in 2013, with recurrence in 2014 and 2021.
- She has chronic anemia since 1 year after her last peptide receptor radionuclide therapy dose and has lost weight gradually from 61 kg at diagnosis to 55 kg currently over the last 13 years.
- Due to increasing back pain, in 2015 she had received 30 Gy external beam palliative radiotherapy to the T3-T10 spinal lesions in 10 sessions, with good pain relief.
- In 2021 she had a 30-minute episode with memory loss and black spot on her vision. She was started on clopidogrel as a precautionary measure.

**Discussion**

Acromegaly due to ectopic secretion of GHRH represents <1% of all patients with acromegaly. It is usually diagnosed by the presence of acromegaly in a patient with a NET and
elevated circulating GHRH. Ectopic secretion of GHRH leads to pituitary hyperplasia manifesting either as a normal or enlarged homogeneous pituitary rather than an adenoma, sometimes with a normal MRI scan [30, 31]. Surgical removal of the NET is the optimal treatment, but any residual excess GHRH secretion can usually be treated with somatostatin analogue therapy [11, 22, 32].

The notable features of this case are the exceptionally long time (22 years) before the tumor demonstrated symptomatic recurrence (although clearly the acromegaly must have been present for many years, and the metastatic disease is likely to have been present at the time of primary lung surgery), the presenting feature of an ocular metastasis (typical of NETs [33]), the initial tumor and endocrine responses to cold and radiolabeled somatostatin analogue, long-term tumor stabilization, the emergence of hyperprolactinemia after prolonged GHRH secretion, and, finally, the use of pegvisomant in acromegaly due to a GHRH-secreting metastatic NET.

In terms of therapy, the use of somatostatin analogues is important in this context, as they are both able to inhibit GH release directly from the hyperplastic pituitary, while also, as in this case, being able to inhibit GHRH secretion from the tumor. Radiolabeled ⁹⁰Y-octreotide was used in 2011 to control the tumor, while currently ¹⁷⁷Lu-labeled analogues are in primary use [34]. However, over time, there was clear evidence of escape. We demonstrate here that the addition of pegvisomant to the somatostatin analogue is valuable, as it was able to control the endocrine features of the tumor and with normalizing IGF-1 potentially reducing tumor growth. This combined therapy, breaking the hypothetical vicious circle of IGF-1 feeding the tumor (Fig. 4), has produced good biochemical control of her acromegaly for the next 5 years. According to RECIST criteria, the patient has demonstrated stable disease of most liver and bone metastases (since 2009), with slight diameter reductions for a few liver lesions (visible in 2010, 2011, and 2014), as well as the detection of some new metastases in the liver (2013) and 2 in the bones (2014), which are suggestive of some disease progression. In April 2018, due to increasing levels of IGF-1, the weekly dose of pegvisomant was doubled, again with a good biochemical response.

Another novelty of our case is also the observation of a progressive rise in prolactin associated with poorer control of acromegaly caused by the GHRH-secreting tumor. GHRH may stimulate release of prolactin secretion not only in patients with acromegaly but also in healthy individuals, especially at high doses [35-37]. Experimental data in transgenic mice support these data, as excess GHRH leads to high prolactin levels [38], while lack of GHRH results in both GH and prolactin deficiency [39]. We believe that the prolonged GHRH stimulation has caused a slow trophic effect on lactotroph cells, and over the years, this has led to slow-rising prolactin levels and some re-enlargement of the gland.

Recent data suggest that patients with pituitary hyperplasia due to a GHRH-secreting tumor show a hypointense T2-weighted MRI signal, which can normalize when GHRH levels return to normal [40]. Our case, with a hypointense T2 signal both at diagnosis and more recently when the GHRH level is still 10× ULN, supports this observation.

William of Ockham, a Franciscan philosopher, theologian, political writer, and a late scholastic thinker from the 13th century, established principle of Ockham’s razor (also spelled Occam’s razor), called the “law of economy” or “law of parsimony” (Lex parsimoniae). He suggested that “entities are not to be multiplied beyond necessity.” In our case, the multiple abnormalities in this patient—an ocular lesion, enlarged pituitary gland, acromegalic physical appearance, elevated IGF-1, and multiple metastasis with a history of lung operation—can all be explained by a single disease, hence fitting Ockham’s principle perfectly (Fig. 5).

In conclusion, we have presented a patient with a bronchial carcinoid who represented 22 years later with an ocular metastasis and was found to have clinical acromegaly, widespread metastatic disease, and grossly elevated levels of GHRH. The prolonged high GHRH levels resulted in a modest prolactin rise over the course of the disease. She was treated with somatostatin analogue injections, radiolabeled octreotide, and, eventually, pegvisomant, with long-term control of both her NET and acromegaly.
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Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in the references.

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Figure 5. Ockham’s razor—multiple presenting abnormalities are unified by a single diagnosis representing the law of parsimony. The image of Sir William of Ockham was adapted from Britannica (https://www.britannica.com/topic/Occams-razor).
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