Case report

Long-standing acromegaly in a patient with a pituitary adenoma not visible on MRI

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ABSTRACT

Introduction: Acromegaly in the course of a pituitary microadenoma or neuroendocrine GHRH-secreting tumour (GHRH, growth hormone-releasing hormone) invisible on MRI is very rare.

Objective: To present the difficulties in determining the cause behind an excessive production of the growth hormone in a patient suffering from long-standing acromegaly, without a pituitary focal lesion that would be visible on MRI.

Case report: The authors describe a case of a 69-year-old female with acromegaly, diagnosed 22 years earlier based on the typical somatic symptoms, and confirmed by the elevated concentration of insulin-like growth factor type 1 and lack of growth hormone suppression in the oral glucose tolerance test. The initial MRI scan (1994) had revealed a hypoechogenic 2 x 3 mm lesion in the anterior lobe of the pituitary gland, whose presence was not reported in the subsequent MRI tests. As ectopic GHRH or growth hormone secretion was suspected, a neuroendocrine tumour was searched for. The 47.7 × 54 × 35.7 mm tumour, located in the thoracic outlet, accumulating tektreotide in receptor scintigraphy, turned out to be a nodular goitre on histopathology. Due to the undetermined location of the source of growth hormone overproduction, failure to measure GHRH levels, and the patient's lack of consent to undergo sella turcica exploration, long-acting release octreotide had been used for many years to manage the patient's condition.

Conclusion: The long-lasting and ineffective search for a neuroendocrine tumour producing GHRH or growth hormone as well as the absence of a focal lesion in the repeated MRI scans render it impossible to unequivocally determine the cause of the patient's acromegaly, and illustrate the difficulties in discovering the source of growth hormone overproduction.

Key words: acromegaly, microadenoma, neuroendocrine tumour, ectopic GHRH secretion

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INTRODUCTION

Around 95–98% of acromegaly cases are caused by the somatotropic pituitary adenoma [1, 2]. 4 to 10 years usually pass in between the emergence of the first symptoms and the final diagnosis of the disease, which is why pituitary adenomas are frequently large (macroadenoma ≥ 1 cm) and easily visible on traditional MRI (magnetic resonance imaging) scans [1, 2]. Acromegaly in the course of a pituitary microadenoma that is not revealed on MRI is very rare, and so far no specific management standards have been defined [3–5]. In a group of 190 acromegaly patients, assessed by Lonser et al. [3], there were only 6 persons (3 females and 3 males) in whose case the tumour could not be visualized with the use of a standard MRI scan (3.2%). Authors suggest that a more sensitive MRI technique should be used in such cases, one that is usually applied for corticotropic microadenomas (SPGR, spoiled-gradient recalled, or VIBE, volumetric interpolated breath-hold examination), or that sella turcica exploration should be considered [3–5].

In the remaining rare cases, acromegaly is a consequence of ectopic GHRH (growth hormone-releasing hormone) secretion by the neoplastic tissue of neuroendocrine tumours [6] or by the hypothalamic tumour, with subsequent uncontrolled GH (growth hormone) release by the somatotropic cells of the pituitary gland or – very rarely – by the GH-secreting neuroendocrine tumour [6–8]. Ghazi et al. [6] indicate that the first documented case of a pulmonary neuroendocrine tumour with concomitant acromegaly was published in 1959 by Altman and Schutz. In the years 1974–2011, ca. 98 similar cases were reported [6]. Those were usually reports of single cases [6, 8, 9], with the exception of a French publication involving 21 different patients [7]. GHRH is usually ectopically secreted by highly differentiated tumours, most likely located within the pancreas or bronchi, but also by the appendix carcinoid, adrenal pheochromocytoma [6], ovarian teratoma [9], paraganglioma and pituitary macroadenoma [6]. Those tumours are mostly large (8–10 cm) and easy to locate with ultrasound, CT (computed tomography) or receptor scintigraphy.

Clinical acromegaly symptoms in the course of ectopic GHRH/GH secretion are no different from the conventional form of the disease. The pituitary gland may be normal or enlarged [6, 7]. GHRH plasma level holds particular importance, with the threshold concentration of 250 to 300 ng/L confirming the diagnosis of acromegaly. GHRH measurement is also aimed at the assessment of the efficacy of surgical treatment and further monitoring of the disease and its relapses [6–8]. No correlation has been found between GHRH concentration and tumour location and size. The treatment of choice is surgery, which leads to recovery or long-term remission, if the resection is complete [6–8].

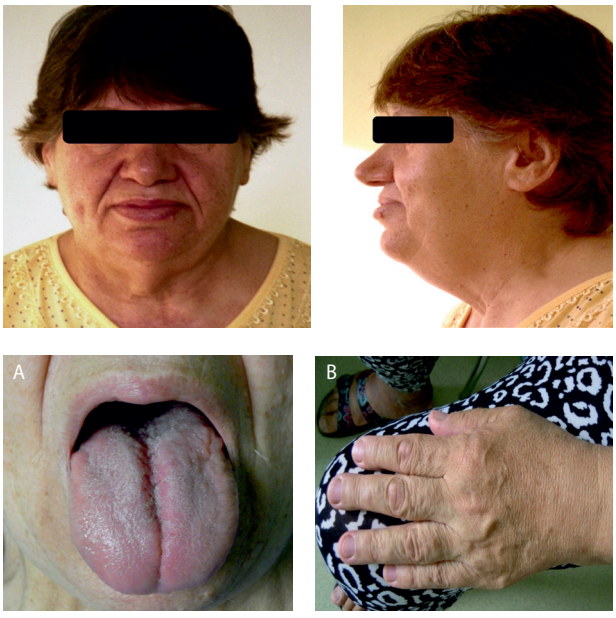
OBJECTIVE

The present paper discusses the difficulties in finding the cause of growth hormone overproduction in a patient with long-standing acromegaly without a focal pituitary lesion visible on conventional MRI scans. For many years, and to no avail, a neuroendocrine tumour was searched for as a source of GHRH or GH secretion.

CASE REPORT

A 69-year-old female patient with acromegaly diagnosed at the age of 47 (22 years earlier) based on the typical somatic symptoms, including pronounced facial features, widened teeth spacing, enlarged tongue, hands and feet (fig. 1). The first symptoms that the patient paid attention to had appeared 4 years before the diagnosis. Aged 43, 2 years after her last childbirth, the patient started suffering from oligomenorrhoea (every 3–4 months), treated with hormone therapy, with no underlying cause determined. At the same time, she started gaining weight, with the increase in her body mass amounting to 30 kg at the time of the diagnosis. Additionally, she observed progressive loss of strength, chronic fatigue, pathological somnolence, vertigo and strong headaches, fainting, and hyperhidrosis of the entire body. A year before the diagnosis she had undergone GI treatment for epigastric pain, hepatitis and hepatomegaly.

FIGURE 1.
Somatic symptoms of acromegaly in the patient discussed.



Acromegaly was diagnosed during the patient's hospital stay following her collapse caused by arterial fibrillation. At the time of diagnosis, the disease was accompanied by the following findings: abnormal glucose tolerance, nodular goitre with normal thyroid function, arterial hypertension and cardiomyopathy in the form of myocardial hypertrophy and grade 2/3 mitral valve regurgitation.

The diagnosis was confirmed based on the elevated IGF-1 (insulin-like growth factor type 1) concentration and lack of GH suppression in OGTT (oral glucose tolerance test). The first MRI scan, performed in 1994, revealed a focal 2 × 3 mm pituitary lesion that failed to be visualized on the subsequent MRI tests performed in the following years (tab. 1). Treatment with bromocriptine was initiated, dosed at 5 to 20 mg/24 h, and continued for 11 years. In 2004, the patient underwent partial strumectomy. Since 2005, she has been followed up on at our Clinic. Due to the diabetes, diagnosed in the meantime, GH suppression in OGTT has not been assessed. Measurement of the IGF-1 level carried out at the time confirmed active acromegaly once again (IGF-1: 446 pg/mL; normal range: 81–225 pg/mL).

TABLE 1.
Pituitary gland assessment on consecutive MRI scans.

No. of examination (year)	MRI assessment
1. (1994)	3 × 2 mm pituitary adenoma with reduced echogenicity.
2. (1996)	A rather large pituitary gland, filling the lumen of the sella turcica, with no focal lesions.
3. (2003)	Normal size pituitary gland, 12 × 8 mm, with slightly heterogeneous signal morphology.
4. (2005)	Pituitary gland of normal width, symmetrical, with homogeneous signal and uniform contrast enhancement, without pathological tissue foci.
5. (2007)	The pituitary gland is quite large, but it is contained in the sella. The division into the glandular and neural parts is distinct. There is no focal lesion indicative of a microadenoma in the glandular lobe. The pedicle of the pituitary gland shows continuity and lack of displacement.
6. (2009)	Normal pituitary gland, 13 × 7 mm, symmetrical, with homogeneous signal and uniform contrast enhancement, with no focal lesions.

In 2005, MRI revealed the pituitary gland, with no focal lesion, tightly filling the sella turcica. As ectopic GHRH or GH secretion was suspected, a search for a neuroendocrine tumour began (tab. 2). In 2006, chest CT revealed a 47.7 × 54 × 35.7 mm tumour in the thoracic outlet, weakly contrast-enhanced, and accumulating tektreotide in receptor scintigraphy (fig. 2A, B; 3).

FIGURE 2.
Thoracic outlet tumour on CT. A – sagittal view; B – horizontal view.

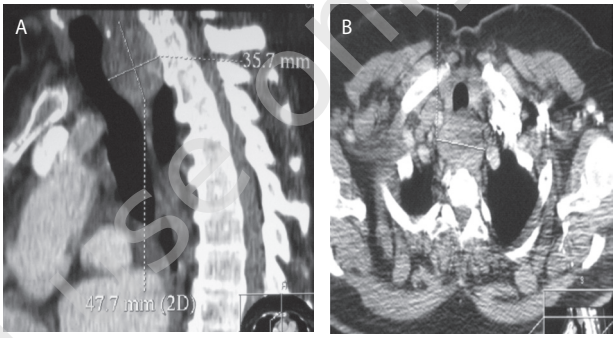
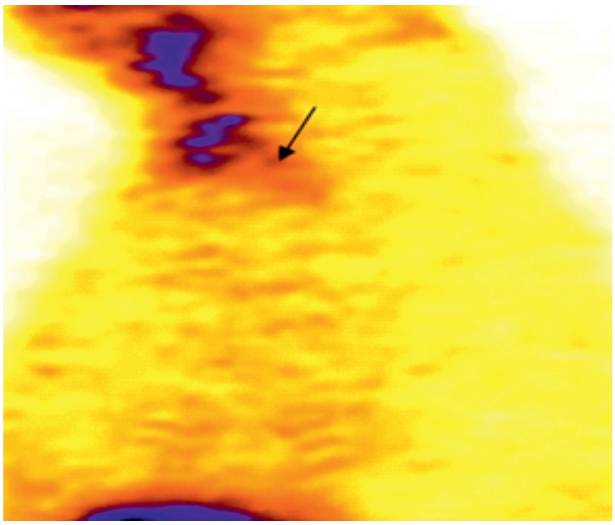


FIGURE 3.
Sagittal section of the SPECT somatostatin receptor scintigraphy. Presence of somatostatin receptors within the mediastinal lesion in the test using ^{99}mTc tektreotide (HYNIC-Tyr3-octreotide).



The patient was referred to a reference centre for further diagnostics (measurement of GHRH levels) and surgical treatment. The post-operative histopathology examination revealed nodular thyroid hyperplasia. Following the surgery, the concentrations of IGF-1 and GH failed to normalize. The patient returned to our clinic, with no further diagnostics or sella turcica exploration recommended at the reference centre. The referral clinic indicated a pituitary microadenoma, not visible on MRI due to its earlier disintegration, as a possible cause of the patient's acromegaly. At our clinic, for lack of the possibility to measure the GHRH levels, treatment with octreotide LAR (long-acting release) was continued, and with periodic dose corrections has been continued

to this day. On periodic conventional MRI scans with contrast, repeatedly performed until 2009, no pituitary adenoma was revealed (tab. 1, fig. 4A, B). Further on, since the time of pacemaker implantation in 2011, due to atrial fibrillation with third degree AV block, no MRI examinations have been performed.

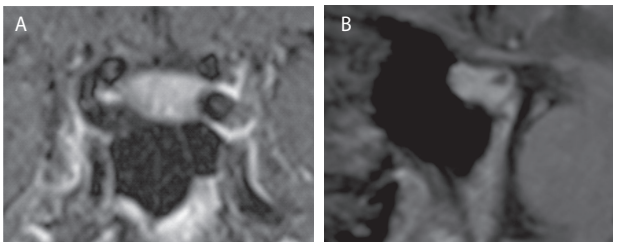
The only lesion revealed in PET/CT with ^{68}Ga-DOTA-TATE, in 2012, was a focal lesion with increased receptor expression, located in the left thyroid lobe. Under ultrasound, a highly vascularized 7 × 5 × 7 mm hypoechogenic nodule was found in that location, whose size doubled one year later, as revealed on a later CT scan. Due to the suspicion of a neuroendocrine tumour, fine needle aspiration biopsy (FNAB) was performed, confirming the benign character of the lesion – nodular thyroid goitre (tab. 2).

In 2011, during the diagnostic process carried out in order to determine the cause of severe iron deficiency anaemia, endometrial cancer was diagnosed. The patient underwent hysterectomy

TABLE 2.
Searching for a neuroendocrine tumour as the cause of acromegaly.

Search area	Year	Examination	Description
Chest and thyroid	03.2004		First strumectomy
	03.2005	chest X-ray	Widened upper right mediastinum
	05.2005	thyroid ultrasound	Status post-strumectomy. Residual right lobe of 11.2 × 9.4 mm, with a 4.8 × 2.9 mm nodule. Left lobe transverse dimension of 23 × 15.8 mm, with 2 hypoechogenic lesions – 6.5 × 5.1 and 9.7 × 6 mm. Reduced thickness, blurred lobar structure. No lymph node involvement.
	11.2005	chest CT	A tissue structure sized 47.7 × 54 × 35.7 mm, weakly contrast-enhanced, located between the spine and the cervical trachea, displacing the cervical oesophagus, and compressing the thyroid. The lesion has a smooth outline. There are isolated non-enlarged lymph nodes of the aortopulmonary window. Myocardial hypertrophy. The CT image indicates a mild intramural hyperplasia of the cervical oesophagus.
	6.03.2006	^{99}mTc scintigraphy with tektreotide (HYNIC-Tyr3--octreotide)	In the region reflecting the lesion revealed on CT, located between the spine and the cervical trachea, isotope accumulation is increased. In the upper segment of the right lung, there is an area of increased radioisotope accumulation, requiring further verification in CT.
	02.2007	Second strumectomy	The mediastinal lesion was removed from cervical access. On histopathology: nodular goitre.
	07.2008	Scintigraphy with somatostatin derivatives	SRS receptor scintigraphy with the use of the SPECT technique, centred on the head, neck and chest. No distinct foci of pathological accumulation. No active pathology with sST2 receptor expression.
	06.2012	PET/CT with ^{68}Ga-DOTA-TATE	A focus of increased receptor expression within the left thyroid lobe.
	07.2012	thyroid ultrasound	Status post double strumectomy. In the left lobe, bordering on the isthmus, there is a well-delineated hypoechogenic nodule, sized 7 × 5 × 7 mm. In the region of mandibular angles, there are isolated lymph nodes with fatty hilum, sized 17 × 5 mm on the right, and 14 × 8 mm on the left.
	09.2012	thyroid Doppler ultrasound	On the border of the isthmus and the left lobe, there is an 8-mm-diameter nodule with good vascularization revealed by colour and power Doppler.
	08.2013	chest CT	Residual right thyroid lobe, sized 25 × 10 × 27 mm; left lobe 26 × 19 × 24 mm, with a 15 × 13 mm nodule showing significant contrast enhancement in the arterial phase – 56 HU, in the venous phase – 109 HU. Isolated supraclavicular lymph nodes of normal size. Isolated enlarged lymph nodes within the mediastinum, max. precarinal – 17 × 24 mm, 14 mm in the right hilus, 13 mm in the left hilus. A small subpleural nodule in the right apex. Cirrhotic lesions in segment V of the right lung. Adhesions between the pleura and diaphragm. No enlarged lymph nodes within the neck.
	02.2014	FNAB of the left thyroid lobe nodule	Benign lesion – nodular thyroid hyperplasia.

FIGURE 4.
MRI (2009) of the patient's pituitary gland. A – coronal view; B – sagittal view.



and brachytherapy. She remains under oncological management, with no signs of disease recurrence. The successful treatment of endometrial cancer has had no impact on the course of the patient's acromegaly.

Over the past 5 years, the patient has been repeatedly hospitalized for anaemia, and is now followed up on at the haematology clinic on suspicion of the myelodysplastic syndrome. The patient's diagnosed anaemia, apart from iron deficiency resulting from malabsorption from the GI tract, is also characterized by ineffective erythropoiesis.

DISCUSSION

The first imaging test should be performed once acromegaly has been confirmed by hormonal tests is MRI of the pituitary gland. Lack of a visible adenoma raises suspicion of ectopic acromegaly. Acromegaly induced by ectopic GHRH production is rare, even though 8–44% of pancreatic NETs (neuroendocrine tumours) and 11–18% of GEP NETs (gastroenteropancreatic neuroendocrine tumours) show GHRH expression [7]. The most accurate method of determining the diagnosis is GHRH blood levels measurement. GHRH is virtually undetectable in pituitary acromegaly, while its concentration in ectopic acromegaly reaches values hundreds- or thousands-fold higher than the normal range. Diagnostic criteria for ectopic acromegaly include: elevated GHRH blood levels, positive immunohistochemistry staining and confirmed presence of GHRH mRNA in tumour cells, extraction of GHRH from tumour cells, normalization of GHRH concentration following complete tumour resection, and others [6].

The time that passes from the initial symptoms of the disease until the final diagnosis is 1 to 22 years, with 8 years being the average. 2/3 of patients are women, in whom acromegaly develops most frequently in the course of pancreatic, bronchial or gastrointestinal neuroendocrine tumours [7]. In sporadic cases, the disease is induced by GH secreted by the pancreatic islet cell tumour, bronchial carcinoid and lymphoma [6].

In rare cases, acromegaly may be caused by a pituitary microadenoma that is not visible on conventional MRI scans [3–5, 10]. Since that method was introduced to visualize pituitary gland tumours, only 4 reports have been published, involving a total of 10 acromegaly cases, where ectopic GHRH or GH secretion was ruled out, and no pituitary adenoma was revealed on MRI [3–5, 10].

Doppman et al. [10] described three of such patients. In 2 of them, the test was performed without a contrasting agent, which might have resulted in its low sensitivity. All adenomas (6, 7 and 10 mm, respectively) were removed during sella exploration. Lonser et al. [3] described 6 patients with acromegaly (including one patient from Doppman's group) without adenoma visible on conventional contrast MRI. In 3 of them, the MRI test was repeated, using the VIBE technique, revealing a 4-milimetre microadenoma in the post-contrast sequence in one of the patients only [3]. In all of the patients from that group, microadenomas, whose biggest dimension was 5 to 6.7 mm (5.6 mm on average), were detected and removed during a surgical procedure. Daud et al. [4] described a patient with a 9-milimetre microadenoma, not visible on conventional contrast MRI and MRI with SPGR, which was resected during sella exploration. In a patient described by Khandelwal et al. [5], a microadenoma infiltrating the dura mater was not revealed on conventional MRI or the VIBE sequence, and was only detected during surgery.

In the patient discussed in our paper, the microadenoma was revealed only on the first conventional MRI scan. It was later never found on any of the subsequent contrast MRI scans. However, the pituitary gland was described as large and tightly filling the sella turcica, which suggested its overstimulation and hyperplasia, and directed our search towards an extra-pituitary source of the disease. Over more than 10 years of imaging follow-up (chest CT, abdominal CT, PET-CT, receptor scintigraphy), several lesions were detected suggestive of a neuroendocrine tumour (tab. 1, 2). In all those cases, the diagnosis was ruled out, following surgery or biopsy. Due to the frequently asymptomatic (18–22 years) course of neuroendocrine tumours, and the long time that passes between the onset of ectopic acromegaly and the final diagnosis [6, 7], the only test that could unequivocally exclude ectopic acromegaly in our patient would be the measurement of GHRH levels.

Another potential cause of acromegaly in our patient could be a somatotropic pituitary microadenoma, revealed only once on conventional MRI. Resolution of the conventional MRI scans used at our clinic is too low for very small microadenomas, and VIBE or SPGR techniques were not available at our centre before 2011,

whereas nowadays the patient cannot be examined with the use of magnetic field. The only remaining method of detecting the microadenoma these days is to explore the sella turcica [3–5], which the patient has not consented to, though.

lesion in the repeated MRI scans render it impossible to unequivocally determine the cause of the patient's acromegaly, and illustrate the difficulties in discovering the source of growth hormone overproduction.

CONCLUSION

The long-lasting and ineffective search for a neuroendocrine tumour producing GHRH or GH as well as the absence of a focal

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