Clinical Case 1

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10.1 Case Report

A 34-year-old woman with a history of oligo-amenorrhea, acne, and hirsutism by age 28 was admitted to the Neuroendocrinology Clinical Center in September 2014. At age 29, polycystic ovary syndrome (PCOS) was diagnosed and the patient started contraceptive pill for 2 years. At age 32, due to primary infertility, the patient conceived after ovarian stimulation, and she safely delivered a healthy baby. No complications were reported during pregnancy and delivery. The patient reported galactorrhea even though she stopped breastfeeding, and she had persistent amenorrhea after the birth of her child. The patient reported a 9.5 kg weight gain in the last year despite diet and exercise, and increased sweating for the last 6 months. She presented with gradually worsening headache in the last 6 months. The headaches generally occurred three times per week. The patient's past medical history included thyroid nodule and uterine leiomyomata diagnosed 4 years earlier.

Because of the persistent galactorrhea and amenorrhea, the patient underwent hormonal evaluation, reporting a mildly elevated prolactin (PRL) levels (68 ng/mL, normal range 5–25 ng/mL), low levels of luteinizing hormone (LH, 1.2 IU/L, normal range 2.4–13 IU/L), follicle-stimulating hormone (FSH, 2.3 IU/L, normal range 3.5–13 IU/L), and estradiol (16 pg/mL, normal range 20–240 pg/mL). The patient was subsequently referred to the Neuroendocrinology Clinical Center for further evaluation.

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At clinical evaluation, abnormal findings included obesity (body mass index 30.2 kg/m^2), acne, hirsutism (modified Ferriman Gallwey score 16/36), and neck and axillary acanthosis. She did not spontaneously complain about acral changes. However, after specific questions, she recognized that her shoe size had increased from size 37 to size 39 during the last 3 years.

She denied significant changes in facial appearance, new spaces between her teeth, snoring, fatigue, joint pain, and paresthesia.

10.2 Differential Diagnosis

Considering the main clinical presentation of the patient, including secondary amenorrhea, galactorrhea, and headache, the prolactinoma and clinically nonfunctioning pituitary adenoma should be considered in the differential diagnosis [1, 2]. Moreover, considering the PCOS-like phenotype associated with acral changes, insulin-mediated pseudoacromegaly should be excluded.

Prolactinomas are the most common of the hormone-secreting pituitary tumors [1] representing approximately 40% of all pituitary tumors, and occur most frequently among women aged 20–50 years [1, 3, 4]. In women of reproductive age, usually the most relevant clinical manifestations are oligomenorrhea or secondary amenorrhea, galactorrhea, and infertility, followed by decreased libido and weight gain [3, 4]. In clinical practice, macroprolactinomas are less common than microprolactinomas and occur more often in men than in women [3]. Mass effects cause headache, hypopituitarism, and visual field defects. Prolactinomas are the most frequent cause of PRL excess even if several other causes should be excluded before the diagnosis is made [4]. Besides prolactinomas, hyperprolactinemia can be associated with a variety of causes, such as pregnancy, hypothyroidism, PCOS, renal insufficiency, and PRL-stimulating drugs, which need to be considered in the differential diagnosis [5]. Since there are multiple causes of hyperprolactinemia, other than prolactinoma, a careful medical history, clinical examination, and measurement of serum thyrotropin and creatinine are required [3].

Clinically nonfunctioning adenomas account for 15–54% of pituitary adenomas [1]. Most patients present with symptoms of mass effect due to their large size (67% are macroadenomas), whereas some patients are completely asymptomatic, detecting the pituitary adenoma as incidental findings (incidentalomas) on magnetic resonance imaging (MRI) or computed tomography scans were performed for other reasons [6]. All patients with clinically nonfunctioning macroadenomas, symptomatic or incidental, should be evaluated for hypopituitarism [1]. Hyperprolactinemia may occur in these patients because of pituitary stalk dysfunction [3, 6].

Pseudoacromegaly is an extremely rare condition characteristic of some patients with physical features resembling acromegaly, usually affecting the face and extremities, without abnormalities in the GH/IGF-I axis [7]. Due to the rarity and variability of these conditions, its correct diagnosis can be challenging [7]. Insulin-mediated pseudoacromegaly is characterized by severe insulin resistance, acanthosis nigricans, and acromegaloid features in the absence of GH and IGF-I excess [7,

8]. Insulin-mediated pseudoacromegaly is associated with a selective post-receptor insulin signaling defect in which the insulin metabolic actions are impaired, but its mitogenic actions are preserved [7, 9]. Therefore, the metabolic actions of insulin are reduced resulting in hyperinsulinemia, while insulin mitogenic actions are preserved leading to acromegaloid features [7]. Insulin and IGF-I exhibit affinity for each other's receptor, and thus, high insulin levels resulting from insulin resistance may act on the type 1 IGF receptor [8]. Genetic abnormalities in the insulin receptor result in hyperinsulinemia, leading to diabetes mellitus and often acromegaloid features, a condition first described in 1976 by Kahn et al. [10]. In particular, the clinical presentation of insulin-mediated pseudoacromegaly may include face coarsening, frontal bossing, macroglossia, separated teeth, prognathism, large ears, acral enlargement, reduced subcutaneous fat on arms and legs, weight gain, acanthosis nigricans, skin tags, acne, hirsutism, hyperhidrosis, oligo-amenorrhea, and PCOS [7, 8, 11]. Adenomatous colonic polyps and multinodular goiter have been reported [8]. Clinical features of these patients overlap with those of acromegaly, but GH suppression on OGTT and IGF-I levels is generally normal. Moreover, these patients usually have increased LH levels and hyperandrogenism [7, 8].

10.3 Diagnostic Aspects

At the clinical evaluation, mild modification of nose, cheekbones, and lips was observed comparing previous photographs of the patient in order to detect the features of acromegaly. The evaluation of the pituitary function showed increased random GH (10.4 ng/mL) and IGF-I (874 ng/mL, normal range 80–290) levels. The oral glucose tolerance test (OGTT) was performed to confirm the diagnosis of acromegaly, resulting in GH nadir of 7.3 ng/mL. Other anterior pituitary hormone tests confirmed secondary hypogonadism (LH, 1.5 IU/L, FSH, 2.4 IU/L, estradiol, 16 pg/mL) and mildly elevated PRL levels (71 ng/mL). The MRI of the hypothalamus–pituitary region with gadolinium showed the presence of an intrasellar pituitary macroadenoma in the left side (14.5 × 13 mm), with a mild suprasellar extension (Fig. 10.1). Visual field testing was normal.

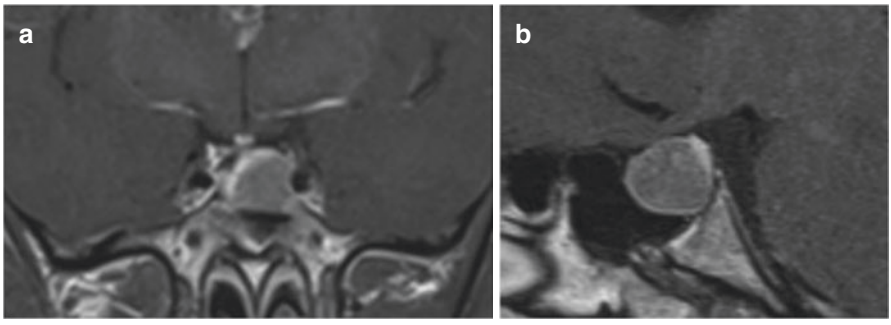

Fig. 10.1 Pituitary MRI images at baseline (coronal (**a**, left) and sagittal (**b**, right))

Table 10.1 Patient profile before and 3 months after neurosurgery

Parameters	Baseline	3 months after surgery
IGF-I (ng/mL)	874	592
GH nadir(ng/mL)	7.3	2.4
LH (IU/L)	1.5	4.6
FSH (IU/L)	2.5	6.1
Estradiol (pg/mL)	16	81
PRL (ng/mL)	71	13
Cortisol (ng/mL)	103	103
TSH (μU/mL)	2	2.4
Free T4 (ng/dL)	0.98	1.07

The assessment of acromegaly complications showed biochemical hyperandrogenism and confirmed the presence of an isoechoic thyroid nodule of 9 mm of maximal diameter on the thyroid ultrasound, uterine leiomyomata, and ovarian cysts on the pelvic ultrasound. In line with the standard diagnostic criteria, acromegaly due to a GH-secreting pituitary macroadenoma was diagnosed. Patient's profile at baseline is shown in Table 10.1.

10.4 Treatment

The patient underwent first-line transsphenoidal surgery of the pituitary macroadenoma in November 2014. Histology of the excised specimen revealed moderate amounts of sparsely granular eosinophilic cytoplasm. Immunohistochemistry was positive for GH and negative for other pituitary hormones. Ki 67 index was <2%.

Her 3 months postoperative evaluation revealed elevated IGF-I levels (592 ng/ml, normal range 80–290) and GH nadir during OGTT was 2.6 ng/mL, indicating persistent disease. Secondary hypogonadism resolved after surgery, and restoration of normal menstrual cycle was reported by the patient 2 months after surgery. Patient's profile 3 months after surgery is shown in Table 10.1. Postoperative MRI of the pituitary revealed millimetric parasellar area (4 mm in maximum diameter) in the left side of the pituitary (Fig. 10.2). Therefore, octreotide LAR treatment was initiated postoperatively, at the dose of 30 mg every 4 weeks. It was then increased stepwise, up to 40 mg every 4 weeks. The lowest IGF-I achieved during LAR treatment was 375 ng/mL (Fig. 10.3), indicating partial resistance to first-generation somatostatin analogs (SSA). LAR therapy was stopped in October 2015. Due to persistently uncontrolled acromegaly, despite high dose of LAR, pegvisomant (PEG) monotherapy was started, considering the small pituitary residual tumor. The dose of PEG was up-titrated up to 20 mg/day, achieving a disease control. Within a few months of PEG therapy, there was a significant clinical improvement.

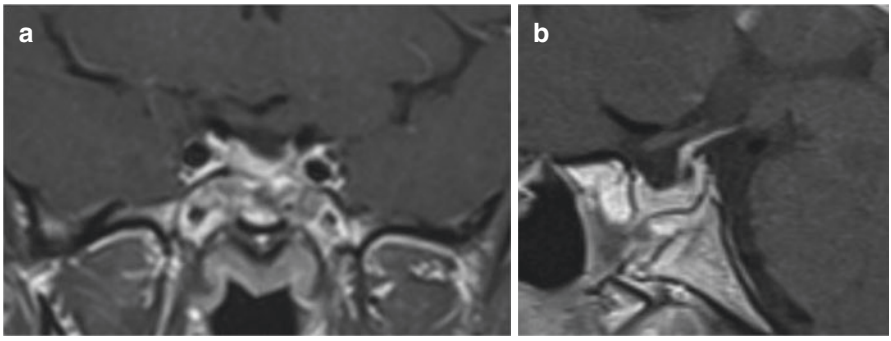

Fig. 10.2 Pituitary MRI images 3 months after surgery (coronal (**a**, left) and sagittal (**b**, right))

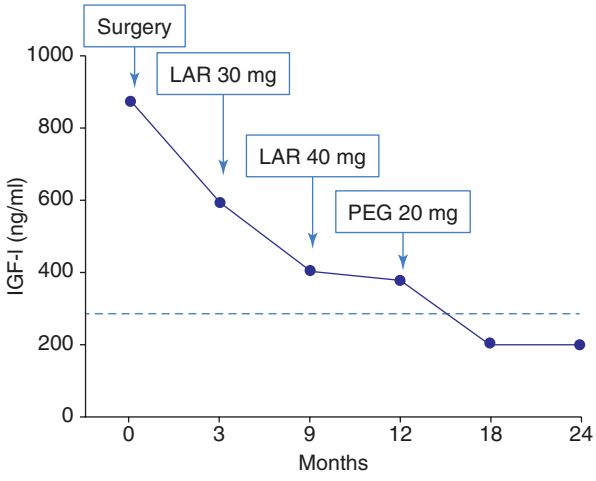

Fig. 10.3 IGF-I levels thought the follow-up. LAR: octreotide LAR; PEG: pegvisomant

10.5 Follow-Up

Within a month of starting PEG 20 mg/day, her IGF-I levels dropped to the normal range, remaining within the normal range for age over the follow-up, although tumor size remained unchanged. PEG was well tolerated. Patient's symptoms have significantly improved, and the patient reported normal menstrual cycle. At age 38, the patient spontaneously conceived. PEG therapy was discontinued after pregnancy confirmation, and the patient was regularly followed during pregnancy. She safely delivered a healthy baby; no complications were reported during pregnancy and delivery. The patient breastfed for 3 months, and then, PEG therapy was resumed.

10.6 Learning Points

- Although acromegaly manifests with distinct physical characteristics, diagnosis of the disease in its early stages can be difficult due to its insidious nature, meaning that neither the patient and their families nor their physicians may notice these changes [12].
- Acromegaly features develop insidiously over decades, often resulting in a delay of 7–10 years or more in diagnosis after the estimated onset of symptoms [13, 14]. Among clinical features, female reproductive disorders, including menstrual abnormalities, galactorrhea, and decreased libido, are commonly complained in acromegaly [13, 14]. Particularly, women with acromegaly often present with menstrual irregularity, mainly represented by oligo-amenorrhea, associated with anovulation and infertility [15, 16].
- A direct action of GH and IGF-I excess on the pituitary–gonadal axis and the tumor mass effect per se have been proposed as potential mechanisms responsible for the occurrence of hyperprolactinemia and for the impairment in gonadotrophin secretion, leading to ovarian dysfunction and infertility [16–19]. Moreover, IGF-I excess has been found associated with overt PCOS or to a PCOS-like phenotype in 50% of acromegalic women [20].
- Evidence from literature has shown menstrual disturbances to occur in 40–80% of acromegalic women [16]. This wide variation in prevalence has been attributed mainly to the insidious onset of the disease and to the delay in diagnosis [18]. However, an earlier diagnosis and the availability of a wide spectrum of effective treatments for acromegaly could positively impact on the female fertility outcome in acromegaly [21].
- Treatment of acromegaly aims to normalize GH and IGF-I levels, control tumor mass, and decrease the risk of developing systemic comorbidities, thereby reducing mortality [13, 22, 23].
- Transsphenoidal adenomectomy remains a cornerstone treatment for GH-secreting pituitary tumors and is the treatment of choice except in those patients with high surgical risk, who refuse surgery or who have invasive, unresectable tumors [22, 23]. In patients with persistent disease despite surgical resection of the adenoma, medical therapy is recommended and first-generation SSA are the first-line medical therapy in most patients with acromegaly [22, 23].
- According to Endocrine Society Clinical Practice Guidelines [22], the GH receptor antagonist PEG is indicated as a second-line or third-line therapy, mostly in patients in whom surgery has failed or in those who show a poor response to first-line SSA.
- Currently, no medication is officially approved and recommended for acromegaly during pregnancy [24, 25]; however, based on a case-by-case analysis of patients the use of medical treatment during pregnancy should be weighed upon the risk-to-benefit ratio, balancing the risk of tumor enlargement, acromegaly symptoms, and maternal/fetal complications [24, 25]. Safety of PEG during pregnancy is yet to be clarified, since only few case reports in the literature have documented uneventful pregnancies following treatment with PEG [26–28].

Questions and Answers

In pregnant women with acromegaly:

(a) Acromegaly medical therapy should be discontinued and administered only for patients with macroadenomas.
(b) **Acromegaly medical therapy should be discontinued and administered only for tumor and headache control.**
(c) Acromegaly medical therapy with somatostatin analogs and pegvisomant should be discontinued and dopamine agonist should be administered for tumor and headache control.
(d) The dosage of acromegaly medical therapy should be reduced in all patients.

The GH receptor antagonist (PEG) is indicated:

(a) As third-line therapy, after surgery in patients who show a poor response to first-line SSA.
(b) Only in patients with persistent disease after surgery.
(c) **As a second- or third-line therapy, mostly in patients in whom surgery has failed or in those who show a poor response to first-line SSA.**
(d) Only in patients resistant to first-line therapy with conventional SSA.

First-line surgery:

(a) Is indicated in all patients with visible pituitary adenoma.
(b) Is the treatment of choice in the majority of patients with acromegaly except in those patients with high surgical risk or who refuse surgery.
(c) Is the treatment of choice in the majority of patients with acromegaly except in those patients with invasive and unresectable tumors.
(d) **b + c.**

Among clinical features of acromegaly:

(a) **Female reproductive disorders are commonly complained in acromegaly women, including menstrual abnormalities, galactorrhea, and decreased libido.**
(b) Up to 80% of women with acromegaly present with menstrual irregularity and hyperprolactinemia.
(c) Menstrual disturbances occur in all young acromegalic women.
(d) PCOS-like phenotype has been reported in the majority of acromegalic women.

1) In women with acromegaly onset during the fertile period:
   (a) Menstrual cycle disorders do not improve despite disease control achieved with treatment.
   (b) The most frequent alteration of the menstrual cycle is polymenorrhea.

(c) **Menstrual irregularities are often associated with anovulation and infertility.**
(d) Hyperprolactinemia and galactorrhea rarely occur.

2) PCOS-like phenotype in women with acromegaly:
(a) Is rarely found at diagnosis in young women.
(b) **Is determined by the direct effect on the ovary of the IGF-1 excess and indirectly by the insulin resistance and hyperinsulinism.**
(c) Differs from classical PCOS due to the absence of clinical and biochemical hyperandrogenism.
(d) Seldom is associated with infertility in these patients.

3) Follow-up of acromegaly during pregnancy requires:
(a) Monthly IGF-1 evaluation.
(b) MRI during the second trimester.
(c) Monitoring of GH but not IGF-1.
(d) **Assessments of the possible growth of the adenoma using the visual field.**

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