CLINICAL VIGNETTE

The Importance of Complete Pituitary Laboratory Assessment in Secondary Amenorrhea

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Case Presentation

A 41-year-old woman with past medical history that included prediabetes and depression presented to endocrinology with one-year of secondary amenorrhea. She reported a previously regular 28-day menstrual cycle since puberty. She had modified her lifestyle with increased exercise and healthy eating in the last year to prevent progression of her prediabetes. She complained of chronic left sided shoulder pain, but otherwise was asymptomatic. Specifically, she denied any change in her facial features, skin, hand and feet size, increased diaphoresis or snoring.

Physical examination demonstrated a normal blood pressure of 100/69 mmHg and a BMI of 23kg/m^2. The patient's appearance was unremarkable and specifically exhibited no acral changes such as frontal bossing, teeth spacing, macroglossia, skin tags, acanthosis nigricans, or enlargement or deformity of hands or feet. Left shoulder examination was within normal limits. Visual fields were intact on confrontation.

Initial labs by her primary care physician showed a negative pregnancy test, normal TSH and, prolactin levels with an undetectable estradiol and low normal FSH. The initial differential diagnosis for her hypogonadotropic hypogonadism included functional hypothalamic amenorrhea, hyperprolactinemia, hypothyroidism, along with rarer endocrine conditions such as Cushing Disease, acromegaly and hypophysitis. Given the importance of a full pituitary laboratory evaluation, even in the absence of suggestive symptomatology, subsequent testing included measurement of Free T4, IGF-1, and HPA axis function with early morning plasma ACTH and serum cortisol. These were all normal except for her IGF-1 level which was significantly elevated at 471 ng/mL (age- and sex-matched ref range; nl 52 - 328 ng/mL) which equated to a z-score of 2.9 SDs.

Repeat IGF-1 level was again elevated at 485 ng/mL and a growth hormone suppression test with 75g of glucose was performed to confirm the diagnosis of acromegaly. Baseline growth hormone level was 6.84 ng/mL and failed to suppress to the expected value of 0.4ng/dl with a nadir GH of 6.43ng/ml at 1 hour. MRI imaging of the sella with and without contrast showed a 9 mm x 11mm x 12 mm hypoenhancing lesion in the left sella turcica which exhibited mild mass effect on the optic chiasm (Figure 1).

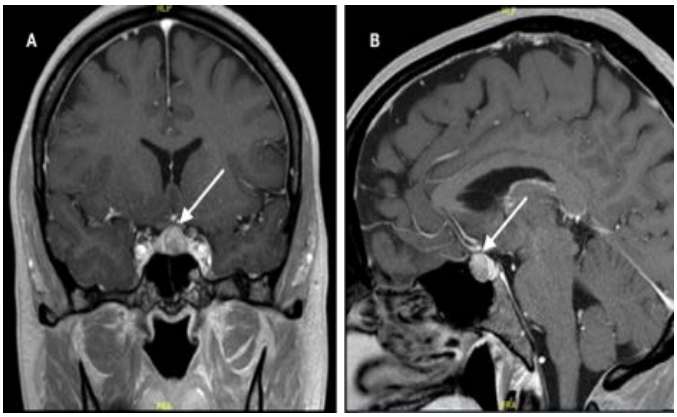

Figure 1. T1 weighted, post contrast coronal (A) and sagittal (B) MRI images of the sella turcica showing pituitary lesion (white arrows).

The patient underwent a trans-nasal trans-sphenoidal (TNTS) resection of the GH-secreting pituitary macroadenoma. Pathology confirmed a diffusely expressing growth hormone-secreting adenoma. Immediate post-operative GH was 1.59 ng/mL, which indicates a high likelihood of remission. She has since experienced a return of menstrual periods, improvement in joint pains and overall improved sense of wellbeing.

Discussion

Secondary amenorrhea is defined as the absence of regular menses for three months or absence of irregular menses for six months. Evaluation of secondary amenorrhea should be guided by the history and physical examination. As a first step, pregnancy should be ruled out in all cases of secondary amenorrhea. Thyroid disease, hyperprolactinemia and ovarian failure should also be excluded by measurement of TSH, prolactin and FSH, respectively. Other rarer causes of secondary amenorrhea such as outflow obstruction due to prior surgery or infection, hyperandrogenism due to polycystic ovarian syndrome (POCS) or non-classical congenital adrenal

hyperplasia, and pituitary disorders such as ACTH and GH secreting adenomas should also be considered.

Acromegaly, usually due to a growth hormone (GH) secreting pituitary tumor is a rare condition with an incidence of 3 to 4 cases per million per year.[1] The resultant overproduction of liver-derived Insulin-like growth factor -1 (IGF-1) leads to increased acral growth, coarsening of facial features, soft tissue swelling with arthralgia and increased diaphoresis. In reality, acromegaly affects virtually every organ system and causes various complications that include depression, hypertension, insulin resistance, goiter, colon polyps, arthritis, and gonadal dysfunction.[2]

A major challenge is the delay between the patient noting their first symptom and the time of diagnosis may be nearly 8 years. As one might predict, a longer duration of disease-related symptoms prior to diagnosis worsens outcome,[3] with increased likelihood of irreversible pathology and deformities. Delay in diagnosis is due to disease rarity, failed recognition of early symptoms by health care professionals and the inherently insidious nature of disease progression with many non-specific symptoms.

Gonadal dysfunction is common in women diagnosed with acromegaly and in one multicenter study 29/47 (62%) of premenopausal women had signs and symptoms of gonadal dysfunction at the time of diagnosis. These included oligo-menorrhea, amenorrhea, galactorrhea, hirsutism, infertility and decreased libido. Of interest, the mechanisms of hypogonadism in acromegaly are multifactorial. In the prior study, 24% had central hypogonadism caused by direct tumor mass effect or associated hyperprolactinemia whereas in others, gonadal dysfunction was attributed to direct effects of GH and IGF-1 on the ovaries and polycystic ovarian syndrome.[4]

First line treatment of acromegaly is generally surgical re-section of the pituitary tumor. In the rare patient who is unsuitable for surgery due to severe medical comorbidities or those with extensive locally invasive disease, medical therapy with a somatostatin receptor ligand can be considered first line. Additionally, given 90% of these GH-secreting adenomas are larger than 1cm, complete remission following surgery alone is only attainable in ~50-55% of patients and therefore SRL and/or growth hormone antagonist (pegvisomant) therapy is generally needed in the post-operative setting. In the afore-mentioned study by Dogansen et al. where the acromegaly remission rate was 66%, central gonadal dysfunction resolved in 55% of patients and hypogonadism due to other mechanisms resolved in 83% of patients.

This patient's initial work-up showed central hypogonadism, prompting consideration of several causes including pituitary lesions, infiltrative disease such as sarcoidosis, and infectious processes such as tuberculosis, among others. The case highlights the importance of a complete pituitary panel in the setting of patients presenting with central endocrine dys-function even if they do not exhibit clear manifestations of conditions such as GH and/or cortisol excess. As the prevalence of pituitary adenomas in the general population is about 10% and half of these are nonfunctional, imaging of the sella is often indicated to exclude a mass lesion in the hypothalamic-pituitary region.

In the above case, the inclusion of IGF-1 measurement as part of the routine evaluation of this patient's central hypogonadism, despite a lack of acromegaly symptoms or signs, resulted in the correct diagnosis and potentially sparing her from development of physical manifestations and organ damage from GH excess. This case highlights the importance of obtaining a full pituitary panel when pituitary pathology is suspected, either due to symptoms, biochemistry or imaging abnormalities. This prac-tice could lead to the diagnosis of morbid diseases, such as acromegaly or Cushing, in their early or subclinical phases prior to lasting health detriments.

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