Chapter 2
Acromegaly, Awareness Is Paramount for Early Diagnosis: Highlights of Diagnosis and Treatment Challenges

Jessica Brzana, Christine G. Yedinak, and Maria Fleseriu

Objectives

- To highlight clinical features of acromegaly at presentation, to facilitate early diagnosis.
- To review the multi-modal approach in the management of acromegaly: surgical indications and medical treatment.

J. Brzana, M.D.
Department of Medicine, Division of Endocrinology, Diabetes and Clinical Nutrition, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Code BTE28, Portland, OR 97239, USA

C.G. Yedinak, D.N.P.
Department of Neurological Surgery, Oregon Health & Science University, 3303 SW Bond Ave, Mail Code CH8N Portland, OR 97239, USA

M. Fleseriu, M.D. (✉)
Department of Medicine, Division of Endocrinology, Diabetes and Clinical Nutrition, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Code BTE28, Portland, OR 97239, USA

Department of Neurological Surgery, Oregon Health & Science University, 3303 SW Bond Ave, Mail Code CH8N, Portland, OR 97239, USA

OHSU Northwest Pituitary Center, 3303 SW Bond Ave, Mail Code CH8N, Portland, OR 97239, USA
e-mail: fleseriu@ohsu.edu

T.F. Davies (ed.), *A Case-Based Guide to Clinical Endocrinology*,
DOI 10.1007/978-1-4939-2059-4_2

Case Presentation

A 31-year-old male presented to a new neurologist for management of a long-standing "absence" seizure disorder with new monthly breakthrough seizures. Diagnosed at 12 years of age, seizures were reportedly poorly controlled until aged 19 years of age, when there was some improvement after treatment with Depakote. The patient reported migraine headaches with "visual symptoms" over several years and recent worsening, in addition to new diagnoses of renal calculi, sleep apnea, carpal tunnel syndrome, and hypertension prior to this presentation. He also noted a 2–3 year history of increasing fatigue, anxiety, worsening memory, profuse sweating, new onset of diffuse and generalized joint pains, and increased central adiposity. In the previous year, he had been troubled by the development of gynecomastia and had undergone breast reduction surgery. Furthermore, he had undergone lip-reductive cosmetic surgery in the same year due to the large size of his lips.

Brain magnetic resonance (MR) imaging at 19 years of age was apparently undertaken, however the patient was unaware of any abnormal findings and MR imaging had not been repeated since that time.

The neurologist, concerned about vision symptoms, selected to repeat evaluation elements and include brain imaging. MR imaging revealed an "incidental" hypoenhancing sellar lesion $2.5 \times 2.6 \times 2.3$ cm in size with bilateral cavernous sinus invasion (Fig. 2.1) indicative of a pituitary macroadenoma. The lesion had compressed and induced superior displacement of the optic chiasm. The patient was subsequently referred to the multidisciplinary Oregon Health & Science University, Northwest Pituitary Center for further assessment and treatment. On evaluation, the patient noted that while he was tall at 6′ 8″ in height, other family members were also on average quite tall. During the initial clinic visit evaluation, he also admitted to some changes in facial features and rounding of the shape of his face as well as a significant increase in ring and shoe size. Further questioning revealed; oily skin, more abundant skin tags, profuse sweating, and the return of more frequent and more severe headaches. A physical exam revealed typical signs indicative of acromegaly: large hands and large wide feet, significant prognathia, frontal bossing, a large tongue, and several gaps between his teeth. Pulmonary and cardiac auscultations were unremarkable. Examination of his skin showed multiple skin tags in his axilla, which demonstrated acanthosis nigricans. Visual field (VF) testing by confrontation suggested bitemporal field deficits. Formal VF testing by a neuro-ophthalmologist confirmed the finding of bitemporal hemianopsia.

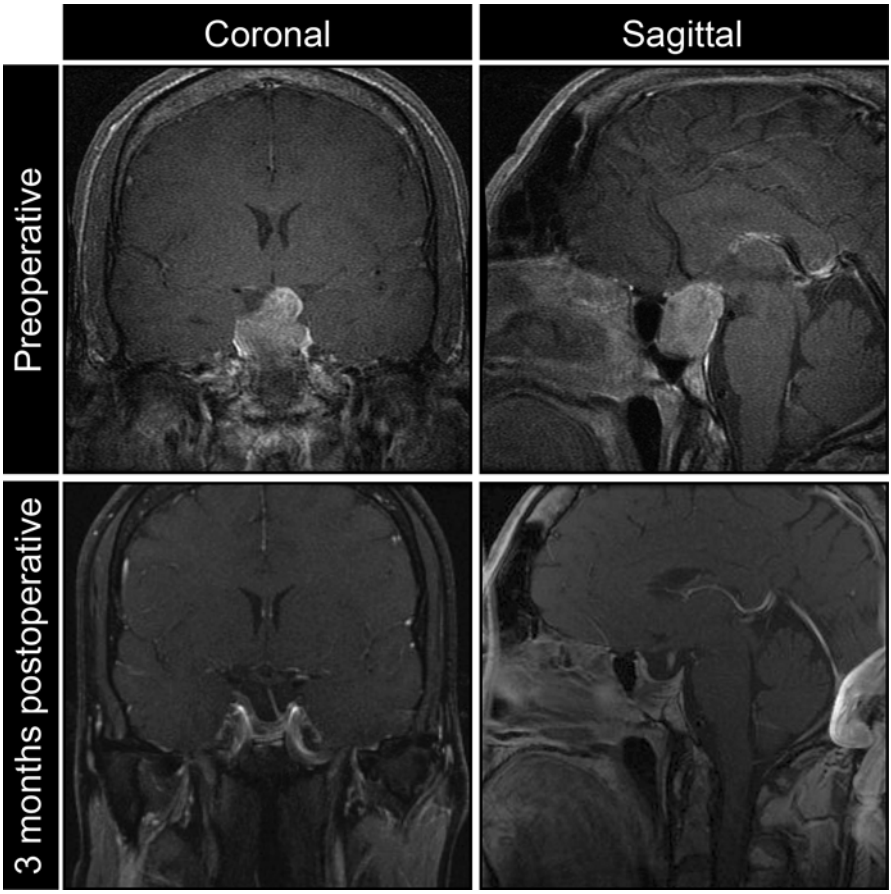

Fig. 2.1 Contrast-enhanced T1-weighted coronal and sagittal MR images; preoperative and 3 months postoperative

Why Does Acromegaly Fail to Be Diagnosed for Years?

Growth hormone (GH) is the most abundant of the pituitary hormones and GH secretory cells (somatotrophs) make up to 50 % of total anterior pituitary cells. GH hypersecretion is usually the result of somatotroph adenomas. Ectopic GH or GH-releasing hormone (GHrH) hypersecretion is very rare.

Clinical features of GH excess are usually progressive and insidious with a mean delay in diagnosis of 10 years or more. Mean age at diagnosis is on average 42 years, with both genders affected equally. Characteristic soft tissue proliferation with local bone overgrowth in the skull and mandible become clinically more striking over time, but often occur so gradually that they are unnoticed and unrecognized by

family members and medical providers alike. Patients most commonly report growth of hands and feet and may present for orthodenture for bite abnormalities and increasing gaps between their teeth (diastema). Tufting of the distal phalanges, carpel tunnel syndrome, peripheral neuropathies, joint remodeling, and paresthesias occur. Once the epiphyses of the long bones are fused, linear growth is arrested. Spinal cord or nerve root compression from bony over growth, cardiomyopathy, and left ventricular mass enlargement leading to hypertension, cardiac arrhythmias, and valvular dysfunction are all possible. Facial features become course and the skin becomes thickened and oily with hypertrichosis and acne. Often profuse sweating associated with minimal or no physical activity is reported. Upper airway obstruction and sleep apnea commonly develop from soft tissue overgrowth. Patients report fatigue, weight gain, heat intolerance, and have often developed a decreased libido and impotence.

In the case we describe, the patient had several clear features of acromegaly that were possibly overlooked for more than 10 years. Furthermore, there was the unusual history of cosmetic procedures including a lip reduction and breast reduction surgery. A detailed history of developing symptoms such as profuse sweating, increased ring size and shoe size, and a diagnosis of obstructive sleep apnea in a tall, slim, young, and otherwise healthy patient should immediately prompt a hormonal evaluation. Unfortunately, in this case, hormonal evaluation was not undertaken when these features were developing. If a diagnosis had been made earlier, this patient would most likely have avoided the development of vision loss and joint damage and he may have avoided several cosmetic procedures. Additionally, early alterations from excess GH causes joint thickness, which can be reversed with treatment, whereas later boney complications are irreversible even with disease control and in the case of this patient may translate to permanent skeletal disabilities.

How Was the Diagnosis of GH Excess (Acromegaly) Made?

Laboratory studies collected at the time of initial evaluation showed a marked elevation in the patient's IGF-1 levels; 1,569 ng/mL (upper limited of normal for equivalent age and sex 331 ng/mL, Table 2.1). An afternoon random GH level draw was 39.4 ng/mL (normal <5 ng/mL). Additional confirmatory testing drawn the following day (before any results available) showed that his GH level did not suppress after administration of an oral glucose load: his nadir GH level during the 2-h evaluation test was 20.9 ng/mL.

Age and gender matched IGF-1 levels are elevated in acromegaly patients and as such provides a useful screening test. A single random GH value is not a reliable screening method due to the pulsitivity of GH secretion by the pituitary. In addition to evaluating IGF-1, dynamic testing of GH is needed for confirmation of GH excess in most cases. Failure of GH to suppress after a 75 g oral glucose load to <1.0, or <0.4 ng/mL (as assessed by newer assays), confirms an acromegaly diagnosis. Nevertheless, there are acromegaly cases that present with an elevated IGF-1 and a

Table 2.1 Patient laboratory results collected at various treatment endpoints

	Time (min)	GH (ng/mL)	IGF-1 (ng/mL; normal range)
Preoperative	Baseline[a]	31	1,569 (53–131)
	30	27.5	
	60	26.5	
	90	23.8	
	120	20.9	
Postoperative	Baseline[a]	2.4	415 (53–331)
	30	1.2	
	60	0.8	
	90	0.9	
	120	0.9	
SSA therapy	Mean 5 points GH profile	1.6	385 (53–331)
Combination therapy		_	131 (53–331)

[a]Pre-glucose administration

suppressible GH after glucose administration. This test is less reliable in the setting of uncontrolled diabetes mellitus (DM), which is a frequent comorbidity in acromegaly patients. In the case we present, the patient had a significantly elevated IGF-1 level, which, in corroboration with his multiple clinical features and symptoms, secured a diagnosis of acromegaly. An oral glucose tolerance test (OGTT) substantiated these findings, but in retrospect, an OGTT was not absolutely necessary diagnostically in this particular patient.

What Additional Evaluation Should Be Performed?

After having determined acromegaly as a diagnosis or when evaluating any patient found to have a pituitary macroadenoma, a full evaluation of pituitary function is recommended. It is important to also evaluate prolactin (PRL) levels when making a new acromegaly diagnosis. This patient's PRL was found to be mildly elevated at 29 ng/mL (normal range, 3–13 ng/mL). This was felt consistent with mass effect on the pituitary stalk from the adenoma with associated interruption of the normal tonic inhibition of PRL by dopamine.

Many GH secreting tumors also secrete PRL due to somatotroph and lactotroph cells having a common progenitor cell. It is therefore helpful to distinguish a pure somatotroph adenoma from a mammosomatotroph or a tumor with two distinct cell lines. Conversely, IGF-1 levels should also be measured in any patient presenting with evidence of a prolactinoma.

Additional biochemical assessments in the case we present included: a cortrosyn stimulation test to evaluate hypothalamic–pituitary–adrenal (HPA) axis function, which revealed a baseline cortisol of 4 mcg/dL and with stimulation up to 11 mcg/dL

(stimulation to <18 mcg/dL is considered an inadequate adrenal response). His baseline ACTH level was low at 11 pg/mL thus, confirming a diagnosis of central adrenal insufficiency (AI). Thyroid function evaluation revealed a low Free T4 at 0.5 ng/dL (normal range, 0.6–1.2 ng/dL) with a corresponding normal range TSH of 2 mIU/L (normal range, 0.4–4.5 mIU/L), which was clearly inappropriate for the low free T4 and indicative of central hypothyroidism. Total serum testosterone drawn in the morning was in the low to normal range with inappropriately low to normal luteinizing hormone and follicle-stimulating hormone. This biochemical evaluation was consistent with a diagnosis of probable central hypogonadism.

How Is Acromegaly Treated?

Surgery is the first-line therapy for most patients with acromegaly. In the presence of a pituitary macroadenoma with optic chiasm displacement, a surgical approach for decompression and subsequent resection or at least tumor debulking is recommended. After initiation of replacement glucocorticoid (GC) therapy, the patient underwent semi urgent transsphenoidal surgery (TSS) due to his VF deficit. His pathology was positive for pituitary tumor cells that stained strongly (>90 %) for GH, and PRL was found in scattered cells in the sample (<10 %). Staining for other pituitary hormones was negative. The pathology report described cytokeratin staining as occurring in round perinuclear structures called fibrous bodies and as such his tumor was classified as a sparsely granulated somatotroph adenoma (Fig. 2.2).

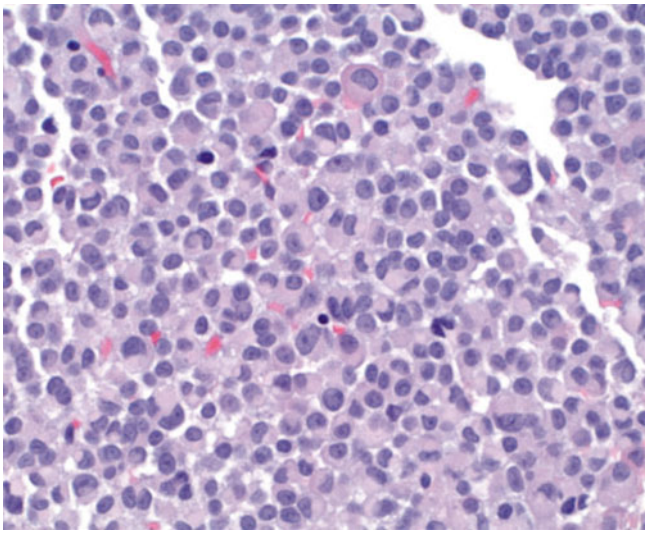

Fig. 2.2 Immunostaining for tumor cell types (magnification ×400). Sparsely granulated adenoma: cytokeratin immunostaining highlights fibrous bodies, a histological "dot–like" appearance, typically seen in these sparsely granulated tumors (cytokeratin-IHC stain)

In experienced hands, surgical remission from acromegaly can be achieved in 70–80 % of cases with microadenomas and <50 % of patients with macroadenomas at presentation. However, 40–60 % of patients surgically treated will, at some time, experience persistent or recurrent disease which requires addition of either medical or radiation therapy.

After surgery, despite a decrease in GH level within 24 h, normalization of IGF-1 level can take up to 3 months or more. Thus a diagnosis of remission vs. persistent disease should not be determined any earlier than 2–3 months postoperatively. It is apparent from several new epidemiologic studies that previous criteria for cure or remission were loosely defined. Based on new data associated with mortality rates in retrospective studies, new cut-offs have been defined: normal age and sex IGF-1 and GH suppression after a 75 g oral glucose load to <0.4 ng/mL (using newer assays).

In the case we present, the patient showed significant improvement in many of his symptoms including headache and fatigue; however, he continued to experience arthritic pain and sweating. His 3-month postoperative IGF-1 level remained elevated at 415 ng/mL (normal range, 53–331 ng/mL) although GH nadir was dramatically lower, albeit not normal (Table 2.1). Postoperative brain MR imaging at 3 months showed residual tumor (Fig. 2.1).

Repeat surgery could be indicated if there is residual tumor that is surgically accessible and there is a significant likelihood for surgical cure, or if there is persistent mass effect upon the optic chiasm. Further surgery was not indicated in this patient owing to residual tumor in the cavernous sinus, an area not surgically accessible. A decision was made that adjuvant medical therapy to achieve disease control was required.

Radiotherapy is considered a third-line treatment when medical therapy is not effective or not well tolerated and/or if the cost of long-term medical therapy is a concern. After radiation, medical therapy usually needs to be maintained until biochemical control is achieved and may be necessary for upwards of 5–10 years.

Somatostatin receptor analogues (SSAs) have been considered the cornerstone of medical therapy to treat acromegaly. Control of GH and IGF-1 excess has been reportedly achieved in approximately 50 % of patients who are naïve to medical therapy, and clinically significant tumor shrinkage (>20 %) has been reported in up to 75 % of patients treated with SSAs. Commercially available SSAs bind to tumor cell somatostatin receptors, most specifically somatostatin receptor subtype 2 (SSTR2a). Studies have shown correlation between tumors that stain for SSTR2a and the degree of responsiveness to SSA therapy; this highlights the importance and usefulness of a detailed immunohistochemical pathologic assessment of tumor tissue.

For most patients, Federal Drug Administration (FDA) approved and recommended starting SSA doses are 20 mg for octreotide LAR (long acting release) and 90 mg for lanreotide administered by injection every 28 days. Subsequent dose titrations, based on both biochemical and clinical response to therapy, are usually required. Currently, the maximum FDA approved dose is 30 mg for octreotide LAR and 120 mg for lanreotide, although octreotide LAR has been extensively used in doses up to 40 mg in clinical practice and clinical trials. Patients require close

monitoring and dose optimization of SSA therapy should be performed at 3- to 4-month intervals. Additionally, it is important to monitor liver function tests, HbA_{1c} and thyroid function.

In the case we present, the patient was initially treated with lanreotide at 90 mg subcutaneously every 28 days, and titrated after 4 months to 120 mg. He tolerated therapy well and experienced clinical improvement, although normalization of IGF-1 at 376 ng/mL (normal range; 53–331 ng/mL) and GH were not achieved.

It has been determined that while taking a SSA, the value of nadir GH after an OGGT is unreliable, we therefore recommend using random GH and if possible 5-point GH profiles for an integrated estimation of GH secretion. The patient's HbA_{1c} increased from 4.9 to 5.9 on treatment.

Treatment Options If Disease Is Uncontrolled Despite SSA Optimization

The goal of acromegaly therapy is to normalize GH levels, limit comorbidities, and reduce the known increased morbidity and mortality associated with persistent GH excess. Increased mortality associated with acromegaly is most often secondary to cardiovascular or pulmonary disease.

If disease control is not achieved with SSA therapy, options include switching to alternative therapy or combination therapy. It is well established that a combined treatment regimen of pegvisomant and SSA is effective for disease control in patients who are partially resistant to SSA monotherapy.

In this patient we selected combination therapy with a SSA and the GH receptor antagonist, pegvisomant.

Pegvisomant is a genetically engineered analog of GH, which inhibits GH action by preventing functional dimerization and IGF-1 production. In contrast with SSA, pegvisomant does not reduce GH secretion by the pituitary tumor, but effectively blocks the systemic effects of GH. In addition, it improves glucose tolerance and insulin sensitivity. Observational studies, which are closer to real life scenarios, have shown that pegvisomant is successful in lowering IGF-1 levels in approximately 70 % of cases. This is lower than initial studies where disease control was reported in more than 90 % of patients and is thought to be due to the use of lower treatment doses. There has been a concern that treatment with pegvisomant could cause residual tumor growth, but this risk does not seem to exceed that of other treatment modalities.

With the addition pegvisomant at 10 mg subcutaneous injection daily, in parallel with a reduction in lanreotide dose to 90 mg every 30 days, our patient was able to achieve a normal IGF-1 value for his age and gender of 131 ng/mL (normal range, 53–331 ng/mL). Once disease control was achieved, we continued to monitor his IGF-1 levels every 6 months as well as periodically assessment his HPA, HP-thyroid, HP-gonadal axes, and liver function tests (LFTs).

It is notable that elevated liver enzymes have been reported with the use of pegvisomant as mono and in combination therapy, however, our patient continued to have normal LFTs throughout treatment. In cases with uncommon but pronounced elevations in LFTs, pegvisomant treatment should be stopped. Other side effects such as mild erythemathous reactions at the injection site are commonly observed in the first months of treatment and quickly disappeared. The patient's HbA_{1c} decreased to 5.4 on combination therapy.

Due to the known presence of residual tumor in the cavernous sinus, he was initially re-evaluated every 6 months with MR imaging, and subsequent yearly MR imaging studies were stable. Biochemical control was maintained on this combination therapy and there were no signs of tumor growth at last follow-up 3½ years after surgery.

Overall, combination therapy is generally well tolerated. By using combination therapy, lower doses of both agents with minimization of the side effects associated with higher doses and improved biochemical control can be achieved. The effects of combination therapy on tumor shrinkage require further study. Combination treatment has the potential to increase compliance and reduce cost as well as reduce impact of possible tumor rebound after stopping SSA.

Complications

Acromegaly is associated with serious morbidity and mortality, if not well controlled. Increased risk of mortality associated with cardiovascular and cerebrovascular atherosclerosis is estimated at 36–62 % and respiratory diseases up to 25 % increase over the normal population. The classic comorbidities may have variable presentation; it is important that ongoing evaluation include assessment of each comorbidity to ensure they are directly addressed in patient management.

In the case we present, a sleep study was performed, which revealed sleep apnea syndrome, and a trial of nasal continuous positive airway pressure was initiated. A colonoscopy was performed and demonstrated multiple colon polyps, which were removed and found to be benign. An echocardiogram showed mild concentric left ventricular hypertrophy, but normal ejection fraction.

Cardiac disease and hypertension are present in more than 60 % of acromegaly patients. Several studies reported increased prevalence of traditional cardiovascular risk factors and early development of endothelial dysfunction and of structural vascular alterations, with subsequent increased risk of coronary artery disease. Furthermore, a large proportion of patients have "acromegalic cardiomyopathy," while valvulopathies and arrhythmias have also been reported and may contribute to the deterioration of cardiac function. The control of GH/IGF-I secretion seems to reverse some cardiovascular abnormalities and could restore normal life expectancy. Cardiovascular risk markers, including lipids, should be monitored and treated aggressively.

Sleep apnea syndrome is present in approximately 70 % of subjects with active acromegaly. Although sleep apnea may improve, it may persist despite biochemical control. Metabolic derangements associated with cardiovascular consequences are also common in acromegaly.

Pre-cancerous or malignant polyps may be found in the colon and given the increase in incidence of colon polyps and the data that malignancies appear to be more aggressive in patients with uncontrolled acromegaly; a screening colonoscopy should be performed.

Panhypopituitarism is likewise more common in this population and all pituitary deficiencies need be appropriately replaced. Regrettably, the musculoskeletal abnormalities are generally not reversible with treatment.

Conclusion

The appropriate treatment approach for any patient should be optimized to take into consideration tumor size, location within the sella and surrounding structures, symptoms, comorbid conditions and patient preferences, and long-term cost.

Once acromegaly/GH excess is considered in the differential diagnosis, it is not difficult to confirm a diagnosis. An acromegaly patient who presents with a VF deficit should be a thing of the past and delayed diagnosis eradicated.

Lessons Learned

- Acromegaly often presents with nonspecific symptoms and conditions. Clinical presentations like carpal tunnel syndrome, sleep apnea, and symptoms of headache, sweating, increase in ring and shoe size should raise suspicion for acromegaly.
- Elevated IGF-1 and abnormal GH suppression to glucose are appropriate screening tests, each respectively confirmatory of a diagnosis. It is essential to use an age and sex adjusted value for IGF-1. Similarly, is important to use a highly sensitive GH assay and to use criteria that reflects the capabilities of new more sensitive assays.
- Treatment of acromegaly is complex and in most cases requires a stepwise, multimodal approach to control disease progression. Therapeutic goals include suppressing GH hypersecretion, normalizing IGF-1 levels, reducing tumor mass, and alleviating comorbidities. Transsphenoidal surgery remains the first line of therapy in the majority of cases with medication reserved for persistent GH excess after surgery or as a primary therapy in selected cases.
- SSAs represent the mainstay of acromegaly medical therapy. In patients who are inadequately controlled with conventional SSA therapy alone, combination therapy with pegvisomant could provide significant additional biochemical control.

While combination therapy results in significantly reduced weekly pegvisomant doses compared to monotherapy, there is wide variability in pegvisomant doses required.

- The advantages and disadvantages of each treatment should be evaluated to provide individually tailored care. It is important to consider the long-term cost: benefit ratio of combination therapy and the overall burden of uncontrolled disease and complications.
- Early diagnosis and intervention represents an important factor toward reducing morbidity and mortality and preventing comorbidities.

Questions

1. A 28-year-old female has been referred to endocrinology because of infertility and irregular menses. Biochemical evaluation reveals an IGF-1 level that is 3 times over ULN and post-glucose GH nadir measurements of 1.4 ng/mL. Which of the following is the most accurate interpretation of her assessment?

   (A) Patient has irregular menses due to intense exercise
   (B) IGF-1 and post-glucose GH nadir are above normal range for a 28-year-old woman and suggestive of acromegaly
   (C) IGF-1 is elevated, but post-glucose nadir levels are normal; thus the patient does not have acromegaly
   (D) She needs repeat testing after she is started on estrogen progesterone treatment to normalize her menses

2. A patient presented with several signs and symptoms suggestive of acromegaly. Biochemical evaluation revealed significantly elevated IGF-1 levels. The following are correct about IGF-1 levels in acromegaly, *except*:

   (A) Will not decrease in response to pegvisomant treatment because the drug blocks only growth hormone receptors
   (B) IGF1 levels correlate with disease severity
   (C) It is important to adjust IGF1 levels for age and sex
   (D) Will normalize with successful treatment

3. A 38-year-old male is receiving a growth hormone receptor antagonist, pegvisomant, after unsuccessful treatment with surgery, radiation, and somatostatin receptor ligands. Clinical studies showed biochemical control with pegvisomant in a high proportion of patients. Which of the following surrogate markers of disease activity should be monitored to best assess treatment response?

   (A) IGF-1 and GH
   (B) Neither IGF-1 or GH; clinical response will be sufficient
   (C) Only IGF-1; GH might be unreliable
   (D) Only tumor size by MRI

4. Pasireotide is a new somatostatin receptor ligand (somatostatin analogue) with higher affinity for somatostatin receptor type 5. Based on recent phase III clinical trials data on treatment with pasireotide in acromegaly, which of the following statements is incorrect?

   (A) Patients on pasireotide LAR were more likely to experience hyperglycemia compared to octreotide LAR
   (B) Pasireotide achieved additional biochemical control in patients not controlled on octreotide or lanreotide
   (C) Pasireotide does not act at the tumor level; thus tumor shrinkage is not expected
   (D) Monitoring pituitary function prior to initiation of therapy, as well as periodically during treatment, as clinically appropriate, is recommended

Answers to Questions

1. (B)
2. (A)
3. (C)
3. (C)

Suggested Reading

1. Carmichael JD, Bonert VS, Mirocha JM, Melmed S. The utility of oral glucose tolerance testing for diagnosis and assessment of treatment outcomes in 166 patients with acromegaly. J Clin Endocrinol Metab. 2009;94:523–7.
2. Fleseriu M. Clinical efficacy and safety results for dose escalation of somatostatin receptor ligands in patients with acromegaly: a literature review. Pituitary. 2011;14:184–93.
3. Fleseriu M. The role of combination medical therapy in acromegaly: hope for the nonresponsive patient. Curr Opin Endocrinol Diabetes Obes. 2013;20:321–9.
4. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, et al. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab. 2010;95:3141–8.
5. Katznelson L. Approach to the patient with persistent acromegaly after pituitary surgery. J Clin Endocrinol Metab. 2010;95:4114–23.
6. Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly–2011 update. Endocr Pract. 2011;17 Suppl 4:1–44.
7. Mathioudakis N, Salvatori R. Management options for persistent postoperative acromegaly. Neurosurg Clin N Am. 2012;23:621–38.
8. Melmed S, Casanueva FF, Klibanski A, Bronstein MD, Chanson P, Lamberts SW, et al. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary. 2013;16:294–302.
9. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab. 2009;94:1509–17.