Treating a Growing Problem: A Closer Look at Acromegaly

Lisa Nachtigall, MD (Moderator)
Nicholas Tritos, MD, DSc
Brooke Swearingen, MD
Goal

• Address key challenges faced by physicians who treat acromegaly
• Review recent advances that may improve patients’ lives
Patient

- 34-year-old woman
- Irregular menses, galactorrhea, and headache
- Sweats, increasing size of hands and feet, new spaces between her teeth, wedding ring had to be resized
- Reported increasing anxiety
Differential Diagnosis

- Coarsening of features
  - Acral enlargement
- Excessive growth during adolescence
- Compare old photographs
- Use of software to analyze facial features

Differential Diagnosis

- Uncommon conditions that can mimic aspects of acromegaly and/or gigantism:
  - Sotos syndrome
  - Pachydermoperiostosis (primary hypertrophic osteoarthropathy)
  - Acromegaloidism in a subset of patients with severe (type A) insulin resistance
## Preoperative Biochemical Evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>959</td>
<td>114-492 ng/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>40.0</td>
<td>0-20 ng/ml</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.8</td>
<td>0.9-1.8 ng/dl</td>
</tr>
<tr>
<td>TSH</td>
<td>1.6</td>
<td>0.4-5.0 uU/ml</td>
</tr>
<tr>
<td>Stimulated cortisol*</td>
<td>25</td>
<td>≥18 ug/dl</td>
</tr>
<tr>
<td>LH</td>
<td>0.8</td>
<td>.6-19 U/L</td>
</tr>
<tr>
<td>FSH</td>
<td>3.4</td>
<td>.3-20 U/L</td>
</tr>
<tr>
<td>Estradiol</td>
<td>&lt; 20</td>
<td>30-370 pg/ml</td>
</tr>
<tr>
<td>Hemoglobin AIC</td>
<td>6.5</td>
<td>3.8-6.5 %</td>
</tr>
<tr>
<td>OGTT nadir GH</td>
<td>72</td>
<td>&lt; 1.0 ng/ml</td>
</tr>
</tbody>
</table>

*On cosyntropin stimulation testing

Reference ranges are laboratory dependent and subject to change

Preoperative MRI

- Sellar and suprasellar mass lesion
- Widened remodeled sella
- Mild patchy enhancement
- No hemorrhage
- Questionable left cavernous sinus invasion
- Mild mass effect on the optic chiasm
- Not present here
  - Diffusely thickened skull
  - Prominent frontal sinuses
Benefits of Pretreatment

- Improvement in remission rate
  - Retrospective studies show variable benefit
  - Two recent prospective studies show some benefit
- May improve comorbid presentation
  - Patients with cardiac-related disease, severe sleep apnea, and narrow upper airways may be improved by pretreatment

Postoperative MRI

- Substantial tumor debulking was achieved
- There is no longer any compression of the chiasm
- There is a small tumor residual in the left cavernous sinus
**Evaluation: 6-Week Postoperative**

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Pituitary MRI minimal residual tumor
Normal visual fields
*On cosyntropin stimulation testing
Reference ranges are laboratory dependent and subject to change

Complications

- Hypertension
- Insulin resistance; impaired glucose tolerance; diabetes mellitus
- Dyslipidemia (including hypertriglyceridemia)
- Sleep apnea (obstructive vs. central)
- Cardiac: cardiomyopathy; CAD; arrhythmias; valvular heart disease; congestive heart failure
- Stroke
- Kyphosis; increased risk of vertebral fractures
- Arthropathy (increased risk of osteoarthritis)
- Carpal tunnel syndrome
- Colon polyps (prevalence) and colon cancer (possibly)
- Controlling GH excess (normal IGF-1 and low GH levels) is essential in order to mitigate excess mortality associated with acromegaly

Treatment Outline

- Surgery (TSS) is the primary treatment of choice for most patients
- Role for primary medical therapy with SSA in select cases (no local mass effect; invasive tumors that cannot be completely resected; patient preference)
- Medical therapy is usually a second-line treatment for patients not cured by surgery. Medical options include: SSA, dopamine agonists, growth hormone receptor antagonist
- Radiation therapy is generally a third-line option

Options for Medical Therapy

- **Somatostatin Analogs**
  - Octreotide and octreotide LAR
  - Lanreotide depot

- **Can achieve biochemical control in up to 60% of patients. Adverse effects:** GI symptoms, hyperglycemia/hypoglycemia, hair loss, bradycardia

- **Dopamine agonists:**
  - bromocriptine
  - cabergoline
    - Used off-label. Achieve biochemical control in 20% of patients; most beneficial in patients with mild disease. Adverse effects include nausea, dizziness, psychiatric manifestations

- **GH receptor (GHR) antagonists**
  - pegvisomant
    - Can control growth hormone excess in up to 95% of patients. Has no effect on the tumor.

Combination Therapy

- Can be beneficial in patients not well controlled on single-agent therapy, including:
  - Somatostatin receptor analog plus pegvisomant
  - Somatostatin receptor analog plus cabergoline
  - Cabergoline plus pegvisomant
Two forms of radiotherapy:
- Conventional fractionated
  - Gradual decline in GH – may take >10 years to achieve control
  - Tumor size is slightly decreased
- Radiosurgery
  - More effective, more rapid onset of effect
  - Can take from 4 to 5 years to achieve biochemical control

Patient Medical Therapy

- She was given octreotide LAR 20 mg x 1
- Had mild persistent stomach pain and diarrhea through the month
- After 1 month of octreotide LAR 20 mg, her IGF-1 was 560 ng/mL (114 to 492)
Which Would Be Most Appropriate as the Next Step in Therapy for Acromegaly?

A. Increase dose of octreotide LAR
   - Would hesitate to increase SA when GI adverse effects already present on lower dose

B. Consider her a nonresponder to SA and suggest radiation
   - She does show some responsiveness to SA at this dose and at 1 month may not reveal full impact of this dose on IGF-1- which may further improve at 3 months after dose

C. Continue octreotide LAR 20 mg; obtain IGF-1 after 3 months of SA
   - Reasonable to see if GI adverse effects wane and if IGF-1 improves during 3-month interval

D. Consider her a nonresponder to SA and change to a different medical therapy
   - GI adverse effects are mild and may improve with time & full impact of SA not yet clear (after only 1 month) & residual tumor more likely to be controlled with SA would not change drug yet

E. Tell her that a monthly visit to the medical center is the only way to receive a long-acting SA
   - Lanreotide depot is available as injection given at home by self or partner if medical practitioner approves and octreotide LAR is available through a home nurse visiting program in many locations

Answer: C
Follow-up Course

- On octreotide LAR 20 mg, persistent GI symptoms
- After 3 months, her IGF-1 was still above normal
- Noticing hair loss, stopped the SSA for 2 months
- Headaches and anxiety increased
- IGF-1 increased to approximately postoperative level (660 ng/mL)
- MRI showed slight increase in tumor size with enlargement in area of left cavernous sinus
What Should Be the Next Step in Therapy?

A. Increase dose of octreotide LAR to maximal dose (30 mg monthly) and follow IGF-1
   - She has already proven noncompliance due to adverse effects

B. Suggest radiation therapy now
   - This is reasonable since tumor is growing but it will likely take several years after radiation therapy before IGF-1 or GH suppression is normal

C. Start cabergoline
   - Given degree of GH elevation & increase in tumor size, cabergoline alone unlikely to achieve optimal control; valvular disease associated with acromegaly and possibly with DA

D. Start pegvisomant
   - This is reasonable for controlling IGF-1 levels but will not control tumor, which is growing so it would be appropriate to combine with radiation therapy

E. B and D
   - Combining radiation therapy and GH receptor antagonist would likely control IGF-1 levels and tumor growth. Once radiation therapy had an opportunity to work, typically several years after radiosurgery, pegvisomant can be withdrawn

Answer: E
Management Goals

• Goals in postoperative management of acromegaly include:
  – Controlling tumor growth
  – Normalizing GH excess/IGF-1
Prevalence of Normal IGF-1 and GH<2.5: Pasireotide LAR vs. Octreotide LAR

Investigational Oral Octreotide

- Octreotide acetate is the active peptide.
- Oily suspension (medium chain fatty acids) enhances intestinal absorption by increasing permeability of intestinal tight junctions.
- In 75 healthy volunteers, pharmacokinetic profile similar to sc octreotide (20 mg oral = 100 µg sc).
- Safety and adverse effects comparable to injectable.
- Suppressed basal and stimulated GH.
- Phase 3 trial in acromegaly: open-labeled multicenter trial results to be presented in 2014.

Thank you Dr. Tritos and Dr. Swearingen for your discussions.

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