CLINICAL VIGNETTE

Growing Pains – A Case of Acromegaly

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Case Presentation

A 47-year-old man presented as a new patient with left sided chest pain, left neck pain which radiated down his left arm, as well as left leg and foot pain. He reported having these symptoms for over 7 years. The symptoms occurred at rest but were more intense with stress. He also described mild left arm weakness and left leg numbness associated with the pain. He was not exercising due to a right knee injury and subsequent arthroscopy. His other concerns included an increased appetite and weight gain. He was unable to control his eating and was depressed. He had been seen by a psychiatrist who specialized in weight loss and was prescribed Lisdexamfetamine. Other prior testing included a treadmill stress test which revealed good exercise tolerance and no ischemic EKG changes.

His exam was notable for lower jaw protrusion, thick lips, a thick neck, and broad fingers. He was asked to produce a prior photo and found a picture from 3 - 4 years ago on his phone, which showed similar increased jaw protrusion. When asked he commented that his shoe size increased from 10 to 11 recently and had increased a full four sizes over the past 12 years. As his fingers were thick, he was also asked about his ring size and he acknowledged that he stopped wearing rings including his wedding band as they were too tight. He wore glasses and noted that the nose pieces needed to be enlarged. He also reported his speech had changed over the last 10 years. Other symptoms include increased perspiration and skin tags on his neck and axillae.

Past medical history was notable for obstructive sleep apnea diagnosed eight years ago. He was not using CPAP after a facial infection from the mask. He also had obesity, hypercholesterolemia, and elevated A1c. Surgical history was notable for right knee menisectomy, laparoscopic cholecystectomy, and wisdom teeth extraction.

Family history included multiple family members with Type 2 diabetes mellitus and coronary artery disease in both parents.

On physical examination, he was afebrile with blood pressure of 120/90. He was 5’4" and 208 pounds, with body mass index of 35.77. His head and neck examination revealed coarse facial features including a broad nasal bridge, thick lips, and a slight protrusion of the lower jaw. Oropharyngeal examination revealed widening of the spaces between his teeth. Thyroid was not enlarged. Cardiac and lung exams were normal and abdominal examination revealed no tenderness or organomegaly.

Musculoskeletal examination was remarkable for broad hands and feet with thick fingers and he had multiple neck and axillary skin tags. Neurological exam was normal.

Laboratory testing included a comprehensive metabolic panel with an elevated fasting glucose of 101 mg/dL and slightly elevated Hgb A1c of 5.9%. Complete blood count and thyroid stimulating hormone level were normal. LDL cholesterol was 154 mg/dL, HDL cholesterol 43 mg/dL, with triglycerides of 208 mg/dL. Based on the constellation of the patient’s symptoms, past history, and physical appearance, an insulin-like growth factor-1 (IGF-1) was obtained and was elevated to 560 ng/mL (reference range 52 - 328 ng/mL).

EKG and stress testing were normal.

With elevated IGF-1 level, pituitary MRI was scheduled and demonstrated a 5.6 x 4.0 mm hypoenhancing lesion along the right aspect of the pituitary gland.

Additional testing to fully assess his pituitary function included normal prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), and adrenocorticotropic hormone (ACTH) levels. Morning cortisol level was slightly low at 5 ug/dL (reference range 6.0 - 18.4 ug/dL). Random growth hormone (GH) was elevated at 1.44 ng/mL (reference range 0.01 - 0.97 ng/mL).

Discussion

Acromegaly is a disease characterized by the hypersecretion of growth hormone (GH) which in turn stimulates production of insulin-like growth factor-1 (IGF-1) primarily by the liver as well as the kidney, pituitary gland, muscle, and gastrointestinal tract. The majority of patients with acromegaly have a benign somatroph (growth hormone secreting) pituitary adenoma. In one report, 69% of patients with suspected acromegaly had a pituitary mass on MRI.[1] The majority are considered macroadenomas with diameter $\geq$ 10 mm or more. In patients without a clear mass, most still have a somatotroph adenoma too small to be detected. Cure for microadenomas is significantly greater than that for macroadenomas.[2] One patient had a microadenoma.

Acromegaly is rare, with prevalence between 40 - 125 per million. The wide range is likely an underestimate of the true

prevalence of the disease. One study screened 6773 unselected primary care patients with IGF-1 levels and detected 7 new cases of acromegaly. This suggests prevalence closer to 1000 per million.[3]

Acromegaly can rarely be caused by growth-hormone releasing hormone (GHRH) production by the hypothalamus, ectopic GHRH production, and ectopic GH secretion.

IGF-1 is the most accurate test to diagnose acromegaly. Growth hormone levels vary throughout the day and are influenced by food intake, sleep, and exercise. An elevated IGF-1 level in a patient with a typical clinical presentation confirms the diagnosis of acromegaly as with our patient.

Clinical Presentation

Acromegaly has insidious onset and effects may often go undetected for 10 - 12 years before diagnosis. Delayed diagnosis may be the result of gradual incremental changes in body features which are easily overlooked. In addition, symptoms are often attributed to other common disorders with excess GH production and not attributed to acromegaly as the unifying underlying diagnosis.

The most common universal clinical manifestation is acral enlargement of the hands, feet, and fingers as well as coarsening of facial features. Facial changes include enlargement of the nose and frontal bones, jaw (macrognathia), mandibular prognathism (protrusion of the mandible), and separation of the maxillary teeth. Soft tissue changes include enlargement of the lips and tongue. Skin changes include skin thickening, hyperhidrosis, increased oily texture, acanthosis nigricans, and skin tags.

Increased mortality in acromegaly is due to the associated comorbidities. Cardiovascular complications occur in 60% of patients with acromegaly.[3] These include hypertension, cardiomyopathy complicated by biventricular hypertrophy, congestive heart failure, and arrhythmias. Up to 80% of patients have sleep disorders with obstructive sleep apnea the most common. Gastrointestinal complications include increased risk for diverticulosis, adenomatous polyps, and colon cancer. Increased IGF-1 and GH levels lead to abnormal glucose regulation and the development of diabetes mellitus in 12 - 37% of patients.[4]

Musculoskeletal complications include arthropathy and joint disease, carpal tunnel syndrome, proximal myopathy, and fibromyalgia. Approximately 70% of patients, have joint changes and pain at the time of diagnosis. Excess GH and IGF-1 levels stimulate growth of the articular cartilage and supporting ligaments. Approximately 50% of patients have axial arthropathy involving the cervical and lumbar spine, with joint space widening and severe osteophytosis. These joint changes can lead to hypomobility and functional restriction of articular movement.[5]

In our patient with atypical chest pain, it is possible that enlargement of the costal cartilages may have contributed to his discomfort. This can be seen in chest radiographs presumably due to growth hormone mediated endochondral bone formation and periosteal bone formation.[6] However, chest pain is an uncommon presentation for acromegaly.

Acromegaly is also associated with increased bone turnover markers. Most studies suggest cortical bone mass increases in acromegaly, while trabecular bone mass remains stable. Bone quality may be the major determinant in fracture risk in these patients.[7] As in the normal population, gonadal status, age, and gender are major influencers of bone mineral density.

A pituitary adenoma may increase in size enough to cause compression of local structures. Visual field defects resulting from impingement of the optic chiasm can cause bitemporal hemianopsia. Other compressive symptoms include cranial nerve palsies, headache, and decreased secretion of other pituitary hormones.

Treatment

Transsphenoidal surgery is the treatment of choice for growth hormone secreting pituitary microadenomas and also for macroadenomas compressing vital structures such as the optic tracts which are amenable to full resection. The early cure rate is 80-90% for microadenomas. Postoperative evaluation includes rechecking IGF-1 and GH levels as well as pituitary MRI 12 weeks after surgery.

If residual disease is detected, repeat surgery may be indicated. The alternative is medical therapy with either a long-acting somatostatin analog, or pegvisomant. Octreotide and lanreotide are analogs of somatostatin, which inhibit GH secretion by binding to receptors. They are generally well tolerated but are associated with gastrointestinal symptoms and increased risk for gallbladder disease. Pegvisomant is a GH receptor antagonist. It is a pegylated growth hormone analog, which increases half-life. The substitution of eight amino acids in the GH-binding site 1, and substitution at binding site 2, results in increased GH receptor affinity at site 1 on the GH receptor and decreased affinity at site 2. This inhibits binding of native GH, but does not activate intracellular signaling.[8] Elevated liver function tests were reported in 2.5% of registry patients. Monthly liver tests are recommended for the first six months followed by every six month checks.[9]

Dopamine agonists such as cabergoline are less effective than somatostatin analogs. Their main advantage is that they can be taken orally.

Finally, radiation therapy can be considered for patients who do not achieve effective control with surgery or medical therapy. However, it can take years to see a reduction in IGF-1 levels and adenoma size.

The goals of treatment include reduction of IGF-1 and GH to normal levels, control of adenoma size, and improvement in symptoms and metabolic abnormalities. Fortunately, soft tissue overgrowth and metabolic abnormalities often improve, as well as decreases in obstructive sleep apnea, swelling, and arthralgias. However, bony changes and some joint symptoms are not reversible.

In summary, while acromegaly is rare, it is important to test for it in patients with typical clinical manifestations, especially those with acral or facial features. It is also recommended in patients who have a cluster of associated conditions without typical features. These conditions include obstructive sleep apnea, Type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension.[10]

Our patient underwent a transphenoidal resection of his pituitary microadenoma. Two months after his surgery, the patient reported improvement in chest, neck, back, and left arm pain, and decreased swelling of his hands and feet. He still noted persistent sciatica. The greatest improvement was in his sleep quality. He commented "I have seen a big improvement on my sleep apnea, I don't snore that much and I am able to sleep better which allows me to wake up more rested."

Awareness of acromegaly and its comorbidities can lead to earlier diagnosis and reduction associated complications and mortality. The treatment for the disease includes biochemical control and treatment of associated conditions.[11]

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