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Case Report

Early Onset GH Excess: Somatotroph Adenoma in a Young Adult

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Abstract

GH-secreting pituitary adenomas can cause gigantism or acromegaly, determined by onset before or after epiphyseal fusion of the distal ends of the radius and ulna. Overlapping phenotypes can occur when the condition presents peripubertally. Gigantism is associated with identifiable hereditary causes and genetic mutations in almost 50% of cases; genetic testing should be considered in patients with gigantism and early-onset acromegaly, especially (but not only) when pituitary tumors have aggressive features and/or are refractory to standard treatments. Here, we present a case of a young adult with a giant somatotroph adenoma resistant to multiple treatment modalities and negative for mutations in *AIP*, which encodes aryl hydrocarbon receptor-interacting protein.

Key Words: acromegaly, gigantism, pituitary, genetics

Abbreviations: BMI, body mass index; MEN, multiple endocrine neoplasia; MRI, magnetic resonance imaging; X-LAG, X-linked acrogigantism.

Introduction

GH excess is a condition driven by pituitary GH hypersecretion in 98% of cases, caused by a pituitary adenoma [1] or pituitary hyperplasia. The clinical picture derived from GH excess is called gigantism if the onset occurs before epiphyseal fusion, or acromegaly if it occurs thereafter. The key distinction between gigantism and acromegaly relates primarily to changes in height in association with the disorder (significant in the former, none or minimal in the latter). Gigantism is also known to present more often with aggressive tumors that are less responsive to treatment and is associated with an underlying genetic mutation in 50% of cases [2]. Acromegaly is most commonly sporadic; however, several genetic syndromes have been linked to acromegaly. The identification of a driving genetic mutation can be helpful in directing medical therapy, although surgery (with or without radiation) remains the mainstay of treatment for most GH-secreting pituitary adenomas [2]. In this report, we describe the case of an aggressive somatotroph adenoma in a teenager presenting with overlapping features of both gigantism and acromegaly and requiring multiple treatment modalities to achieve control.

Case Presentation

A 17-year-old female was referred to endocrinology with a history of blurred vision and weight gain over several months. Her review of systems was remarkable for a 12-kg weight gain in the 5 months before presentation, despite being very active and with no changes in her diet; she reported that her fingers had enlarged and her shoe size had increased by 1 size over the preceding 6 months; her menstrual cycle had become progressively more irregular, whereas it was previously regular for 5 years since menarche at aged 12 years; she noted increased sweating and heat intolerance; and height measurements documented a 2.5-cm linear growth over the preceding year compared with 1 cm the 2 years prior. Her growth charts around the time of diagnosis showed a growth acceleration and increase in her height percentile (Fig. 1). She had not noticed snoring, arthralgias, or increased spacing between her teeth. Her medical and surgical histories included a remote intussusception repair and celiac disease. Her family history was notable for triple-negative breast cancer in her mother and type 2 diabetes mellitus in her maternal uncle; it was negative for pituitary disorders. She was not on any medications.

Diagnostic Assessment

An initial assessment for irregular menses performed before her presentation to endocrinology demonstrated an elevated free testosterone level of 7.1 pg/mL (0.02 nmol/L; normal range, 0.5-3.9 pg/mL), hemoglobin A1c in the prediabetes range, 6.3% (normal <5.7%), and an elevated prolactin level, 63.38 ng/mL (normal range, 2.8-29.2 ng/mL). During the initial endocrine visit, her vital signs were notable for a blood pressure of 131/90 mm Hg, a height of 177.8 cm (99th percentile), and a body mass index (BMI) of 23.68 kg/m^2. On physical examination, she was noted to have an enlarged tongue and widening of the nose, a diffusely enlarged thyroid with no appreciable discrete nodules or cervical lymphadenopathy, left-sided expressible galactorrhea, Tanner stage 4-5 breast development, enlarged hands and feet, and a decreased

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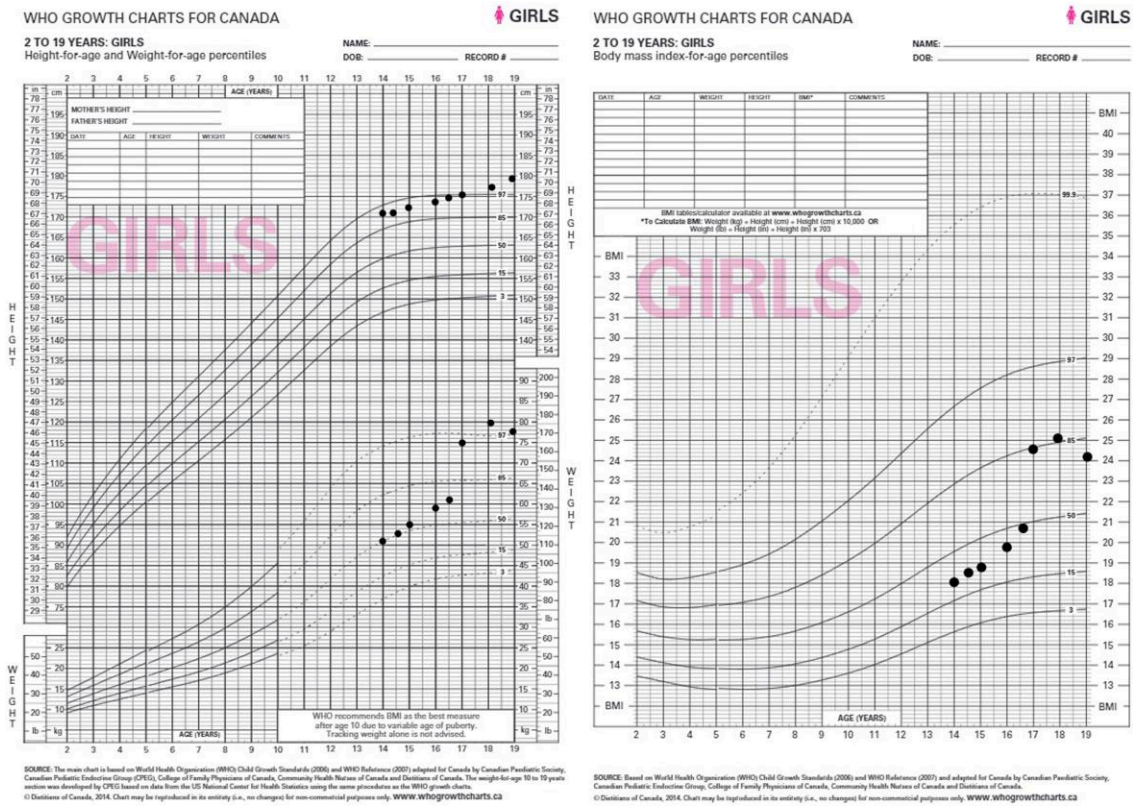

Figure 1. Growth charts for girls aged 2 through 19 years for height, weight, and BMI. The patient's data were reported for ages 14 to 19 years. It is notable that the patient's height percentile was leveling off between the 85th and 97th percentile by age 14 to 16 years, but then increased to exceed the 97th percentile between ages 17 and 19 years.

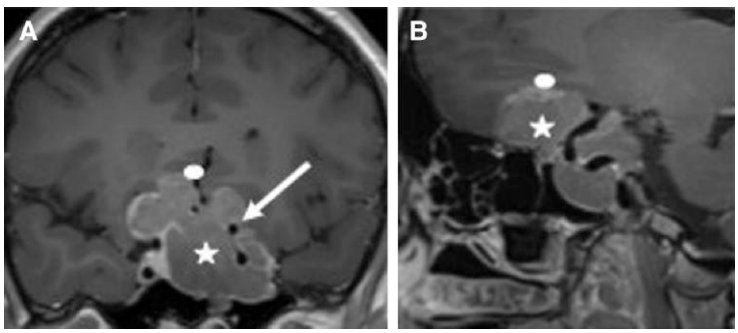

Figure 2. (A) Coronal and (B) sagittal views of MRI scan of the brain performed with a pituitary protocol, demonstrating a giant pituitary adenoma (stars) invading the cavernous sinus (arrow) and compressing the optic chiasm (ovals).

visual field on the right to the confrontation test. Her predicted height, based on her parents' heights, was 173.8 cm. Figure 1 shows her growth charts (height, weight, and BMI) between ages 14 and 19 years. A deviation from her percentile height and a growth acceleration compared with her prior growth plateau was noted between ages 17 and 19. Her laboratory studies demonstrated normal electrolytes and kidney function, significantly elevated IGF-1 (1285 ng/mL [168.34 nmol/L]; reference range, 188-512 ng/mL) and random human GH levels (54 ng/nL; reference range, 0.01-3.61 ng/mL), worsening hyperprolactinemia (113.6 ng/mL [4939 pmol]; reference range, 3.8-20.1 ng/mL), intact hypothalamic-pituitary-adrenal axis (random cortisol 22.8 µg/mL [629.05 nmol/L]; reference range, 6.2–19.4 µg/mL), borderline central hypothyroidism (TSH 1.43 uIU/mL (normal) with concurrent free T4 0.8 ng/dL [10.3 pmol/L]; reference range, 0.8-1.8 ng/dL), and central hypogonadism (LH 1.36 mIU/mL and FSH 2.97 mIU/mL) with amenorrhea. Magnetic resonance imaging of the pituitary gland with and without contrast showed a large, $4.2 \times 2.5 \times 3.5$ cm enhancing mass centered within the sella turcica, causing pituitary and infundibulum displacement and with extrasellar extension and left cavernous sinus, prepontine cistern, sphenoid sinus, and optic chiasm involvement (Fig. 2). Given the patient's age and these results, a bone age study was performed, which showed a bone age consistent with age 17 years, within 2 SD of her chronological age, with fused epiphyses. She was diagnosed with acromegaly/gigantism complicated by hyperprolactinemia (possibly from pituitary stalk effect or to tumoral

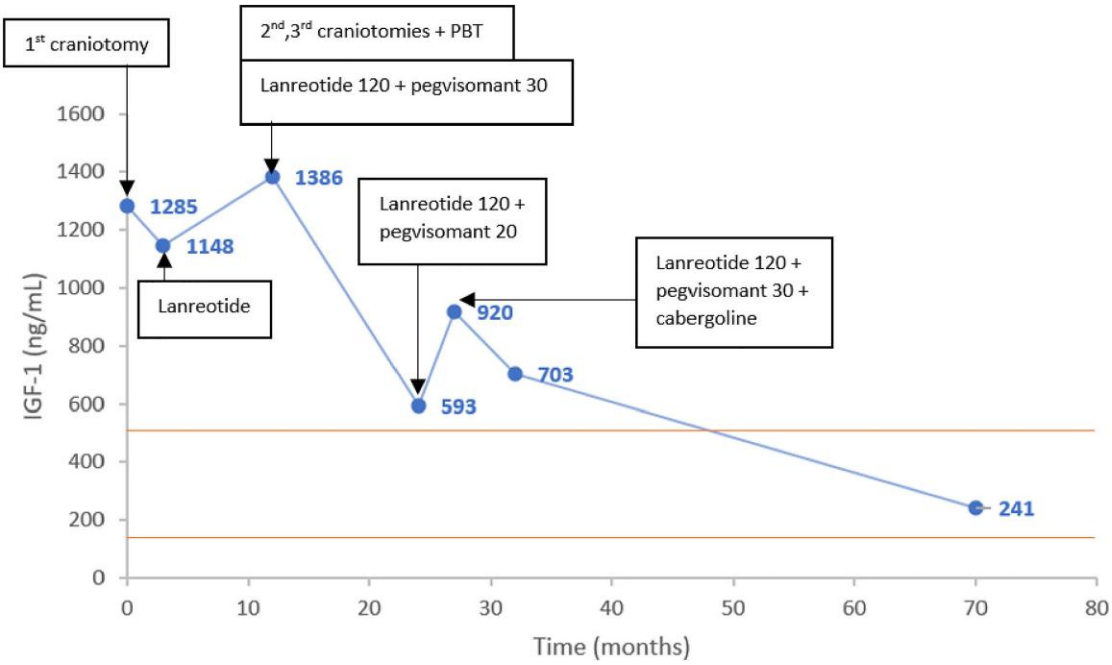

Figure 3. Patient's clinical course over time (expressed in months on the X axis) reporting IGF-1 levels (expressed in ng/mL on the Y axis) and treatment interventions. Abbreviation: PBT, proton beam radiation.

prolactin cosecretion) and hypogonadotropic hypogonadism and was referred to neurosurgery for consideration of surgical pituitary adenoma resection. The treatment course is described in detail in the following section; tumor pathology is reported here because it is pertinent to the subsequent diagnostic assessment. The pituitary adenoma was classified based on the World Health Organization 2004 classification [3], as the first surgery occurred before 2017, after which the more recent World Health Organization pituitary adenoma classification [4] was adopted by most centers. The patient was found to have an atypical somatotroph (GH-secreting) macroadenoma strongly positive for GH, mildly positive (scattered cells) for prolactin, expressing TP53 in 10% of the cells, and with a Ki-67 index of 15% (>3% is indicative of aggressive adenomas). Tumor granularity was not reported. Of note, her prior elevated testosterone was attributed to GH-induced insulin resistance and subsequent androgenization.

Treatment

Figure 3 shows the treatment course for the patient. Given her diagnosis of acromegaly/gigantism and the extensive nature of the pituitary adenoma, she first underwent a craniotomy for partial tumor resection. Surgery was complicated by transient (less than 2 months in duration) diabetes insipidus, requiring desmopressin treatment only temporarily. She developed overt central hypothyroidism and was started on levothyroxine 125 mcg daily, she had persistent hypogonadism treated with oral contraceptive pills, and she developed new postoperative central adrenal insufficiency treated with glucocorticoid replacement. Three months postoperatively, serum IGF-1 had decreased only minimally (from 1285 to 1148 ng/mL) and subsequently increased to a level higher than baseline (1386 ng/mL) by 12 months postoperatively, despite treatment with escalating doses of lanreotide to the maximum dose (120 mg monthly) started 2 months postoperatively, and subsequent addition of pegvisomant that was titrated up to 30 mg daily. As her tumor had again progressed, she underwent second and third craniotomies (4 months apart because of evidence of interim tumor increase on subsequent imaging) for further tumor resection that was, however, never total because of its substantial size and invasiveness. After her third surgery, she received proton beam radiation (37.4 Gr total), divided into 24 fractions. Lanreotide was discontinued during radiation therapy and restarted afterward at the same dose (120 mg monthly). Nearly 2 years after her third surgery (and 3 years after the initial diagnosis), the patient's IGF-1 level had decreased to 866 ng/mL (113.44 nmol/L), showing improved but nonetheless suboptimal control. Her IGF-1 subsequently improved further to 593 ng/mL (77.68 nmol/L), likely reflecting pegvisomant effectiveness, as an attempt to reduce the medication to 20 mg daily failed with a rise in IGF-1 to 920 ng/mL (120.52 nmol/L). Thus, the patient was maintained on maximum doses of both lanreotide and pegvisomant, and her medical treatment was further augmented with cabergoline, titrated to 1 mg twice weekly, with subsequent achievement and maintenance of normal IGF-1 levels for several years. Her serum GH level was monitored for 2 years after surgery and was consistently elevated, ranging between 34 and 144 ng/mL (reference range, 0.01-3.61 ng/mL); however, IGF-1 levels were used for titration of medical therapy. Her most recent IGF-1, measured 6 years after diagnosis, was in the normal range (241 ng/mL [31.57 nmol/L]). Figure 4 presents this patient's most recent pituitary magnetic resonance imaging (MRI) scan (performed 6 years after the initial diagnosis), which demonstrated stable, yet persistent, residual tumor. As a consequence of her pituitary adenoma, excessive GH exposure, and side effects of surgical and medical treatment, she developed several comorbidities, including central hypothyroidism, central hypogonadism, persistent hyperprolactinemia requiring cabergoline, central adrenal insufficiency, prediabetes

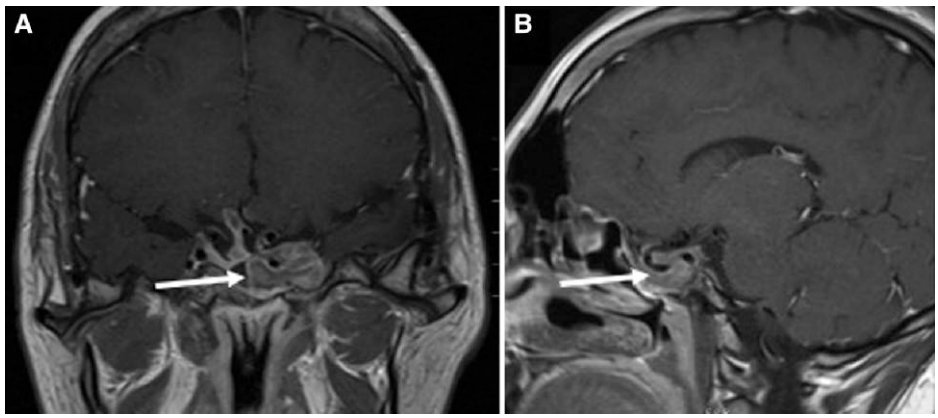

Figure 4. MRI scan of the brain performed with a pituitary protocol, showing (A) coronal and (B) sagittal views, demonstrating the residual tumor present six years after the initial diagnosis (arrows).

mellitus requiring metformin, and hypertension, and she was treated accordingly. Soon after her diagnosis, she underwent genetic testing, as recommended by guidelines in 2016 [5], for aryl hydrocarbon receptor-interacting protein (*AIP*) gene mutations that did not detect any pathogenic mutations, variants of unknown significance, or duplications or deletions. *MEN1* was not analyzed for mutations; her calcium and phosphorus levels have always been within normal ranges; thus, the clinical suspicion for multiple endocrine neoplasia type 1 (MEN-1) was low.

Outcome and Follow-up

We have extensively described our patient's clinical course, treatment, and monitoring (performed through IGF-1 levels and serial pituitary MRIs) as well as treatment actions taken to manage persistent and recurrent pituitary adenoma and GH excess. Her tumor has been stable for the past year, and she is currently monitored with pituitary MRI and pituitary and biochemical testing (including IGF-1 levels). Pegvisomant has been tapered to 20 mg daily recently, but other medications have not changed.

Discussion

This is a case of early-onset GH excess, resulting in a combination of both gigantism and acromegaly. A notable aspect of this case is that this patient's GH excess likely started during puberty and led to a limited acceleration in linear growth (sufficient to cause an increase in height percentile) shortly before epiphyseal fusion. The diagnosis of gigantism is often delayed by many years [6], and her bone age study was not performed until the time of diagnosis of acromegaly, after her epiphyses had fused. Gigantism and early-onset acromegaly are associated with more aggressive tumors and worse prognosis, compared with GH-secreting pituitary adenomas diagnosed in the elderly population (>65 years of age) [7]. Up to 49% of cases of gigantism are now recognized to be associated with an identifiable genetic background [5, 6, 8], with mutations in *AIP* being the most frequent (29%), followed by mutations in *GPR101* associated with X-linked acrogigantism (X-LAG) (10%), McCune-Albright syndrome (mutations in *GNAS*) (5%), Carney complex (mutation in *PRKAR1A*) (1%), and MEN-1 (mutations in *MEN1*) (1%) [6]. More rarely, gigantism can occur in MEN-4 (mutations in *CDKN1B*) and pheochromocytoma/paraganglioma/pituitary adenoma association (mutations in *SDHD*) [2]. Early-onset GH-secreting adenomas can be part of any of these syndromic pictures. Familial isolated pituitary adenoma can be secondary to loss-of-function mutations in *AIP* or gain-of-function mutations in *GPR101* causing X-LAG; however, the onset of X-LAG is usually before the age of 4 years [2]. Even when there is no family history suggestive of a hereditary cause of GH excess, genetic testing should be pursued when patients present with pituitary adenomas with aggressive features, sparsely granulated histology, at a very young age, and/or resistant to standard treatment [9]. Indeed, it has been suggested that, given the high rate (close to 50%) of mutations in patients with pituitary gigantism, genetic testing should be performed for every patient [10]. In the context of this patient, she had a very aggressive pituitary adenoma requiring multiple treatment modalities, onset was at a relatively young age (although not in early childhood), and her tumor was found to express both GH and prolactin. Of note, although prolactin levels are usually higher than 100 ng/mL in macroprolactinomas, tumors cosecreting GH and prolactin can present with varying degrees of hyperprolactinemia. Although mixed lactosomatotroph adenomas are found with a higher prevalence in X-LAG, the onset of GH excess in this patient at aged 17 years makes it less likely to be caused by a germline *GPR101* mutation and she does not meet the current criteria for genetic screening for X-LAG [10]. She did undergo genetic testing for *AIP* mutations, which was negative. The genetics of pituitary adenomas is a rapidly advancing field, recommendations are evolving, and consideration of genetic testing may need to be revisited periodically; providers should consider further genetic testing when indicated by updated guidelines. Recent recommendations suggest testing for both *AIP* and *MEN1* mutations in patients with an established diagnosis of GH excess with onset between age 5 and 30 years, and no other syndromic features or family history of pituitary adenomas [2, 10]. It is also recommended to test any patient with a diagnosis of gigantism and concurrent personal family history of other tumors or syndromic features for MAS (*GNAS* mosaicism), Carney complex (*PRKAR1A* mutations), neurofibromatosis 1, Von Hippel-Lindau syndrome, and MEN-4 [2, 10]. Given this patient's aggressive GH-secreting pituitary adenoma and young age at diagnosis,

current guidelines would recommend genetic testing for *MEN1* in addition to *AIP*.

In conclusion, gigantism and early-onset acromegaly are aggressive diseases that significantly impact quality of life and increase morbidity and mortality. They are often associated with hereditary syndromes and known genetic mutations, so genetic testing for these patients must be considered and frequently revisited according to the most up-to-date guidelines.

Learning Points

- GH excess is a clinical condition associated with increased morbidity and mortality.
- GH secreting pituitary adenomas account for 98% of cases of GH excess and define 2 distinct clinical pictures based on the age of onset: gigantism (onset before epiphyseal fusion) and acromegaly (onset after epiphyseal fusion).
- Overlap between gigantism and acromegaly occurs when the disease onset occurs during pubertal transition.
- Up to 49% of pituitary gigantism is associated with known genetic mutations and syndromes.
- Genetic testing is of crucial importance when a family history of GH excess is present, at younger ages, and for patients with invasive adenomas.

Contributors

All authors made individual contributions to authorship. U.B.K. was involved in the diagnosis and management of this patient. F.G. and U.B.K. conceived the manuscript idea and wrote the manuscript. F.G. completed the manuscript submission. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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