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Case Report

Change in the immunophenotype of a somatotroph adenoma resulting in gigantism

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Abstract

Background: Examining the pathologic progression of a pituitary adenoma from the point of a prepubescent child to an adult with gigantism affords us an opportunity to consider why patients may develop secretory or functioning tumors and raises questions about whether therapeutic interventions and surveillance strategies could be made to avoid irreversible phenotypic changes.

Case Description: A patient underwent a sublabial transsphenoidal resection for a clinically non-functioning macroadenoma in 1999. He underwent radiation treatment and was transiently given growth hormone (GH) supplementation as an adolescent. His growth rapidly traversed several percentiles and he was found to have elevated GH levels. The patient became symptomatic and was taken for a second neurosurgical procedure. Pathology and immunohistochemical staining demonstrated a significantly higher proportion of somatotroph cells and dense granularity; he was diagnosed with a functional somatotroph adenoma.

Conclusions: While it is likely that the described observations reflect the manifestations of a functional somatotroph adenoma in development, it is possible that pubertal growth, GH supplementation, its removal, or radiation therapy contributed to the described endocrine and pathologic changes.

Key Words: Gigantism, growth hormone, non-functional adenoma, pituitary adenoma, somatotroph adenoma

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INTRODUCTION

Excessive levels of growth hormone (GH) prior to pubertal closure of the epiphyseal plates, over time, can lead to aberrant somatic growth and features consistent with gigantism. Pituitary tumors, if large enough, may produce more immediate symptoms such as headache or visual changes from either optic nerve compression or cranial neuropathies. From natural history data, we know that non-functional pituitary adenomas can present with signs of pituitary insufficiency in 44%, visual field deficits in 14%, apoplexy in 14%, and chronic headache in 7%.[7] Changes in hormonal secretion by pituitary adenomas are a recognized but rare phenomenon.[6,17] Examining the pathologic progression of a pituitary adenoma from the point of a prepubescent child to an adult with gigantism affords us an opportunity to consider why patients may develop secretory or functioning tumors and raises questions

about whether a diagnosis and therapy can be made prior to irreversible clinical changes. The following case report uniquely demonstrates a change in corticotroph adenoma secretory activity based on clinical/growth curve data and histopathologic evidence, in parallel with a child's growth.

CASE REPORT

The patient presented at the age of 12 with headache and visual changes. Pre-operative endocrine lab values were within normal limits. The patient had an insulin-like growth factor-1 (IGF-1) level of 182 and a serum growth hormone (GH) level of 7.2 following stimulation with L-3,4-dihydroxyphenylalanine (L-DOPA; upper and lower limits 5 ng/ml and 10 ng/ml, respectively.[14]) Imaging revealed a large sellar enhancing lesion with lateral extension [Figure 1]. He underwent a sublabial transsphenoidal operative approach for biopsy and resection in 1999 at our pediatric institution—The Children's Hospital of Philadelphia. Pathology demonstrated a soft avascular mass with <5% GH reactivity (Western blot analysis; ThemoFisher Scientific, Waltham, MA, USA). This non-functioning, sparsely granulated somatotroph adenoma was treated with 6 weeks of intensity-modulated radiation therapy (IMRT) directed to a 3.8 cm remnant in the left cavernous sinus, 4600 rads, 2 months after surgery. Endocrine evaluation after treatment was notable for hypothyroidism and GH deficiency [Table 1]. The patient's tumor demonstrated a decrease in size at 6 months and 1 year post-op. At age 14, the patient's tumor remnant appeared stable on magnetic resonance imaging (MRI). He was started on human growth hormone (HGH; 0.3 mg/kg/week) in addition to thyroid replacement therapy at that time. Table 1 depicts the patient's clinical course through development.

At 16, he had no sign of axillary or facial hair. He was given testosterone injections as treatment for low levels (serum testosterone 50, given 100 mcg IM × 4 doses). At age 17.3, the patient's IGF-1 level was 283 ng/ml [normal range 268-430 ng/ml for Tanner V, up to age 18]. At 17.5, the patient self-discontinued the human GH supplementation. His IGF-1 level was 335 at that time. At age 18.5, he started developing headaches. The IGF-1 level had increased to 424. MRI obtained at the time showed an increase in size of the sellar mass. By age 19, he had full axillary and facial hair. His growth trajectory had jumped several percentiles in this range, both in height and weight (Refer to Figure 2). At this point, he remained only on thyroid replacement therapy. At age 22.5, the patient began experiencing headaches and associated visual changes. Labs obtained at the time were notable for an IGF-1 of 835 ng/ml (normal range 281-510 ng/ml). He presented to Pennsylvania Hospital with this history and was taken to the operating room for an endoscopic transsphenoidal resection (2009). Figure 3 demonstrates the patient's pathological specimen. At this time, pathology and immunohistochemical staining demonstrated a much higher proportion (70-80% based on immunoreactivity analysis) of somatotroph cells and what was deemed a clinically functioning, densely granulated somatotroph adenoma (Western blot analysis; ThemoFisher Scientific). Microscopic analysis demonstrated fragments of homogenous cells with uniform round to oval nuclei and finely stippled chromatin. Mitotic activity was sparse and necrosis was not seen. There were no adjacent fragments of normal gland or tissue demonstrating hyperplasia. Immunohistochemical stains to thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, GH, and adrenocorticotropic hormone (ACTH)

Table 1: Clinical and developmental characteristics of patient

Date	Age (years)	Age (months)	Clinical/development	Endocrine	Medication
3/1999	12.8	153.6		IGF-1 182; GH 7.2	
4/1999	12.9	154.8			
6/1999	13	156		I-DOPA stim ->GH 2.9	
4/2000	13.9	166.8	Tanner II pubic; Tanner II/III genital		HGH
7/2001	15.1	181.2	Tanner III pubic; Tanner V genital		HGH
8/2002	16.3	195.6	No growth of facial/axillary hair		HGH, testosterone
9/2003	17.3	207.6		IGF-1 283	HGH (dose decreased by half), testosterone
3/2004	17.8	213.6		IGF-1 335	HGH STOPPED, testosterone
11/2005	19.5	234		IGF-1 424	Testosterone STOPPED
4/2006	19.9	238.8	Facial/axillary hair; normal sexual function		
12/2008	22.5	270		IGF-1 835	
2/2009	22.7	272.4			
4/2009	22.9	274.8		IGF-1 735	Somatostatin
10/2009	23.4	280.8		IGF-1 441	Somatostatin
8/2011	25.2	302.4		IGF-1 249	Somatostatin

The gray cells indicate the point at which the patient underwent transsphenoidal surgery. Human growth hormone (HGH) supplementation was initiated at age 13.9. Dosing of HGH was coincident with testosterone supplementation. The patient stopped taking HGH at age 17.8. IGF-1 level was elevated leading up to the second operation, but was controlled afterward. Note the administration of somatostatin post-op

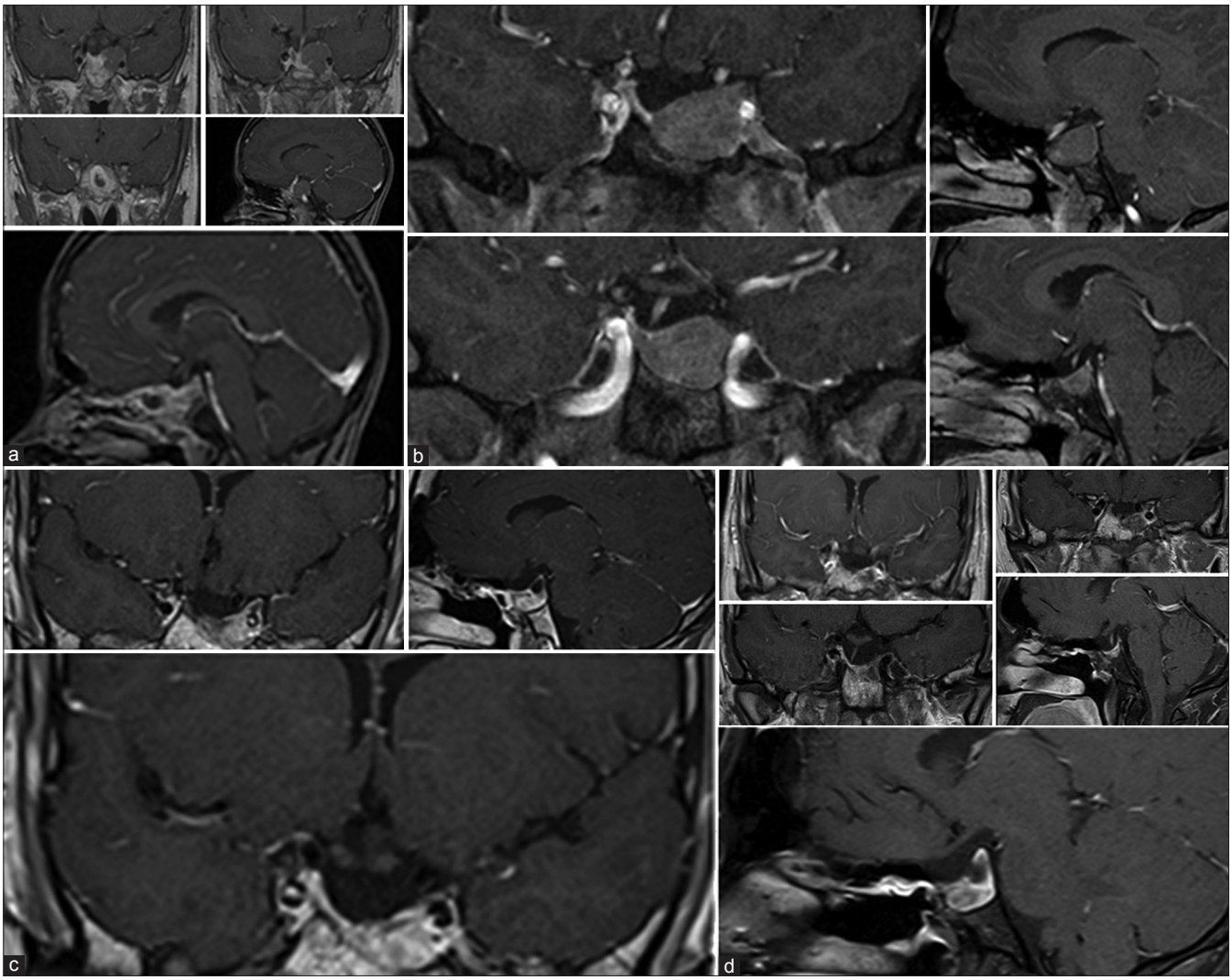

Figure 1: MR imaging. (a) Pre-operative from 5/1999. (b) Recurrent adenoma, 2008. (c) MRI s/p endoscopic endonasal approach (2nd operation), 2009. (d) Recent MRI, 12/2012

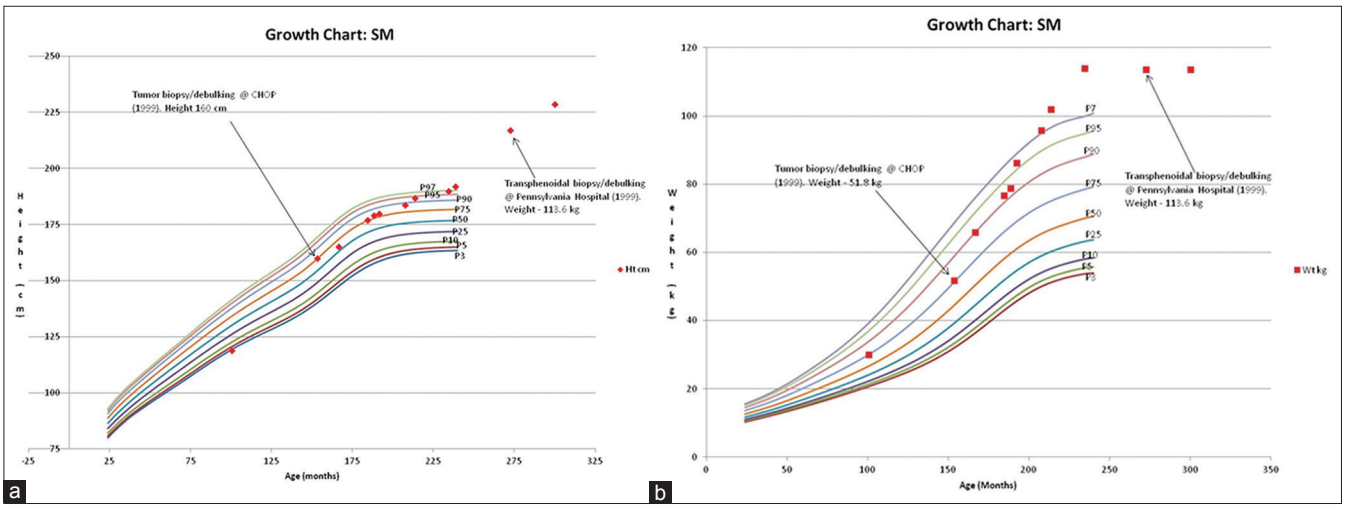

Figure 2: Growth chart. (a) Stature with age. (b) Weight with age. The CDC growth chart for males (age 2-20) is indicated by percentile. Percentiles are indicated as P where P3 represents the third percentile and so forth

were performed with adequate controls. The cells showed strong positive staining for GH immunostain only.

At this point, the patient had known residual tumor in the left cavernous sinus that was deemed inoperable. He

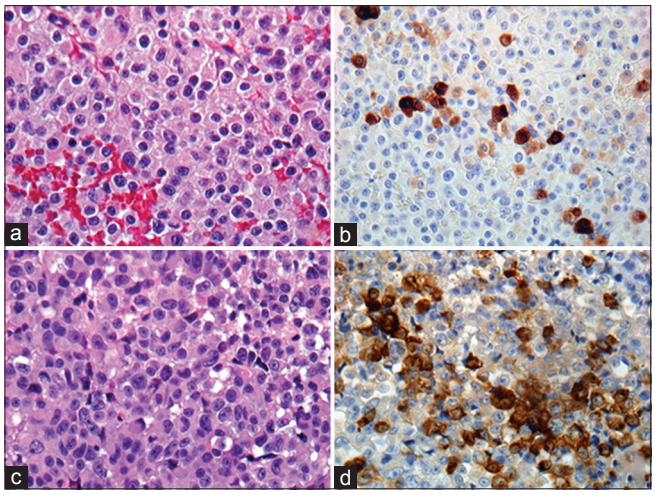

Figure 3: Non-functioning adenoma and recurrent, functioning adenoma. (a) Histological examination from the first resection showed sheets of a uniform population of neoplastic cells with loss of the normal adenohypophysis architecture, ×200. (b) Several cells stained positive for GH immunohistochemistry (sparse granulation), 200×. Second resection after 9 years showed similar histological features HandE, ×200 (c) and a more diffuse positivity for GH immunohistochemistry (dense granulation), ×200 (d)

was started on Octreotide postoperatively and remains on this medication. His serum IGF-1 levels have decreased to 309 (normal range 155–432 ng/ml) as of 4/2012. Clinically, he has a 6-foot 4-inch stature and weighs approximately 300 lbs.

DISCUSSION

Changes in pituitary tumor secretory activity in recurrent, previously non-functional tumors have been reported sparsely in the form of rare adult cases. These have suggested transformation from non-functional to functional ACTH-secreting (corticotroph) tumors.[5,20] One large series examined 65 recurrent pituitary adenomas from 1023 patients undergoing operations for resection of pituitary tumors. All patients were identified within 9 years and all except one underwent repeat surgery. Five (7.7%) of the recurrent tumors had different immunophenotypes. Only one of these patients had a non-functional pituitary adenoma which recurred in the form of a functional corticotroph tumor.[17] Transformation of a benign silent or non-functional somatotroph adenoma to a functional variant has been described in a single adult patient. The reported 41-year-old patient was diagnosed incidentally with a sellar mass. Following surgery, he was found to have a somatotroph adenoma, non-functional based on clinical and laboratory data. Five years later, he presented with acromegalic features and underwent repeated transsphenoidal surgery. Pathological specimens showed strong immunoreactivity for GH. However, isolated cells were also positive for prolactin, TSH, and α-subunit.[6]

Up to one-third of somatotroph adenomas are considered clinically silent or nonfunctional.[21] Somatotroph adenomas can be classified into five different groups based on secretory activity according to the presence of granulated cells (either densely or sparsely granulated based on the presence of secretory granules within the cytoplasm of cells) and immunoreactivity to hormones.[18] Although non-functioning pituitary adenomas have been shown to be monoclonal in origin and share a common cellular lineage,[1,13] the pathological classification of somatotroph adenomas does not clearly define the clinical behavior of tumor subtypes.

The sparse GH reactivity (less than 5%) observed in the non-functioning adenoma by our pathologists following the patient's first operation was consistent with the patient's lack of endocrinologic symptoms. Immunohistochemistry performed following the patient's second operation was consistent with the clinical and laboratory findings of excess GH. Increased immunoreactivity for other hormones was not demonstrated. Although possible, it does not seem likely that subtotal sampling reasonably explains the observed histopathologic and clinical findings.

A combination of epigenetic and genetic factors may contribute to tumorigenesis in the pituitary gland.[12,16] While it is likely that the described observations reflect the manifestations of a functional somatotroph adenoma in development, exogenous factors such as GH supplementation/removal[2,10,11] or postoperative radiation therapy[9,17]may have led to the development of phenotypic changes. In a report by Dessimoz and colleagues,[8] a patient with a known microprolactinoma on dopamine agonist therapy developed acromegaly and GH autonomous secretion. In this case, the patient developed acromegaly several years after being diagnosed with a prolactinoma by laboratory and radiological data; the patient underwent surgery due to an increase in the size of the tumor and a negative response to somatostatin. Although the report does not demonstrate a change in pathology and immunohistochemistry, the patient's phenotype and progression of laboratory data suggest that de-differentiation and/or iatrogenic suppression of a subpopulation of cells could have led to a change in phenotype. It has been suggested that the same factors maintaining the homeostatic functions served by the hypothalamus-pituitary–end organ axis may impact tumorigenesis.[12,19] Exogenous medications, autocrine, and/or paracrine effectors could alter intracellular signal transduction impacting tumor growth and hormonal expression.[3,4,12,16,19] Data specifically demonstrating growth hormone releasing hormone (GHRH) receptor expression/heterogeneity and allosteric regulation may account for transformational behaviors of nonfunctional

tumors.[15] Pubertal secretion of GH may suggest a role in transformation from a non-functional state, but to our knowledge, there are no existing reports that clearly demonstrate this.

Regardless of the cause, pre-pubertal effects of excessive GH release will result in irreversible phenotypic changes. The above case suggests that patients with clinically non-functioning somatotroph adenomas may exist in an asymptomatic but susceptible state; adjuvant measures and observational strategies should be carefully considered, particularly in a developing patient.

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