JCEM Case Reports, 2023, **1**, 1–4
https://doi.org/10.1210/jcemcr/luad034
Advance access publication 21 April 2023
Case Report

Atypical Course of a Patient With AIP-Positive Acromegaly: From GH Excess to GH Deficiency and Back to GH Excess

Keren-Sandyn García-de-la-Torre, Jacobo Kerbel, Amayrani Cano-Zaragoza, and Moisés Mercado

Endocrinology Service and Endocrine Research Unit, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City 06720, Mexico

Correspondence: Moisés Mercado, MD, Endocrinology Service and Endocrine Research Unit, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Av Cuauhtemoc 330, Colonia Doctores, Mexico City 06720, Mexico.
Email: mmercadoa@yahoo.com; moises.mercado@endocrinologia.org.mx.

Abstract

Acromegaly/giantism results from the chronic excess of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), in more than 96% of cases, due to a GH-secreting pituitary adenoma. Primary treatment of choice is transsphenoidal resection of the adenoma. More than 30% to 40% of operated cases require adjunctive forms of treatment, be it pharmacological or radiotherapeutical. The multimodal treatment of acromegaly has resulted in substantial improvements in the quality of life and life expectancy of these patients. We herein present the complex case of a patient with acromegaly due to a mammosomatotrope adenoma, with a germ-line AIP (aryl hydrocarbon receptor–interacting protein) mutation, who had a chronic and protracted course of more than 15 years during which he was treated with surgery, somatostatin receptor ligands, dopamine agonist, and the GH receptor antagonist pegvisomant. At one point, he was able to come off medications and was even found to be transiently GH-deficient, only to develop acromegaly again after a couple of years.

Key Words: acromegaly, gigantism, GH, IGF-1, octreotide, cabergoline, pegvisomant, impulse control disorder

Abbreviations: AIP, aryl hydrocarbon receptor–interacting protein; CAB, cabergoline; DA, dopamine agonist; GH, growth hormone; ICD, impulse control disorder; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; PEG, pegvisomant; PRL, prolactin; rhGH, recombinant human growth hormone; SRL, somatostatin receptor ligand; ULN, upper limit of normal.

Introduction

Acromegaly/gigantism is a rare condition resulting from growth hormone (GH) hypersecretion by a pituitary tumor [1]. It is a systemic, chronic, and progressive disease with multiple comorbidities, so early diagnosis and appropriate treatment are essential to improve quality of life and reduce its high risk of mortality [1]. We herein present the complex case of a patient with acromegaly due to a mammosomatotrope adenoma, harboring a germline mutation of the gene encoding AIP (aryl hydrocarbon receptor–interacting protein), who had a chronic and protracted course of over 15 years. After undergoing unsuccessful transsphenoidal surgery, he was treated with somatostatin receptor ligands (SRLs), dopamine agonists (DAs), and the GH receptor antagonist pegvisomant (PEG), with a remarkable response in terms of GH and insulin-like growth factor-1 (IGF-1) control, as well as with significant tumor shrinkage. At one point, he was able to come off medications and later was found to be transiently GH deficient, only to develop acromegaly again after a couple of years.

Case Presentation

This previously healthy young man presented at age 18 years with a 4-year history of a progressive increment in linear growth, headache, as well as enlarged hands, feet, and nose and coarsening features. Shortly after, he developed hyperhidrosis and hand numbness and weakness suggestive of carpal tunnel syndrome. He was initially evaluated at another hospital, where he was found to have an elevated GH and IGF-1 along with a magnetic resonance imaging (MRI) scan showing a large pituitary lesion extending cephalically and laterally into the left cavernous sinus. An unsuccessful transsphenoidal resection of the pituitary lesion was attempted, about which we have little information. Apparently, an intraoperative hemorrhage precluded the resection of the lesion, and the patient developed severe diabetes insipidus with urinary volumes above 500 mL/h. When he came to us, his acromegaly was fully active, and he had evidence of panhypopituitarism as well as permanent diabetes insipidus. At the time of presentation, he was a senior high school student, who did not smoke or drink alcohol and who never used drugs. Born to a nonconsanguineous marriage, he has 2 half siblings, and his family history is unremarkable. On physical exam, his blood pressure was 160/100 mm Hg, pulse 87 per minute, weight 98 kg, height 1.80 m (body mass index 30), midparental height 1.63 m. Marked acromegaloid facies, with enlarged hands, feet, and nose, macroglossia, and diastema. Acanthosis nigricans was evident in the posterior cervical area, as well as in both axillae. He had a palpable

Received: 12 January 2023. **Editorial Decision:** 7 March 2023. **Corrected and Typeset:** 21 April 2023

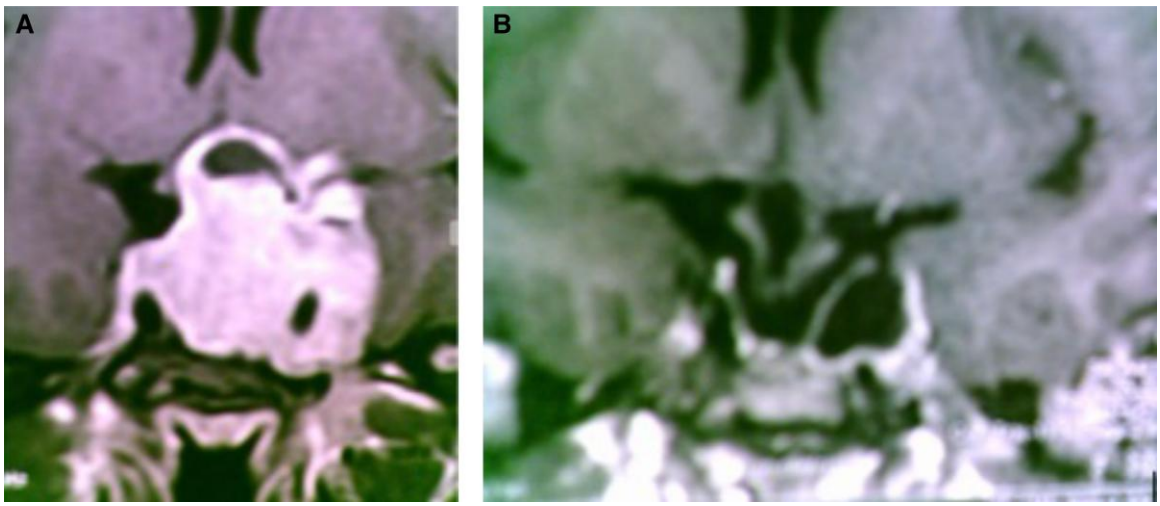

Figure 1. A, Magnetic resonance imaging (MRI) from January 2005, after unsuccessful pituitary surgery and before pharmacological therapy showing a 2.16 × 2.09 cm, predominantly solid lesion with a cystic component, isointense on T1, with suprasellar extension, displacing the optic chiasm cephalically and extending into the left cavernous sinus. B, MRI from August 2005 after treatment with octreotide LAR and cabergoline, showing a 90% reduction in tumor size, with herniation of the optic chiasm and a partial empty sella.

thyroid gland. Cardiopulmonary exam was unremarkable. Visual fields by confrontation were normal.

Diagnostic Assessment

When we first saw the patient, he was already on glucocorticoid (prednisone 5 mg daily) and thyroid hormone (levothyroxine 100 µg daily) replacement. Our initial hormonal assessment revealed a basal GH of 7.1 ng/mL (21.3 mIU/L), a nadir postglucose GH of 6.7 ng/mL (20.1 mIU/L), and an IGF-1 of 1330 ng/mL (173.8 nmol/L, 2.9× upper limit of normal [ULN]). Free thyroxine was 1.7 ng/dL (21.9 pmol/L), prolactin (PRL) 1265 ng/mL (26 615 mIU/L), follicle-stimulating hormone 1.2 mIU/mL, luteinizing hormone 0.8 mIU/mL, and total testosterone 187 ng/dL (14.7 nmol/L). Sellar MRI revealed a 2.16 × 2.09 cm (anterior-posterior and cephaloncaudal diameters, respectively) predominantly solid lesion with a cystic component, isointense on T1, with suprasellar extension, displacing the optic chiasm cephalically and extending into the left cavernous sinus (Fig. 1). He tested negative for *GNAS* (the gene encoding guanine nucleotide-binding protein alpha-stimulating activity polypeptide) and *Menin* mutations but was found to harbor a heterozygous, germline, pathogenic mutation of the gene encoding AIP (c.910 C > T, p.Arg304*). His parents and siblings were also genetically evaluated, and only his father was found to be positive for the same *AIP* gene mutation but without any clinical or biochemical evidence of acromegaly.

Treatment

The patient was kept on levothyroxine replacement and was started on octreotide LAR 40 mg every 4 weeks and cabergoline (CAB) 3 mg weekly; hydrocortisone 10 mg in the morning, 5 mg in the afternoon, and 5 mg in the evening; testosterone enanthate 250 mg monthly; and desmopressin 0.1 mg twice daily. Eight months later, his pituitary tumor showed a 90% reduction in size (see Fig. 1), along with a significant reduction, albeit not normalization of his GH, IGF-1, and PRL levels (PRL 98 ng/mL [2085 mIU/L], GH 4.7 ng/mL [2 mIU/L], IGF-1 711 ng/mL [92.9 nmol/L] or 1.6× ULN) (Fig. 2). The GH receptor antagonist PEG was added at a dose of 10 mg 3 times a week. Three months later, his IGF-1 normalized but his transaminases were found to be elevated (aspartate transaminase 634 IU/L and alanine transaminase 246 IU/L) so PEG was stopped. He was kept on octreotide LAR and CAB and a few months later GH, IGF-1, and PRL came down to normal, despite having discontinued the GH receptor antagonist. Furthermore, we were able to gradually decrease the dose of both the SRL and the DA over the course of 1 year.

Outcome and Follow-up

Over the next 2 years the patient continued to be in remission, without any medications. He then developed progressive fatigue and headaches, his IGF-1 was repeatedly below the lower limit of normal, and his GH failed to rise above 0.5 ng/mL during an insulin-induced hypoglycemia test. He was started on recombinant human GH (rhGH) at a dose of 600 µg daily; his fatigue resolved, and his IGF-1 was kept within normal limits. After a couple of years, his IGF-1 and PRL started to rise again despite the discontinuation of the rhGH (IGF-1 402 ng/mL, 1.6× ULN, PRL 301 ng/mL). It was decided to restart acromegaly treatment with CAB only at a dose of 2 mg/weekly with a significant reduction of his IGF-1 levels and resolution of his hyperprolactinemia. During the following 3 months he developed progressively worse depression, and his behavior became generally inappropriate. He became a compulsive shopper, and he began bringing home street dogs (at one point he had accumulated 9). After having argued with his mother, he unsuccessfully attempted suicide. A diagnosis of impulse control disorder (ICD) was established, the DA was discontinued, and he was started on octreotide LAR 20 mg monthly. His IGF-1 became rapidly controlled, but his PRL remained slightly elevated. The SRL injection interval was gradually increased and after a few months he was again able to come off it while maintaining a normal IGF-1. He is currently doing well on multiple hormonal replacement but off any acromegaly treatment.

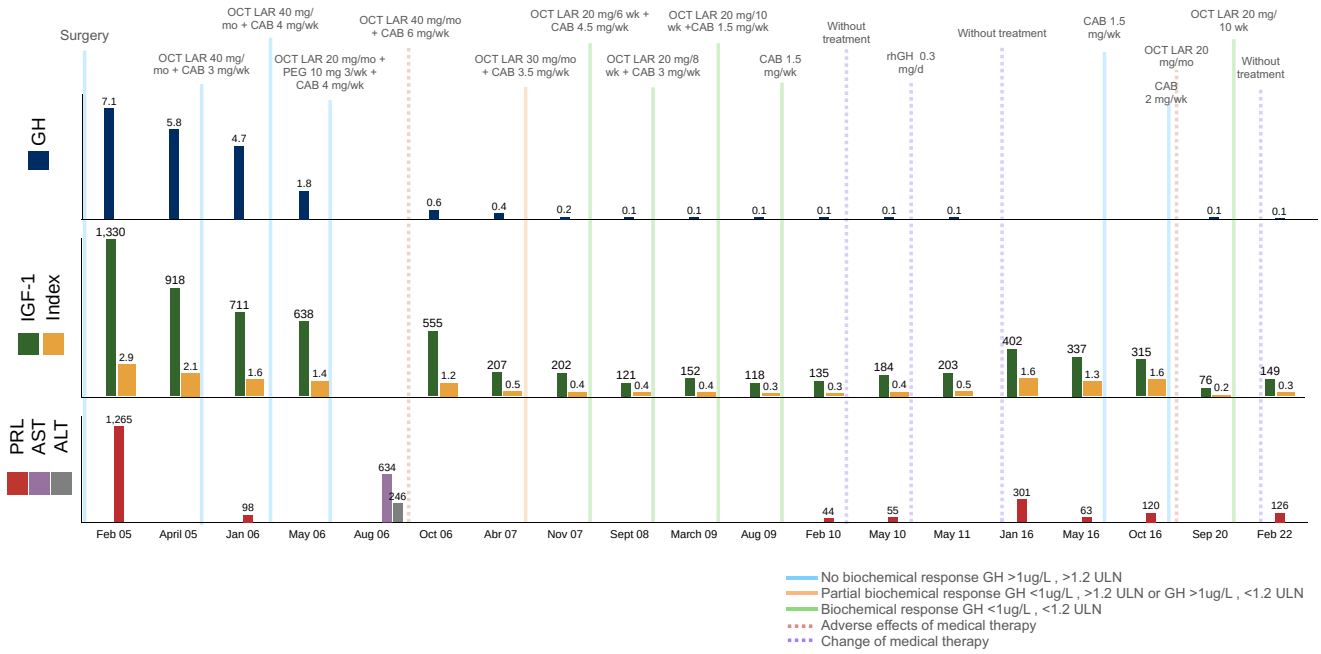

Figure 2. Biochemical response to treatment over time, from February 2005 to February 2022. ALT, alanine transaminase; AST, aspartate transaminase; CAB, cabergoline; GH, growth hormone; IGF-1, insulin-like growth factor-1; Oct LAR, octreotide LAR; PEG, pegvisomant; PRL, prolactin; rhGH, recombinant human growth hormone.

Discussion

This patient underscores how complex and protracted the course of acromegaly can be. First, it must be said that in all likelihood, he harbored a mammosomatotrophinoma, despite our not being able to document it histologically or immunohistochemically. We based this assumption on the very high PRL level he had on presentation and the fact that acromegaly patients with germline *AIP* mutations have tumors that frequently cosecrete GH and PRL [2, 3]. Patients with acromegaly/gigantism occurring in the context of germline *AIP* mutations are usually younger, have larger and more invasive tumors, and are usually less responsive to SRLs [2, 3]. It was based on the patient's tumor size and invasiveness, as well as on his elevated PRL level, that it was decided to start him on combination therapy with CAB and octreotide LAR. Somewhat to our surprise, his response was spectacular with more than 90% tumor shrinkage and a significant reduction, albeit not normalization, of GH and IGF-1 levels. CAB has been used to treat acromegaly for many years, both as monotherapy and in combination with either octreotide or lanreotide in partially responsive patients to the SRL. According to a meta-analysis that included 3 prospective and 2 retrospective studies, comprising more than 70 patients treated with CAB at a mean dose of 2.5 mg per week as add-up therapy to ongoing SRL, 51% achieved a normal age-adjusted IGF-1 after a median follow up of 7.5 months [4]. Several individual studies evaluating the efficacy of combination therapy with CAB and SRL that have been published since report IGF-1 normalization rates ranging from 37% to 40% [5]. It has been argued that acromegaly patients who respond to CAB, either as monotherapy or in combination with SRL, usually have IGF-1 levels below 1.5 x ULN [4, 5]. Despite the almost complete disappearance of the pituitary tumor and the normalization of PRL concentrations, 6 months after combination therapy our patient had marginally abnormal GH and IGF-1 levels, which prompted us to add PEG. Three months after receiving triple therapy, his IGF-1 normalized but his liver enzymes rose, so the GH receptor antagonist was stopped. PEG has been used with relative success in combination both with SRL and CAB [6]. Shortly after the addition of PEG, our patient's hepatic aminotransferases became elevated, so the GH receptor antagonist had to be discontinued. Transient elevation of liver enzymes has been known to occur in 2.5% to 15% of patients treated with PEG, both as monotherapy and in combination with SRL [6], but it seldom requires discontinuation of treatment. Despite discontinuation of the GH receptor antagonist, our patient's GH and IGF-1 continued to decline, prompting us to reduce the dose of the SRL by increasing the injection interval progressively until it was stopped. Discontinuation of SRL treatment is possible in only a minority of patients with acromegaly who had been successfully treated for several years [7]. A few months after stopping PEG, CAB was also discontinued and the patient remained in remission for several years until he presented clinical and biochemical evidence of GH deficiency, which was shortly treated with rhGH replacement. GH deficiency develops in 60% of acromegaly patients managed with multimodal treatment and it is usually permanent [8], in contrast to our patient, who after a couple of years again showed evidence of acromegalic activity.

Our patient was started on CAB monotherapy when, after being on GH replacement for 5 years, he showed clinical and biochemical evidence of acromegalic activity. After a couple of months, his symptoms improved and his PRL, GH, and IGF-1 decreased considerably; however, he became progressively depressed and started to display a rather erratic behavior characterized by compulsive shopping and the accumulation of as many as 9 street dogs in his house, culminating in an unsuccessful suicide attempt. He was diagnosed with ICD due to DA therapy, and the CAB was discontinued with a remarkable improvement. ICD, particularly featuring hypersexuality and compulsive shopping,

is increasingly being recognized in prolactinoma patients treated with DAs [9]; however, to our knowledge there is only one study addressing the occurrence of this psychiatric complication in patients with acromegaly [10].

This young man was initially treated at a private hospital by a neurosurgeon with very limited experience in pituitary tumors. Operative notes mention a persistent hemorrhage occurring early during the procedure that compromised the patient hemodynamically and eventually rendered him panhypopituitary; the tumor itself was not touched, not even biopsied. This is perhaps the most important lesson to be learned from this case: Patients with pituitary adenomas should be treated by a multidisciplinary team that includes an experienced neuroendocrinologist and a large-volume pituitary surgeon.

Learning Points

- This case highlights how protracted the course of a patient with acromegaly can be.
- Patients with acromegaly should be managed by a multidisciplinary team that includes an experience neuroendocrinologist and a large-volume pituitary surgeon.
- Perhaps the most atypical feature of this patient is the repeated recurrence of acromegalic activity even after several years of GH deficiency.
- The development of ICD secondary to DAs can occur in patients with acromegaly.

Contributors

K.G. reviewed the clinical, biochemical, and imaging information of the patient, and prepared the first draft of the manuscript; J.K. and A.C. performed the literature search and contributed to the preparation of the manuscript, as well as the design and construction of the figure; M.M. was the primary treating endocrinologist and coordinated the project and the preparation of the manuscript. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

The authors have nothing to disclose.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Clinical, laboratory and imaging data are available on request to the corresponding author.

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