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Management Strategies for Mixed GH and Prolactin-Secreting Macroadenomas Following Surgical Failure: A Case Report

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Abstract

Introduction: Acromegaly is a rare endocrine disorder characterized by excessive growth hormone (GH) production, leading to various complications. The primary treatment goal is to reduce GH and IGF-I levels, with options including surgical resection, medical therapy (e.g., somatostatin receptor ligands (SRLs), dopamine agonists, and pegvisomant), and radiotherapy. The rate of biochemical control reported varies widely across different studies. ***Case Presentation:*** A 28-year-old woman with clinically evident acromegaly, characterized by physical changes, was referred due to symptoms including snoring, dental spacing, profuse sweating, joint aches, headaches, visual blurring, and amenorrhea. She had no hypertension, galactorrhea, or diabetes mellitus. Clinical examination revealed a clear acromegalic phenotype and a thyroid goiter. Initial tests showed elevated IGF-1(687 µg/L), high prolactin (165 ng/ml), normal glucose tolerance, and normal lipid profile. MRI identified a large hyperintense mass with supra- and latero-sellar extension. Campimetry revealed a bitemporal hemianopsia in both the right and left eyes. The patient underwent transsphenoidal surgery, with histology confirming a GH/PRL adenoma. At 3 months, residual tumor was still present, and IGF-1 levels were elevated. The treatment with cabergoline and lanreotide for four years did not achieve biological or tumor control of the tumor residue, despite dosage increases. However, switching to pasireotide led to the normalization of IGF-1 levels after four months, although this was accompanied by an increase in fasting blood glucose levels. ***Conclusion:*** In summary, this case highlights the effective use of pasireotide, in combination with the dopamine agonist cabergoline, for managing acromegaly in a patient with residual disease. It underscores the importance of personalized treatment plans and the necessity for ongoing monitoring and therapy adjustments to achieve the best possible outcomes.

Keywords: acromegaly, somatostatin receptor ligands, resistance, pasireotide

1. Introduction

Acromegaly is a rare endocrine disorder caused by excessive production of growth hormone (GH), affecting men and women equally (Melmed S., 2009).

Elevated levels of GH and IGF-I lead to various somatic, cardiovascular, endocrine, metabolic, and gastrointestinal complications. Consequently, the primary therapeutic objective in managing acromegaly is to

lower the circulating levels of GH and IGF-I (Pivonello R, Auriemma RS, Grasso LF, et al., 2017; Jane JA Jr, Starke RM, Elzoghby MA, Reames DL, Payne SC, Thorner MO, Marshall JC, Laws ER Jr & Vance ML., 2011).

The main therapeutic options for acromegaly include surgical resection of adenomas, with initial remission rates of over 85% for microadenoma and 40–50% for macroadenoma (Starke RM, Raper DM, Payne SC, Vance ML, Oldfield EH & Jane JA Jr., 2013).

Except in specific cases where it is employed as the primary treatment, medical therapy is typically started for persistent disease following surgery, while radiotherapy is generally reserved as a third-line treatment option (Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al., 2014).

Medical therapy options include long-acting somatostatin receptor ligands (SRLs), dopamine agonists (particularly cabergoline), and the growth hormone receptor antagonist pegvisomant (PEG) (Ben-Shlomo A & Melmed S., 2008).

The percentage of biochemical control achieved varies significantly across different studies (Paragliola RM, Corsello SM & Salvatori R., 2017; Colao A, Auriemma RS, Lombardi G, et al., 2011).

Resistance to SRLs can be defined as the inability to meet biochemical control criteria (GH levels < 1.0 μg/L and normal age-adjusted IGF-1) and either an increase in tumor volume or less than a 20% reduction in tumor volume after at least 12 months of treatment (Colao A, Auriemma RS, Lombardi G, et al., 2011).

It has been suggested that the inadequate response to SSAs may be linked to low expression levels of somatostatin receptor subtypes (SSTRs) (Paragliola RM, Corsello SM & Salvatori R., 2017).

2. Case Presentation

A 28-year-old woman with clinically evident acromegaly was referred to our department due to the physical changes over the years, that had been noticed by the family.

She reported snoring, dental spacing, profuse sweating, joint aches, occasional headache visual blurring, galactorrhea and amenorrhea. She had normal blood pressure, with normal glucose tolerance.

At clinical examination, the patient showed a clear acromegalic phenotype, with prominence of the brow, enlargement of the nose, thickening of the lips, prognathism, macroglossia, acral enlargement, evident thyroid goiter.

Initial testing revealed IGF-1 at 687 μg/L (normal range: 150-343), with GH-nadir during an oral glucose tolerance test (OGTT) > 1ng/ml, prolactin 165 ng/ml (normal: < 20 ng/ml), estradiol level at 176 pg/ml with normal gonadotrophins, parathyroid hormone 18 pg/ml (normal: 10-65 pg/ml). The diagnosis of corticotropin deficiency and thyrotropin deficiency have been made. The patient showed normal glucose tolerance (fasting glucose 4.54 mmol/l), and normal lipid profile.

Magnetic resonance imaging (MRI) revealed a large hyperintense mass of 33*29mm with supra- and latero-sellar extension (pushing upwards the optic chiasm with bilateral, involvement of the cavernous sinus).

Campimetry revealed a bitemporal hemianopsia in both the right and left eyes.

The patient underwent a transsphenoidal surgery, without complications. Histologically, the tumor was classified as GH/PRL adenoma, with a Ki-67 labeling index < 1%.

At 3 months, the MRI evaluation revealed a persistence of a residual tissue process lateralized to the right invading the cavernous sinus measuring 15**15*18 mm, with IGF-1 at 557 ng/ml.

The patient was put on cabergoline 1 mg weekly and lanreotide90 mg monthly (34 injections).

MRI showed an almost unchanged tumor mass, and IGF-1 was above the normal level during the follow up.

Treatment was modified by increasing cabergoline to 2.25 mg/weekly and lanreotide to 120 mg/monthly. A further, very small, decrease in hormonal levels was obtained, but without reaching the target, as follows (Figure1).

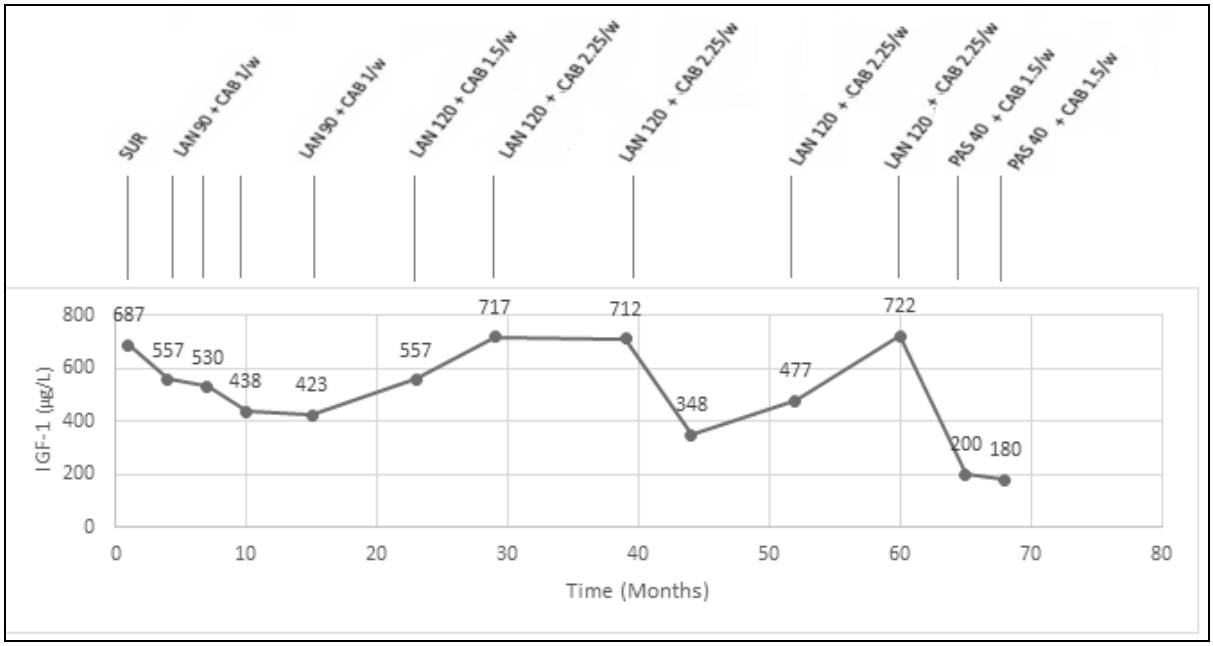

Figure 1. IGF-1 levels during the entire clinical follow-up of the patient

Given the failure to achieve therapeutic goals, the patient was put on Pasireotide 40 mg monthly. Four months after starting the treatment, we observed a normalization of the IGF-1 levels. No side effects were reported, except for a quite significant increase in fasting glucose (6.44 mmol/l).

3. Discussion

This case report highlights the effective use of pasireotide in combination with a dopamine agonist for managing a patient with acromegaly and post-surgical residual disease. The patient initially failed to achieve control with first-generation SRLs and underwent further treatment with pasireotide and cabergoline.

3.1 Tailoring Post-Surgical Management

For patients with residual acromegaly after surgery, a tailored approach to treatment is crucial.

First-generation somatostatin analogs (SSAs; long-acting octreotide and lanreotide Autogel) are the current standard of medical care for acromegaly (Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, et al., 2018; Colao A, Auriemma RS, Pivonello R, Kasuki L & Gadelha MR., 2016).

Long-acting octreotide and lanreotide Autogel, both first-generation somatostatin analogs, are the current standard treatments for acromegaly. Nevertheless, research indicates that up to 70% of patients do not achieve biochemical control with these first-generation SSAs (Bruns C, Lewis I, Briner U, Meno-Tetang G & Weckbecker G., 2002). In contrast, pasireotide, a second-generation SSA with a multi-receptor targeting mechanism, demonstrates a higher affinity for somatostatin receptor subtype 5 compared to octreotide and lanreotide, while maintaining a similar affinity for subtype 2. These two subtypes are the most commonly found on somatotroph adenomas (Corica G, Ceraudo M, Campana C, Nista F, Cocchiara F, Boschetti M, Zona G, Criminelli D, Ferone D & Gatto F., 2020).

Initially, our patient was treated with lanreotide, a first-generation SRL. Lanreotide, like octreotide, can be effective in controlling GH-secreting tumors, but the efficacy is often limited in cases of substantial residual disease or biochemical resistance.

According to a research conducted by Gadelha et al. (2020), switching to long-acting pasireotide resulted in biochemical control for some patients, and this control was maintained with ongoing treatment. The long-term safety of long-acting pasireotide was consistent with its established safety profile. These findings support the use of long-acting pasireotide for certain patients with acromegaly who remain uncontrolled on first-generation somatostatin analogs (Gadelha M, Bex M, Colao A, Pedroza García EM, Poiana C, Jimenez-Sanchez M, Yener S, et al., 2020).

In a randomized, double-blind, phase 3 trial involving 358 patients with acromegaly who had not previously undergone pharmaceutical treatment, pasireotide long-acting release (pasireotide-LAR) demonstrated superior biochemical control compared to octreotide long-acting repeatable (Colao A, Bronstein MD, Freda P, et al.,

2014). Specifically, 31.3% of patients treated with pasireotide-LAR achieved mean growth hormone concentrations below 2.5 μg/L and normalized IGF-1 levels, versus 19.2% of those receiving octreotide. The odds ratio was 1.94 (95% CI 1.19–3.17, p=0.007), indicating a statistically significant advantage for pasireotide-LAR.

In recent years, numerous in vitro and in vivo studies have investigated the factors affecting the response to first-generation SRLs treatments (Gatto F, Biermasz NR, Feelders RA, et al., 2016). These studies have identified several potential clinical, histopathological, and molecular markers that may indicate resistance.

Regarding clinical determinants, factors such as gender, age, and levels of GH and IGF-1 at diagnosis have been linked to the response to SRLs treatment. Specifically, younger male patients and those with higher GH and IGF-1 levels at diagnosis tend to show greater resistance to SRLs therapy (Paragliola RM, Corsello SM & Salvatori R., 2017).

3.2 Incorporating Dopamine Agonists

Dopamine agonists, such as cabergoline, are often used as adjunctive therapy in acromegaly, particularly when there is co-secretion of prolactin or in cases where SRLs alone are insufficient. Cabergoline primarily targets dopamine receptors to inhibit GH and prolactin secretion.

In this case, the addition of pasireotide resulted in a significant reduction in IGF-1 levels, demonstrating its effectiveness in controlling GH hypersecretion. The synergy between pasireotide and cabergoline likely stems from their complementary mechanisms. While pasireotide directly inhibits GH secretion through its receptor activity, cabergoline's dopaminergic effects add another layer of hormonal control, particularly in cases with prolactin co-secretion (Ben-Shlomo A, Liu NA & Melmed S., 2017).

Although the initial response to the combination of lanreotide and cabergoline was inadequate, the switch to pasireotide, combined with an increased dose of cabergoline, led to substantial clinical improvement. This suggests that pasireotide's broader receptor binding profile and its ability to modulate receptor signaling pathways effectively enhanced treatment outcomes. The dosing schedule of cabergoline and pasireotide also played a role in achieving better control of IGF-1 levels, reflecting the importance of optimizing treatment regimens in resistant cases.

3.3 Monitoring and Side Effects

Pasireotide, while effective, can impact glucose metabolism due to its high affinity for SSTR5, which influences insulin secretion (Gadelha MR, Gu F, Bronstein MD, Brue TC, Fleseriu M, Shimon I, van der Lely AJ, Ravichandran S, Kandra A, Pedroncelli AM & Colao AAL., 2020). This effect necessitates careful monitoring of the patient's glucose levels to manage potential side effects. The combination of pasireotide with cabergoline requires ongoing evaluation to balance treatment efficacy with the management of adverse effects.

The efficacy of pasireotide in controlling GH and IGF-I levels is attributed to its activation of SST_2 and SST_5, which are most prevalent on somatotroph adenomas (Zambre Y, Ling Z, Chen MC, Hou X, Woon CW, Culler M, Taylor JE, Coy DH, Van Schravendijk C, Schuit F. et al., 1999). Both of these receptors also play important roles in blood glucose regulation. Insulin secretion is mediated by both SST_2 and SST_5, whereas glucagon secretion is mediated mainly by SST_2 (Zambre Y, Ling Z, Chen MC, Hou X, Woon CW, Culler M, Taylor JE, Coy DH, Van Schravendijk C, Schuit F. et al., 1999). As pasireotide has a higher affinity for SST_5 than for SST_2, insulin is suppressed to a greater degree than glucagon, which results in increased glucose levels (Schmid HA & Brueggen J., 2012).

4. Conclusion

In summary, this case illustrates the successful use of pasireotide in combination with a dopamine agonist like cabergoline for controlling acromegaly in a patient with residual disease. This approach underscores the importance of personalized treatment strategies and the need for careful monitoring and adjustment of therapy to achieve optimal outcomes.

Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient Consent

Written and informed consent was obtained from the patients for publication of the submitted article.

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