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Challenges in the management of resistant acromegaly: Experience of multi-modal therapy in Sri Lanka: A case report

Dilrukshi M. D. S. A. [1], Dissanayake H. A. [1], Dissanayake P. [1], Sumanatilleke M. R. [1] , Pathmanathan S. [1], Somasundaram N. P. [1]

[1] National Hospital of Sri Lanka

Abstract

Background:

Acromegaly is a rare endocrine disorder that is associated with significant systemic morbidity and mortality. A substantial proportion of patients are unable to achieve long-term biochemical and/or tumour control despite the standard treatment [surgery and 1st generation somatostatin analog (SSA)] and develop systemic complications that depend on the duration of exposure to excess growth hormone (GH). 'Early multi-modal therapy' and 'personalized treatment' are novel concepts in the management of acromegaly based on advancements in the knowledge regarding the condition.

Case description:

A 37-year-old female was noted to have characteristic features of acromegaly when she presented with an acute febrile illness to a tertiary care centre in Sri Lanka. She had worsening headaches, increased sweating, generalized ill health along with a history of secondary amenorrhoea and galactorrhoea. Endocrine work up confirmed acromegaly with severe GH burden and prolactin co-secretion from a Knosp grade 4 pituitary-macroadenoma. The disease was complicated with poorly controlled diabetes, hypertension, and bilateral knee joint osteoarthritis. Trans-sphenoidal surgery (TSS) and subsequent cabergoline therapy failed to achieve significant biochemical and/or tumour control. Repeat TSS was not planned as per patient preference and conventional external beam radiotherapy (EBRT) and subsequent octreotide (1st generation SSA) therapy was offered which were useful in achieving satisfactory control of the residual tumour burden but failed to achieve biochemical remission. Add-on therapy with pegvisomant (a Growth hormone-receptor antagonist) was arranged through Pfizer compassionate use programme that helped to achieve normal IGF-1 levels and subsequent satisfactory blood glucose and blood pressure control without any significant adverse effects.

Conclusions:

This case highlights successful use of multi-modal therapy in managing resistant acromegaly in a resource-limited setting and the first experience of GHRA-Pegvisomant use in Sri Lanka.

Keywords : Resistant acromegaly, 1st generation somatostatin analog-octreotide, Growth hormone receptor antagonist-Pegvisomant, Multi-modal therapy

Correspondence email: dilrukmatharage@gmail.com

https://orcid.org/0000-0002-6309-7140

Introduction

Acromegaly is a rare endocrine disorder with an annual incidence of 2-11 cases per million population [1]. It occurs due to excessive secretion of growth hormone (GH) and consequent increase in IGF-1 [1]. Sporadic GH-secreting pituitary adenoma is the commonest cause [2,3]. Acromegaly is associated with significant morbidity, which include mass effects of the tumor (headache, visual impairment, cranial nerve palsy, hypopituitarism) and systemic effect of GH / IGF-1 excess like hypertension (40%), cardiac hypertrophy and arrhythmia (40%), diabetes (DM) (19-52%), obstructive sleep apnea (OSA) (60%), arthropathy (75%) cancer and increased mortality that is likely driven by cardiovascular disease and cancers [4].

Treatment goals of acromegaly are controlling the tumor mass and normalizing the GH/IGF-1 levels thereby reducing the risk / or improving co-morbidities and reducing / or normalizing mortality. With the advancement of knowledge about the disease, improved GH/IGF-1 assays, and the discovery of new pharmacological agents, the management of acromegaly has progressed towards more 'personalized treatment' and 'multimodal therapy'. Yet, the proportion of patients that remain biochemically uncontrolled disease is still as high as 20% [5], and may be higher in resource limited settings. Limitations in therapeutic options, assay variability affecting the assessment of biochemical control, and notable heterogeneity in patient and tumor-related factors are challenges to successful disease control. Additionally, limited access to specific treatment and diagnostic-modalities is a significant and the most impactful challenge faced in the resource-limited setting like in Sri Lanka.

Pegvisomant is a growth hormone receptor antagonist which has shown high efficacy in biochemical control of acromegaly [1]. We report the first patient in Sri Lanka to be treated with pegvisomant.

Case presentation

A 37-year-old female was admitted to a tertiary-care centre in Sri Lanka in July 2015 with an acute febrile illness. She reported secondary amenorrhoea and expressible galactorrhoea for 2 months |with generalized headache, malaise, and ill-health. She was the tallest in her family but no alteration in facial appearance had been noted by the family members. Her height was 170 cm, weight 72 kg and blood pressure (BP) was 140/70 mmHg. She had enlarged nose, lips, and tongue, prominent supra-orbital ridges, prognathism, large hands and feet and positive Tinel sign bilaterally. No skin tags or acanthosis nigricans was noted. Her visual fields were full.

Laboratory work-up confirmed acromegaly (Table 1), with possible co-secretion of prolactin complicated with diabetes mellitus (DM) and hypertension. Magnetic resonance imaging of the pituitary with contrast (CE-MRI) showed a large lobulated mass (2.5×2.4cm, isointense in T1W images with contrast-enhancing, hyperintense in T2W images) in the pituitary fossa suggesting an adenoma. There was a central area of hemorrhage suggestive of apoplexy and right-sided cavernous sinus invasion (Knosp grade 4). No optic chiasm compression was noted despite the supra-sellar extension (Figure 1). She underwent trans-sphenoidal surgery (TSS) of the tumour in September 2015 and histology confirmed a pituitary adenoma without atypical or malignant features.

She was started on dopamine agonist (DA), cabergoline 0.5 mg daily immediately following the TSS considering the co-secretion of prolactin. Despite completed improvement of headache and reduced severity of sweating after the TSS, biochemical improvement was negligeable and post-operative imaging at 3-months showed a significant residual tumor. Patient declined re-do surgery and SSA was not immediately available. Therefore, she was offered external beam radiotherapy (EBRT) in April 2016.

Her GH level started to fall after one year of EBRT, but IGF-1 remained persistently elevated with poor blood glucose (BG) and blood pressure (BP) control. From June 2019, she was started on subcutaneous (SC) octreotide long-acting release (LAR) preparation (initial dose of 20 mg monthly that increased to 30 mg monthly) with a satisfactory tumor control (Figure 2) at one year of treatment, but persistent sub-optimal IGF-1 control. Given the limited-resource setting, treatment escalation was not possible, hence, we applied for Pfizer compassionate use SOMAVERT®(Pegvisomant) program on behalf of the patient to arrange pegvisomant free of charge. She was commenced pegvisomant 10 mg daily subcutaneous injections in May 2020 through this program with normalization of IGF-1 level and satisfactory control of BG and BP, though there were subtle fluctuations in IGF-1 levels observed when the medication had to discontinue for a few months due to the difficulties caused by the COVID-19 pandemic (Figure 3). During the initial 6-month period of pegvisomant therapy, her liver enzymes were

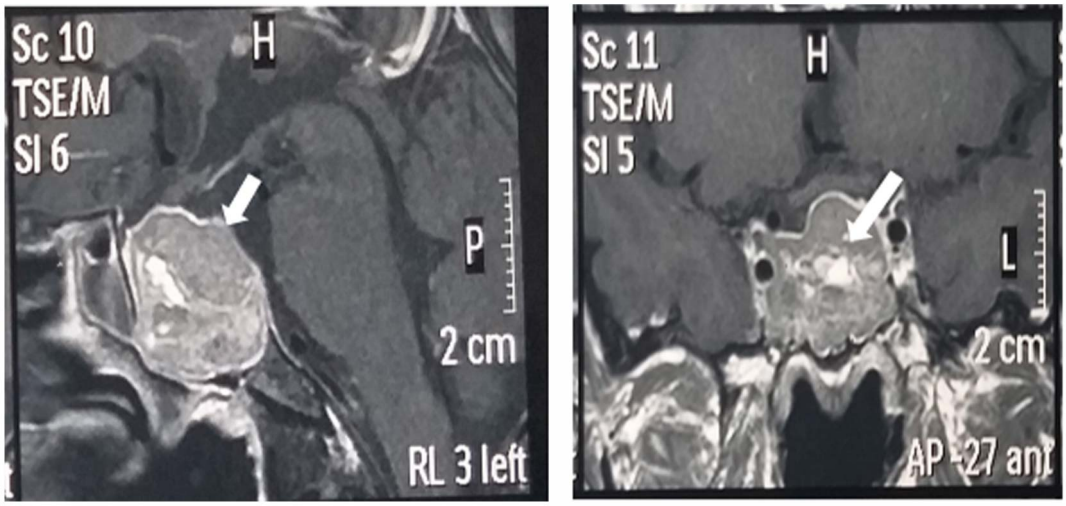

Figure 1 : CE-MRI pituitary: **(a)** saggital view. large lobulated contrast-enhancing mass lesion (2.5×2.4cm) arising from the pituitary gland (white arrow)
(b) coronal view: A central area of haemorrhage seen (white arrow). Laterally mass lesion extends up to cavernous sinuses with invasion into the right cavernous sinus (white arrow head).

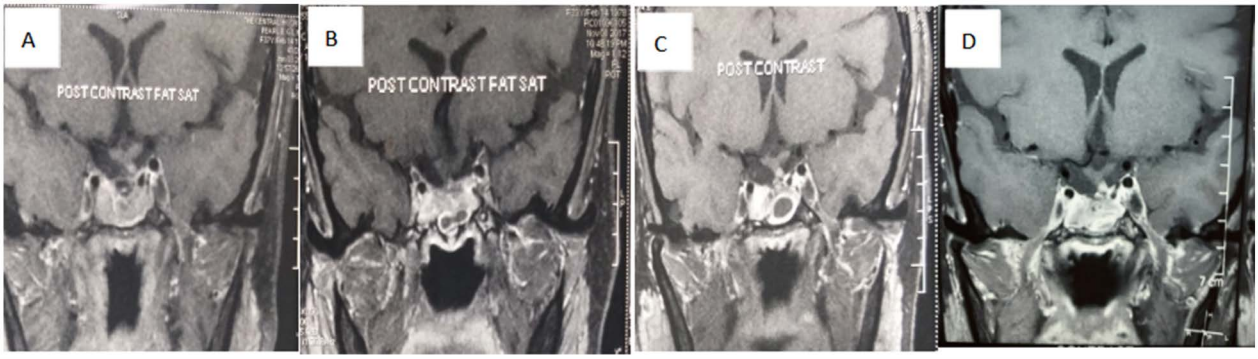

Figure 2 : Changes in CE-MRI tumour control with the disease
A - post-op 3months, **B** - 2years post-op (2017), **C** - at 3years (2018) and **D** - at 6years (2021)

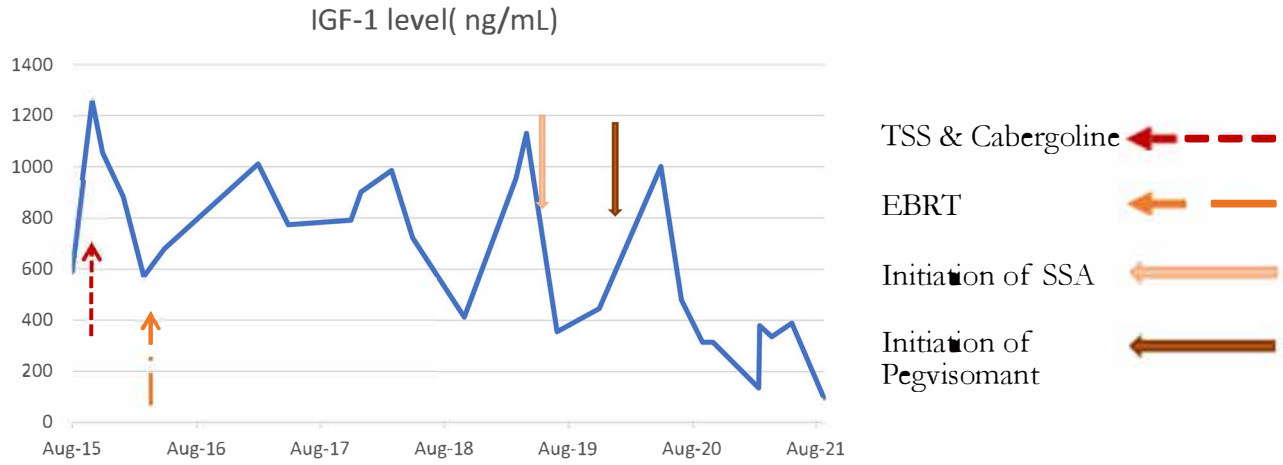

Figure 3 : Biochemical control during the disease course: IGF-1 level

transiently and mildly elevated, resolving later, without a need to discontinue treatment | However, she did not develop any lipohypertrophy at the injection sites. Tumor size remained unchanged after 6 months of treatment.

Bilateral knee joint osteoarthritis persisted despite the good biochemical control. She had secondary adrenal insufficiency, hypothyroidism, and hypogonadism following TSS that was managed with appropriate hormone replacement.

Discussion

This case report describes the first patient with acromegaly to be treated with pegvisomant in Sri Lanka. The patient had residual pituitary macroadenoma following surgery and persistent biochemical disease activity with poorly controlled diabetes and hypertension despite treatment with cabergoline, octreotide LAR and EBRT. Given the future risks for cardiovascular disease and cancer, it was prudent that disease activity was controlled.

A marked heterogeneity in the response to available treatment is observed in patients with acromegaly. Surgery, being the only treatment with a possible cure has shown variable remission rates; 34-85% overall, 75-90% for microadenoma, 45-70% for macroadenoma, and 50-60% with repeat surgery [1]. Re-do surgery was declined by the patient and even if done, would have been unlikely to produce complete tumor clearance in the presence of cavernous infiltration. Hence the need for additional interventions.

Conventional radiotherapy (external beam radiotherapy [EBRT]) has shown a remission rate of ~50-60% but has a considerable latency period before manifesting the effect [12]. Stereotactic radiotherapy (SRT) has superior efficacy and fewer adverse effects compared to EBRT achieving biochemical control in 17-82% and tumor control in 37-100% [1,4]. However, latter was not available in Sri Lanka. We offered EBRT shortly after surgery. However, anticipating the delayed response the patient was also commenced on medical therapy.

DAs are beneficial in controlling mild disease with ~35% of patients achieve biochemical control with monotherapy and >50% in combination with 1st generation SSA [2]. Its efficacy in more aggressive acromegaly is not known. Nevertheless, we offered it immediately after surgery given prolactin co-secretion with an acceptable safety profile. However, the patient showed only an incomplete response.

There is a significant heterogeneity in overall efficacy of first-generation SSAs (octreotide LAR and lanreotide autogel) ranging from 25-70% for biochemical control and ~80% for tumor control while treatment resistance is observed in ~25% of patients [7,11]. Pasireotide (a second-generation SSA) has shown superior efficacy in achieving biochemical and tumor control compared to 1st generation SSA, in treatment naïve patients and in patients resistant to 1st generation SSA. However, deterioration of diabetes control is a concern [7]. Our patient received octreotide LAR. However, the biochemical response was incomplete.

Pegvisomant has shown normalization of IGF-1 in up to 97% of patients in clinical trials [13] and up to 60% in the 'real world setting' [14]. Efficacy is further increased with combination therapy with SSA [7]. Transient elevation of liver enzymes may occur in up to 3% and needs monitoring. However, treatment discontinuation due to transaminitis is < 1% and liver failure has not been reported. During 10-year follow up in ACROSTUDY, 6.8% of patients experienced enlargement of the pituitary adenoma [15]. Furthermore, pegvisomant has shown improvement of diabetes control independent of IGF-1 reduction [15].

Several factors may predict response to treatment in acromegaly and guide a personalized approach to management and triaging patients to early multi-modal therapy. Younger age at presentation, larger tumor size and higher baseline IGF-1 levels predict treatment-resistant aggressive disease [16]. Women with acromegaly have larger, more invasive tumors compared to men independent of age, and therefore are more likely to remain uncured after surgery [7]. In contrast, female sex, older age, and lower baseline IGF-1 levels predict better biochemical control with first generation SSA therapy [7]. Tumour hypointensity on T2W MRI, dense granularity of GH vesicles (demonstrated by perinuclear staining pattern in Cam 5.2 immunohistochemistry) and SSTR2a receptor positivity are also predictive of increased response to SSA. In contrast, high Ki-67% index, a marker of aggressiveness of the tumor, predicts poor response to 1st generation SSA [17]., Responsiveness to DA is predicted by high prolactin level and mild IGF-1 elevation. Higher pre-treatment IGF-1 levels, female sex, obesity and diabetes are associated with higher pegvisomant dose requirement [1, 7].

Our patient had characteristics of aggressive disease;

Table 1 : Basic and specific laboratory workup

Parameter	Patient's value	Reference range
Haemoglobin	9.6	12-15 g/dL
Blood picture	Normochromic normocytic anemia	
Serum Creatinine	0.68	0.6 – 1.2 mg/dL
Serum sodium	139	135 – 148 mmol/L
Serum potassium	4.2	3.5 – 5.2 mmol/L
Ionized calcium	1.31	1.12-1.32 mmol/L
HbA1c	8.5%	< 5.7%
IGF 1	1257	76-271 ng/mL (Normal range for age & sex matched)
FT4	13.1	10-23 nmol/L
TSH	1.96	0.4 – 4.1 mIU/L
FSH	3.73	
LH	0.806	
Serum prolactin	6475	28 – 525 mIU/L
Serum cortisol	183	nmol/L
75g oral glucose tolerance test	GH (ng/mL)	
Basal	60.1	Note: glucose at baseline 103 mg/dL, peaked at 90 min to 196 mg/dL. Expected normal GH response is < 1 ng/mL
30	61.6	
60	57.2	
90	68.7	
120	72.3	
150	73.8	

female sex, younger age of onset, large tumor with cavernous sinus invasion, and significantly elevated GH/IGF-1 levels at diagnosis. Therefore, we rapidly escalated her treatment (early multi-modal therapy). Furthermore, radiological features (hyperintensity in T2W MRI) predicted weaker response to SSA, hence the need for treatment with pegvisomant.

A clear benefit in tumour control and biochemical control was observed with EBRT in our patient, however given the expected latency period, bridging treatment with medical therapy was prudent to reduce effects of significantly elevated IGF-1 burden as early as possible, ie. poorly controlled BG and BP. Treatment with pegvisomant brought about a significant biochemical response, with IGF-1 normalizing for the first time since diagnosis. Overall, our patient tolerated pegvisomant well except for a transient mild rise in liver enzymes which completely resolved without requiring discontinuation of the medication. Repeat MRI of pituitary did not show any tumor enlargement, very likely due to ongoing

effects of octreotide and EBRT.

The main concern in using pegvisomant in our context is the substantial cost (unit prize for pegvisomant[10mg] was 150.16 USD in 2020). However, patients with resistant acromegaly are at high risk of adverse cardiovascular outcomes, cancer, poor quality of life and shortened life expectancy all of which have economic consequences. It may be reasonable to consider pegvisomant in highly selected patients, based on clinical, radiological, biochemical and histological characteristics as well as response to available treatment options.

Conclusion

Treatment-resistance is common among patients with acromegaly. Personalized approach with early multimodal therapy is useful in achieving early disease control. Limited access to new treatment and diagnostic modalities is the major challenge encountered in management of acromegaly in resource-limited setting.

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