Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign):
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: August 2019
Date of report submission: March 2021

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: What to do if the patient continued to be Big?

Case history:

A 48-year-old decoration worker was referred to the Medical Clinic of our hospital in September 2012. He was noted to be acromegalic by ophthalmologist with coarse facial features, prominent supra-orbital ridge, enlargement of nose, prognathism, increase in inter-dental separation and dental malocclusion. In retrospect, he had increase in shoe size (European size 43 at presentation as compared to size 41 at his thirties) over the years. Loud snoring was also noticed by his wife. He did not complain of any joint pain, malaise, headache, excessive sweating, or visual disturbance. He shaved daily and denied erectile dysfunction or loss of libido.

The patient's past medical history was notable for alpha thalassemia trait, pterygium of right eye with excision done in June 2012 and history of benign gastric ulcer in 2011. He was married with an 8-year-old daughter. There was no family history of endocrine disorders.

Apart from the acromegalic features previously described, physical examination also showed spade-like hands with doughy palms and macroglossia. The patient's voice was cavernous and heavy sweating was noted over the hands. Visual field was normal by confrontation test. Goiter was absent. Tinel's sign for carpal tunnel syndrome was negative. No skin tags were found and there were no signs of arthropathy. Blood pressure was 110/78 mmHg.

Laboratory investigations revealed elevated insulin-like-growth factor 1 (IGF-1) at 809.3 ug/L (reference range: 50-317 ug/L). Random growth hormone (GH) was elevated at 72 ng/ml (reference range: ≤8.0 ng/ml).

GH was non-suppressible upon 75-gram oral glucose tolerance test (OGTT) with nadir GH level of 60 ng/ml at 1 hour. Low dose short Synacthen test showed inadequate serum cortisol response from 238 nmol/L at 0 minutes to 449 nmol/L at 30 minutes. Prolactin was elevated at 352 mIU/L (reference range: 56-278 mIU/L). Thyroid function tests, follicle stimulating hormone (FSH, luteinizing hormone (LH), adrenocorticotropic hormone (ACTH) and testosterone levels were unremarkable. He was not diabetic and lipid profile was normal. A polysomnography confirmed severe obstructive sleep apnea (OSA) with apnea-hypopnea index of 62.3/hour. Magnetic resonance imaging (MRI) of pituitary gland in January 2013 (Figure 1) showed a 1.2cm x 1.2cm x 2cm mass at the left pituitary gland with infra-sellar extension, consistent with a macroadenoma.

A diagnosis of acromegaly caused by a GH-secreting pituitary macroadenoma was made. Comorbid OSA, secondary adrenal insufficiency and mild hyperprolactinemia which could be due to stalk effect or tumor co-secretion, were also present. The patient was put on oral hydrocortisone replacement and started on continuous positive airway pressure (CPAP) therapy. He was subsequently referred to Neurosurgery. Trans-sphenoidal excision of pituitary tumor was performed in April 2013. Pathology findings were consistent with pituitary adenoma.

Three months after the surgery, IGF-1 was found to be persistently elevated at 497 ug/L. GH remained non-suppressible after 75-gram OGTT with nadir GH of 9.6 ng/ml at 2 hours. Cabergoline was commenced for persistently active disease and was titrated up to 2 mg weekly. Follow-up MRI of pituitary gland in December 2013 and October 2014 showed complete removal of the previous tumor and post-operative changes only.

However, the patient's disease remained uncontrolled over the next year. His IGF-1 levels were increasing despite up-titration of cabergoline. Repeat surgical exploration of the pituitary gland was pursued by the neurosurgical team in December 2014. A small piece of suspected tumorous tissue was resected while pathological examination revealed normal pituitary tissue only. Activity of the disease as measured by GH and IGF-1 was unchanged. Subsequently cabergoline was switched to monthly long-acting octreotide injection for disease control.

Further follow-up MRI pituitary in February 2015 showed probable 0.9 cm microadenoma at postero-inferior corner of sphenoid sinus extending to clivus. The patient was then referred for stereotactic radiosurgery, which was performed by Oncology team in October 2015. However, the disease remained active at more than 3 years post-radiosurgery as evidenced by a rebound elevation of GH and IGF-1 upon trial of octreotide withdrawal. Octreotide therapy was therefore continued and normalization of serial IGF-1 and GH levels was achieved in the past 2 years. Meanwhile, follow-up MRI pituitary in April 2019 and April 2020 showed static size of the adenoma. Last but not least, the patient's symptoms of soft tissue overgrowth were ameliorating and the medical treatment was well tolerated by the patient. He would be continuously monitored for disease

remission in longer term and post-radiation hypopituitarism.

Discussion and literature review

This case illustrated the complexity of managing a patient with persistently active acromegaly after trans-sphenoidal surgery.

Although tumor resection via trans-sphenoidal surgery is recommended the first line treatment in most patients with acromegaly caused by a GH-secreting pituitary adenoma, remission rate can only be achieved in about 50-70% of patients harboring macroadenoma even in specialized referral center. These figures dramatically decrease when the tumor is invasive or very large (e.g. >4 cm), in patients with very high preoperative GH levels and in neurosurgical unit with small patient volume and less experienced.[1]

In any circumstance where adjuvant therapy is pursued, active disease should be confirmed by proper endocrine assessment. This is accomplished by measurement of age-adjusted IGF-1 and GH at approximately 12 weeks after surgery. An elevated IGF-1 level, together with high basal GH >1ng/L or non-suppressed nadir GH >0.4ng/L after a glucose load, is highly suggestive of residual disease. These cutoffs are associated with increased mortality, increased morbidities and risk of relapse after surgery in patients with acromegaly and argue for the need of additional therapy. A repeat MRI of the sellar region should also be pursued not earlier than 12 weeks for anatomical delineation of any residual tumor.[2]

After confirming persistently active acromegaly as in our patient, consideration should be made to select the most appropriate therapy on a case-by-case basis. Indeed, the selection of adjuvant therapy after failed trans-sphenoidal surgery is complex and a multidisciplinary team approach is recommended. Multiple factors including patient factors (e.g., age, co-morbidities), tumor factors (e.g., residual size and location of tumor) and disease factors (e.g., degree of biochemical activity) have to be taken into account. A thorough clinical, biochemical, radiological and

pathology assessment is required for optimal personalized management. The overall goals of therapy include biochemical control, control of tumor mass effects, improvement of symptoms and signs of the disease and reversal of comorbidities and mortality risk.

Viable options for persistent acromegaly after pituitary surgery included surgical re-exploration, medical therapy and radiotherapy. Table 1 shows a proposed algorithm for treatment of persistent acromegaly after surgery.

Firstly, for repeated surgery, the results are generally less favorable than those in primary operations but still a 50–60% remission rate has been described in small and retrospective series.[3] This was accompanied by an increased rate of complications, such as transient diabetes insipidus and meningitis, but no increase in mortality. Factors favoring a second pituitary operation for persistent disease include persistent mass effect on the optic chiasm, the need for debulking large tumors to improve response to medical treatment and a residual intrasellar tumor where complete resection is deemed possible. Patient's age, comorbidities and preference should also be taken into account.

On the other hand, major guidelines recommend medical therapy for patients with persistent disease despite surgical resection of the adenoma as well as for patients in whom surgery is not appropriate. First-line medical treatment includes dopamine agonist, namely cabergoline and first-generation somatostatin receptor ligands including long-acting octreotide and lanreotide. Second-line medical treatment includes pegvisomant, a GH receptor antagonist and pasireotide, a second-generation somatostatin receptor ligand.

Cabergoline monotherapy results in biochemical control rates of approximately 35%. However, the benefits are largely limited to patients with mildly elevated levels of IGF1 at baseline, with the greatest benefit seen in those with IGF1 levels ≤1.5 times the upper limit of normal (ULN). Prolactin co-secretion does not predict the response with dopamine agonist. In general, cabergoline is considered as a first-line medical therapy or as an addition to first-generation somatostatin receptor ligants in patients with IGF1 levels <2-2.5 times the ULN.[4]

Somatostatin receptor ligands (SRLs) are suggested to be used in patients with higher IGF1 levels. Rate of Biochemical control is approximately 55% with the first-generation SRLs octreotide and lanretotide.[7] Octreotide long-acting release (LAR) is administered once monthly by intramuscular injection, and lanreotide autogel is administered once monthly subcutaneously. Efficacy rates are similar for the two agents. More recently, an oral form of octreotide (oral octreotide capsules) has been approved in the United States. It is indicated as long-term maintenance treatment in patients with acromegaly who have responded to octreotide or lanreotide, obviating the need for deep intramuscular injection. Its efficacy is comparable to the injectable form of first generation SRLs.[5]

Pegvisomant is a GH receptor antagonist. Pegvisomant monotherapy administered as second-line therapy yields biochemical control rates more than 90% in clinical trials and around 60% in real-world surveillance studies.[6] It is considered when patient has minimal or no response to first-line medical treatment, or has impaired glucose metabolism due to SRLs. However, it is very expensive and currently not available in Hong Kong.

Pasireotide is a multireceptor-targeted somatostatin analogue with higher affinity to somatostatin receptor type 1, 2, 3 and 5. Biochemical control rates with pasireotide are higher than those achieved with octreotide in patients who have not previously been treated with an SRL.[7] However, normalized levels of IGF1 are still achieved in fewer than half of patients treated with pasireotide, and nearly 70% of patients treated with pasireotide exhibited hyperglycemia-associated adverse effects. In patients who are previously treated and do not respond to first generation SRLs, biochemical control may be achieved in 15-20% of patients after switching to treatment with pasireotide. However, predictors for pasireotide effectiveness are not clearly defined. Therefore, pasireotide is considered a second-line therapy in patients with inadequately controlled disease on octreotide or lanreotide who showed improvement in biochemical control after switching to pasireotide.[8] Combination therapy can also be considered in patients failing monotherapy. Amongst various combinations, pegvisomant with SRLs has yielded the highest biochemical control rates, with rate exceeding 70% with the pegvisomant-pasireotide combination.[9]

Radiotherapy is considered in patients whose disease is not controlled by surgery or medical therapy. Radiation can be administered as a single dose ("stereotactic radiosurgery," or SRS) or fractionated radiotherapy (FRT). The most commonly used stereotactic method used is the Gamma Knife. In a meta-analysis, median time to achieve disease control was 3.0 years for FRT and 2.1 years for SRS, and the 10-year remission rate was 48% and 52% for FRT and SRS, respectively. 29% of patients developed hypopituitarism at a median of 29.5 months with SRS.[10]

In our patient, cabergoline was chosen as the initial adjuvant medical therapy in our patient in view of the modestly elevated IGF-1, lower cost and availability in our center. The second operation was an exploratory one in the absence of a definite tumor shown on MRI imaging. He responded favorably to long-acting octreotide, a first generation SRL, with normalization of IGF-1 and GH. Radiosurgery was performed in an attempt to alleviate the burden of lifelong treatment of parenteral treatment and address the cost concern.

In conclusion, the management of acromegaly depends on multi-disciplinary team approach with close collaboration among endocrinologists, neurosurgeons, radiologists and oncologists. Adequate knowledge of the multiple comorbidities, signs and symptoms, and biochemical parameters is important for determination of disease activity, choices of interventions and continuous surveillance.

Tables and figures (where applicable) (no more than two figures)

Figure 1. MRI (January 2013) confirmed pituitary tumor with a size of 1.2cm x 1.2cm x 2cm.

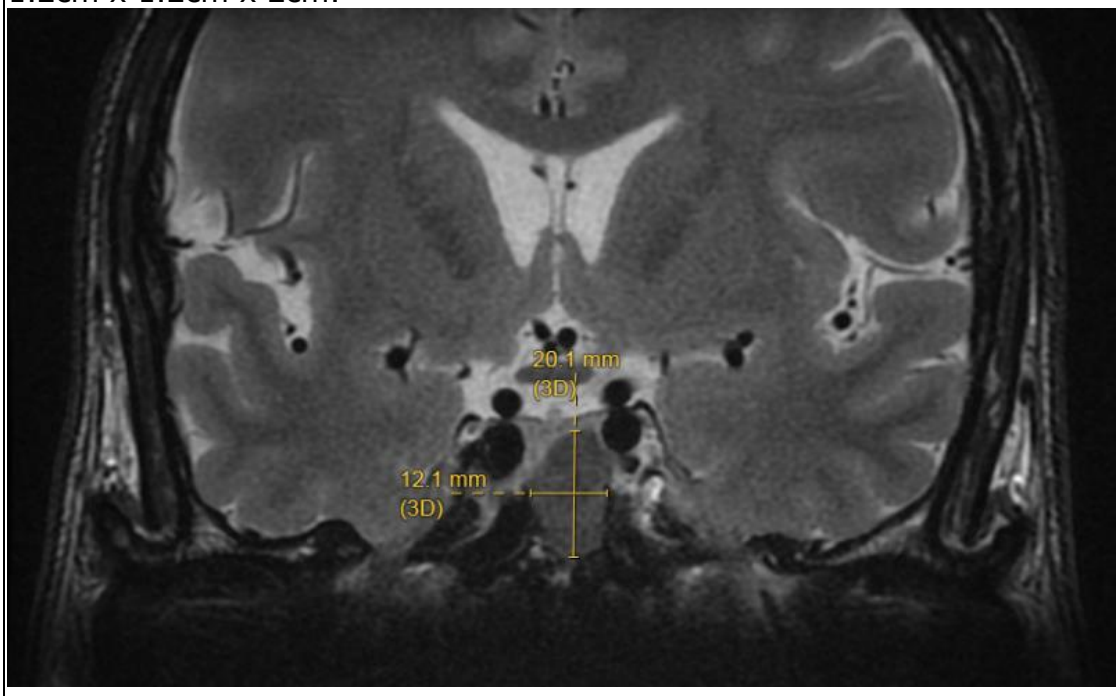
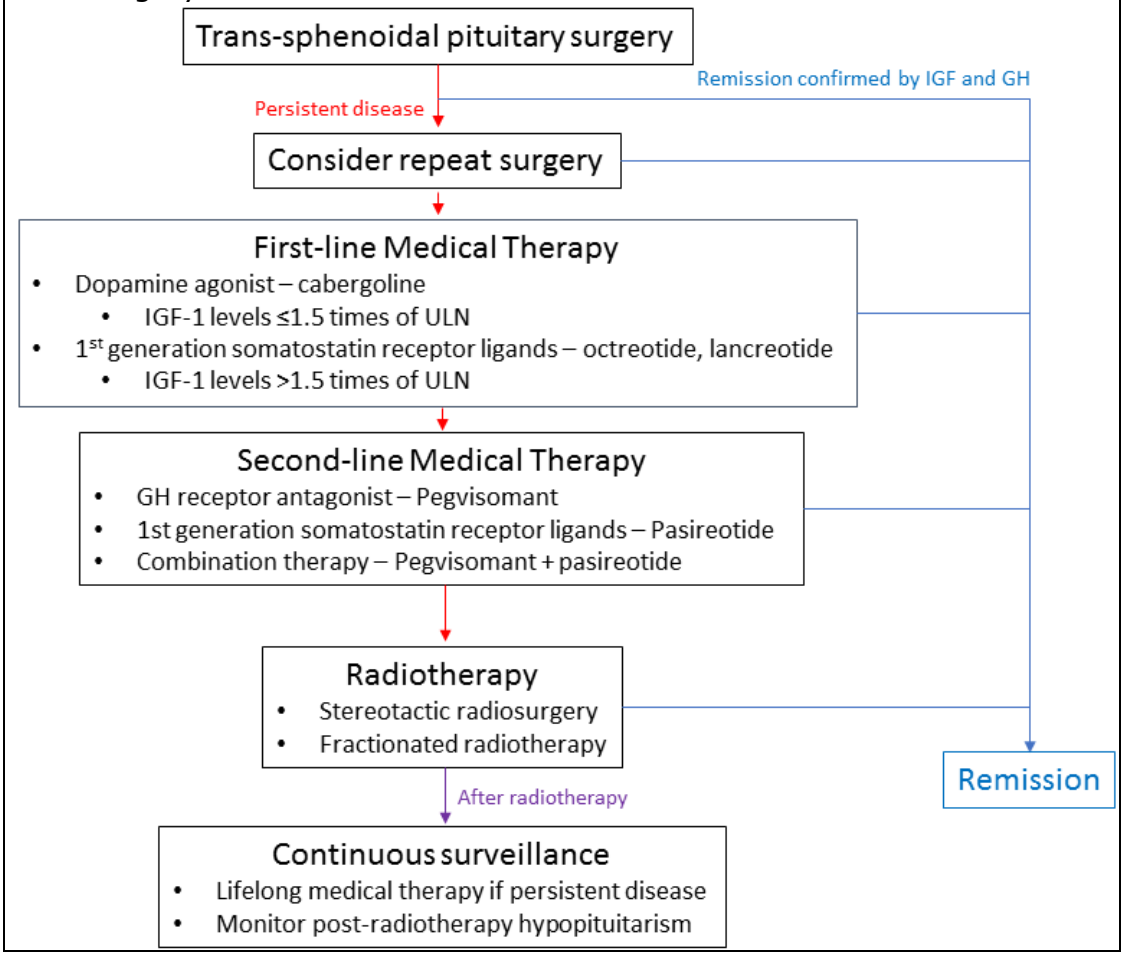


Table 1. A proposed algorithm for treatment of persistent acromegaly after surgery



Reference (not more than 10)

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generation somatostatin analogues (PAPE study). J Clin Endocrinol Metab 103(2):586 – 595.
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No of words in Case History and Discussion (excluding references): 1863
(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

_____
(signature of Trainee)

Endorsed by Supervisor *

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