

Acromegaly with empty sella syndrome

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Summary

Acromegaly is a rare, chronic progressive disorder with characteristic clinical features caused by persistent hypersecretion of growth hormone (GH), mostly from a pituitary adenoma (95%). Occasionally, ectopic production of GH or growth hormone-releasing hormone (GHRH) with resultant GH hypersecretion may lead to acromegaly. Sometimes localizing the source of GH hypersecretion may prove difficult. Rarely, acromegaly has been found in patients with an empty sella (ES) secondary to prior pituitary radiation and/or surgery. However, acromegaly in patients with primary empty sella (PES) is exceedingly rarely and has only been described in a few cases. We describe a 47-year-old male who presented with overt features of acromegaly (macroglossia, prognathism, increased hand and feet size). Biochemically, both the serum GH (21.6 µg/L) and insulin-like growth factor 1 (635 µg/L) were elevated. In addition, there was a paradoxical elevation of GH following a 75 g oral glucose load. Pituitary MRI demonstrated an ES. In order to exclude an ectopic source of GH hypersecretion, further biochemical tests and imaging were done, which were unremarkable. Notably, increased uptake in the sella turcica on the ⁶⁸Gallium DOTATATE PET/CT confirmed the ES as the likely source of GH secretion. As no overt lesion was noted, medical treatment (octreotide acetate) was initiated with a good clinical and biochemical response. At his 3 month follow-up, he reported an improvement in symptoms (fatigue and headache), however he still complained of low libido. Due to a persistently low testosterone level at follow-up, a long-acting testosterone was initiated. His GH level normalised, and IGF-1 has significantly reduced.

Learning points:

- The commonest cause of acromegaly is due to GH hypersecretion from pituitary adenomas (95%).
- Acromegaly has rarely been found in patients with ES.
- It is important to exclude a past history suggestive of pituitary apoplexy.
- Extra-pituitary source of GH such as ectopic production of GHRH with resultant GH hypersecretion needs to be excluded.
- In such cases, since there is no resectable mass, medical therapy is the primary treatment option.

Background

Acromegaly is a rare pituitary disorder caused by growth hormone GH hypersecretion. The estimated prevalence is 30–70 individuals per million with an annual incidence of 3–4 cases per million (1). Circulating GH stimulates insulin-like growth factor 1 (IGF-1) production by the

liver and systemic tissues, which mediates the somatic and metabolic effects of GH.

Hypersecretion of GH leads to excessive production of IGF-1 and hence acromegaly, a multisystem disease. The characteristic features include (in descending order

of frequency) acral and facial changes, hyperhidrosis, headaches, paraesthesia, sexual dysfunction, hypertension, goiter, and rarely, visual field defects (2). Acromegaly is associated with multiple co-morbidities including (but not limited to) hypertension, cardiac failure, arrhythmias, obstructive sleep apnoea, type 2 diabetes mellitus, arthritis, and carpal tunnel syndrome. If left untreated, mortality associated with cardiovascular, cerebrovascular, and pulmonary dysfunction increases, and life expectancy is reduced by up to 30% (3, 4).

The aetiology of acromegaly is due to GH hypersecretion from pituitary adenomas (95%) and in rare cases, ectopic production of GH or growth hormone releasing hormone (GHRH) with resultant GH hypersecretion. Localizing the source of GH hypersecretion may prove difficult sometimes. Rarely, acromegaly has been found in patients with an empty sella (ES) secondary to prior pituitary radiation and/or surgery (5, 6, 7). However, this has rarely been described in patients with a primary empty sella (PES) (8, 9, 10).

We describe a case of a 47-year-old male who presented with clinical and biochemical features of acromegaly, who had an ES on pituitary MRI.

Case presentation

A 47-year-old unemployed African man presented to the endocrine clinic with a history of fatigue, headaches, and low libido. He reported no nausea, vomiting, or any change in vision. There was no other significant medical, family, or drug history. In addition, he had no prior history of pituitary imaging, surgery, or head and neck radiation. Upon further questioning, he admitted to coarsening of his facial features which were also noted in comparison to photographs of him at a younger age. Furthermore, he reported difficulties with putting on his wedding ring for the last 5 years and having to purchase new shoes (US size 11) as his previous pairs (US size 9) no longer fit him.

On examination, he was 1.88 m (74 inches) tall, weighed 106 kg with a BMI of 30 kg/m². Blood pressure, heart rate, respiratory rate, and temperature were all normal. The patient had an acromegalic appearance with coarse facial features, a big nose, prognathism, malocclusion of his teeth, enlarged tongue and lips (Figs 1 and 2). His hands were large and spade-like, with thickened sausage-shaped fingers (Fig. 3), with oily and sweaty skin. Systemic cardio-respiratory and abdominal examinations were otherwise unremarkable. He had no palpable goitre and visual fields, visual acuity and fundoscopy were normal.



Figure 1

Face showing coarse facial features, prominent brow, big nose, and enlarged thick lips.

Investigation

Biochemical investigations highlighted elevated GH and IGF-1 levels (Table 1). There was a paradoxical elevation of GH following a 75 g oral glucose load (Table 2). The gonadal axis revealed a low testosterone level with inappropriately normal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Prolactin levels (post-PEG precipitation) were elevated but were below 100 µg/L. The remainder of the pituitary panel investigations (adrenocorticotropic hormone (ACTH), cortisol, tetraiodothyronine (T4), and thyroid-stimulating hormone (TSH)) was normal (Table 1).

MRI of the brain revealed cerebrospinal fluid intensity signal in the sella confines with enlargement and remodelling of bony sella turcica, in keeping with an ES (Figs. 4, 5, 6). In order to exclude an ectopic source of the GH hypersecretion, further biochemical (plasma chromogranin A and calcitonin, 24-h urine metanephrines



Figure 2
Side view highlighting prognathism and large ears.



Figure 3
Acral enlargement of the hand highlighting large spade-like hand with thick sausage like fingers.

and normetanephrines) and imaging (neck, chest, and abdominal CT) tests were performed, all were unremarkable.

Whole-body ^{68}Ga DOTATATE PET/CT revealed uptake in the pituitary gland in keeping with physiological somatostatin expression within the sella turcica (Fig. 7).

Based on the biochemical and radiological findings, a diagnosis of acromegaly with an ES was made.

Treatment

The patient was started on medical therapy. A monthly long-acting somatostatin analogue (octreotide acetate 20 mg i.m. injection) was initiated.

Outcome and follow-up

At his 3 month follow-up, he reported an improvement in symptoms (fatigue and headache), however he still complained of low libido. Due to a persistently low testosterone level at follow-up, a long-acting testosterone therapy (250 mg testosterone undecanoate) was started. His GH level normalized, and IGF-1 has significantly reduced (Table 1). In the absence of therapy, the prolactin level has improved.

The patient will continue to be monitored and his biochemistry and imaging will be repeated at his 6-month follow-up appointment.

Discussion

ES refers to a neuro-radiological entity characterized by a cerebrospinal fluid-filled sella turcica, with the normal pituitary gland compressed to the rim of the fossa (11). ES may be classified as primary (PES) or secondary (SES) based on the aetiology. PES is rare and occurs in individuals with no prior pituitary disease. Its aetiology is unclear but has been linked to incompetence or absence of the diaphragma sella, chronic intracranial hypertension, or temporary expansion followed by the regression of the pituitary gland (12). SES is related to pathological processes within the sella region; such as pituitary atrophy after medical treatment, surgery, radiotherapy, apoplexy, postpartum pituitary necrosis, pituitary infections, autoimmune diseases of the pituitary, malignancies, and trauma (13).

Contrary to conventional belief, ES is frequently associated with a variety of neurological and endocrine disturbances. Most patients with PES syndrome are found to have a normal pituitary function, while about 30% have



Table 1 Summary of biochemical results.

Variable	Result	3 month follow-up	Reference range
Growth hormone (GH)	21.6	2.0	<0.03–2.47 µg/L
Insulin-like growth factor (IGF-1)	635	275	53.0–215 µg/L
Post PEG prolactin	35.0	21.3	3.0–11.6 µg/L
Luteinising hormone (LH)	2.6	1.3	1.7–8.6 IU/L
Follicle-stimulating hormone (FSH)	10.9	9.8	1.5–12.4 IU/L
Testosterone	5.2	8.5	8.8–27.9 nmol/L
Thyroid-stimulating hormone (TSH)	0.56	1.79	0.35–4.95 mIU/L
Tetraiodothyronine (T4)	17.0	13.5	9.1–19.0 pmol/L
Adrenocorticotrophic hormone (ACTH)	4.3	3.6	1.6–13.9 pmol/L
Cortisol	173	214	133–537 nmol/L
Chromogranin A	56.9		0–84.7 ng/mL
Calcitonin	2.1		<11.8 ng/L
24-h urine metanephrines	1187		480–2424 nmol/24 h
Normetanephrine:creatinine	102.87		28–158 nmol/mmol creatinine
24-h urine metanephrines	731		264–1729 nmol/24 h
Metanephrine:creatinine	71.14		15–89 nmol/mmol creatinine

Bold values are to highlight the abnormal parameters

varying degrees of hypopituitarism (14). Acromegaly has occasionally been found in patients with SES following prior pituitary irradiation and/or surgery. However, acromegaly in patients with PES is exceedingly rare and limited to a handful of case reports and a few retrospective studies. In a single retrospective study of 76 patients with ES, only 3 patients were diagnosed with acromegaly (9, 15, 16, 17, 18). Following this, three retrospective studies conducted between 2004 and 2017 reported acromegaly with ES in 20.3% (19), 22% (20), and 15.4% (21) of cases, respectively.

The most commonly held hypothesis concerning the aetiology of acromegaly with PES includes an undetectable microadenoma in the pituitary tissue lining the sella as the source of excess GH production or silent infarction of a pituitary mass or adenoma with the development of a partial or total ES (22). Other hypotheses cite downward growth of an adenoma, enlargement of the sella and sella floor remodelling through compression or direct effect on the bone from elevated GH and IGF-1 levels (19, 20).

Our patient has an ES without a history of a prior pituitary procedure or head and neck radiation. As such, we postulate he most likely had a prior pituitary microadenoma, which underwent asymptomatic and silent infarction and

subsequent development of a total ES. It is evident that the infarct did not totally ablate the hyperfunctioning tissue in this patient, as demonstrated by elevated, non-suppressible GH levels and uptake shown in the pituitary fossa on the ⁶⁸Gallium DOTATATE PET/CT scan.

Pituitary adenomas are associated with headaches, but so too is ES. A number of patients with PES present with headaches, which are described as lateral, persistent, and datable for years (23). Our patient's presentation of headache may be multifactorial including a possible initial pituitary adenoma, an ES, or directly from an elevated GH level.

Table 2 75 g oral acromegaly glucose tolerance test.

	Glucose (mmol/L)	Growth hormone (µg/L)
Reference range (min)		<0.03–2.47
0	6.7	8.7
30	9.1	8.2
60	9.1	7.8
90	7.2	7.7
120	4.4	9.4

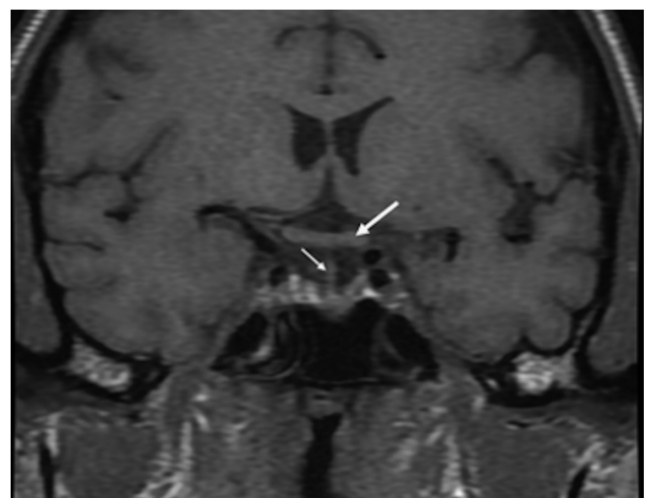


Figure 4

Coronal T1 weighted cut demonstrating empty sella with optic chiasm (large arrow) and pituitary stalk (small arrow) extending to the residual thinned and flattened pituitary tissue visible along the base of the sella.

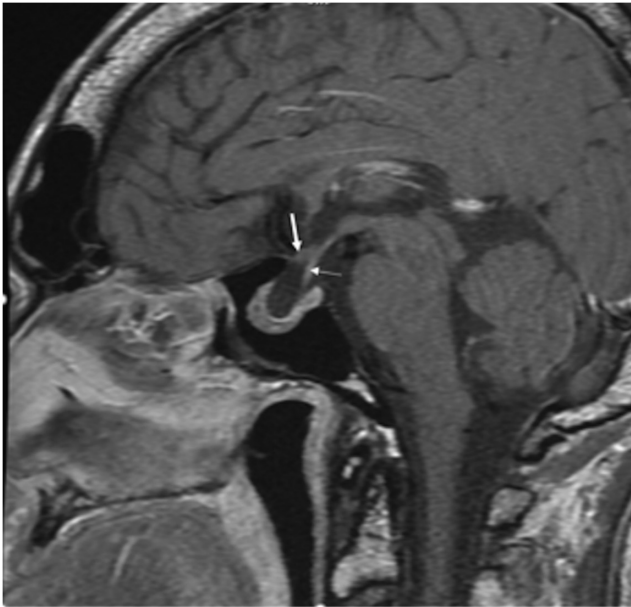


Figure 5
Sagittal T1 weighted cut demonstrating empty sella with optic chiasm (large arrow) and pituitary stalk (small arrow) extending to the residual thinned and flattened pituitary tissue visible along the base of the sella.

Ectopic acromegaly occurs due to the secretion of GHRH or rarely GH from extra-pituitary tumors (24). When compared to a pituitary cause of acromegaly where GHRH levels may be normal or more often suppressed, in the case of ectopic GHRH secretion, serum GHRH levels are raised (25, 26, 27). Typically, ectopic tumours secreting GHRH or GH are located within the chest or abdominal cavity and are easily detectable by conventional radiological techniques

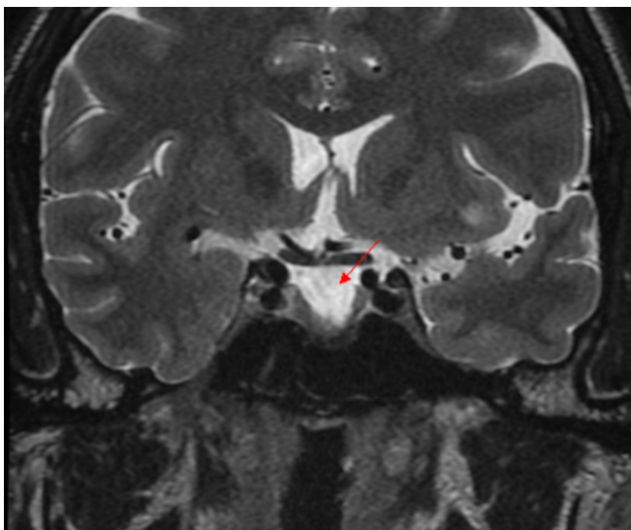


Figure 6
Coronal T2 weighted cut demonstrating empty sella (arrow).

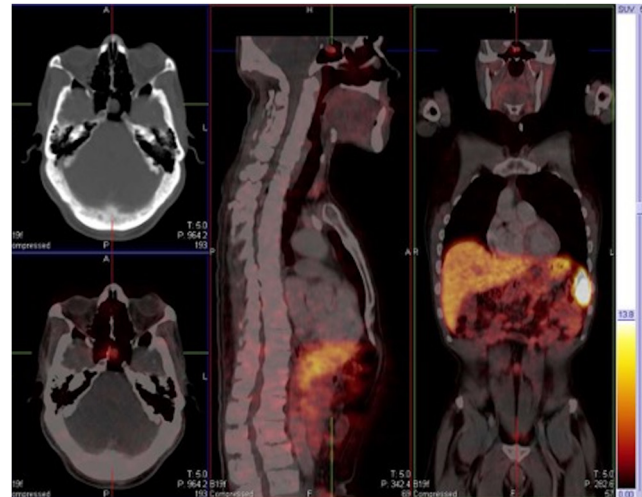


Figure 7
⁶⁸Gallium DOTATATE PET/CT showing receptor activity in the pituitary gland due to physiological somatostatin receptor expression.

(CT or MRI). As these tumours suppress somatostatin receptors, they may also be detected using somatostatin scintigraphy, which is particularly useful in the detection of smaller tumours, or metastatic disease (27).

In our case, due to the normal neck, chest, and abdominal CT and as the ⁶⁸Gallium DOTATATE PET/CT scan which did not demonstrate extra-pituitary uptake, it is unlikely an ectopic source of GHRH or GH secretion was present.

Since no resectable pituitary mass is present, medical management with somatostatin analogues remains the only viable treatment option that may be offered to patients with acromegaly and an ES.

Conclusion

Whilst the underlying mechanism remains unclear, the co-existence of acromegaly and ES is not rare. However, PES with acromegaly is exceedingly rare. This case demonstrates that despite ES syndrome, the source of GH hypersecretion can still be from the pituitary fossa. In such cases, an undetectable microadenoma in the pituitary tissue lining the sella is thought to be the source of excess GH production.

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 informed consent was obtained from the patient for submission of the publication and accompanying images.

Author contribution statement

R Daya wrote the first draft of the manuscript. R Daya, F Seedat, S Bulbulia, K Purbhoo, and Z Bayat edited the submitted manuscript. Z Bayat supervised the overall preparation of the manuscript. All authors reviewed the final manuscript and reviewed it for publication.

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