Brief Communication

# Plurihormone secreting pituitary macroadenoma masquerading as thyrotoxicosis: Clinical presentation and diagnostic challenges

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## ABSTRACT

Thyroid stimulating hormone (TSH) secreting adenomas are the rarest type of pituitary adenomas (1:1000000 in the population; 0.2-2.8% of adenomas). Plurihormonal thyrotropic adenomas are even rarer usually having cosecretion of growth hormone (GH) and prolactin. We report perhaps for the first time, TSH, GH, adrenocorticotrophic hormone (ACTH) and gonadotropins secreting pituitary macroadenoma diagnosed in a 40 year lady presenting with features of thyrotoxicosis for 5 months, amenorrhea for 3 months and newly diagnosed diabetes and hypertension for 2 months along with headache, nausea, and vomiting, who had acromegaloid habitus, grade-II goitre, increased uptake on Technitium-99 pertechnate thyroid scan (4.1%; normal: 0.24-3.34%), with increased T3 (5.98 pg/ml; 1.5-4.1), increased T4 (2.34 ng/dl; 0.9-1.8), inappropriately high TSH (2.32 μIU/ml; 0.4-4.2), insulin like growth factor-1 (711 ng/ml; 109-264), non-suppressed post-glucose GH (15.9 ng/ml; <1 ng/ml), normal estradiol (52 pg/ml; 21-251), inappropriately high luteinizing hormone (53.5 mIU/ml; 1.1-11.6), inappropriately high follicle stimulating hormone (59 mIU/ml; 3-14.4), non-suppressed overnight dexamethasone cortisol (5.8 mcg/dl; <2), elevated ACTH (58 pg/ml 5-15), withdrawal bleed on progestrogen challenge, bitemporal hemianopia on automated perimetry and pituitary macroadenoma on MRI imaging of sella. Thyroid hormone resistance was ruled out by documenting normal sex hormone binding globulin and ferritin levels. Her clinical and biochemical phenotype was not suggestive of multiple hormone resistance seen in pseudohypoparathyroidism. This report intends to highlight the challenges in the diagnosis of plurihormonal thyrotropic adenoma.

**Key words:** Gonadotropins, growth hormone, pituitary adenoma, plurihormonal, thyroid stimulating hormone

## Introduction

Plurihormonal adenomas (PhAs) are monomorphous, bimorphous or polymorphous tumors, usually monoclonal in origin, having complex immunohistochemistry profiles of the seven different hormones secreted from the pituitary, along with biochemical and phenotypic evidence of secretion of two or more different hormones.[1] Prolactin along with growth hormone (GH) secretion is the most common type of PhA.[1] Thyroid stimulating hormone (TSH) secreting adenomas are the rarest type of pituitary adenomas (prevalence of 1:1000000 in the population; 0.2-2.8% of adenomas), usually macroadenoma, and up to 30% have associated secretion of other hormones like GH and prolactin and very rarely luteinizing hormone (LH) and follicle stimulating hormone (FSH).[2]

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## Case Report

SD, 40 year lady, newly diagnosed diabetic (on metformin 1 g/day) and hypertensive (on amlodipine 5 mg/day) with 5 months history of progressively worsening tremors and palpitation and 3 months amenorrhea was referred to an endocrine clinic with the diagnosis of thyrotoxocosis. She complained of headache, nausea, and occasional vomiting. Examination was significant for tachycardia (120/m),

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hypertension (BP-160/100 mm Hg), fine tremors, increased sweating, acromegaloid habitus (prominent frontal ridges, fleshy nose, bulbous lips, coarsened facial features, stubby fingers with large and broad hands) and grade-II soft diffuse goitre [Figure 1a and b]. Investigations revealed elevated free T3 and free T4 with an inappropriately normal TSH, on repeated testing. Technetium-99 pertechnate thyroid scan with uptake revealed diffuse increased uptake at 5 min (4.1%; normal: 0.24-3.34%). insulin -like growth factor-1 was increased with serum GH not suppressible on the glucose challenge. Overnight dexamethasone suppression test was positive with an inappropriately high plasma adrenocorticotrophic (ACTH) hormone [Table 1]. She had withdrawal bleeding following progestogen challenge test (medroxyprogesterone acetate 20 mg/day for 10 days). Her serum estradiol (E2) was increased with an inappropriately high LH and FSH [Table 1]. Her serum sex hormone binding globulin (198 mM/L; normal: 48-142 mM/L) and feritin (322 ng/ml; 8.6-72 ng/ml) were raised. Hemoglobin was 11.2 g%. Anti-thyroid peroxidase (anti-TPO) antibody was absent (10 IU/ml; normal <35). Thyroid function testing was normal in her first -degree relatives. Blood glucose charting revealed persistent fasting and post-prandial hyperglycemia with HbA1c of 7.8%. Pituitary imaging revealed pituitary macroadenoma with predominant suprasellar extension compressing the optic chiasm [Figure 2]. Automated perimetry showed bitemporal hemianopia. Her symptoms improved with carbimazole 30 mg/day and propranolol 80 mg/day. Hyperglycemia was controlled with gliclazide 80 mg/day and metformin 1.5 g/day. Patient was referred to the neurosurgeon for translabial trans-sphenoidal resection of pituitary macroadenoma.


**Figure 1:** (a) Profile of patient showing acromegaloid facies and (b) Picture of hand of patient showing enlargement with coarsening as compared to normal hand

## Discussion

Autonomous secretion of TSH, GH, ACTH and gonadotropins were documented in our patient. The main differential diagnosis of autonomous secretion of TSH seen in thyrotropic adenoma is thyroid hormone resistance (THR). THR is primarily dominantly inherited, mainly

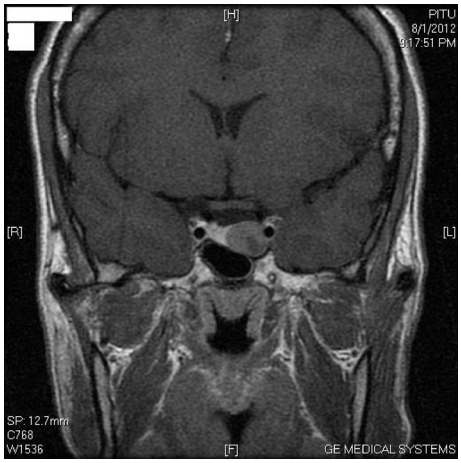


**Figure 2:** MRI hypothalamo-pituitary region showing pituitary macroadenoma

**Table 1: Hormonal profile of patient with pleurihormone secreting pituitary adenoma**

| Parameter | |
|---|---|
| Free T3 (pg/ml) (1.5-4.1) | 5.98 |
| Free T4 (ng/dl) (0.8-1.9) | 2.34 |
| Thyroid stimulating hormone (μIU/ml) (0.4-4.2) | 2.32 |
| Growth hormone (basal) (ng/ml) | 18 |
| Growth hormone (1 h post 75 g glucose) (ng/ml) (<1) | 15.9 |
| IGF-1 (ng/ml) (109-264) | 711 |
| 8 am cortisol (mcg/dl) | 18.2 |
| ONDST cortisol (mcg/dl) (<2) | 5.8 |
| Adrenocorticotrophic hormone (pg/ml) (5-15) | 57.8 |
| Prolactin (ng/ml) (1-25) | 12.1 |
| Luteinizing hormone (LH) (mIU/ml) (1.1-11.6) | 53.5 |
| Follicle stimulating hormone (FSH) (mIU/ml) (3-14.4) | 59 |
| Estradiol (pg/ml) (21-251) (follicular phase) | 52 |

T3: tri-iodothyronine, T4: tetra-iodothyronine, IGF: insulin like growth factor, Hormonal estimation was done using chemiluminescence assay (Immulite-1000, Siemens, Gwynedd, UK), ONDST: Overnight dexamethasone suppression test

seen in children. Patients can be hypothyroid, euthyroid, or thyrotoxic depending on the pattern of THR. Increased circulating T3, T4, and TSH with thyrotoxic features is seen due to pituitary resistance of thyroid hormone action, which is commonly associated with hepatic resistance characterized by normal Sex hormone binding globulin (SHBG) and ferritin levels.[3] THR was ruled out in our patient in the absence of similar history in her family members, increased SHBG and ferritin ruling out hepatic resistance, and documentation of pituitary macroadenoma on MRI brain. Werner's test has been used classically to differentiate THR from TSHoma, but is limited by poor sensitivity and specificity, and is not commonly used.[2] In Werner's test, circulating T3 is suppressed by oral T3 administration (80-100 μg/day for 8-10 days) in patients with THR but not TSHomas who have autonomous secretion.[3] Availability of ultra sensitive TSH assays have made the diagnosis of thyrotropic adenomas easier. Autonomous secretion of GH, cortisol and gonadotropins seen in our patient, can also be due to resistance to action of GH, ACTH and gonadotropins. Such a phenotype can be seen in patients of pseudohypoparathyroidism-Ia (PHP-Ia). PHP-Ia was ruled out in our patient because of lack of Albright hereditary osteodystrophy phenotype, metastatic calcification, lack of hypocalcemia and hyperphosphatemia, and normal iPTH levels. PHP-Ia patients with gonadotropin resistance are usually hypoestrogenic and hypothyroid, in contrast to our patient.[4]

One of the limitations of this report is the lack of estimation of alpha-subunit (aSU) and the surgical outcome of the adenoma. Recent studies have however, shown that aSU is elevated in only 60% of thyrotroph adenomas.[5] Surgery is the primary treatment for thyrotropic adenomas with a recent study showing 58.3% remission rate after 1 year.[5] Thyrotopic adenomas are more fibrotic (increased TGF-β production) which may worsen the surgical outcomes. Somatostatin analogues are useful in suppressing TSH secretion in patients not achieving remission following surgery and/or radiotherapy.[5]

Plurihormonal thyrotropic adenomas usually present with features of thyrotoxicosis, in contrast to monohormonal thyrotropic adenoma who are clinically and bio chemically euthyroid and present with compressive features of large invasive pituitary adenoma.[2] This is perhaps the first report of a plurihormonal thyrotropic macroadenoma secreting TSH, GH, ACTH and gonadotropins presenting with thyrotoxicosis, acromegaly, new onset diabetes and hypertension, and local compressive effects.

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