Pituitary Lesions and Elevated TSH: A Case Series Exploring Diagnostic Variability

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Key Clinical Message:

In cases of pituitary lesions with elevated TSH, a comprehensive diagnostic approach that includes biochemical, clinical, and radiological assessment is essential. Not all pituitary masses are adenomas. Pituitary hyperplasia secondary to primary hypothyroidism can mimic adenomas, particularly prolactinomas, due to associated hyperprolactinemia. Thyroxine replacement therapy often reduces pituitary hyperplasia, making hormonal profiling essential to avoid unnecessary surgical interventions. Patient compliance with hormone therapy is also a key factor, as non-compliance can lead to persistent symptoms and impact outcomes. Early specialist involvement and a multidisciplinary approach are beneficial in these complex cases to ensure accurate diagnosis and timely intervention.

Introduction :

The pituitary gland, often called the "master gland" of the body, regulates numerous essential functions by releasing various hormones. Structurally, the gland is divided into an anterior and a posterior lobe. The anterior lobe produces several vital hormones, including human growth hormone (HGH or GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. The posterior lobe produces oxytocin and antidiuretic hormone (ADH). The hypothalamus controls all these hormones, which regulate their release through specific signaling chemicals.

Pituitary adenomas, or benign tumors of the pituitary gland, can be classified by size—macroadenomas are more significant than 10 mm, while microadenomas are smaller. They are also categorized as either secreting or non-secreting, depending on whether they actively release hormones. The most common secreting adenoma is prolactinoma, which overproduces prolactin (1). Pituitary hyperplasia, on the other hand, involves the overgrowth of pituitary cells and may affect either specific hormone-producing cells or the entire gland. Both adenomas and hyperplasia can present as a pituitary mass on imaging, which can complicate diagnosis.

In primary hypothyroidism, inadequate thyroid hormone production can result in elevated TSH levels and pituitary hyperplasia due to loss of negative feedback in the hypothalamic-pituitary-thyroid axis. Studies indicate that 25-81% of hypothyroid patients present with pituitary hyperplasia (2). Additionally, thyroid-stimulating hormone (TSH)-secreting adenomas, or TSHomas, are rare, accounting for only 0.5% to 3% of all pituitary tumors (3). These tumors are typically characterized by elevated levels of free thyroid hormones (FT4 and FT3) in the presence of non-suppressed TSH, often presenting clinically with symptoms of hyperthyroidism (4). Differentiating between TSHomas, thyroid hormone resistance, and other causes of elevated TSH can be challenging.

This case series presents three patients with elevated TSH and pituitary lesions, each with a unique clinical outcome and treatment pathway. Although their initial symptoms were similar varying diagnoses led to distinct management strategies. This series highlights the diverse presentations of pituitary lesions with elevated TSH and underscores the importance of systematic evaluation to avoid misdiagnosis and unnecessary surgical interventions.

Case Discussions:

Case Number 1:

Case History/Examination:

A 24-year-old female with no comorbidities presented with complaints of Galactorrhea and menstrual irregularities for 1.5 years. She had been using norethisterone for her menstrual issues. She reported a weight gain of 20 kilograms over the past 18 months, accompanied by polyuria, mild headache, myalgia, and numbness in her upper limbs. She had a history of delivering a child via C-section 3 years ago but had no other notable past medical or surgical history. Physical examination was unremarkable.

Her complete pituitary profile was checked, which showed high TSH and low Free T4. Her lab results are shown in the table below **(Table 1).**

These labs were significant for hypothyroidism, so there was a suspicion of pituitary hyperplasia with hypothyroidism, but prolactin levels were also high, so the possibility of pituitary macroadenoma could not be ruled out completely

An MRI of the brain was done a few days before her presentation in the clinic. It showed an enhancing mass in the sellar and suprasellar locations, measuring 11x 16 x 14 mm (AP x TR x CC). An associated mass effect causing downsloping of the sellar floor into the sphenoid sinus was noted. The mass was also compressing the pituitary stalk. Findings were suggestive of pituitary macroadenoma. Images of the MRI brain are shown below in **Figures 1 and 2.**

As per the multidisciplinary team meeting, it was planned to start her on levothyroxine 100mcg daily and assess the response in an interval MRI brain in 2 to 3 months. Hence, she was advised levothyroxine, which she took regularly with good compliance.

MRI of the brain repeated after 2 months showed interval resolution of the enlarged pituitary gland. It measures 5.7 x 9x 12 mm (CC x AP x Transverse) against the previous 14 x 10 x 17mm measurements. It showed a good treatment response to levothyroxine. Radiological images of the MRI brain are shown below. The arrow shows the complete resolution of the mass shown before **(Figures 3 and 4).**

After starting levothyroxine, the patient's symptoms resolved significantly. Her menstrual cycle normalized, and she became pregnant with her second child. The pregnancy was uneventful, resulting in the delivery of a healthy baby. Her issues with galactorrhea and body pain also resolved. She was advised to return for a follow-up MRI in four months; however, she missed this appointment due to her pregnancy. Lab results showed marked improvement after two months, especially in her TSH levels **(Table 2).**

Differential Diagnosis:

In this patient, differential diagnoses included prolactinoma, as elevated prolactin with galactorrhea suggests this common pituitary tumor, and primary hypothyroidism with pituitary hyperplasia, where prolonged hypothyroidism can cause pituitary enlargement that may mimic a macroadenoma and often regresses with thyroid hormone therapy, as observed here. Medication-induced hyperprolactinemia, from norethisterone used for menstrual irregularities, could also contribute. Given her improvement on levothyroxine, pituitary hyperplasia due to hypothyroidism appears most likely.

Conclusion and Results (Outcome and follow-up):

At her one-year follow-up, the patient was completely asymptomatic. Her menstrual cycle had remained regular, her weight was stable, she had no headaches, and she was compliant with her levothyroxine regimen. Her lab parameters continued to be within normal ranges **(Table 3).**

Initially, a pituitary adenoma was suspected based on misleading MRI findings. This case highlights the importance of thoroughly assessing lab parameters before relying on imaging alone, as her blood test results ultimately prevented unnecessary surgical intervention.

Case Number 2:

Case History/ Examination:

A 22-year-old female with no significant medical history presented with a three-year history of headaches and three months of vomiting. She also reported five months of amenorrhea, with a negative pregnancy test and stable weight, though she experienced generalized body aches during this period. She had no galactorrhea, changes in hand or foot size, or hirsutism. She had no medical or surgical history and wore glasses for reduced visual acuity. Her physical examination was unremarkable.

Her blood work revealed an elevated thyroid-stimulating hormone (TSH) level and a local doctor started her on thyroxine 50 mcg daily. A complete pituitary profile was conducted, as shown in **Table 4** , which confirmed significantly elevated TSH levels while the rest of her pituitary profile was within normal limits.

MRI brain was performed to investigate the underlying cause of her symptoms, which included prolonged headaches, vomiting, and amenorrhea. These symptoms, coupled with her elevated TSH levels and pituitary profile findings, raised suspicion of a possible pituitary or central hormonal disorder. Imaging revealed a bulky pituitary gland with a mild upward convexity and a slight deviation of the pituitary stalk to the left. There was no compression of the optic chiasm. A small, hypo- to non-enhancing lesion measuring approximately 7 x 6 x 5 mm was identified in the anterior part of the pituitary gland on the right side of the midline. The rest of the pituitary gland showed homogeneous enhancement, with no invasion into the cavernous sinus **(Figure 5 and 6).**

Her thyroxine increased to 150mcg daily. She was kept on follow-up as per a multidisciplinary meeting in which neurosurgeons and endocrinologists decided to follow her repeat thyroid profile and brain imaging.

A follow-up MRI performed six months later showed that the pituitary gland remained persistently bulky with mild upward convexity, with the pituitary stalk now in the midline. There was no compression of the optic chiasm. The small, hypo- to non-enhancing lesion was re-demonstrated in the anterior part of the pituitary gland on the right side of the midline, measuring approximately 6.5 x 4.7 x 4.5 mm. The remainder of the pituitary gland showed homogeneous enhancement, with no cavernous sinus invasion, consistent with a stable pituitary microadenoma on the right side of the midline **(Figure 7 and 8).**

Approximately eight months after her symptoms began, the patient started experiencing brief episodes of loss of consciousness, followed by spontaneous recovery, often accompanied by headaches. A neurologist diagnosed her with epilepsy and initiated treatment with levetiracetam. The orofacial team managed her headaches. Specialists determined that these symptoms were unrelated to her pituitary lesions, as the pituitary mass was too small to cause such issues. However, she had been non-compliant with her thyroxine medication, resulting in persistently elevated TSH levels and the continued presence of the pituitary adenoma. Her thyroid tests at that time are shown in **Table 5.**

Her thyroxine dose was subsequently increased to 200 mcg for six days per week and 150 mcg on one day, emphasizing reinforcing medication compliance. Her lab results at the two-year follow-up are shown in

Table 6.

Differential Diagnosis:

In this case, differential diagnoses include primary hypothyroidism with pituitary hyperplasia, as chronic elevated TSH from untreated hypothyroidism can cause pituitary enlargement. A TSH-secreting pituitary

adenoma (TSHoma) is less likely, as thyroxine therapy normalized TSH, which wouldn't occur with a true TSHoma. The stable, non-enhancing lesion may represent a non-functional pituitary microadenoma coexisting with hypothyroidism, while secondary hypothyroidism due to compression by the lesion is improbable given the lesion's small size and lack of compression. Granulomatous diseases, like sarcoidosis, can involve the pituitary, causing headaches and endocrine dysfunction, though they often present with more extensive hormonal deficiencies than isolated TSH elevation.

Conclusion and Results (Outcome and follow-up):

Her symptoms improved significantly as her TSH levels normalized. A follow-up MRI after two years showed a reduction in the size of the pituitary adenoma, although complete resolution was not achieved. The MRI report indicated a decrease in the non-enhancing lesion on the right side of the pituitary gland, now measuring 6.8 x 6.7 x 5 mm, compared to the previous measurement of 7.3 x 6.8 x 6.4 mm. Additionally, the pituitary gland showed a slight size reduction, now measuring 19 x 6 mm, down from 20 x 8 mm on the previous scan **(Figure 9 and 10).**

This case suggests that the pituitary adenoma developed secondary to primary hypothyroidism. While the hyperplasia resolved with medical treatment, the adenoma remained present despite normalization of thyroid hormone levels. It was suspected that the patient had both pituitary adenoma and hyperplasia; the hyperplasia responded to treatment, but the adenoma persisted.

Case Number 3:

Case History/Examination:

A 37-year-old male presented to the clinic with palpitations, weight loss, and easy fatigability. On examination, he appeared thin, with a BMI of 19 kg/m^2, and exhibited resting tachycardia with a regular pulse of 104 bpm. He had tremors in his outstretched hands and bilateral neck swelling with an audible thyroid bruit. There were no eye signs of hyperthyroidism or evidence of pretibial myxedema. He had been treated for thyrotoxicosis over the past seven years outside the hospital, receiving anti-thyroid medications and radioactive iodine (RAI) therapy. After RAI, he was started on levothyroxine. Despite gradually increasing the levothyroxine to the maximum dose, his TSH levels remained elevated, and symptoms of hyperthyroidism persisted. Initial workup showed a TSH of 48 μIU/mL (normal range: 0.35–5.5 μIU/mL), FT4 of 4.8 ng/dL (normal range for adults >20 years: 0.89–1.76 ng/dL), and FT3 exceeding 20 pg/mL (normal range: 2.4–4.2 pg/mL). The elevated FT4 and FT3 levels, alongside non-suppressed TSH, suggested a central cause of hyperthyroidism. The rest of the pituitary hormones were in the normal range except for raised testosterone with inappropriately average values of LH and FSH (Table 7)

Brain MRI revealed a 9 x 12 mm mass in the sellar region

(Figure 11).

Based on the clinical, biochemical, and radiological findings, a TSH-secreting adenoma (TSHoma) diagnosis was made. Octreotide was administered; however, thyroid function tests (TFT) showed no improvement, even at the maximum dose of octreotide LAR. As other somatostatin analogs were unavailable in the country, carbimazole was given to stabilize TFT levels before surgery.

Differential Diagnosis:

The differential diagnoses for this case include a TSH-secreting pituitary adenoma (TSHoma), which is supported by the elevated FT4 and FT3 levels, persistent hyperthyroid symptoms, and the sellar mass on MRI, making it the most likely diagnosis. Resistance to thyroid hormone (RTH) is another consideration, as it can cause elevated thyroid hormones with unsuppressed or high TSH, but typically lacks the clinical symptoms of hyperthyroidism, such as tachycardia and tremors, and does not show a pituitary mass on imaging. Exogenous thyroid hormone ingestion (factitious thyrotoxicosis) could also lead to high FT4 and FT3, but would typically suppress TSH and is unlikely to be associated with a pituitary mass. Lastly,

multinodular goiter with autonomous thyroid function could cause elevated thyroid hormones with a mildly elevated TSH, but this diagnosis is improbable due to the absence of multinodular findings

Conclusion and Results (Outcome and follow-up):

After four weeks, the patient achieved a euthyroid state and subsequently underwent endoscopic transsphenoidal surgery. Postoperatively, serum TSH, FT4, and FT3 levels decreased to within the normal range.

This case illustrates that the elevated TSH was due to the rare condition of TSHoma, which required timely surgical intervention. However, due to a misdiagnosis and prior treatment with thyroxine replacement, the patient's symptoms were initially aggravated, delaying appropriate management.

Discussion:

This case series presents three patients with similar complaints and radiological findings of pituitary lesions, yet with distinct underlying causes and treatment outcomes. The cases highlight the need for a thorough and systematic approach to diagnosis, incorporating clinical, biochemical, and radiological findings. Comparison of the three has been provided in the table 8.

The mechanism of secretion of thyroid hormones is basically controlled by hypothalamus. Thyrotropin releasing hormone (TRH) from hypothalamus stimulates thyrotrophs cells in anterior pituitary to release thyroid stimulating hormone, which ultimately acts on TSH receptors on thyroid gland and releases Thyroxine (T4) and triiodothyronine (T3) hormones. This mechanism is controlled by a feedback response. Thyroid hormones produced from thyroid glands give negative feedback to hypothalamus so that TRH secretion can be reduced and vice versa. In primary hypothyroidism, this negative feedback response is lost because thyroid gland is not able to produce enough T3 and T4, as a result of which hypothalamus keeps on producing TRH which stimulates thyrotropes of pituitary gland, causing its hyperplasia and increasing TSH levels. This TRH can also cause an increased rate of growth of lactotroph cells in addition to thyrotropes cells which is the reason behind hyperprolactinemia in primary hypothyroidism (6). It can be easily mis diagnosed as a prolactinoma if we do not have the hormonal profile to identify hypothyroidism.

The etiology of pituitary adenoma still needs to be clarified. It can be sporadic or genetic. Sometimes, it is a part of a syndrome like MEN 1 or a secondary effect of another condition like hypothyroidism, as in our cases. Hypothyroidism itself is commonly due to iodine deficiency in certain regions, while in developed countries, it is more often linked to autoimmune diseases like Hashimoto's thyroiditis. Other causes include Medications (e.g., amiodarone, carbamazepine, lithium), Post-thyroidectomy effects, Radioiodine ablation, Neck or chest radiation, and Genetic factors.

Pituitary hyperplasia due to hypothyroidism was initially seen in 1851 when an autopsy of a cretin was done (5). It has been seen that the incidence of pituitary hyperplasia with primary hypothyroidism has not been apparent. Still, more literature is being done to understand the etiology behind this relation more clearly. The risk of pituitary hyperplasia with hypothyroidism can range from 25-81% (6), and features of hyperprolactinemia are seen in 36% of people with primary hypothyroidism (7). This is similar to our case number 1 presented above, which presented with symptoms of hyperprolactinemia (galactorrhea, menstrual irregularities), but it was due to primary hypothyroidism.

Patients of hypothyroidism with pituitary involvement usually present with galactorrhea, irregular menstrual cycle, infertility, weight gain, fatigue, loss of appetite, dry skin, constipation, short stature, and delayed puberty in children (8). The initial investigation should focus on biochemical testing of pituitary hormones, including serum prolactin, thyroid profile (TSH, T3, T4), cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone levels. If the hormonal profile does not indicate hypothyroidism but shows elevated levels of another hormone, such as prolactin, brain imaging (MRI or CT) should be considered. Importantly, radiological imaging alone cannot reliably distinguish between pituitary adenoma and hyperplasia (8). Our Case 2 illustrates a patient whose pituitary lesion, secondary to hypothyroidism, comprised both hyperplasia and a persistent adenoma that remained despite thyroxine treatment.

Medical management with thyroxine hormone supplementation is the treatment for such patients. When thyroxine levels rise, they produce a negative feedback response to the hypothalamus, reducing TRH and TSH hormone levels. This treatment typically resolves pituitary hyperplasia (7). Ongoing follow-up is crucial to assess treatment efficacy, and repeat MRI imaging can help evaluate pituitary mass size. If the mass does not respond to thyroxine therapy, a pituitary adenoma should be considered.

TSH-secreting pituitary adenomas are a rare cause of hyperthyroidism, accounting for less than 1% of all functioning pituitary adenomas [3]. While the presence of a pituitary adenoma in a patient with inappropriately elevated TSH levels can suggest TSHoma, this finding alone is not diagnostic, as incidental pituitary tumors are detected in up to 10% of normal subjects on MRI (10). Dynamic tests to diagnose TSHoma include both stimulatory and inhibitory tests, including the TRH stimulation and T3 inhibitory tests. The T3 suppression test (T3 inhibitory test), where failure to suppress TSH following T3 administration, alongside elevated levels of the serum glycoprotein hormone alpha subunit (α-GSU), strongly supports a TSHoma diagnosis (11). Elevated alpha subunit concentration or a high alpha subunit/TSH molar ratio is typically present in patients with TSHoma.

Resistance to thyroid hormones (RTH) is most commonly caused by mutations in the THRB gene on chromosome 3. The mutant thyroid hormone receptor beta protein has either reduced affinity for T3 or abnormal interaction with cofactors involved in thyroid hormone action, making the target tissues refractory to thyroid hormones [12]. Patients with THRB mutations have variable clinical presentation. They may be clinically euthyroid or present with symptoms of hypothyroidism hy, hyperthyroidism, or a combination of thyroid hormone excess and deficiency, depending on the level of THRB and THRA gene expression in the target tissue.

Peripheral metabolic markers, including sex hormone-binding globulin (SHBG), bone-specific alkaline phosphatase (bs-ALP), carboxy-terminal cross-linked telopeptides of type I collagen (ICTP), and ferritin, are typically elevated in cases of TSHoma (13). The liver contains primarily THR β1 THR β3. Raised levels of sex-hormone binding globulins favor TSHoma as the likely etiology of inappropriate secretion of TSH. In case of resistance to thyroid hormone, SHBG should be normal or low because of end-organ resistance. Moreover, tachycardia and weight loss with low BMI favored the diagnosis of TSHoma as these features might be absent in case of resistance to thyroid hormone, depending on the level of gene mutation. Additionally, average IQ is consistent with TSHoma, whereas patients with RTH often experience learning disabilities due to resistance in THR β receptors within the central nervous system. Despite limited access to pituitary dynamic testing in this case, clinical features and biochemical markers pointed to a diagnosis of TSH-secreting pituitary tumor (TSHoma) in our third patient.

The first-line treatment is surgical resection of adenoma. Before surgery, somatostatin analogs are started to optimize TFTs. In patients who are not cured with surgical management, other available options are medical treatment with somatostatin analogs and radiotherapy.

In summary, all three patients had elevated TSH and a pituitary lesion, but their presentations and outcomes differed. Case 1 responded well to medical treatment with thyroxine, whereas Case 2 had a residual adenoma despite thyroxine therapy. In Case 3, a TSHoma was mismanaged initially with thyroxine, delaying the necessary surgical intervention.

Conclusion:

Pituitary lesions (mass/hyperplasia) on radiological findings can have different interpretations. A systematic investigation combining biochemical, clinical, and radiological evidence is essential before initiating therapy. This approach helps prevent unnecessary surgical interventions and avoids delays in necessary surgical treatments. Not every pituitary mass represents an adenoma, particularly a prolactinoma; hyperplasia or other types of pituitary cell adenomas should always be considered as differential diagnoses. Although rare, TSHoma do exist, distinguishing them from thyroid hormone resistance can be challenging. In conclusion, a thorough, multi-faceted approach to diagnosing pituitary lesions is essential for ensuring accurate treatment and optimal patient outcomes .

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Consent :

Written consent was taken from the patient.

Author Contribution :

Amina Jafar: conceptualization, data curation, writing-original draft, writing- reviwe & editing, **Rabia Iqbal** : writing- review & editing**, Wania Rafaey** : Writing- original draft,**Hooria Shumail** : Resources, **Zainab Ajmal** : Writing- original draft, **Ahmad Taimoor Bajwa** : Writing –original draft,**Sabrin Maro** wa: Resources, Supervision, **Ahmed Imran Siddiqi** : Conceptualization, Resources, Writing- original draft, Writing- review & editing

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