

## Case Report

## Refractory Transposing Hyperthyroid Disorder Inducing Tsh-secreting Pituitary Adenoma: A Case Report and Literature Review

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## ABSTRACT

**Introduction:** TSH-secreting pituitary adenomas (TSH-sPAs) or thyrotropinomas are very rare forms of pituitary adenomas (PAs). Although several authors have presented single cases or case series on this occurrence, only few authors have indicated that hyperthyroidism heralded the pathogenesis of TSH-sPA. We also present a case of refractory transposing hyperthyroid disorder inducing TSH-sPA. **Case Presentation:** We present a 47-year-old woman with 20 years' history hyperthyroidism and a visible anterior neck swelling with normal TSH. She was put on anti-thyroid medications that transposed her hyperthyroid state to hypothyroid state with elevated TSH and a pituitary adenoma (PA). The PA was surgically excised via transsphenoidal approach. **Conclusion:** Hyperthyroidism or anti-thyroid medications could be responsible for the trigger of a feedback mechanism that led to over-secretion of TSH and subsequently the development of PA.

## INTRODUCTION

TSH-secreting pituitary adenomas (TSH-sPAs) or thyrotropinomas, are very rare forms of pituitary adenomas (PAs), accounting for about 0.9-1.5% of all pituitary tumors reported in literature (1-4). TSH-sPAs manifesting with hyperthyroidism may appear as clinically insignificant to very grave thyrotoxicosis. Asymptomatic cases as well as diffuse anterior neck swelling with no exophthalmia forms of this disorder has also been reported (2,5). Acromegaly and/or hyperprolactinemia as a result of co-secretion of growth hormone (GH) and/or prolactin (PRL), correspondingly has also been associated with TSH-sPAs (2,3). This presentation is often evident when endocrine workout uncovers elevated levels of free thyroxine (FT4) with normal or high levels TSH, which juxtaposes with the suppressed TSH levels usually seen in other kinds of thyrotoxicosis (2,4-6). Detailed literature search revealed that only hand full of studies (6,7) reported cases of Graves' disease or hyperthyroidism who became euthyroid, but consequently developed a TSH-sPA. Indicating that hyperthyroidism heralded

the pathogenesis of TSH-sPA. We also present a case of refractory transposing hyperthyroid disorder inducing TSH-sPA.

## CASE REPORT

We present a 47-year-old woman with 20 years' history of heat intolerance, excessive sweating, loss of appetite as well as weight. She also had tremors, irritability, menstrual irregularities, photophobia, easy tearing, as well as an anterior neck swelling. When the symptoms started 20 years ago, she presented at her community hospital where her thyroid function test revealed elevated serum free triiodothyronine (FT3), free thyroxine (FT4) and normal TSH. A diagnosis of hyperthyroidism (Graves' disease) was made and she was put on oral methimazole for 6 years. She however defaulted treatment with methimazole so they switched her to oral iodine 131 for 12 years. Two years before presenting at our facility, her symptoms aggravated into lower extremity edema, palpitations, easy fatigability on her normal daily activities. Thyroid

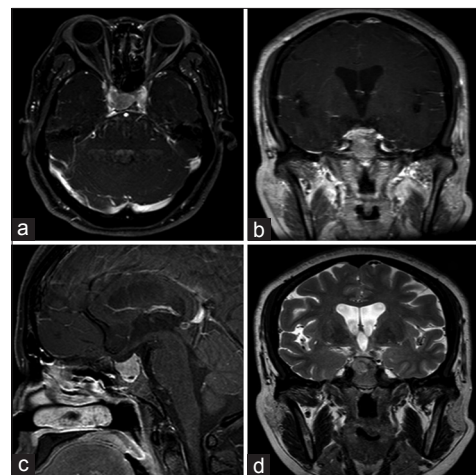
function test repeated revealed normal FT3, FT4 and elevated TSH. A diagnosis of hypothyroidism was made and she was put on oral thyroid 80-120mg qid for two years and switched to euthyrox 150ug qid when thyroid function test became normal. On examination, apart from the signs mentions above, all other systems were essentially normal. Thyroid function done at our facility revealed TSH 16.8mU/l, FT3 4.6pmol/l, FT4 23.25pmol/l. All other endocrine investigations as well as routine laboratory investigations were grossly normal. ECG and CXR done were also normal.

Magnetic resonance imaging (MRI) done however revealed an enlargement of the sella turcica with a mass. The mass was about 1.6 x 1.2 x 1.3cm in size (Figures. 1, a-d), confirmed to the sella and suprasellar region with mixed signal intensities. The mass was significantly enhanced on enhancement scan with heterogeneous patterns and pointing upwards towards the convex suprasellar pool. The mass displaced the pituitary stalk towards the left as well as significant invasion of the right cavernous sinus with no neurological or cranial nerve deficits. There was no enlargement of the brain cistern in all the ventricles as well as midline shift of the brain. The skull bones were all normal. Base on the clinical presentation as well as radiological finding above a working diagnosis of pituitary adenoma (PA) secondary to refractory transposing thyroid disease was made. The patient was then transferred from the endocrine department to the neurosurgical department. The patient as well as her relatives were taken through a series of education and counseling and surgery scheduled.

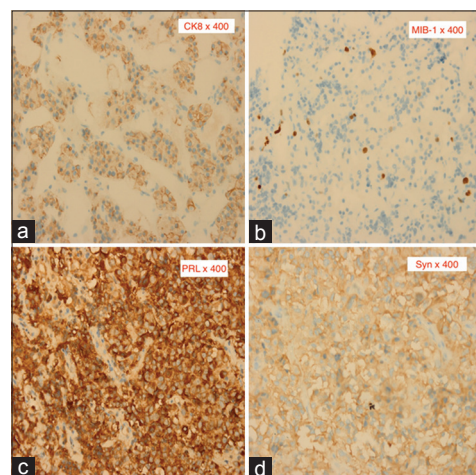
We used the transsphenoidal approach to access the pituitary adenoma, decompressed the optic nerve which was compressed by the tumor, sinus injury repair as well as reconstruction of the skull base to prevent cerebrospinal fluid (CSF) leakage. Intraoperatively, we saw the tumor in the sella and the suprasellar region. It was solid in consistency, brown in color with rich blood supply. We noticed that the stroma displaced the pituitary stalk towards the left as well as significant invasion of the right cavernous sinus. After meticulous excision of the tumor, we notice copious amount of CSF therefore, we reconstructed the skull base adequately to prevent CSF leak. The citrate buffer method of immunohistochemistry staining was utilized. Observation of the color of the antibody staining in the tissue sections were done under microscopy. Our immunohistochemistry staining (Figure. 2) revealed CK8 (+), Syn (+), MIB-1 (positive rate of <1%), PRL (+), CH (focal +), TSH (+), LH (-), ACTH (-), FSH (-) with a significantly reduced reticulocyte staining. Positive CK8, Syn, PRL, CH as well as TSH supports the diagnosis of TSH secreting pituitary adenoma. The patient recovered very well after operation with no CSF leak. She was discharged home seven days after the operation with scheduled out patients visits at neuro-endocrine department every six months. Two years follow up revealed massive regression of the signs and symptoms above with significant improvement of her life.

## DISCUSSION

Hyperthyroidism or Grave's disease occurring mainly in women has an annual incidence of 0.5/1000 populations (6, 8). On



**Figure 1.** a-d; A is T1 axial, b is T1 coronal, c is T1 sagittal while d is T2 coronal MRI showing the pituitary adenoma



**Figure 2.** Is immunohistochemistry staining confirming co-secretion of TSH with PRL, Synaptophysin (Syn), CK8 and MIB-1

the other hand, TSH-sPAs comprises of about 0.9-1.5% all PAs with an annual incidence of 1-8/10 million (6, 9). Consequently, the conviction that these two disorders occurred coincidentally has an estimated incidence of less than 1/100 million, and only four cases with histological substantiation have been described (6,10,11). A hand full of studies have demonstrated that the time interval between the first signs and symptoms of thyroid and/or PA and the accurate diagnosis of a TSH-secreting or co-secreting adenoma is usually very long (several years) (1-3,12,13). Our case also took several years before we identified PA although we noticed hyperthyroid without TSH elevation which transposed into hypothyroidism with TSH elevation.

Nazato et al (2) in their study with eleven (11) patients with TSH secreting tumors noticed that two of their cases had specific signs and symptoms of hyperthyroidism before the diagnosis of PA. They also noticed anterior neck swelling with mild hyperthyroidism in two of their cases (2). Ogawa et al presented case of progressive Graves' disease or hyperthyroidism who consequently developed TSH-sPA after euthyroid state was attained. Our case also attained eu-

thyroid state before we noticed the elevation of TSH and subsequently PA. Ogawa et al (6,14) in an earlier case report indicated that anti-thyroid medicine given under a misdiagnosis of Graves' disease or hyperthyroidism may carry the risk of facilitating TSH-sPA because of a positive feedback system. Nevertheless, studies (7,15) have also shown that TSH is the key factor associated with the regulation of proliferation of thyrocytes. The general clinical presentations as observed in literature is mild signs of thyrotoxicosis as well as neurological deficits as a result of the PA. Anterior neck swelling has reported in almost all cases (7,16,17). Our patient had signs and symptoms thyrotoxicosis and thyroid enlargement before the diagnosis of PA was made with MRI as well as confirmation of TSH-secretion via immunohistochemistry staining. The cardinal symptom for hyperthyroidism is weight loss. Weight loss in hyperthyroidism is a crucial symptom during the natural course of Graves' disease(18). Nevertheless, patients with hyperthyroidism usually have increased appetite and food intake with a desire for carbohydrate-rich food yet have weight loss. the pathophysiological mechanisms underlying this behavior is still a matter of debate(18,19).

MRI is the supreme radiological modality used in the diagnosis of PA because it is able to pinpoint the existence of an adenoma as well as associated features surrounding the adenoma (20,21). Several authors (20,22) have recommended MRI as the gold-standard because it is absolutely superior to computer tomographic scan (CT-Scan) in the diagnosis of PA with a sensitivity of about 88-90 %. MRI principally displays an intra- and suprasellar growing mass with varying signal intensities on T1WI and T2WI, depending on the existence of accompanying features (20). Studies (20,23, 24) have shown that after introduction contrast agent, a mild and homogeneous or heterogeneous contrast enhancement is manifested but usually very challenging to distinguish from normal residual pituitary gland. T2WIs are very advantageous in the assessment of possible compressions of the optic chiasm and hypothalamus by the tumor (20). Furthermore, MRI is able to identify PA even when the sphenoid sinus mucosa is very thick (20,21,24,25).

The gold-standard treatment for TSH-sPAs is certainly transsphenoidal tumor excision (1,14). Many authors (1,14,26,27) have indicated that excision attains total remedy in about 40% of circumstances partly because of the invasiveness and huge size of adenomas as compared to other forms of functioning PA. Nevertheless, combined treatment by means of surgical excision and external radiation attains remedy in 50-80% of patients though comparisons of surgical excision and combined treatment exhibited no substantial transformation in the magnitudes of treated, better-quality, and untreated patients (14,28,29). Many authors (14,27,30,31) support medical management option with somatostatin analogue octreotide or lanreotide hence this treatment modality has yielded positive results. Furthermore, studies (14,32) have proven that octreotide accomplishes PA regression in about 38.5% of cases. Nevertheless, other studies (14,30) have indicated that octreotide accomplishes regularization of hyperthyroidism in 75% of patients as well PA regression in 50%. Somatostatin analogues have

demonstrated not to facilitate interstitial fibrosis of the tumor as compared to dopamine agonists, so preoperative treatment is occasionally advocated to shrink the tumor and/or decrease the intraoperative thyroid crisis. Treatment with anti-thyroid medications that are often used should be circumvented because of the potential risk of positive feedback to the tumors (14,27). The prognostic factors of TSH-sPAs comprise of size, invasiveness of the tumor, duration of signs and symptoms as well as severity of hyperthyroidism (1,14).

Several studies have implicated co-secretion TSH and other hormones in 28-30% of patients with TSH-sPAs (2,7). The tumor most frequently secretes alpha-subunit of the glycoprotein hormones ( $\alpha$ -SU) and occasionally other pituitary hormones, particularly growth hormone (GH) and/or prolactin (PRL) (7,17). Our pathology report demonstrated co-secretion of TSH with PRL, Syn, CK8, CH and MIB-1(Figure. 2) which affirm that the lesion was a TSH.

## CONCLUSION

Hyperthyroidism or anti-thyroid medications could be responsible for the trigger of a feedback mechanism that led to over-secretion of TSH and subsequently the development of PA. The gold-standard treatment modality in our case was surgical excision because of huge size of the adenoma as well as its invasive nature. Two years follow up of our patients revealed regression of the signs and symptoms as well as massive improvement in her quality of life.

## DECLARATION

### Ethics Approval and Consent to Participate

The ethical committee of West China Hospital full approved our case study. The patient and her relatives were informed about our intention to involve him in a case study and she/they agreed to partake in the study. he/they signed the concern form before the operation was carried out according to all surgical protocols.

### Consent for Publication

The patient and her relatives were dually informed about our intention to publish his case and she/they fully consented to the use of his documents. The hospital also consented to the use of this information for publication.

### Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

## AUTHORS' CONTRIBUTIONS

SAR, CB and SZ conceived the project and SAR designed the study. SAR, FW and XY collected patient's data. CL provided the pathology report and pictures. CB provided technical assistance in the study. SAR analyzed the data, prepared the illustrations and wrote the paper. All authors approved the paper for the submission.

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