The 17th European Congress of Endocrinology

# A case of TSH secreting pituitary adenoma with Evans' syndrome

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## Introduction

TSH-secreting pituitary adenomas (TSHomas) are rare tumors. These tumors may lead to the development of hyperthyroidism through a condition called syndrome of inappropriate secretion of TSH (SITSH). In contrast, Evans' syndrome is a rare combination of autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP). A relationship between the pathogenesis of TSHomas and Evans' syndrome is unlikely. However, several recent cases of Evans' syndrome associated with hyperthyroidism caused by autoimmune thyroid diseases, such as Graves' disease, suggest that these two conditions may have a common immunological mechanism. We report here a case of a TSHoma associated with Evans' syndrome. In our case, the hyperthyroidism is due to TSHoma.

## Medical history

A 30-year-old woman was admitted to a nearby hospital due to purpura and ecchymoses on her limbs and body and epistaxis. There was no family history of notable illness, including autoimmune disease. Laboratory results revealed low hemoglobin, hematocrit, red blood cell, and platelet levels. A hematologic disease was suspected, and she was referred to our hospital. She had a history of malocclusion and thyroid gland enlargement 4 years prior to admission.

## Physical examination

Height 163.0 cm, Weight 49.0 kg

| | |
|---|---|
| Vital sign: | BT 37.6 ℃, BP 182/80 mmHg, HR 148 /min, RR 24 /min |
| Eyes: | Conj. palp: anemic Conj. bulb: icteric exophthalmos(-) |
| Face: | thickened lips, prognathism of the mandible |
| Neck: | diffusely enlarged thyroid gland |
| Chest: | Lungs: clearto auscultation bilateral, Heart: regular rhythm, no murmur |
| Abdomen: | soft, no tenderness, normal bowel sound, hepatosplenomegaly |
| Ext.: | scattered ecchymoses, edema(-) |

She presented with hyperthyroidism symptoms, acromegalic features and bleeding tendency.

## Routine laboratory data

| | | | | | |
|---|---|---|---|---|---|
| <Hematological examination> | | | | | |
| WBC | 4900 | /μL | HbA1c | 4.7 | % |
| RBC | 143 | ×10⁴/μL | Glu | 118 | mg/dL |
| Hb | 3.5 | g/dL | Na | 139 | mEq/L |
| Ht | 12.6 | % | K | 3.1 | mEq/L |
| Plt | 0.1 | ×10⁴/μL | Cl | 110 | mEq/L |
| <Blood chemistry> | | | Ca | 8.2 | mg/dL |
| TP | 4.7 | g/dL | P | 3.2 | mg/dL |
| Alb | 2.5 | g/dL | | | |
| GOT | 15 | U/L | <Urinalysis> | | |
| GPT | 7 | U/L | color | yellow | |
| γ-GTP | 12 | U/L | protein | (+) | |
| BUN | 6 | mg/dL | occult blood | (2+) | |
| Cr | 0.29 | mg/dL | glucose | (-) | |
| UA | 4.0 | mg/dL | ketone body | (-) | |
| CRP | < 0.09 | mg/dL | | | |

Laboratory results revealed low hemoglobin, hematocrit, red blood cell, and platelet levels. Malnutrition and abnormal urinalysis were observed.

## Endocrine laboratory data

| | | | | | |
|---|---|---|---|---|---|
| <neurohypophysis> | | | | | |
| ADH | 2.5 | pg/mL | PRL | 6.8 | ng/mL |
| | | | GH | 19.5 | ng/mL |
| <adenohypophysis> | | | IGF-1 | 407 | ng/mL |
| ACTH | 27.8 | pg/mL | FSH | 4.4 | mIU/mL |
| F | 8.9 | μg/dL | LH | < 2.0 | mIU/mL |
| TSH | 4.450 | μIU/mL | E2 | < 25 | pg/mL |
| fT3 | 11.96 | pg/mL | Prog | 0.2 | ng/mL |
| fT4 | 4.03 | ng/dL | | | |

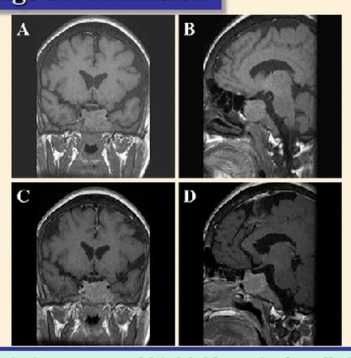
The hormonal examination suggested a syndrome of inappropriate secretion of TSH (SITSH). GH and IGF-1 were also high. The low levels of FSH, LH and E2 implied central hypogonadism.

## Serological findings

| | | | | | |
|---|---|---|---|---|---|
| sIL-2R | 2660 | U/mL | anti nuclear antibody | positive | |
| MPO-ANCA | < 10 | EU | anti GAD antibody | < 0.3 | U/mL |
| PR3-ANCA | < 10 | EU | anti SS-A antibody | < 5.0 | U/mL |
| RF | < 2 | IU/mL | anti SS-B antibody | < 5.0 | U/mL |
| C3c | 37.3 | mg/dL | anti pituitary antibody | negative | |
| C4 | < 1.0 | mg/dL | | | |
| TPOAb | 36 | IU/mL | Coombs' tests | | |
| TgAb | 289 | IU/mL | direct | (+) | |
| TRAb | 0.4 | % | indirect | (+) | |

The serum levels of C3c and C4 were both decreased, and the antinuclear antibody test was positive. The patient also had an increased sIL-2R, anti-thyroid peroxidase antibody and anti-thyroglobulin antibody. The direct/indirect Coombs' test had a positive result. The impression on hematological investigations was hemolytic anemia with thrombocytopenia.

## MRI findings on admission




MRI revealed a pituitary tumor of 34x26x28 mm in the sella involving cavernous sinuses and extending inferior to the sphenoid sinus (A: unenhanced coronal T1-weighted image, B: unenhanced sagittal T1-weighted image, C: postcontrast coronal T1-weighted image, D: postcontrast sagittal T1-weighted image).

## 75gOGTT and octreotide suppression test

75 g OGTT

| min | 0 | 30 | 60 | 120 |
|---|---|---|---|---|
| Glucose (mg/dL) | 83 | 122 | 142 | 102 |
| GH (ng/mL) | 13.6 | 10.1 | 8.21 | 4.36 |

octreotide suppression test

| hour | 0 | 2 | 4 | 6 | 8 |
|---|---|---|---|---|---|
| GH (ng/mL) | 5.57 | 1.52 | 1.67 | 2.13 | 2.44 |

A 75 g OGTT showed no suppression of GH release (RR, nadir GH level < 1 ng/mL). An octreotide suppression test had a positive result (RR, nadir GH level < 2.785 ng/mL).

## Diagnosis and Treatment

### Diagnosis

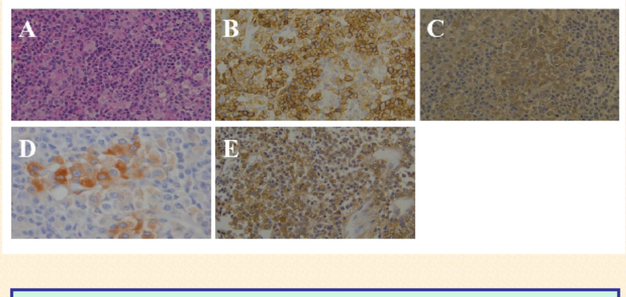
Evans' syndrome and hyperthyroidism due to TSHoma with the adenoma concomitantly secreting GH

### Treatment

Steroid treatment for Evans' syndrome
Octreotide treatment and transsphenoidal surgery for the pituitary adenoma

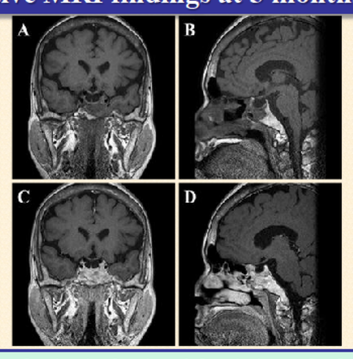
Immediately after admission, immunosuppressive therapy with glucocorticoid for Evans' syndrome was started. She was also treated with octreotide to control the hyperthyroidism caused by the TSH-secreting adenoma before the operation. The patients' laboratory data, including hemoglobin, platelet, TSH, fT3, fT4, GH and IGF-1 levels, were normalized before operation. After surgery, octreotide treatment was discontinued, and immunosuppressive therapy was maintained. The patients' laboratory data, including TSH, fT3, fT4, GH and IGF-1 levels, were normalized, but over the next 5 months, these hormone levels increased again. Thus, she was administered a long-acting octreotide treatment again.

## Histopathological findings



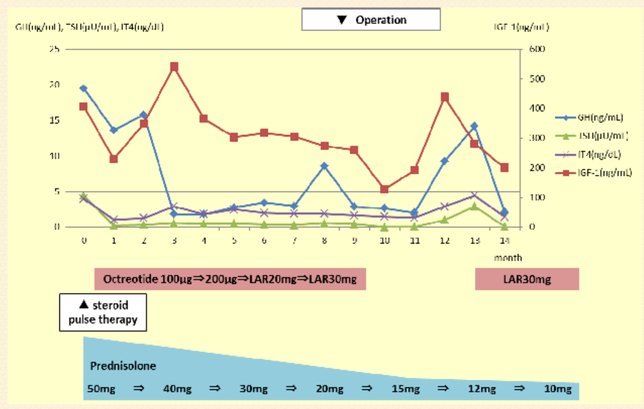

Hematoxylin and eosin staining for the cells in the surgical specimen showed diffuse proliferations of small atypical cells (x 400, A). Also they were diffusely positive for chromogranin A (x 400, B) and α-subunit (x 400, C). Immunostaining for thyroid-stimulating hormone reveals the expression of TSHβ (x 800, D). TSHβ-positive cells were not positive for GH (x 400, E). GH-positive cells were not observed.

## Postoperative MRI findings at 5 months




MRI revealed a reduction in the size of the pituitary gland compared with the size found using MRI at admission (A: unenhanced coronal T1-weighted image, B: unenhanced sagittal T1-weighted image, C: postcontrast coronal T1-weighted image, D: postcontrast sagittal T1-weighted image).

## Clinical course of the patient




## 75g OGTT after surgery

| min | 0 | 30 | 60 | 120 |
|---|---|---|---|---|
| Glucose (mg/dL) | 87 | 160 | 153 | 127 |
| GH (ng/mL) | 15.6 | 15.1 | 8.08 | 3.27 |

GH was not suppressed (RR, nadir GH level < 1 ng/mL).

## Discussion 1

To the best of our knowledge, there is no case report of Evans' syndrome associated with TSHomas. It would be interesting to determine whether these two diseases exist coincidentally. Recent studies suggested that both diseases have the same immunological mechanism, including insufficient suppressor T-cell activity [1] and TSH receptor autoantibodies [2, 3]. Moreover, it was indicated that hemolytic anemia and thrombocytopenia are the results of thyroid hormone stimulation of the activated reticuloendothelial phagocytic system [4]. In our patient, the hyperthyroidism is due to the TSHoma and is not associated with autoimmune disorders, such as Graves' disease. Thus, we speculate that the excess of thyroid hormone itself might promote autoimmunity in Evans' syndrome.

## Discussion 2

An important question, as described above, concerns the extreme rarity of a coincidence between Evans' syndrome and hyperthyroid states, including Grave's disease and TSHomas. Li *et al.* speculated that hyperprolactinemia might contribute to the excessive immune response in SLE and investigated patients with SLE and prolactinomas [5]. However, there was no clear relationship between the degree of increase in prolactin levels, hormone effectiveness, and autoimmune disease activity [5]. The authors suggested that these results were due to genetic differences in the reactivity to prolactin [5]. Similarly, among Evans' syndrome patients, there may be a group of patients with a genetic difference that causes susceptibility to the effects of hyperthyroidism.

## Discussion 3

Another possible etiology in patients with TSHomas and Evans' syndrome is a genetic polymorphism related to the pituitary tumor-transforming gene (PTTG). PTTG1 overexpression was confirmed to have transforming and tumorigenic activity [6]. In addition, a recent genome-wide study suggested a variant in a region, which was between PTTG1 and the microRNA-146a genes, related to SLE susceptibility [7]. This study statistically analyzed three single-nucleotide polymorphisms (SNPs) in SLE patients [7]. One SNP was genetically associated with SLE and potentially important in SLE etiology [7]. With this in mind, there is a possibility that a pituitary tumor might be related to an autoimmune disease.

## Concluding remarks

In summary, we described here a case of TSHoma associated with Evans' syndrome. To the best of our knowledge, there is no case report of Evans' syndrome associated with hyperthyroidism due to TSHoma. Our report suggests that an excess of thyroid hormone itself promotes autoimmunity in Evans' syndrome. Thus, early treatment for hyperthyroidism is necessary in TSHomas because thyroid hormone normalization may prevent the development of Evans' syndrome.

## References

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DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY