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CASE REPORT

# An unusual case of hypopituitarism and transient thyrotoxicosis following asymptomatic pituitary apoplexy

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**Abstract**

Although pituitary function is often impaired in pituitary apoplexy, the development of thyrotoxicosis is rare. We describe an unusual case of hypopituitarism due to pituitary apoplexy coexisting with transient hyperthyroidism. A 74-year-old woman presented with severe fatigue, palpitation, appetite loss, hypotension, and hyponatremia. Endocrine studies showed hyperthyroidism and anterior pituitary hormone deficiencies. A magnetic resonance imaging suggested recent-onset pituitary apoplexy in a pituitary tumor, although the patient had no apoplectic symptoms such as headache and visual disturbance. Thyrotoxicosis and adrenal insufficiency worsened her general condition. Glucocorticoid supplementation improved her clinical symptoms and hyponatremia. Serum anti-thyrotropin receptor and thyroid-stimulating antibody titers were negative, and her thyroid function was spontaneously normalized without antithyroid medication, suggesting painless thyroiditis. Thereafter, her thyroid function decreased because of central hypothyroidism and 75 μg of levothyroxine was needed to maintain thyroid function at the euthyroid stage. The pituitary mass was surgically removed and an old hematoma was detected in the specimen. Considering that painless thyroiditis develops as a result of an autoimmune process, an immune rebound mechanism due to adrenal insufficiency probably caused painless thyroiditis. Although the most common type of thyroid disorder in pituitary apoplexy is central hypothyroidism, thyrotoxicosis caused by painless thyroiditis should be considered even if the patient has pituitary deficiencies. Because thyrotoxicosis with adrenal insufficiency poses a high risk for a life-threatening adrenal crisis, prompt diagnosis and treatment are critical.

## INTRODUCTION

Pituitary apoplexy is a rare disorder caused by hemorrhage, infarction, or hemorrhagic infarction of the pituitary gland or pituitary tumor (Sibal *et al.* 2004; Rajasekaran *et al.* 2010; Leyer *et al.* 2011). It is typically characterized by a sudden onset of severe headache, visual disturbance, and sometimes loss of consciousness. Asymptomatic cases without the typical apoplectic episodes are often seen (Wakai *et al.* 1981; Bonicki *et al.* 1993). Although pituitary function is often impaired in pituitary apoplexy, the development of thyrotoxicosis is rare. Here, we describe a case of hypopituitarism due to asymptomatic pituitary apoplexy with transient hyperthyroidism. Because thyrotoxicosis with adrenal insufficiency poses a high risk for the development of a life-threatening adrenal crisis, prompt diagnosis and treatment are critical.

## CASE REPORT

A 74-year-old woman had been regularly followed up by a general practitioner. She was given 80-mg nicardipine, 10-mg pravastatin, and 100-mg aspirin. She was referred to our hospital because of leg edema. Thereafter, she began to experience severe general fatigue, dizziness, palpitation, nausea, and appetite loss. The antihypertensive drug was discontinued because of hypotension (70/40 mmHg). Laboratory data revealed hyperthyroidism (Figure 1) and hyponatremia; her serum sodium level decreased from 143 to 128 mmoL/L over 1 month. She also had hypercalcemia; her total serum calcium level corrected for albumin level was 11.4 (reference range, 8.7–10.3) mg/dL with low intact parathyroid hormone level (9 [reference range, 10–65] pg/mL). She was hospitalized for poor general condition.

The patient was 157-cm tall and weighed 60 kg. Her blood pressure, pulse rate, and body temperature were 97/58 mmHg, 102/min, and 37.1°C, respectively. No cushingoid or acromegalic features, and no thyroid enlargement or tenderness were observed. Thyroid ultrasound revealed a normal-sized thyroid gland with a diffuse hypoechoic pattern. Head magnetic resonance imaging (MRI) revealed a pituitary mass with isointense T1-weighted and highly intense T2-weighted images (Figure 2a, b). A T2*-weighted image, which helps in detecting hemorrhage (Tosaka *et al.* 2007), showed a low-intensity signal, indicating hemorrhage in the pituitary tumor (Figure 2c). T1-weighted pituitary MRI with gadolinium infusion revealed pituitary macroadenoma (16×25×16 mm) consisting of a non-enhanced cystic lesion surrounded by a solid portion of relatively high signal intensity (Figure 2d, e). These findings suggested recent-onset pituitary apoplexy in a pituitary tumor, although the patient did not have any apoplectic symptoms such as headache and visual disturbance. Emergency surgery was not performed because the patient lacked neurological and visual deficits.

Basal hormone value in the morning and the results of a dynamic pituitary function test are shown in Figure 3a. The very low plasma cortisol levels throughout the day (Figure 3b) and the exaggerated adrenocorticotropin response to corticotropin-releasing hormone (8.8–128.0 pg/mL) were suggestive of a tertiary adrenal insufficiency. The responsiveness of growth hormone, gonadotropins, and thyrotropin to growth hormone-, gonadotropin-, and thyrotropin-releasing hormones were poor. The blunted thyrotropin response was probably caused by thyrotropin deficiency and strong suppression due to hyperthyroidism. These data indicated anterior pituitary hormone deficiencies with hyperprolactinemia.

| | Reference range | Day 1 | Day 6 | Day 8 | Day 19 | Day 33 | Day 42 | Day 54 | Day 89 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **TSH** | (0.54–4.26) | <0.003 | <0.003 | <0.003 | 0.003 | 0.010 | 0.176 | 0.708 | 0.109 | μU/mL |
| **FT3** | (2.39–4.06) | 7.86 | 7.32 | 6.85 | 4.99 | 2.63 | 2.17 | 2.03 | 2.48 | pg/mL |
| **FT4** | (0.71–1.52) | 1.79 | 1.85 | 1.75 | 1.57 | 0.69 | 0.40 | 0.65 | 1.24 | ng/dL |
| **Tg** | (<32.7) | 212.0 | | | | 32.7 | | | | ng/mL |
| **TRAb** | (<1.0) | | <0.4 | | | | | | | IU/L |
| **TSAb** | (<180) | | 141 | | | | | | | % |
| **TPO Ab** | (<0.2) | | <0.3 | | | | | | | U/mL |
| **Tg Ab** | (<0.3) | | 4.6 | | | | | | | U/mL |


**Fig. 1.** The clinical course with respect to thyroid function and levothyroxine dose. Tg, thyroglobulin; TRAb, anti-thyrotropin receptor antibody; TSAb, thyroid-stimulating antibody; TPOAb, anti-thyroid peroxidase antibody; and TgAb, anti-thyroglobulin antibody.

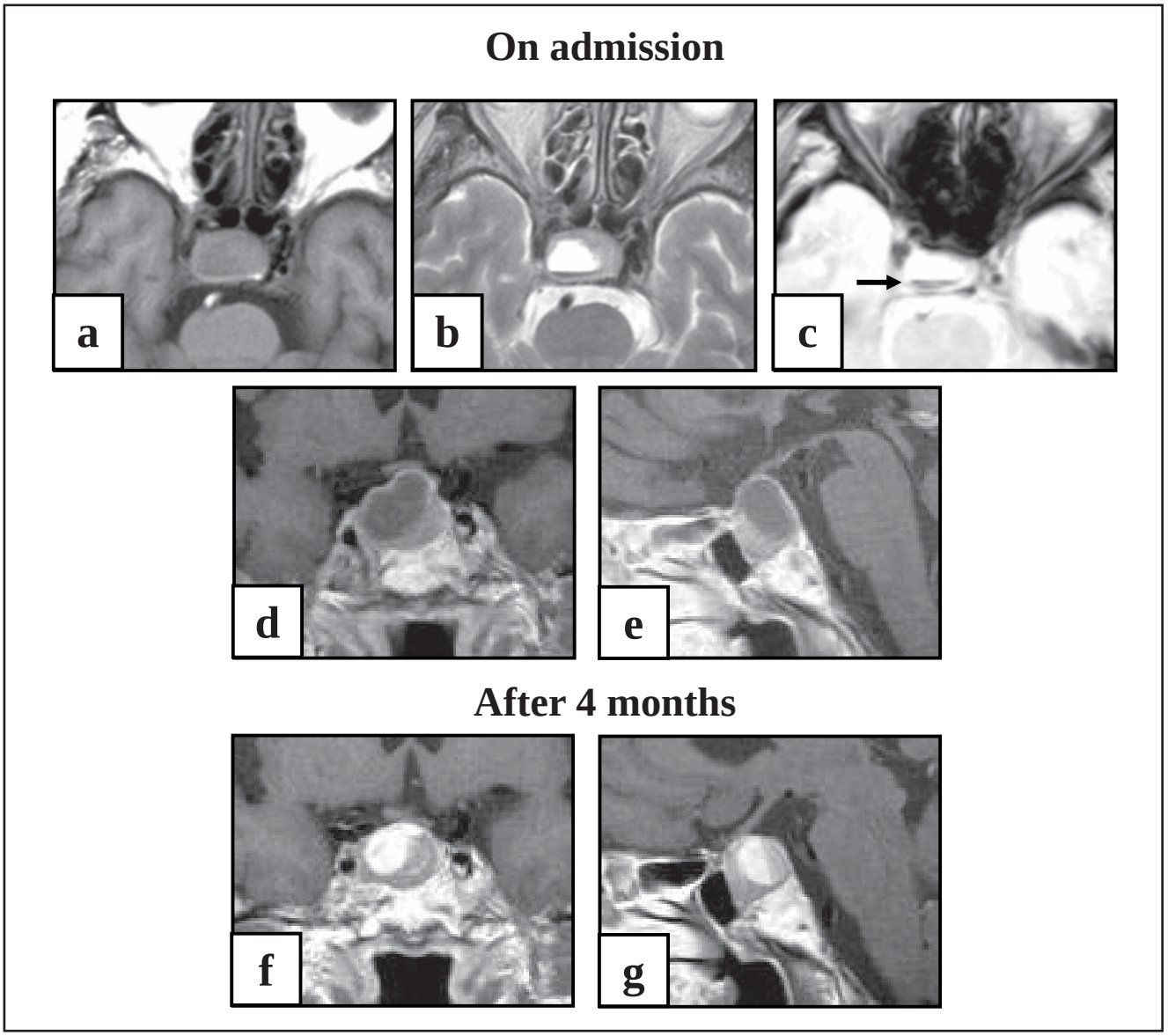


**Fig. 2.** Pituitary MRI. **a**, **b**, Plain images on admission. T1- (**a**), T2- (**b**), and T2*- (**c**) weighted axial images are shown. Marked low-intensity area (arrow) indicates intratumoral hemorrhage. **d–g**, Gadolinium-enhanced T1-weighted images. The MRIs were taken on admission (**d**, **e**) and after 4 months (**f**, **g**).

Hydrocortisone replacement (10 mg/5 mg [morning/evening]) significantly improved her general condition and normalized her serum sodium and calcium levels. Hypercalcemia is a rare electrolyte disorder of adrenal insufficiency. Thyrotoxicosis might have worsened the hypercalcemia associated with adrenal insufficiency because hyperthyroidism increases bone resorption (Strachan *et al.* 2003, Kimura *et al.* 2008). She had no symptoms of diabetes insipidus. Aspirin was discontinued to prevent recurrent bleeding.

Her free triiodothyronine (FT3) and free thyroxine (FT4) levels spontaneously decreased over a short period (days 1–8) in the absence of antithyroid drug therapy (Figure 1). In addition, both serum anti-thyrotropin receptor antibody and thyroid-stimulating antibody titers were negative. These observations suggested painless thyroiditis rather than Graves' disease. In fact, her FT3 and FT4 levels returned to within the reference range at day 33 without medication. The high thyroglobulin levels, probably due to destruction of the thyroid gland, were decreased with the improvement in thyroid function. This is the typical clinical course of painless thyroiditis. Because her thyroid function was expected to decrease due to thyrotropin deficiency, 25-μg levothyroxine was started at day 34. In fact, her FT3 and FT4 levels were below the reference range, with a low thyrotropin level (day 54); 75 μg of levothyroxine was needed to maintain thyroid function at the euthyroid stage.

After 4 months, spontaneous tumor shrinkage with a decreased fluid component but a typical fluid-fluid level pattern was observed (Figure 2f, g). High-intensity

**a** CRH+GRH+GnRH+TRH ⬇

| | reference range | 0 | 30 | 60 | 90 | 120 | min |
|---|---|---|---|---|---|---|---|
| **GH** | (0.001–3.607) | 0.229 | 1.690 | 3.253 | 2.574 | 1.622 | ng/mL |
| **LH** | (5.72–64.31) | <0.10 | <0.10 | 0.16 | 0.22 | 0.28 | mIU/mL |
| **FSH** | (< 157.79) | 0.72 | 1.26 | 1.98 | 2.45 | 2.72 | mIU/mL |
| **Prolactin** | (6.12–30.54) | 63.90 | 95.25 | 90.14 | 85.00 | 82.07 | ng/mL |
| **TSH** | (0.54–4.26) | <0.003 | 0.004 | 0.004 | 0.005 | 0.004 | μIU/mL |
| **ACTH** | (7.2–63.3) | 8.8 | 128.0 | 113.0 | 80.7 | 59.3 | pg/mL |
| **Cortisol** | (4.0–19.3) | 0.9 | 6.9 | 8.1 | 10.1 | 8.7 | μg/dL |
| **IGF-I** | (121–436) | 70 | | | | | ng/mL |

**b**

| | 6h | 12h | 16h | 23h | |
|---|---|---|---|---|---|
| **ACTH** | 7.6 | 11.6 | 8.4 | 7.2 | pg/mL |
| **Cortisol** | 0.8 | 1.3 | 1.2 | 0.8 | μg/dL |

**Fig. 3.** Blood examination on admission and evaluation of pituitary function. **a**, Results of basal hormone value and a combined anterior pituitary function test. Blood samples were obtained in the morning after an overnight fast and a 30-min resting period in the supine position. Reference ranges of the morning hormone levels are shown in parentheses. Hormone values were measured at the suggested times after intravenous administration of 100 μg of corticotropin-releasing hormone (CRH), 100 μg of growth hormone-releasing hormone (GRH), 100 μg of gonadotropin-releasing hormone (GnRH), and 500 μg of thyrotropin-releasing hormone (TRH). **b**, Diurnal variation of plasma ACTH and cortisol levels. IGF-I, insulin-like growth factor I.

signals in the supernatant of the bilayer in T1-weighted image were probably due to intratumoral re-bleeding. Thereafter, the pituitary tumor was slightly enlarged; thus, the patient underwent transsphenoidal surgery. Degraded tumor cells and an old hematoma due to hemorrhage were observed in the removed pituitary mass.

## DISCUSSION

Pituitary apoplexy occurs mainly in a pituitary tumor and is typically characterized by a sudden onset of severe clinical symptoms, such as headache, visual disturbance, and sometimes loss of consciousness. Asymptomatic cases, however, are not so rare and are often difficult to diagnose. For example, in 93 pituitary apoplexies, 42 were asymptomatic (Wakai *et al.* 1981). Of 783 surgical cases of pituitary tumors, 113 were pathologically suggestive of pituitary apoplexies, 74 of which were asymptomatic (Bonicki *et al.* 1993). In the present case, the exact onset of pituitary apoplexy was unclear, and the diagnosis was not made until endocrine disorder was suspected.

Unlike Graves' disease, painless thyroiditis is caused by destruction of the thyroid gland, which leads to characteristic patterns of thyroid fluctuation: transient hyperthyroidism occurs in the early phase, followed by euthyroidism and subsequent hypothyroidism and, finally, euthyroidism. Serum anti-thyrotropin receptor and thyroid-stimulating antibodies are useful for differentiating between Graves' disease and painless thyroiditis. In our patient, the negative tests for both antibodies suggested painless thyroiditis. Although a radioactive iodine uptake scan was not performed, the fluctuation pattern of her thyroid function over several months was consistent with painless thyroiditis. If antithyroid drugs had been prescribed incorrectly during the hyperthyroid state, severe hypothyroidism due to thyrotropin insufficiency would have occurred.

Considering that painless thyroiditis develops as a result of an autoimmune process, an immune rebound mechanism induced by adrenal insufficiency due to pituitary apoplexy might cause painless thyroiditis. In fact, acute changes in cortisol levels caused by steroid tapering (Maruyama *et al.* 1982; Yamakita *et al.* 1993; Morita *et al.* 2001; Kimura *et al.* 2008) or unilateral adrenalectomy for Cushing's syndrome (Haraguchi *et al.* 1984; Takasu *et al.* 1990) can trigger painless thyroiditis. Only 1 report of simultaneous occurrence of pituitary apoplexy and painless thyroiditis has been published so far (Sasaki *et al.* 1991). On the other hand, Punnose *et al.* reported the case of a patient with painless thyroiditis developing soon after the discontinuation of corticosteroid replacement for adrenal insufficiency due to pituitary apoplexy (Punnose *et al.* 2000); unlike our case, steroid tapering after improvement of adrenal insufficiency caused painless thyroiditis. In our case, thyrotoxicosis was thought to be secondary to pituitary apoplexy.

Although the most common type of thyroid disorder in pituitary apoplexy is central hypothyroidism, thyrotoxicosis should be considered even if the patient

has panhypopituitarism. Thyrotoxicosis with adrenal deficiency increases the risk of an adrenal crisis because thyroid hormones accelerate cortisol turnover. Therefore, adrenal deficiency in the presence of thyrotoxicosis is likely to further aggravate the patient's condition, compared with adrenal deficiency without thyrotoxicosis. Although asymptomatic pituitary apoplexy is often difficult to diagnose, prompt diagnosis and glucocorticoid supplementation are essential to avoid a life-threatening adrenal crisis.

### *Conflict of interest*

*The authors declare that they have no conflict of interest.*

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