A Collision Tumor of Pit-1/SF-1-positive Double Pituitary Adenoma and a Craniopharyngioma Coexisting with Graves' Disease

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Abstract

Double or multiple pituitary adenomas expressing different types of transcription factors and collision tumors of pituitary adenomas and craniopharyngiomas are rare. In this report, we present a case of pituitary adenoma of two different cell populations, Pit-1 and SF-1, and an adenoma and craniopharyngioma collision tumor with coexisting Graves' disease. The patient had a 16-mm pituitary tumor with pituitary stalk calcification and optic chiasm compression but no visual dysfunction. Based on hormonal profile results, the tumor in the sella was considered a nonfunctioning pituitary adenoma; nevertheless, the pituitary stalk was invaded by a different lesion, which was later confirmed to be a craniopharyngioma. Using an endoscopic endonasal approach, the pituitary adenoma was removed; however, a small remnant remained medial to the right cavernous sinus. Because the pituitary stalk lesion was isolated from the pituitary adenoma, it was preserved to maintain pituitary function. Three years after the initial surgery, the patient suffered from Graves' disease and was treated with antithyroid medications. However, the intrasellar residual and pituitary stalk lesions gradually increased in size. A second surgery was performed, and the residual intrasellar and stalk lesions were completely removed. As per the initial and second histopathologies, the pituitary adenoma comprised different cell groups positive for thyroid-(TSH) and follicle-stimulating hormones, and each cell group was positive for Pit-1 and SF-1. The pituitary stalk lesion was an adamantinomatous craniopharyngioma. We believe that TSH-producing adenoma was involved in the development of Graves' disease or that treatment for Graves' disease increased TSH-producing adenoma.

Keywords: collision tumor, craniopharyngioma, double pituitary adenoma, Graves' disease, pituitary adenoma

Introduction

The fourth edition of the World Health Organization classification of tumors of endocrine organs published in 2017 introduced the immunohistochemical classification of pituitary tumors using transcription factors such as Pit-1, T-pit, and SF-1.[1] Pituitary adenomas with multiple hormo-

nal activities by the same transcription factor, such as growth hormone (GH) thyroid-stimulating hormone (TSH) prolactin (PRL) and luteinizing hormone (LH) follicle-stimulating hormone (FSH), have been reported to exist in autopsy and surgical case studies.[2] Nonetheless, only a few reports of pituitary adenomas demonstrated overexpression of multiple transcription factors or equivalent multi-
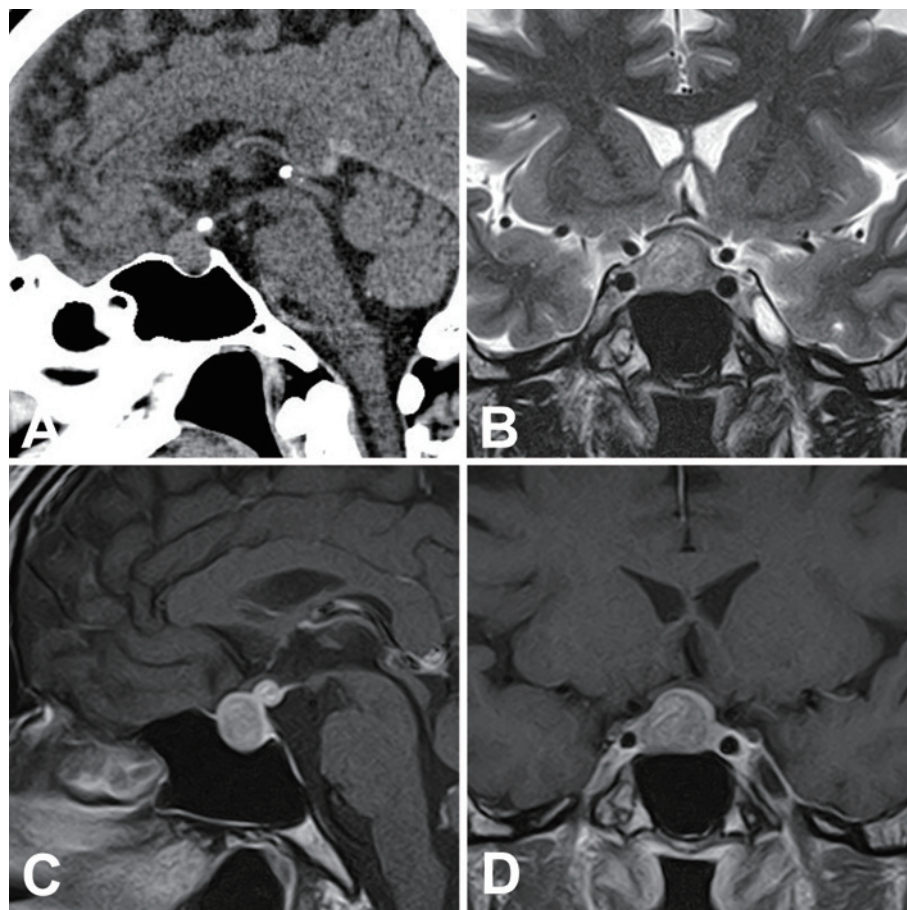
Fig. 1   **Initial preoperative images. A: Plain CT image, sagittal view. B: T2-weighted MR image, coronal view. C: Gadolinium-enhanced T1-weighted MR image, sagittal view. D: Gadolinium-enhanced T1-weighted MR image, coronal view. These images (A–D) show a pituitary tumor with a maximum diameter of 16 mm in the sella compressing the optic chiasm and a 2-mm-diameter cystic lesion at the pituitary stalk, which demonstrates calcification on CT.**

ple hormone-producing properties.[3-5] Collision tumors comprising pituitary adenoma and craniopharyngiomas are also rare.[5-26] This report presents a rare case of a collision tumor of craniopharyngioma and double pituitary adenoma immunohistochemically positive for Pit-1 and SF-1, with coexisting Graves' disease. Informed consent was obtained from all the participants.

Case Report

A 54-year-old man was referred to our department with a pituitary tumor without visual dysfunction or hormonal abnormality. MRI showed that the tumor was compressing the optic chiasm; thus, surgery was recommended to prevent the deterioration of his visual function.

The results of the pituitary-related hormonal assay were as follows: TSH = 1.55 μIU/mL (normal range, 0.34-3.88 μIU/mL), free T3 = 3.16 pg/mL (normal range, 2.13-4.07 pg/mL), free T4 = 0.98 ng/dL (normal range, 0.95-1.74 ng/dL), adrenocorticotropic hormone (ACTH) = 21.6 pg/mL (normal range, 7.2-63.3 pg/mL), cortisol = 3.4 μg/dL (nor-

mal range, 5.3-22.5 μg/dL), PRL = 19.8 ng/mL (normal range, 3.7-16.3 ng/mL), GH = 0.45 ng/mL (normal range, 0-2.47 ng/mL), insulin-like growth factor-1 (IGF-1) = 161 ng/mL (normal range, 84-239 ng/mL), LH = 2.7 mIU/mL (normal range, 0.1-8.7 mIU/mL), and FSH = 10.3 mIU/mL (normal range, 2.0-8.3 mIU/mL). Cortisol showed a decrease in baseline values, and PRL and FSH were slightly elevated above the baseline values. There was no specific family history.

Preoperative MRI showed a pituitary tumor with a maximum diameter of 16 mm in the sella compressing the optic chiasm and a 2-mm-diameter cystic lesion at the pituitary stalk, which demonstrated calcification on CT (Fig. 1 A-D). Based on the hormonal assay results, we considered the intrasellar tumor to be a nonfunctioning pituitary adenoma. However, the cystic lesion in the pituitary stalk was not identical to an intrasellar pituitary adenoma, and another tumor, such as craniopharyngioma, was suspected. The intrasellar tumor was grossly resected using an endoscopic endonasal approach. Since the intrasellar tumor was not continuous with the cystic lesion of the pituitary
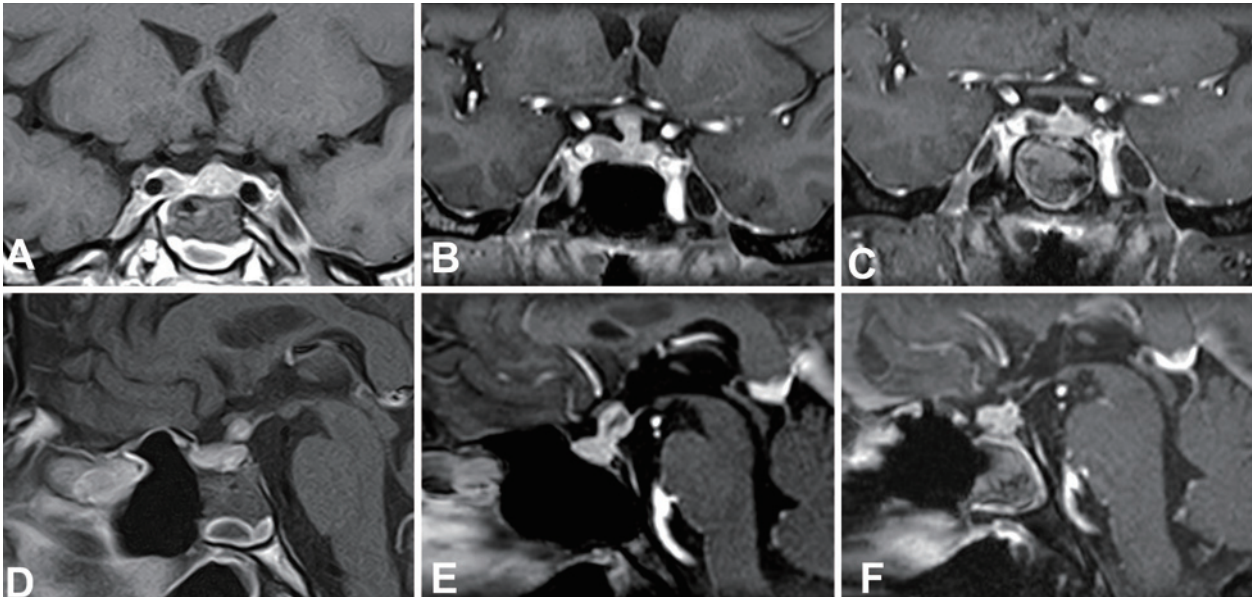
Fig. 2   Initial postoperative, second preoperative, and postoperative images. A–C: Gadolinium-enhanced T1-weighted MR image, coronal view. D–F: Gadolinium-enhanced T1-weighted MR image, sagittal view. Initial postoperative images (A, D) show a small residual pituitary adenoma in the right cavernous sinus medial wall, and the cystic lesion is unchanged. Second preoperative images (B, E) show the cystic components with a 9-mm diameter in the pituitary stalk, and the residual tumor in the sella is enlarged compared to the size after the initial surgery. Second postoperative images (C, F) show no obvious residual tumor both the intrasellar and pituitary stalk lesions and preservation of the pituitary stalk.

stalk and there was a concern that the resection of this lesion would worsen pituitary function due to pituitary stalk injury, we decided to preserve the pituitary stalk cystic lesion and not excise it.

Postoperative MRI revealed a small residual pituitary adenoma in the medial wall of the right cavernous sinus, and the cystic lesion remained unchanged (Fig. 2A, D). The histopathological diagnosis of the intrasellar tumor was a clinically determined nonfunctioning FSH-positive pituitary adenoma (Fig. 3A). Reexamination of this tumor performed after the second surgery revealed two different cell types: a TSH-positive area, which was also Pit-1-positive, and an FSH-positive area, which was SF1-positive (Fig. 3B-F). The SF-1 and Pit1-positive cells were considered to be separate in this tissue section because the area that was not stained for SF-1 in Fig. 3C was stained for Pit-1 in Fig. 3E, F. The patient did not require hormonal replacement therapy during discharge. Furthermore, the patient had no preoperative or postoperative symptoms with high TSH levels.

Postoperative course

Three years after the initial surgery, the patient developed palpitations and shortness of breath. The thyroid hormone levels were elevated under TSH suppression (TSH < 0.01 µIU/mL; free T3, 13.7 pg/mL; free T4, 3.00 ng/dL). Moreover, the test for the thyroid-stimulating autoantibody (TSAb) was positive (675.0%). A diagnosis of probable Graves' disease was made, and the patient started treatment with antithyroid medication (propylthiouracil), by

which hyperthyroidism was controlled. After treatment for Graves' disease, the residual intrasellar tumor and pituitary stalk lesion gradually continued to increase in size (Fig. 2B, E). Accordingly, we decided to perform a second surgery to remove both the stalk and intrasellar lesions 4 years after the initial surgery because the stalk lesion with cystic components was strongly suspected to be a craniopharyngioma.

Present illness (second admission)

The patient was using propylthiouracil 100 mg/day, and the baseline values of pituitary-related hormones were as follows before the second surgery: TSH = 5.14 µIU/mL, free T3 = 2.73 pg/mL, free T4 = 0.83 ng/dL, ACTH = 27.1 pg/mL, cortisol = 10.9 µg/dL, PRL = 12.3 ng/mL, GH = 0.157 ng/mL, IGF-1 = 175 ng/mL, LH = 5.2 mIU/mL, and FSH = 8.8 mIU/mL. TSH and FSH levels were above baseline values, and free T4 showed a decrease in baseline values. Although a preoperative thyrotropin-releasing hormone loading test was not performed, propylthiouracil was discontinued because of hypothyroidism. He was also positive for antithyroid peroxidase antibodies (A-TPO 61.71 IU/mL [normal range ≤ 16 IU/mL], A-TG 19.38 IU/mL [normal range ≤ 28 IU/mL], TRAb 0.922 IU/L [normal range ≤ 2.0 IU/L], and HTG 41.94 ng/mL [normal range ≤ 33.7 ng/mL]). MRI showed cystic components with a 9-mm diameter in the pituitary stalk, and the residual tumor in the sella was enlarged compared to the size after the initial surgery (Fig. 2B, E).
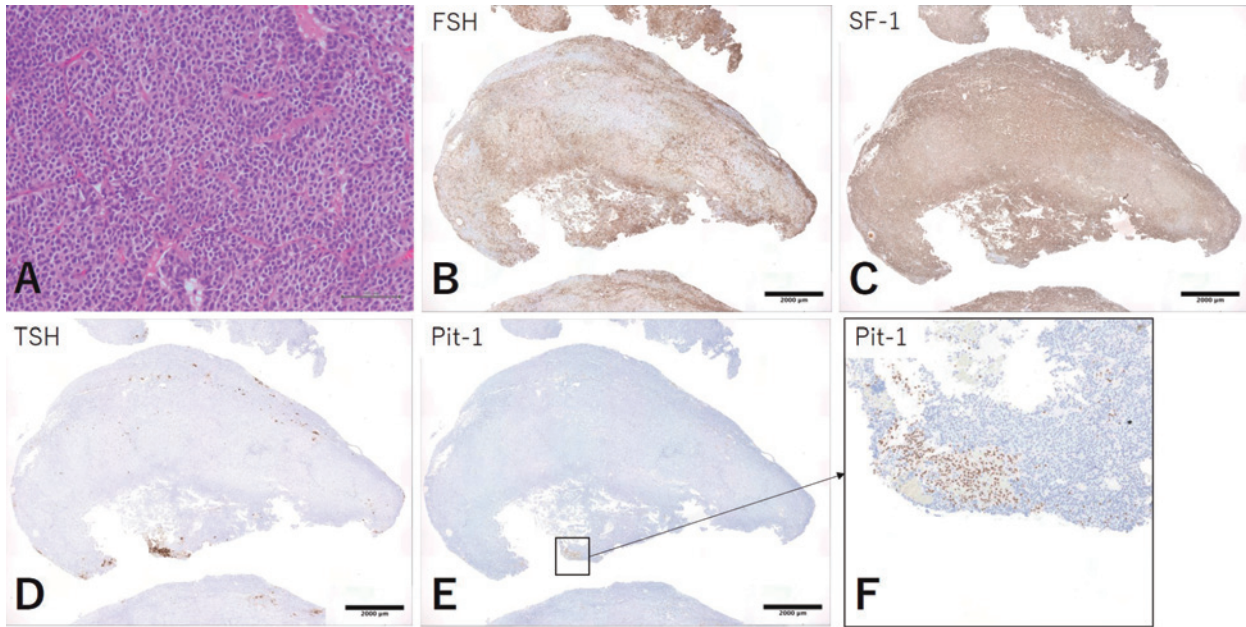
Fig. 3　Immunohistochemistry of tumor samples from the first operation.
Hematoxylin and eosin staining (A) showed tumor cells with relatively small, uniform round nuclei, and acidophilic cytoplasm growing in foci or sheets, and the stroma showed increased fibrous tissue rich in blood vessels. Positive staining for FSH (B), SF-1 (C), TSH (D), and Pit-1 (E, F) showed a small area of TSH-positive cells compared to that in the FSH-positive group. SF-1 was positive, consistent with the FSH-positive cell population, and Pit-1 was positive, consistent with the TSH-positive cell population. Scale bar of A = 100 μm and B, C, D, E = 2000 μm, where F is the enlargement of the area squared in E.

A second endoscopic endonasal tumor resection was performed. After removing the remaining tumor in the sella, there was no continuity between the intrasellar tumor and the pituitary stalk lesion. Thus, the tuberculum sellae was removed, and the cystic lesion of the pituitary stalk was excised. The cystic lesion with the tumor capsule was removed; however, the thinning pituitary stalk was preserved. Postoperative MRI revealed no obvious residual tumor in either the intrasellar or pituitary stalk lesions or preservation of the pituitary stalk (Fig. 2C, F). The histopathological diagnosis of the intrasellar residual tumor was pituitary adenoma with two different types of cells, FSH- and TSH-positive cells, which were immunohistochemically positive for SF-1 and Pit-1, respectively (Fig. 4A-C, E-G). The immunostaining images of SF-1 and Pit-1 showed that different cells were stained (Fig. 4C, F, G). The cystic lesion in the pituitary stalk was diagnosed as adamantinomatous-type craniopharyngioma (Fig. 4D).

The postoperative hormonal assay showed a decrease in TSH levels within baseline values, and free T4 showed a decrease in baseline values (TSH = 0.76 μIU/mL, free T3 = 1.63 pg/mL, free T4 0.66 ng/dL, ACTH = 22.19 pg/mL, cortisol = 8.65 μg/dL, PRL = 13.71 ng/mL, GH = 0.89 ng/mL, IGF-1 = 164 ng/mL, LH = 2.63 mIU/mL, and FSH = 4.36 mIU/mL). The patient required antidiuretic hormone replacement for postoperative diabetes insipidus, but no other hormone replacement was necessary.

Discussion

This report presents a case of a collision tumor between a pituitary adenoma and craniopharyngioma. Immunostaining of the pituitary adenoma showed positive cells for SF-1 and Pit-1, indicating that the pituitary adenoma tissue was a double pituitary adenoma. During the course of the disease, the patient suffered from Graves' disease and was treated with antithyroid medications. The craniopharyngioma and residual adenoma increased in size during the patient's clinical course and required resurgery.

Double pituitary adenomas

Since 1914, different types of multiple or mixed pituitary adenomas have been reported.[27] The definitions of double and multiple pituitary adenomas could be misleading. They can be defined according to either 1) morphology, in which two or more separate tumors are present in the pituitary gland[28,30,31,34-37] or 2) histopathology, in which two or more hormones are identified via immunostaining regardless of the number of pituitary adenomas within the same single pituitary gland.[29-37] A systematic review by Budan et al. reported 63 cases of histologically multiple or double pituitary adenomas of different lineages using immunostaining.[2] These included GH-PRL-TSH and LH-FSH in 31 patients, ACTH and GH-PRL-TSH in 30 patients, and ACTH and LH-FSH in two patients. In a report examining transcription factors, Hagel et al. found that multiple tran-
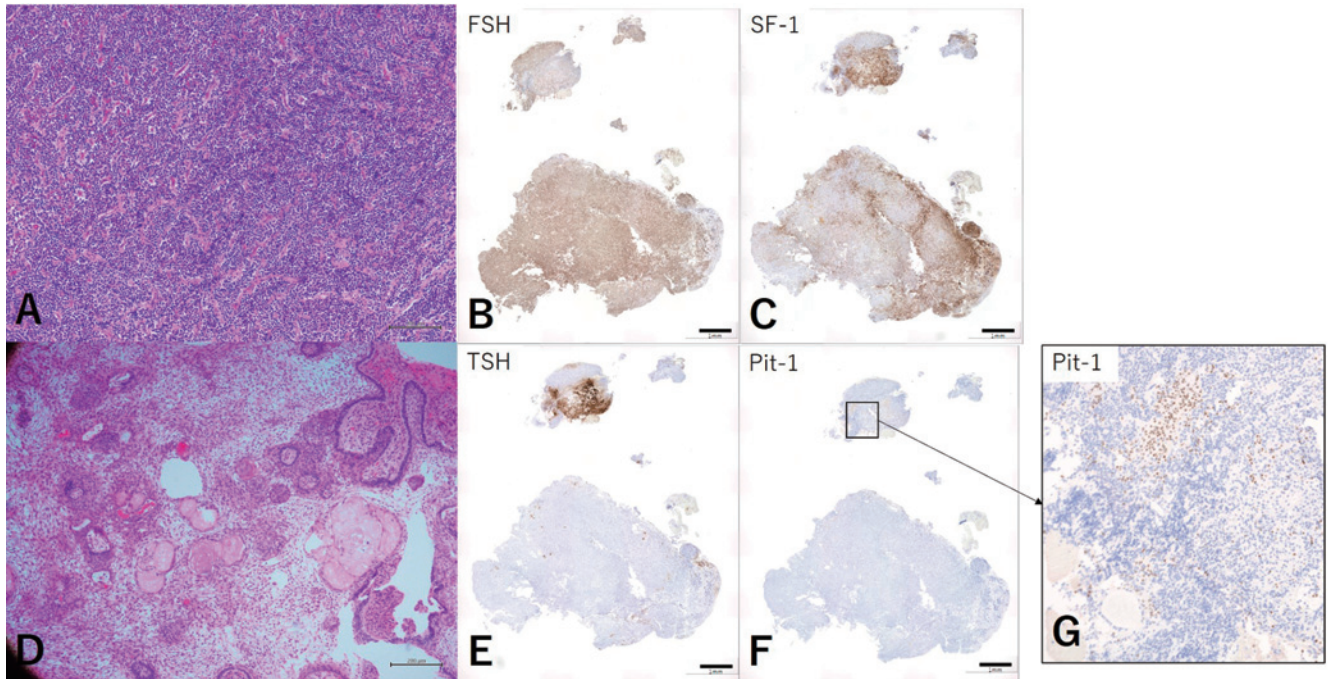
Fig. 4   Immunohistochemistry of tumor samples from the second operation.
Hematoxylin and eosin staining of the residual tumor within the sella (A) showed foci or sheets of cells with acidophilic sporangia with round nuclei and abundant vascular components in the stroma. Immunostaining showed different groups of FSH- (B) and TSH-positive cells (E), and each group of cells was positive for SF-1 (C) and Pit1 (F, G), respectively. There were some areas of mixed FSH- and TSH-positive cells, but immunostaining for other anterior pituitary hormones was negative, signifying a border-line area between FSH- and TSH-producing adenoma rather than normal anterior lobe tissue. Hematoxylin and eosin staining of the pituitary stalk lesion (D) showed that the tissue was composed of basal cells showing a fenestrated arrangement, stellate net-work, stratified squamous-like cells, and wet keratin. Scale bar of A, D = 200 μm, and B, C, E, F = 1 mm, where G is the enlargement of the area squared in F.

scription factors were stained in only 0.3% of patients with pituitary adenomas, for which they performed tissue evalu-ations (9 of 3654).[3] They found immunostaining of Pit-1 and SF-1 in four cases, T-pit and Pit-1 in three, and T-pit and SF-1 in two. However, based on these reports, it was not determined whether double pituitary adenomas ex-pressing multiple transcription factors comprise a single adenoma or whether they are separate adenomas.

The mechanism underlying the histological development of double or multiple pituitary adenomas remains unclear. However, several theories have been proposed, including the coincidental multicentric development of multiple monoclonal tumors,[36] the transformation of the same ade-noma cells into different adenomas,[37] and the development of a second tumor by stimulation of a GH-producing ade-noma.[38]

There have been reports of double pituitary adenomas in which different transcription factors were positive dur-ing the first and second surgeries.[4] In the current case, the tumor specimen from the first surgery was re-examined and was found to be a double tumor. Furthermore, the two histologically distinct adenomas were indistinguishable on imaging.

Collision tumor of pituitary adenoma with craniopha-ryngioma

The first case of a collision tumor of a pituitary ade-noma with a craniopharyngioma was reported in 1971,[7] and to date, 22 cases have been reported.[5-26] The histologi-cal diagnosis of pituitary adenoma in 22 reported cases was GH positive in one case,[22] ACTH positive in three,[16,21,25] PRL positive in six,[7-11,13,19] gonadotropin positive in three,[6,14,15] multiple in one,[5] none in four,[12,17,20,24] and un-known in four.[7,18,23,26] All craniopharyngiomas were of the adamantinomatous type, except for one that was papillary type.[26] Yoshida et al. reported a patient with multiple pi-tuitary adenomas associated with craniopharyngioma.[5] This is a rare report in which all three transcription fac-tors were positive. To the best of our knowledge, the cur-rent case is the 23rd to be reported, and the second case of a collision tumor involving a craniopharyngioma and a double pituitary adenoma.

In cases of prolactinomas associated with craniopharyn-giomas, it is hypothesized that pituitary stalk compression by the craniopharyngioma and reduction of central dopaminergic input in the hypothalamus may contribute to the development of prolactinomas.[13] Regarding the GH

lesions, GH-related receptor expression in craniopharyngioma is involved in tumor growth and recurrence, and tumor cell growth is promoted in the presence of GH and IGF-1 in vitro and inhibited under tamoxifen.[39] Therefore, in GH- or PRL-producing adenomas combined with craniopharyngiomas, tumor enlargement is possible because of their interaction.

In this case, the patient was diagnosed with gonadotroph adenoma during the initial surgery. However, because the pituitary adenoma was positive for TSH and FSH at the second surgery, the initial specimen was restained and a TSH-positive area was found, indicating a double pituitary adenoma from the initial stage of the disease. Although there are reports of the involvement of high TSH levels in the development of thyroid cancer,[40] there are no reports of TSH involvement in the development or growth of cancer in other parts of the body, including brain tumors.

Association between TSH-producing adenoma and Graves' disease

TSH-producing adenomas (TSHomas) cause hyperthyroidism, usually with elevated fT3 and fT4 levels, and no TSH suppression. Reports of TSHomas linked to Graves' disease are rare, with only approximately 10 cases reported.[41,42] Excessive TSH secretion promotes the production of anti-idiotypic antibodies and induces Graves' disease, but the treatment of TSHomas may improve Graves' disease.[42-44] Conversely, using antithyroid medications to treat Graves' disease may increase TSHoma because thyroid hormone levels are lowered and TSH secretion is stimulated.[44,45] Because hyperthyroidism, in this case, was not due to the syndrome of inappropriate secretion of TSH, we considered that TSHoma was not symptomatic. However, the slightly higher preoperative TSH level and lower postoperative value in the second surgery suggested that TSH was overproduced, suggesting that the administration of antithyroid medication may have induced TSHoma growth.

Although collision tumors involving craniopharyngiomas and pituitary adenomas are rare, it is even rarer for pituitary adenomas to be histologically double tumors. Moreover, a TSHoma and its increased hormonal production can possibly affect the development and treatment of Graves' disease.

Conflicts of Interest Disclosure

All authors have no conflicts of interest to declare.

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