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# A Rare Case of Recurrent Pituitary Collision Tumors

**Almoutaz Shakally,[1] Naoyuki Tahara,[2,3] Brent Clark,[4] Ramachandra Tummala,[5] Emiro Caicedo-Granados,[6] Yasuhiko Kawakami,[2,3] and Takako Araki[1]**

*[1]Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, University of Minnesota, Minneapolis, Minnesota 55455; [2]Department of Genetics, Cell Biology and Development, University of Minnesota, Minneapolis, Minnesota 55455; [3]Stem Cell Institute, University of Minnesota, Minneapolis, Minnesota 55455; [4]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota 55455; [5]Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota 55455; and [6]Department of Otolaryngology, Head and Neck Surgery, University of Minnesota, Minneapolis, Minnesota 55455.*

**ORCiD numbers:** 0000-0002-1905-2906 (R. Tummala); 0000-0002-0043-9705 (Y. Kawakami); 0000-0002-4451-1668 (T. Araki).

Pituitary collision tumors are sporadically reported and rare. We present a case of pituitary collision tumors with nonfunctioning pituitary adenoma (NFPA) and craniopharyngioma. In order to look for any common activated pathway, we examined WNT/β-CATENIN signaling activation, known to be involved in tumorigenesis in both craniopharyngioma and NFPA. We found nuclear accumulation of β-CATENIN protein and expression of LEF1 protein, markers of active β-CATENIN signaling in the craniopharyngioma but not in the pituitary adenomas. In our case, the NFPA is invasive macroadenoma, which is a frequently identified type of pituitary adenoma in collision tumor cases. Recurrence of this tumor was first observed after 8 years of follow-up. Based on this case, we suggest that pituitary collision tumors require long-term follow-up.



Collision tumors are defined as 2 histologically distinct tumors that occur at the same location. These uncommon tumors have been found in a variety of organs, including the adrenal gland, pancreas, breast, colon, esophagus, stomach, and uterus [1–10]. Very rarely, collision tumors have also been reported in the pituitary [11–21]. A combination of adenoma and craniopharyngioma is one of the most frequent combinations of pituitary collision tumors. Clinical features of pituitary collision tumors are not well known. It is unknown whether pituitary collision tumors recur and whether activation of a signaling pathway common to the different tumor types underlies their pathology.

The NFPA is the most common type of pituitary tumor. There are 2 subtypes of NFPA: adenomas of null cells that are negative for immunostaining of hormones and silent pituitary adenomas that express but do not oversecrete hormones. A majority of silent NFPAs are derived from gonadotrophs, which stain positive for luteinizing hormone and/or follicle stimulating hormone (FSH). Despite intensive molecular investigations, mechanisms of pathogenesis of NFPA are not completely understood [22, 23]. However, evidence suggests that high levels of expression of β-CATENIN protein contribute to the development of NFPA [24, 25].

Craniopharyngiomas are categorized into 2 types; the more common adamantinomatous type and the less common papillary type. It has been reported that more than 70% of adamantinomatous craniopharyngiomas harbor mutations in *CTNNB1,* the gene encoding β-CATENIN [26–28]. β-CATENIN is a central component of WNT/β-CATENIN signaling.

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Aberrant activation of β-catenin signaling by mutations in *CTNNB1* contributes to tumor progression and increased recurrence of the tumors [29].

Here we report the first recorded case of recurrence of pituitary collision tumors. An initial NFPA was followed by the development of a craniopharyngioma after 8 years, and then a recurrence of a second NFPA. We also describe clinical characteristics of pituitary collision tumors based on literature research.

## Case Report

A 41-year-old male presented with a 2-month history of fatigue, headache, and decline in visual acuity. Ophthalmological evaluation showed moderate left temporal field cut with an afferent pupillary defect and atrophy of the left optic nerve. Brain magnetic resonance imaging (MRI) showed a heterogeneous enhancing mass arising from the *sella turcica*, measuring 31 × 26 × 37 mm, with significant upward displacement of the chiasm, especially on the left aspect with invasion of the right cavernous sinus. (Fig. 1A, arrow). Initial hormonal evaluations showed insulin-like growth factor-1, prolactin with dilution, thyroid stimulating hormone, free thyroxine, and morning cortisol levels to be normal. Total testosterone level was decreased to 200 ng/dl (reference range 240–950 ng/dl).

Endoscopic trans-sphenoidal resection of the pituitary tumor was performed without complications. Histopathological analysis of the resected tumor revealed that it was an

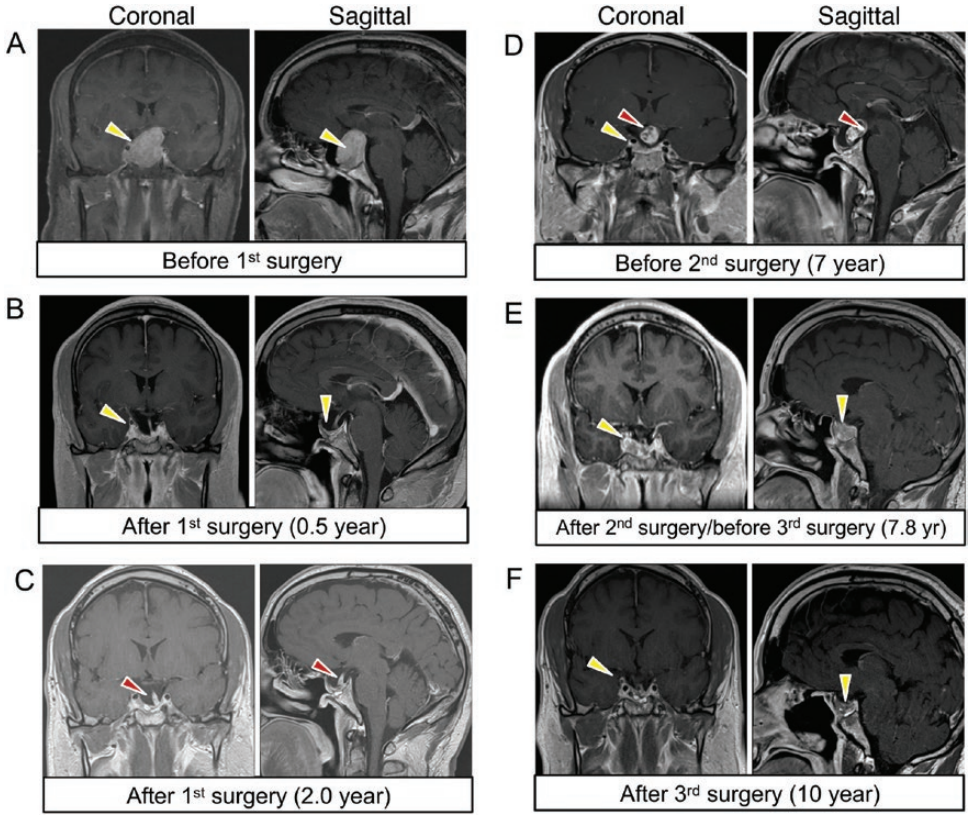


**Figure 1.** Brain MRI throughout the clinical course. Brain MRI of coronal (left) and sagittal (right) images T1-weighted with gadolinium contrast. **A:** MRI images before the first surgery show a large solid sellar mass with suprasellar extension causing optic chiasm compression and extension to the cavernous sinus. **B:** MRI images after the first surgery show resection of the tumor. **C:** MRI images 2 years after the first surgery. **D:** MRI images before the second surgery. **E:** MRI images after the second surgery/before the third surgery. **F:** MRI images after the third surgery. Yellow and red arrowheads indicate NPFA and craniopharyngioma, respectively. MRI indicates magnetic resonance imaging.

NFPA (Fig. 2A). A postoperative MRI did not show any residual tumor (Fig. 1B). MRIs were repeated 2 years after the surgery and did not detect recurrence (Fig. 1C). However, 7 years after surgery, there was a new lesion 15 × 17 × 26 mm sized T1 hypointense, T2 hyperintense, cystic, and lobulated lesion with heterogenous contrast enhancement involving the pituitary stalk (Fig. 1D). Therefore, a second endoscopic trans-sphenoidal surgery was performed, which again successfully removed the tumor without complications. Histopathology revealed a squamous epithelial neoplasm with keratin pearls and calcifications, which is characteristic of an adamantinomatous craniopharyngioma (Fig. 2B).

Nine months postoperatively, MRI showed no tumor above the *sella turcica*; however, a new tumor was found in the right side of the *sella turcica*, with extension into the right cavernous sinus (Fig. 1E). Therefore, a third trans-sphenoidal surgery was performed, and the tumor was again successfully removed (Fig. 1F). Postoperatively, the patient developed mild secondary hypothyroidism, persistent secondary hypogonadism, and mild growth hormone deficiency, which were managed well with hormone replacement therapies. Histopathological analysis showed that the tumor exhibited a pattern characteristic to

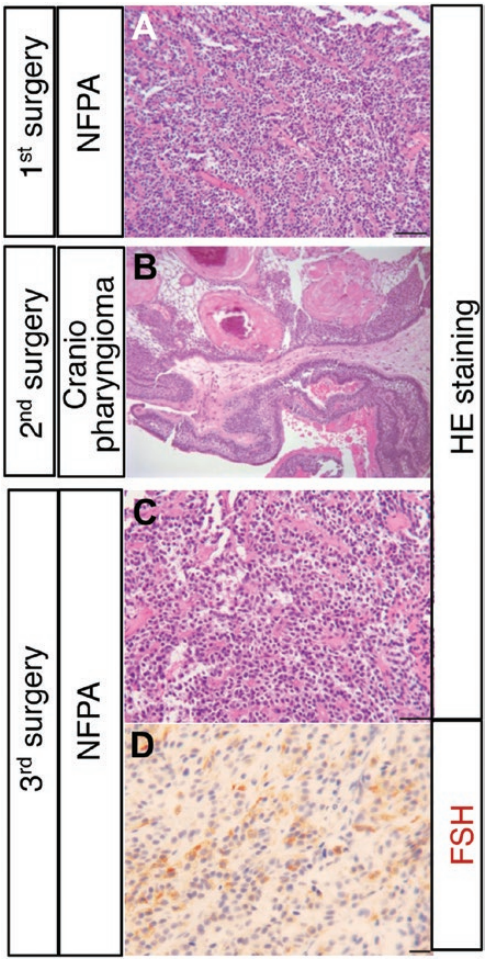


**Figure 2.** Stained surgical specimens during the clinical course. **A–C:** Hematoxylin and eosin-stained images. **A:** Histopathology of the first resection specimen shows a classical pituitary adenoma. There are sheets of bland epithelial cells with loss of the acinar pattern seen in normal adenohypophysis. **B:** Histopathology from the second resection shows adamantintomatous craniopharyngioma. There are keratin pearls and foci of calcification in the upper half of the figure. **C:** Histopathology from the third resection shows a classical pituitary adenoma. **D:** Immunohistochemistry of follicle stimulating hormone (FSH) on (**C**). Cells of the pituitary adenoma exhibit nuclear cytoplasmic and nuclear staining for FSH. Scale bars: 50 μm (**A–C**). Scale bar: 25 μm (**D**).

pituitary adenoma, similar to the tumor from the first surgery, and also stained positive for FSH (Fig. 2C and 2D). This recurrence of NFPA could be a regrowth of the original tumor, given that we observed a subtle hypoenhanced lesion by MRI prior to the second surgery (Fig. 1D yellow arrow).

We also performed confocal immunofluorescent analysis of tumors from the first and second surgeries for β-CATENIN (mouse anti-Active-β-CATENIN: Millipore, #05-665, 1/250 dilution), a protein associated with the cell membrane for adherence junction formation, and LEF1 (lymphoid enhancer-binding factor 1; rabbit anti-LEF1, Cell Signaling Technology, 2230P, 1/100 dilution), a target of WNT/β-CATENIN signaling (Fig. 3) [30]. Cytosolic/nuclear localization of β-CATENIN is a hallmark of activation of WNT/β-CATENIN signaling. In the craniopharyngioma, LEF1-positive cells are also positive for nuclear β-catenin (Fig. 3E –3H and 3M–3P), while membrane β-catenin was detected in both LEF1-positive

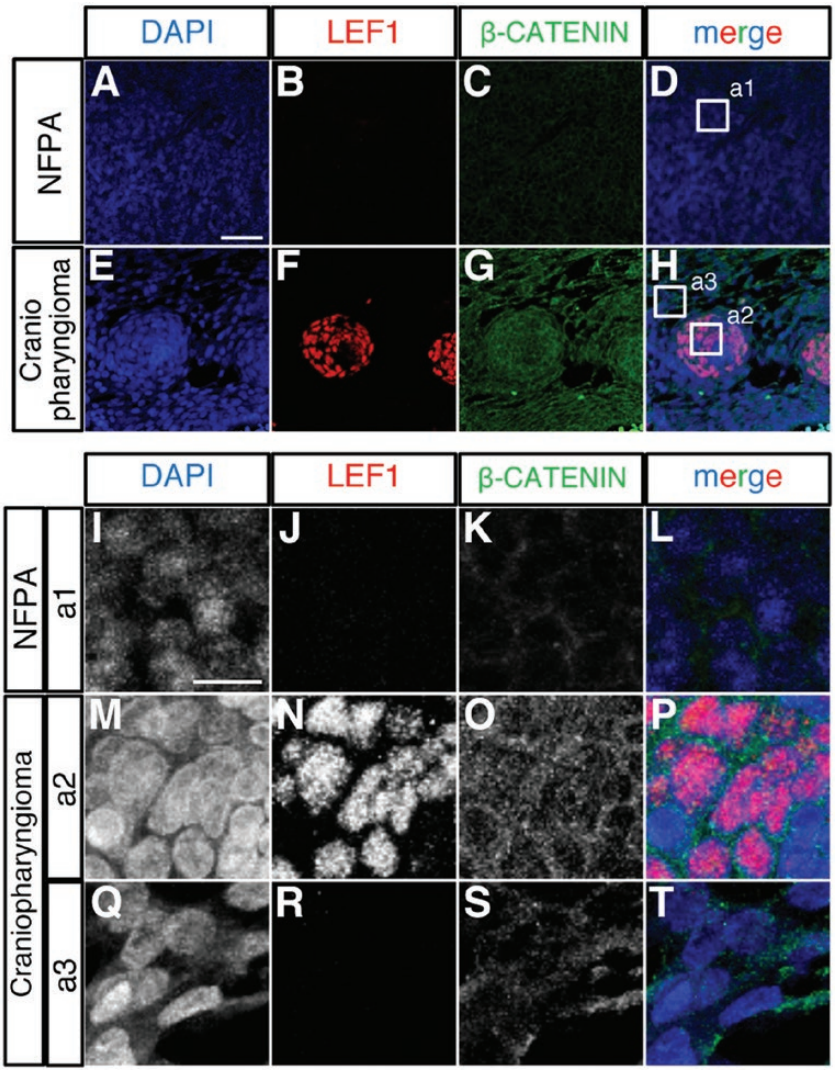


**Figure 3.** Immunofluorescence analysis of LEF1 and β-CATENIN in the collision tumor. Immunofluorescence of β-CATENIN and LEF1 on sections of NFPA (first resection, **A–D**) and craniopharyngioma (second resection, **E–H**). Craniopharyngioma samples exhibit strong LEF1 staining. **I–T:** Higher magnification images of a1 (**D**), and a2 and a3 (**H**). In NFPA, LEF1 signals were not detected (**J**) and β-CATENIN was detected only in the plasma membrane (**K**). In craniopharyngioma, LEF1 and cytoplasmic/nuclear β-CATENIN are co-present (**N–P**). In cells without LEF1, cytoplasmic/nuclear β-CATENIN was not detected (**R–T**). Scale bars: 50 μm (**A–H**). Scale bars: 10 μm (**I–T**).

and LEF1-negative cells (Fig. 3Q–3T). In the NFPA, neither cytoplasmic/nuclear β-catenin nor LEF1 were detected (Fig. 3A–3D and 3I–3L). In this case, these results demonstrated that WNT/β-CATENIN signaling is activated in the craniopharyngioma but not in the NFPA.

Due to the concern of recurrence, we plan to follow this patient indefinitely with MRI scans every 1 to 2 years.

## Discussion

We describe a case of collision tumors in the pituitary. Collision tumors are characterized by development of 2 distinct types of tumors in the same region. Although they are rare [11–21], co-existence of multiple tumors (up to 3 types) in the pituitary has been observed in up to 0.9% of autopsy cases from all causes of death [31]. It is possible that undiagnosed collision tumors may be more frequent than reported.

In pituitary collision tumors, the co-existence of craniopharyngioma and adenoma is the second most common combinations after a combination of a Rathke's cleft cyst and adenoma. Among adenomas, prolactinoma is the most frequent, and NFPA is the second most frequent. To date, 14 cases (including this case) of pituitary collision tumors consisting of pituitary adenomas and craniopharyngioma have been reported worldwide [11–21]. All cases involved pituitary macroadenoma (> 10 mm). Especially large adenomas (> 30 mm) with histologically invasive features were reported in 7 cases (50%) [11–17, 19–21].

It is not known if 1 tumor type is more likely develop early than another tumor type in collision tumors. We speculate that pituitary adenomas are more likely to develop earlier than craniopharyngioma for the following reasons: with the combination of craniopharyngioma and adenoma, the majority of cases (6/10 well-described cases) exhibit a pattern of small "islands" of craniopharyngioma that are found within the large adenomas. In 3 cases of collision tumors (including our case), there was a lag between the discoveries of the initial tumor and the subsequent tumor(s) [11, 15]. In all of these cases, an adenoma was found first, followed by a craniopharyngioma. Different cases report different lag periods in the detection of 2 types of tumors: 4 months [15], 10 months [11], and 7 years in the present case. However, by retrospectively examining MRI images, we noticed a pituitary stalk enlargement 2 years after the first surgery (Fig. 1C). This observation suggests that the actual lag between the development of pituitary adenoma and craniopharyngioma could have been shorter.

The mechanism of pituitary collision tumor development remains unknown. There might be common causes of tumorigenesis in both tumor types. We investigated whether aberrant activation of WNT/β-catenin signaling could be this common mechanism by measuring WNT/β-catenin signaling activation in both NFPA and craniopharyngioma. A previous study reported activation of WNT/β-catenin signaling in adenoma but not in craniopharyngioma [13]. In contrast, our case showed that WNT/β-catenin signaling was activated in craniopharyngioma, but not in NFPA. Our result (and a previous report) suggest that activation of WNT/β-catenin signaling does not always serve as a common mechanism of tumorigenesis between the 2 types of tumors in the collision tumors [13].

Aberrant activation of WNT signaling by mutations in the *CTNNB1* gene in craniopharyngioma has been previously reported [26–28]. β-catenin signaling promotes cell proliferation, and its activation could contribute to tumorigenesis of craniopharyngioma [32]. Consistent with these reports, the craniopharyngioma reported in this case exhibited strong LEF1 staining and accumulation of cytoplasmic/nuclear β-CATENIN, indicative of activation of β-CATENIN signaling. In contrast, expression patterns and potential roles of β-CATENIN in NFPA development are controversial [24, 33–36]. A study described that nuclear β-CATENIN was observed in 57% (n = 21/37) of NFPA cases [35]. Another study compared NFPA and normal pituitary glands using proteomics approaches and showed increased expression of WNT signaling-related proteins SFRP1, PITX2, and CYCLIN D1 in NFPA [24]. But the other study failed to detect *CTNNB1* mutations in NFPA [34]. In our case, WNT/β-catenin signaling was not activated in NFPA, suggesting that activation of

WNT/β-catenin signaling is not a common mechanism of the 2 types of tumors in the collision tumors reported here.

This is the first published report to describe tumor recurrence in a pituitary collision tumor case. This may be due to the short follow-up periods included in previous reports. In the 13 previously reported pituitary collision tumor cases, the average follow-up term was less than 1 year (7 months) [11–21]. Our case has the longest reported follow-up (11 years) and shows evidence of recurrence of the NFPA component. The latency period of NFPA in this report is longer than that of the average of solitary NFPA from previous meta-analysis (8 years vs 1–5 years) [37], suggesting that we may need longer follow-up on NFPA that is part of a set of collision tumors than on solitary NFPA. For further recurrence, adjuvant radiation therapy could be an option.

In conclusion, we present the first case of recurrence of pituitary collision tumors. Development of pituitary collision tumors is rare, and they may occur within large, aggressive pituitary adenomas. Collision tumors of the pituitary may require long-term follow-up to monitor for recurrence of either or both tumor types.

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## Additional Information

***Correspondence:***Takako Araki MD, Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, University of Minnesota, MMC 101, 420 Delaware Street, SE, Minneapolis, MN 55455, USA. E-mail: taraki@umn.edu.

***Disclosure Summary:*** The authors have nothing to disclose.

***Data Availability:*** All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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