

# Long-Term Follow-Up of Growth Hormone-Producing Pituitary Carcinoma With Multiple Spinal Metastases Following Multiple Surgeries: Case Report

Toshihide TANAKA,<sup>1</sup> Naoki KATO,<sup>1</sup> Ken AOKI,<sup>1</sup> Mitsuyoshi WATANABE,<sup>1</sup>  
Takao ARAI,<sup>1</sup> Yuzuru HASEGAWA,<sup>1</sup> and Toshiaki ABE<sup>2</sup>

<sup>1</sup>*Department of Neurosurgery, Jikei University School of Medicine Kashiwa Hospital, Kashiwa, Chiba;*

<sup>2</sup>*Department of Neurosurgery, Jikei University School of Medicine, Tokyo*

## Abstract

This report describes a rare case of a patient with growth hormone (GH)-secreting pituitary adenoma with malignant transformation resulting in multiple metastases to the dura mater of the cerebral convexity and high cervical spine. The patient was a 60-year-old man with a previous history of pituitary adenoma with suprasellar extension who had undergone transsphenoidal surgery, craniotomy for a convexity tumor, and suboccipital craniotomy for a cerebellar tumor. Thirteen years after the initial surgery, suboccipital craniotomy for a cervicomedullary junction tumor and cervicospinal surgery for a metastatic tumor was performed. Histologic findings of resected specimens demonstrated that the primary pituitary tumor was typical adenoma (similar to specimens from the initial surgery) but that the cerebellar and the dural tumor from the high cervical spine had a high incidence of mitotic figures, and cellular anaplasia with nuclear polymorphism and necrosis. In addition, the serum levels of GH were noted to have decreased with recurrence of the tumor. It was concluded that patients with pituitary adenoma, even when benign, must be carefully followed for signs of malignant transformation, and spinal or distant metastases.

Key words: pituitary carcinoma, growth hormone-producing adenoma (GHoma), acromegaly, dural metastasis, spinal dissemination

## Introduction

Pituitary adenomas are generally benign. Recurrence and distant metastases of the pituitary adenoma to the spinal dura are rare and may indicate transformation to pituitary carcinoma. Malignant pituitary adenoma is a rare tumor that accounts for a small percentage of all cases of pituitary adenoma. Growth hormone (GH)-secreting pituitary adenoma is usually benign, and distant metastases are extremely rare.<sup>1,11,17,23)</sup>

In the current World Health Organization (WHO) classification of pituitary adenomas, subarachnoid spread is an indicator of malignant transformation. The pathogenesis of malignant pituitary tumors is poorly understood, and there is insufficient information regarding reliable prognostic markers of malignant transformation and appropriate treatment strategies for these tumors. Of note, radiation therapy for residual or recurrent pituitary tumors might induce malignant transformation.<sup>2,13)</sup>

According to previous reports, most patients with pituitary adenoma who experience recurrences (including intracranial and spinal metastases) have undergone multiple previous surgeries and have received prolonged radiotherapy.<sup>1,2,5,6,9,11,13,14,16,21,22,24)</sup> Further, cerebral spinal fluid (CSF) leakage following transsphenoidal surgery may increase the risk of subsequent subarachnoid dissemination of the tumor.<sup>16)</sup>

Taya et al.<sup>23)</sup> previously described a patient with GH-producing adenoma (GHoma) with intracranial dissemination who was treated with surgery 7 years after transsphenoidal surgery for pituitary adenoma. The present report was a follow-up report of Taya et al.'s article describing a case of a patient who developed multiple supratentorial, cerebellar, and cervical spine dural metastases at 13 years after initial surgical operation for pituitary adenoma.

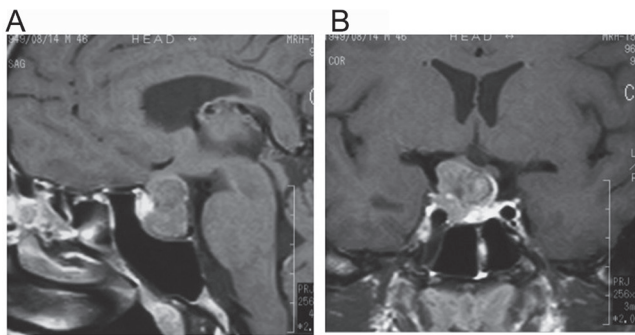
## Case Report

### I. Clinical course

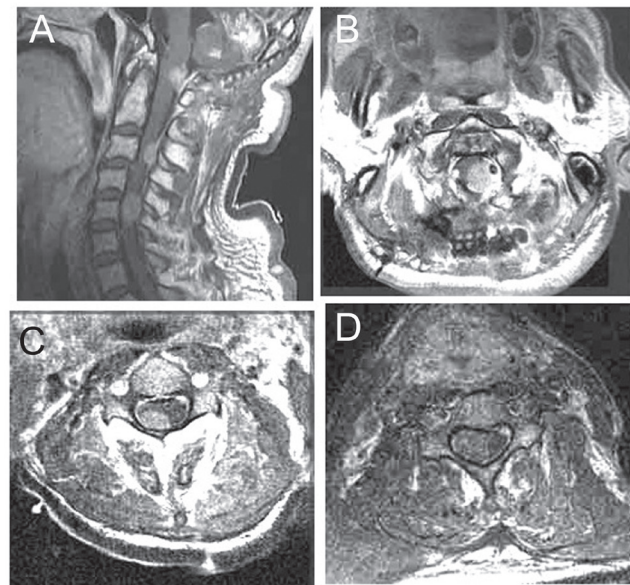
The patient was a 60-year-old man who suffered

from visual disturbance in March 1996, as previously described.<sup>23)</sup> Magnetic resonance (MR) imaging showed an intrasellar tumor (Fig. 1A, B). Transsphenoidal sellar surgery was performed, and histologic examination revealed a benign GH-secreting pituitary adenoma.<sup>23)</sup> After the initial surgery, nine surgical operations in total were performed via the transcranial route for recurrent pituitary tumor between October 1996 and September 2009 followed by gamma knife and cyber knife as previously described.<sup>23)</sup>

The patient developed progressive tetraparesis in October 2009. His muscle tone was flaccid, and superficial sensation was also abnormal. Endocrinologic examination showed that serum levels of GH and somatomedin C were



**Fig. 1** Initial gadolinium-enhanced T<sub>1</sub>-weighted magnetic resonance (MR) imaging demonstrating the tumor in the sella. (A: sagittal image, B: coronal image).



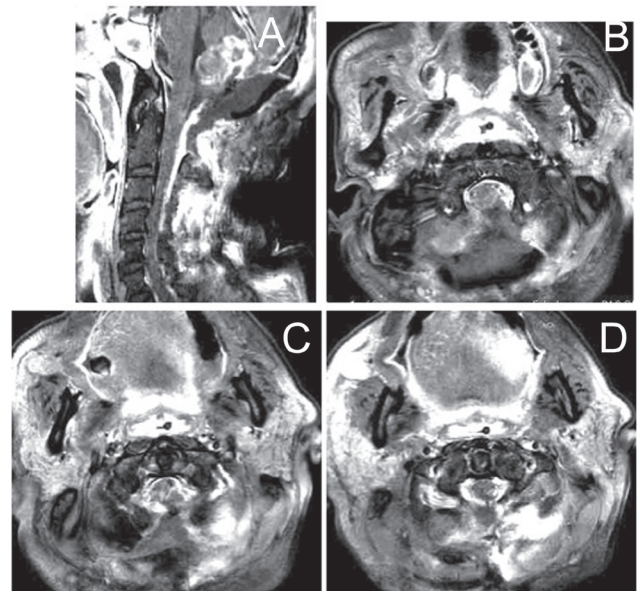
**Fig. 2** Gadolinium-enhanced T<sub>1</sub>-weighted magnetic resonance (MR) imaging well-demarcated tumors on the dorsal side of the cervicomedullary junction, the C3 and the C5. (A: sagittal image, B–D: axial image).

80.4 ng/ml and 562.0 ng/ml, respectively.

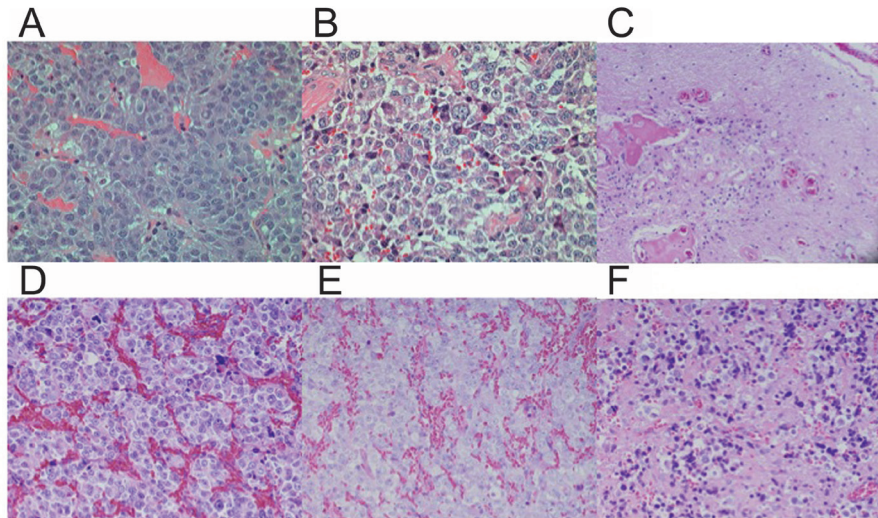
MR imaging of the brain and cervical cord showed a gadolinium-enhanced solid tumor at the cervicomedullary junction, compressing the medulla (Fig. 2A, B). In addition, extramedullary solid tumors at the level of the C3 and the C5 were also seen (Fig. 2C, D). A two-stage operation was performed. The tumor in the cervicomedullary junction was completely removed via a midline suboccipital craniotomy. The tumor was located in the subdural space, adhering to the medulla and to the dura at the posterior rim of the foramen magnum. The arachnoid was intact; thus, the tumor was easily separated from the medulla but was still tightly adherent to the dura. Two days later, the tumors at the levels of C3 and C5 were removed via C1–C5 laminectomy. These tumors were also located in the subdural space and were tightly adherent to the dura. The arachnoid was intact; thus, the tumors were easily separated from the cervical cord. Postoperative MR imaging revealed that the tumors had been completely removed (Fig. 3). The patient's motor function improved, and he was transferred to a rehabilitation facility. However, his ability to conduct activities of daily living gradually deteriorated, and he died 14 years after the first surgery. An autopsy was not performed.

## II. Histologic findings

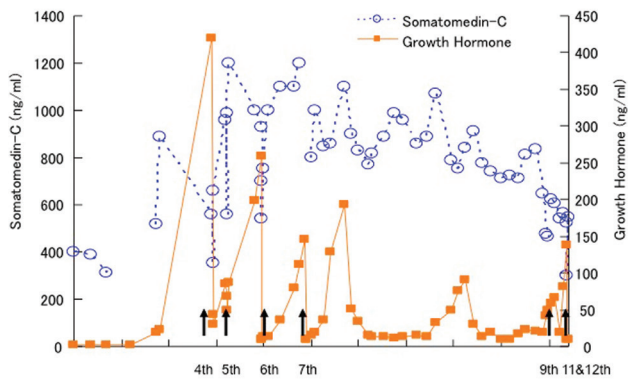
Histologic examination revealed that the tumors in the pituitary fossa consisted of uniformly sized cells with uniform round nuclei (Fig. 4A). These findings were



**Fig. 3** Postoperative magnetic resonance (MR) imaging revealing complete removal of the tumors. (A: sagittal image, B–D: axial image).



**Fig. 4** Photograph of histopathologic findings from the tumors. A: The intrasellar tumor obtained from the initial surgery showed findings that are typical of pituitary adenoma. B: The parietal tumor obtained from the fourth surgery shows sheets of cells with pleomorphic nuclei with abundant cytoplasm and mitoses. C: The cerebellar tumor shows necrosis. D: The tumor in the medulla shows sheets of cells with round nuclei and sporadic mitoses with abundant microcapillaries. E: The tumor in the C3 shows faint staining of nuclei with hematoxylin with abundant mitoses with abundant microcapillaries. F: The tumor in the C5 shows a cluster of the tumor cells with pleomorphic nuclei and necrosis.



**Fig. 5** Time course of serum levels of growth hormone (GH) and somatomedin C. Serum level of GH declined gradually with recurrence of the tumor.

consistent with those of the pituitary adenoma.

The tumor in the parietal lobe (the second surgery) displayed moderately pleomorphic nuclei and amphophilic cytoplasm (Fig. 4B). MIB-1 index was 7% (data not shown).

The tumor in the cerebellum had marked necrosis (Fig. 4C). The tumor in the medulla and the C3 had cells with hyperchromatic nuclei that intermingled with connective tissue including abundant capillaries (Fig. 4D, E). Mitotic figures were frequent. The tumors in the C5 displayed tumor cells with pleomorphism and

poor differentiation (Fig. 4F). Histologic diagnosis was pituitary carcinoma.

### III. Time course of serum levels of GH

Serum levels of GH and somatomedin C are shown in Fig. 5. Levels of GH declined with progressive dissemination of the tumor and corresponded to the histologic findings of differentiation of the adenoma (Fig. 5).

## Discussion

Pituitary carcinomas are rare, representing approximately 0.1% to 0.5% of all pituitary tumors.<sup>2,12</sup> Most of these lesions are endocrinologically active.<sup>12</sup>

According to previous reports,<sup>4,17,23</sup> the diagnosis of the pituitary carcinoma can be difficult when based on histologic findings alone. A number of pathologic features, such as a high mitotic rate, cellular anaplasia with nuclear pleomorphism, lack of encapsulation, and the presence of necrosis and hemorrhage, are typically associated with malignant tumors.

Clinical features of aggressive behavior, such as distant metastases, are indicators of a malignant transformation of the pituitary tumor. Bayindir et al.<sup>4</sup> defined pituitary tumors that have metastasized outside the central nervous system as “malignant tumors” and locally infiltrative tumors as “invasive adenomas.” The pathogenesis of pituitary carcinoma is unclear, and there are no reliable markers that predict later malignant behavior.<sup>4,8,9</sup> Final diagnosis is based on histologic findings of recurrent



tumors, which reveal increasing atypical or mitotic tumor cells.<sup>18)</sup>

The interval from diagnosis of the primary lesion to detection of intracranial dissemination or spinal metastases of the disease ranged from 2 months to 18 years in previous reports, and multiple spinal metastatic lesions tended to appear 5–6 years after the patients' most recent intrasellar operation.<sup>8,9,22)</sup> As Taya et al.<sup>23)</sup> reported, the present case developed intracranial dissemination at 5 years after transsphenoidal surgery and then developed multiple spinal metastases 5 years after Taya's article was published.

Multiple surgical operations may fragment tumors and open arachnoid barriers, especially in the initial transsphenoidal surgery, freeing tumor cells to float passively into the CSF.<sup>3,7,16,20)</sup> Lehman et al. described such a case as "synchronous subarachnoid drop" metastases from a pituitary adenoma with multiple recurrences.<sup>16)</sup> This phenomenon supports the idea that seeding of tumor cells into the subarachnoid space is followed by gravitational or bulk flow spread to the dependent part of the thecal sac. Postoperative CSF leakage may, therefore, facilitate subarachnoid dissemination.

In all the reported cases of pituitary adenoma with spinal metastasis, patients have undergone multiple different craniotomies. Therefore, it is difficult to determine whether these spinal metastases were caused by mechanical dissemination of surgical manipulation or arose from spread via the systemic circulation or via the venous channel in the dura mater. Indeed, most cases of pituitary adenomas with intracranial or spinal metastases, including cases that would otherwise be considered benign, have occurred among patients who had previously undergone surgery. Therefore, a pituitary adenoma with malignant potential may not always be necessary for dissemination of the tumor.

Most pituitary adenomas that display subarachnoid spread secrete adrenocorticotrophic hormone (ACTH),<sup>5,13,18,25)</sup> prolactin,<sup>10,15,20)</sup> or GH.<sup>1,11,16,23)</sup> It is noteworthy that the incidence of metastatic tumor is exceedingly high in patients with ACTH-secreting adenomas when compared with other types of pituitary adenomas.<sup>5,13,18,25)</sup>

The present case was a patient with a GH-secreting adenoma with multiple dural metastases. In addition, histologic findings of the spinal tumors included numerous mitotic figures, pleomorphism, hemorrhage, and necrosis, all of which corresponded with the diagnostic criteria of a malignant pituitary tumor. Serum levels of GH decreased as the tumor progressed, which was thought to be a sign that the tumor cells dedifferentiated. In contrast to previously reported cases, radiation and stereotactic gamma knife surgery were attempted, but this strategy resulted in radiation-resistant tumors.

Although radiation has been implicated in the development of fibrosarcoma, it has never been demonstrated

to induce malignant changes in pituitary adenoma.<sup>6)</sup> According to previous reported cases of pituitary carcinoma associated with spinal metastases, most patients have undergone surgery combined with postoperative radiotherapy.<sup>1,2,5,6,9,11,13,14,16,21,22,24)</sup> The present case showed cerebrospinal metastases after radiation and gamma knife treatment. Based on these findings, it is suspected that repeated radiation therapy for the pituitary and intracranial tumors may have induced malignant transformation and the multiple spinal metastases.

Dopaminergic drugs, such as bromocriptine and cabergoline have inhibitory effects of GH-secreting pituitary adenoma.<sup>19)</sup> In spite of bromocriptine and cabergoline therapy attempted in the present case, progressive malignant transformation occurred along with a decrease in serum level of GH. The recurrent tumor was resistant to dopaminergic agents, probably due to poorly differentiated carcinoma (malignant transformed adenoma) with decreased serum level of GH.

Radiotherapy and combination chemotherapy are not effective in the treatment of malignant pituitary adenoma with CSF dissemination or distant metastasis. Surgery is rarely curative, but repeated resection of recurrent metastases has been reported to prolong survival in several cases. Repeated recurrence and residual tumors should be carefully followed and treated at early stages, because spinal metastases, especially those involving the high cervical spine, result in poor prognosis due to respiratory compromise.

Pituitary carcinoma is rare. However, an awareness of this diagnosis is important in patients with previously diagnosed pituitary adenoma who present with neurologic dysfunction or other signs of disseminated malignancy.

## Conflicts of Interest Disclosure

All authors have no conflict of interest. All authors who are members of the Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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Address reprint requests to: Toshihide Tanaka, MD, PhD, Department of Neurosurgery, Jikei University School of Medicine Kashiwa Hospital, 163-1 Kashiwa-shita, Kashiwa, Chiba 277-8567, Japan.  
e-mail: ttanaka@jikei.ac.jp