

Case report

Pituitary carcinoma with intraspinal metastasis: report of two cases and review of the literature

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Abstract: Pituitary carcinomas are rare malignant neoplasms with diagnostic and management challenges. Patients with pituitary carcinomas have extremely poor outcomes. In this report, the authors describe two cases of pituitary carcinomas with intraspinal metastasis (Case 1: 42-year-old man with a history of pituitary adenoma 16 years ago developed an intraspinal lesion at C4-C5; Case 2: 26-year-old women with a history of growth hormone-producing pituitary adenoma 9 years ago developed intraspinal lesion in the sacral canal). Both patients underwent spine surgery. The intraspinal lesions were confirmed as metastatic pituitary carcinomas based on the histomorphology and immunohistochemical stains. The authors reviewed the literature for the diagnosis, treatment, and prognosis of intraspinal metastasis from pituitary carcinomas.

Keywords: Pituitary carcinoma, intraspinal metastasis, pituitary adenoma, management

Introduction

Most pituitary neoplasms are benign adenomas. The overall estimated prevalence of pituitary adenomas in the general population is 16.7% (14.4% in autopsy studies, 22.5% in neuroimaging studies) [1]. Pituitary carcinomas are uncommon and comprise less than 1% of pituitary tumors. A diagnosis of pituitary carcinoma can only be made when there is central nerve system (CNS) dissemination or distant metastasis. Pituitary carcinomas with intraspinal metastasis are extremely rare. To date, less than 20 patients with intraspinal metastasis have been reported [2-15].

We present two cases of pituitary carcinoma with intraspinal metastasis, and have reviewed the literature relevant with the diagnosis, treatment and prognosis of pituitary carcinomas with intraspinal metastasis.

Case report

Case 1

A 42-year-old male was diagnosed with a pituitary adenoma 16 years ago. The tumor was

removed through a subfrontal craniotomy at a local hospital in 1998 and was confirmed as a benign pituitary adenoma on histological examination. He did not receive radiation therapy after the first surgery.

He was admitted to our hospital in 2008 because of 1 year history of left ear tinnitus and intermittent occipital pain. No neurological dysfunction was found. There was no obvious abnormality on neurological examination or endocrinological examination. His brain Magnetic resonance imaging (MRI) showed an abnormal signal in the left cerebello-pontine angle region, which was isointense on T1 weighted images (T1WI), hyperintense on T2 weighted images (T2WI), and homogeneously enhancing after Gd-DTPA injection. The tumor was subtotally resected via left retrosigmoid approach since the tumor was adhered to cranial nerves. During the operation, the tumor was reddish-brown in color, and soft with focal cystic degeneration. The tumor had morphological features of pituitary neoplasm with immunopositivity for NSE, synaptophysin and adrenocorticotrophic hormone (ACTH), which was consistent with metastatic pituitary carcinoma

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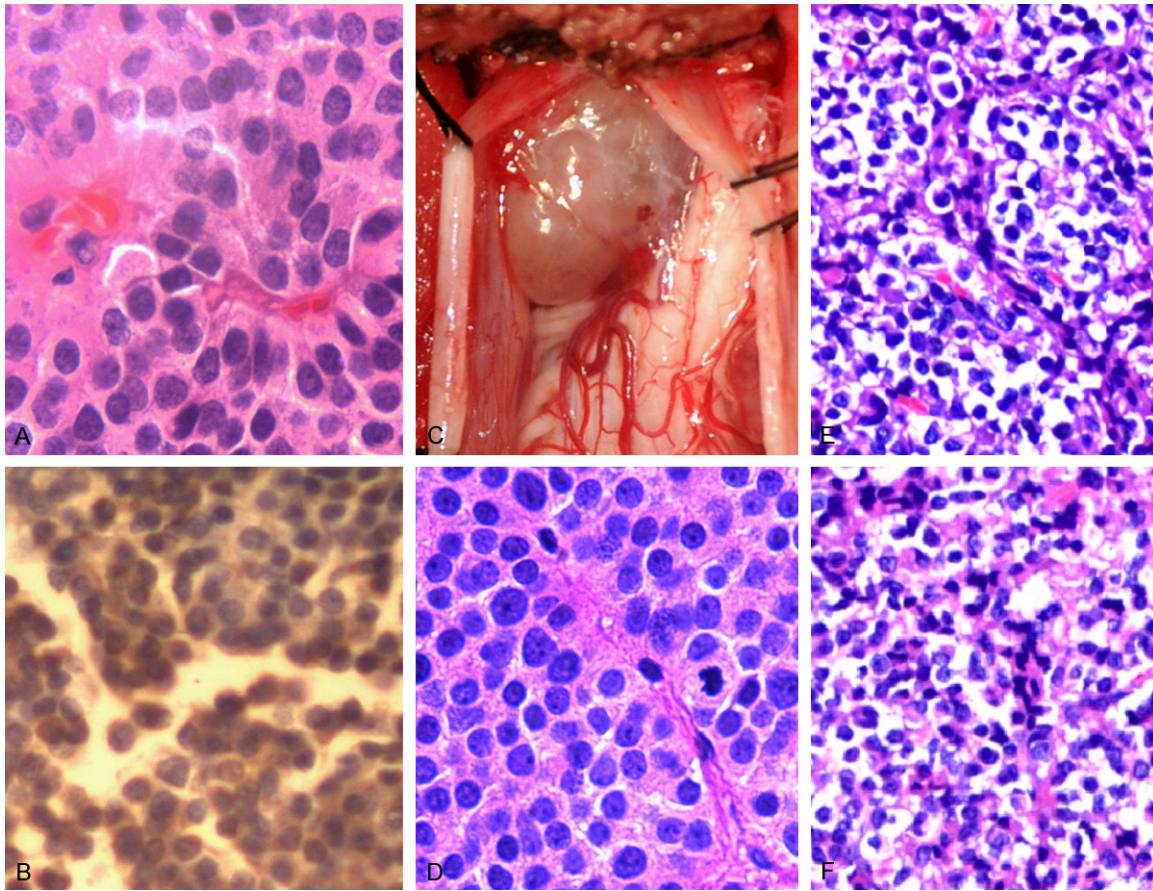


Figure 1. Pathological findings of pituitary carcinoma. The first patient: A. Tumor from cerebello-pontine angle at the second operation exhibits sheets of tumor cells with abundant eosinophilic granular cytoplasm. The tumor cell nuclei are relative monotonous with “salt-and-pepper” chromatin. 400 X, Hematoxylin and eosin (H&E) stain. B. ACTH immunohistochemical stain show tumor cells are positive for ACTH. C. A well-circumscribed pinkish grey intradural extramedullary mass is located on the right side of C4 level of cervical spinal cord. D. Tumor from C4-C5 level of spinal cord shows sheets of tumor cells with abundant eosinophilic granular cytoplasm and “salt-and-pepper” chromatin. Rare mitoses are seen. 400 X, H&E stain. The second patient: E. The recurrent pituitary tumor exhibits lobulated tumor cells with clear cytoplasm and dark nuclei. 200 X, Hematoxylin and eosin (H&E) stain. F. Metastatic tumor in sacral canal shows similar morphology to the pituitary tumor. 200 X, H&E stain.

(**Figure 1A, 1B**). Radiation therapy was offered, but the patient refused it.

In 2000, he experienced right extremity numbness for several months and was admitted into our hospital. He had a decreased light touch and pain sensation in the right arm. MRI showed an intradural extramedullary mass at the level of C4-C5 (**Figure 2A**). The patient underwent cervical posterior medial approach for the resection of the intraspinal tumor. The pinkish grey well-circumscribed mass was located at the right side of the C4 level of cervical spinal cord. The mass was soft with modest blood supply, measuring 3 × 2 × 2 cm (**Figure 1C**). The patient was discharged with almost

complete recovery from his previous symptoms. Histological examination showed that a cellular neoplasm is positive for synaptophysin and ACTH, but is negative for other pituitary hormones. Rare mitoses are noted in the tumor. The Ki-67 labeling index is 4%. The findings were consistent with metastatic pituitary carcinoma (**Figure 1D**). Postoperative MRI showed that the tumor was totally resected (**Figure 2B**).

In 2013, he presented with blurred vision. MRI revealed a sellar tumor measuring 1.5 cm in diameter. The patient underwent subfrontal craniotomy for tumor resection on May 23rd in 2013. The morphology of the sellar tumor was similar to that of previous metastatic pituitary

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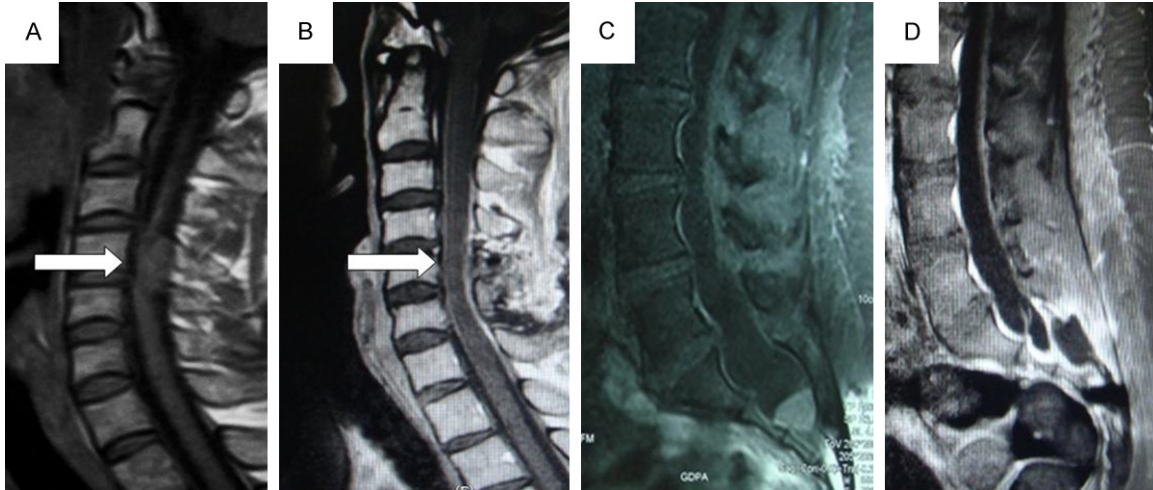


Figure 2. MRI findings of pituitary carcinoma. The First patient: A. MRI shows an intradural extramedullary mass (arrow) at the level of C4-C5, which is isointense on T1WI. B. Postoperative MRI shows no residual tumor (arrow). The second patient: C. MRI shows a homogeneously enhancing mass in the sacral canal on T1 post-contrast image. D. Postoperative MRI shows no residual tumor on T1 post-contrast image.

carcinoma. There was no recurrence after a 17-month follow-up.

Case 2

A 26-year-old female presented with acromegaly and amenorrhea 9 years ago. A sellar tumor was noted and removed with a right frontotemporal craniotomy in 2006. The tumor was diagnosed as a pituitary adenoma. In 2012, she developed a recurrent pituitary tumor and presented with acromegaly and amenorrhea. Her serum growth hormone (GH) (121.0 ng/ml) and insulin-like growth factor 1 (IGF-1) (1127.0 ng/ml) were elevated. Preoperative MRI demonstrated multiple lesions in anterior fossa and sellar region with mild enhancement after gadolinium injection. During the surgery, the tumor was soft and pinkish-grey in color. Since some of tumor tissue tightly adhered to the anterior cerebral artery, subtotal resection was achieved. The histological features are consistent with recurrent pituitary adenoma (**Figure 1E**). Tumor cells are positive for synaptophysin and growth hormone, but they are negative for other pituitary hormones. The Ki-67 labeling index is approximately 3%. The serum GH (37.8 ng/ml) significantly decreased after operation.

During the hospitalization, she also declared numbness on the left lateral thigh for 6 years. The spine MRI showed a hyperintense well-defined mass in the sacral canal (**Figure 2C**).

Two weeks later, the patient underwent laminectomy at S2-S3 level in order to remove the tumor. During the operation, the tumor was found inside the sacral canal. It was relatively firm in texture and sharply demarcated, and had modest blood supply. At the periphery, the tumor adhered to the bilateral nerve bundles. The histomorphology of the tumor was similar to that of previous surgeries (**Figure 1F**). The Ki-67 labeling index was 1-2%. Postoperative MRI showed no residual tumor on T1 post-contrast image (**Figure 2D**). The serum GH reduced to 29 ng/ml before discharge.

In April 2014, the patient developed a recurrent tumor in the sellar region and was subsequently treated with stereotactic radiation. Recently, the serum growth hormone was 9.5 ng/ml. There was no progression after a 10-month follow-up.

Discussion

Pituitary adenoma is one of the most common intracranial tumors, representing 10% to 15% of all intracranial neoplasms [16]. Pituitary adenomas have excellent prognosis after gross total resection. About 5% of pituitary adenomas show aggressive features and involve adjacent intracranial structures such as cavernous sinus, internal carotid artery or hypothalamus, which are classified as invasive pituitary adenomas (IPA). However, pituitary

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Table 1. Summary of pituitary carcinomas with intraspinal metastasis

Author (Year)	Age, Sex	Hormone production	Metastatic sites	Duration*
Salassa (1959) [2]	46, M	ACTH	Spinal cord	5 years (2 months)
Epstein (1964) [3]	29, M	NONE	Cauda equina	14 years (2 years)
Zafar (1984) [4]	56, M	ACTH	Spinal cord	Initial found (5 years)
Landgraf (1985) [5]	44, M	PRL	Cauda equina	4 years (6 months)
Hashimoto (1986) [6]	50, F	GH	Spinal cord	2 years (3 months)
Gabrilove (1986) [7]	37, M	ACTH	Cauda equina	5 years (7 months)
Sakamoto (1990) [8]	37, F	NONE	Spinal cord (C3-C7)	2 years (4 months)
Popovic (1991) [9]	56, F	PRL	Spinal cord (L1-L2)	12 years (3 months)
Frost (1995) [10]	33, M	ACTH	Spinal cord (C1-C2)	6 years (4 years)
Popadic (1999) [11]	51, M	PRL	Cauda equina	4 years (-)
Lehman (2003) [12]	49, M	NONE	Foramen magnum and cauda equina	18 years (-)
Ayuk (2005) [13]	68, M	NONE	Spinal cord (C2-4)	4 years (-)
Arnold (2012) [14]	61, F	ACTH	Spinal cord (L2-3)	22 years (-)
Takeuchi (2014) [15]	57, M	ACTH	Cauda equina	11 years (-)
Present case 1	42, M	ACTH	Spinal cord (C4-C5)	12 years (-)
Present case 2	26, F	GH	Cauda equina	6 years (-)

ACTH-Adrenocorticotropic hormone; GH-Growth hormone; PRL-prolactin. *Interval from the onset of initial symptom to intraspinal metastasis. The time in parentheses is the duration from the diagnosis of metastasis to death. If the patient is still alive when it is reported, "-" is put in parentheses.

carcinoma is still a very rare tumor and comprises less than 1% of all pituitary tumors [17]. According to WHO 2004 Tumours of Endocrine Organs Classification, The Ki-67 labeling index > 3% and p53 immunoreactivity might indicate that the tumor is more aggressive [18]. The Ki-67 labeling index of more than 10% suggests that the tumor has malignant potential [19]. p53 is currently used as an indicator for micrometastases. Some studies show that p53 are expressed in all pituitary carcinoma, but it is negative in benign adenomas [20]. Mitotic figures are more commonly seen in pituitary carcinoma (66.7%) than in pituitary adenoma (3.9%) and IPA (21.4%) [21]. However, the diagnosis of pituitary carcinoma still relies on the presence of cerebrospinal and/or systemic metastasis.

There are three different scenarios of pituitary carcinomas: 1) The original tumor is malignant, invades surrounding tissue, and has distant metastasis. 2) Histologically, the original pituitary tumor is benign; the recurrent tumor undergoes malignant transformation and develops distant metastasis. Usually the metastatic tumor has frank malignant histomorphology. The incubation time is 2-10 years. 3) Recurrent tumor and metastatic tumor have similar histology without obvious malignant

transformation [17]. Both of our cases belong to the third scenario. Recurrent tumors and metastatic tumors all have bland morphology similar to conventional pituitary adenoma. The Ki-67 labeling indexes from both cases are lower than 5%.

Pituitary carcinomas with intraspinal metastasis are quite rare. Only 14 cases are reported in English literature except our two cases (**Table 1**). They were 5 women and 11 men between 26 to 68 years old at the time of diagnosis of intraspinal metastases with the median age of 47.5 years [2-15]. Usually there is a long latency period between the primary diagnosis of pituitary tumor and the occurrence of intraspinal metastases, with an average of 7.9 years (2 to 22 years) [2-15]. Approximately 50% of patients survive less than 1 year after the diagnosis of pituitary carcinoma. Some patients survive more than 10 years. Our patients are still alive at 10 and 17 months respectively after the diagnosis of intraspinal metastasis. ACTH-producing tumors consist of almost half of pituitary carcinomas with intraspinal metastasis. In general, ACTH-producing pituitary carcinomas are the second most common tumors after prolactin-producing tumors. Only 50% of patients with ACTH-producing carcinomas develop Cushing's disease [22]. Only 5% of pituitary car-

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cinomas are GH-producing tumors. Our first patient has an ACTH-producing pituitary carcinoma based on the immunohistochemical stain. However, the patient has normal serum ACTH and does not develop Cushing's disease. Our second patient has a GH-producing pituitary carcinoma with manifestations of acromegaly and elevation of serum GH level.

Many researchers agree that pituitary carcinomas should be treated with local resection of the primary tumor and metastatic foci followed by radiation therapy. Compared with conventional radiotherapy, radiosurgery offers safe and effective treatment for recurrent or residual pituitary adenomas [23]. These patients require close postoperative follow-up.

Temozolomide (TMZ) is an oral alkylating agent, currently the first-line chemotherapy drug for malignant glioma [24]. It is reported that TMZ can induce apoptosis of pituitary adenomas confirmed by immunohistochemistry and electron microscopy techniques [25]. All pituitary carcinoma subtypes seem to be effectively controlled by TMZ with a tumoral and/or hormonal response in nine of 15 (~60%) treated cases. Tumor volume is significantly reduced and hormone level is decreased after three treatment cycles (Classic therapeutic doses of 150-200 mg/m² per day, for 5 days in a 28-day treatment cycle). The long-term effects of TMZ therapy requires further investigation [26].

In summary, sine the rarity of pituitary carcinoma with intraspinal metastasis precludes the likelihood of large-scale randomized clinical trials, the diagnosis and treatment of pituitary carcinoma is still very challenging and needs further investigation. Based on available case reports, multimodal therapy with surgery, radiation therapy, and chemotherapy is the treatment of choice for pituitary carcinomas with intraspinal metastasis. Post-treatment follow-up for early identification of recurrent sellar region lesions or new metastatic foci is essential for all patients.

Disclosure of conflict of interest

None.

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