



Sellar Neuroblastoma Mimicking Pituitary Adenoma

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Abstract. *Objective and importance:* Primary intracranial neuroblastomas are rare. They generally arise in the supratentorial parenchyma or paraventricular region. Even more rare are primary sellar neuroblastomas. We present a neuroblastoma that arose in the sellar region and mimicked a non-functioning pituitary adenoma. *Clinical presentation:* This 33-year-old man presented with bitemporal hemianopsia. MRI showed a sellar mass with suprasellar extension mimicking a pituitary adenoma. *Intervention:* Because of tumor recurrence and dissemination to the cervical region, he underwent 6 operations and radiosurgery. Detailed histologic examination confirmed the diagnosis of neuroblastoma. Postoperative conventional radiotherapy was effective in reducing the size of the tumor. *Conclusion:* Neuroblastoma should be considered in the differential diagnosis of patients with sellar lesions.

Key Words. neuroblastoma, pituitary tumors, sellar lesions, sella turcica, radiotherapy

Esthesioneuroblastoma (olfactory neuroblastoma) is an uncommon but well-recognized type of neuroectodermal tumor arising in the nasal cavity. These tumors result in nasal obstruction or epistaxis [1, 2]. The even more rare primary intracranial neuroblastomas arise in supratentorial parenchyma or paraventricular region [3, 4]. Primary sellar neuroblastomas are extremely rare and to our knowledge, only 3 cases have been reported so far [5–7].

We now report a neuroblastoma that arose primarily in the sellar region and mimicked a pituitary adenoma.

Case Report

History and examination

In 1998, this 33-year-old man was admitted to another hospital complaining of headache and bitemporal hemianopsia. MRI revealed a sellar mass with suprasellar extension. It was hypointense on T1-weighted and hyperintense on T2-weighted MRI images; there was weak heterogeneous enhancement after contrast medium administration (Fig. 1a). Under a presumptive diagnosis of pituitary macroadenoma he underwent a 1st operation via the transsphenoidal approach; the postoperative pathological diagnosis based on the hematoxylin-eosin staining (H & E) was chromophobic pituitary adenoma. Within the next 16 months, the tumor regrew to

almost its preoperative size and he underwent a 2nd operation via craniotomy. The pathological diagnosis, again based on H & E, was also chromophobic pituitary adenoma. In the course of the next 3 years, the tumor showed rapid regrowth with invasion into the surrounding tissue despite 3 additional efforts of surgical removal. The pathological diagnoses included neuroblastoma, central neurocytoma, and chromophobic pituitary adenoma. In 2000, gamma-knife radiosurgery (GKS) was performed with a marginal dose of 15 Gy. However, none of the treatments were able to control tumor regrowth.

In August 2002, he was referred to our hospital after developing left oculomotor nerve palsy due to tumor regrowth. MRI showed a large, invasive sellar mass lesion invading both cavernous sinuses and extending to the sphenoid sinus and frontal base. In addition there was a cervical mass in the ventral part of the C1 region (Fig. 1b). Endocrine examination disclosed panhypopituitarism. A 6th operation, subtotal removal of the soft tumor, was performed via the transsphenoidal approach to reduce the tumor size and to provide symptom relief.

Pathological findings

Surgical specimens from his 5 prior operations were available for re-examination at our Institute. Light microscopic examination of the current specimen revealed a cellular tumor composed of small cells arranged in a diffuse pattern (Fig. 2a-1). No normal tissue was recognized. The tumor cells were round with a spherical chromatin-rich nucleus and a sparse chromophobic, slightly acidophilic cytoplasm. There were anuclear areas suggestive of the gathering of cellular processes. In some areas, spindle-shaped cells were arranged as perivascular pseudo-rosettes (Fig. 2a-2). Mild cellular and nuclear pleomorphism and occasional mitotic figures were also noted. Few scattered nuclei exhibited signs of apoptosis. Immunohistochemistry revealed diffuse cytoplasmic immunopositivity for NCAM, neuron-specific enolase, and synaptophysin.

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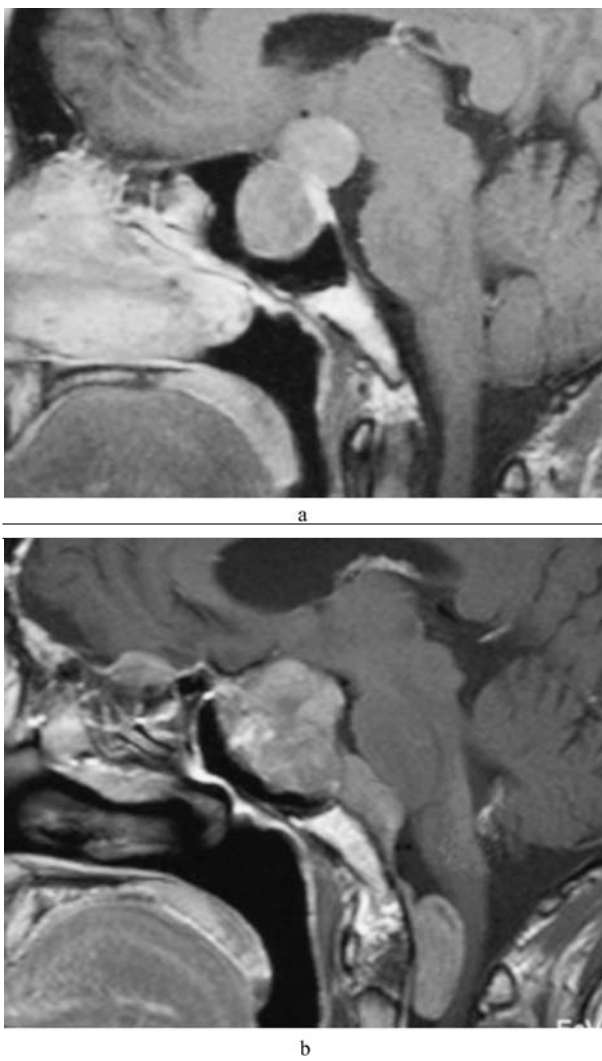


Fig. 1. a. Pretreatment MRI demonstrates a pituitary tumor with suprasellar extension. There was weak heterogeneous enhancement after contrast medium administration. The MRI finding closely resembled those of pituitary adenoma. b. Preoperative MRI obtained at our hospital showed a huge, invasive pituitary tumor extending to the sphenoid sinus and frontal base. There was a disseminated cervical mass in the C1 region.

Immunostaining for cytokeratin was negative, except for a few cells in the matrix of the 3rd surgical specimen. The tumor was immunonegative for S100 protein, GFAP, laminin, low molecular weight keratin, vimentin, GH, PRL, ACTH, LH, FSH, TSH, alpha subunit, desmin and neurofilament antigen. There was diffuse positivity for Ki-67 (MIB-1); the index was approximately 30%. Immunostaining for the tumor suppressor gene P53 was negative; immunostaining for P27, a cell-cycle inhibitor was positive in only a few cells. The surgical specimens obtained at his 1st operation and reexamined histologically showed the same findings as

the examination of the 6th operative specimens. On electron microscopic (EM) examination, the tumor cells exhibited round nuclei and relatively scanty cytoplasm with small Golgi complexes and mitochondria (Fig. 2b-1). Several areas of the tumor were composed of tightly packed neurites filled with dense-core vesi-

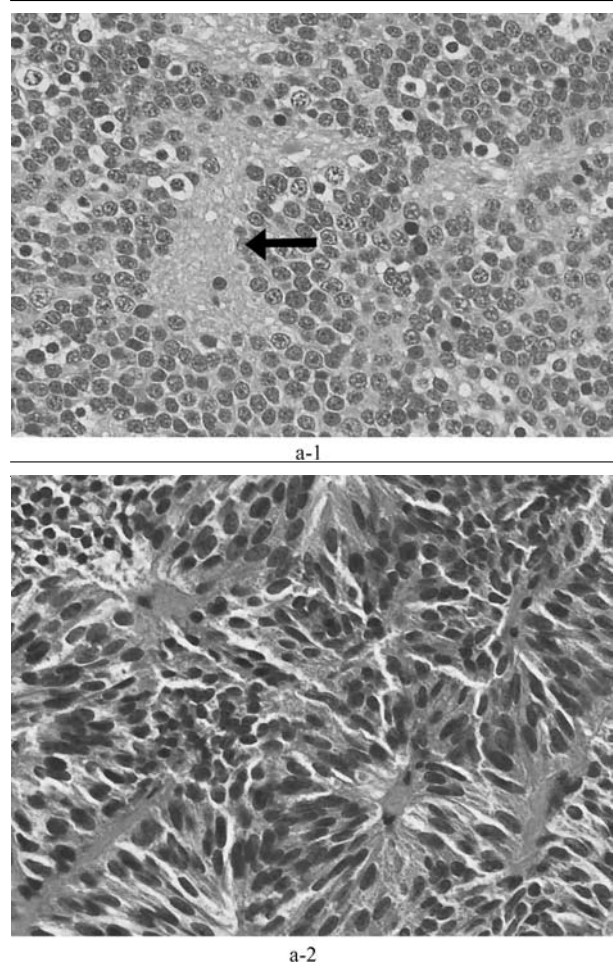
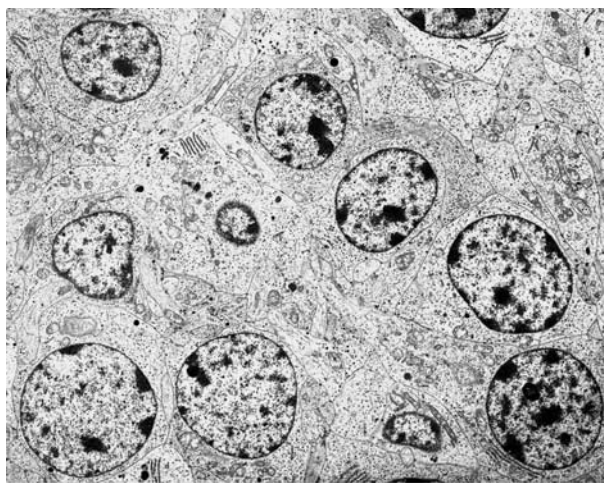
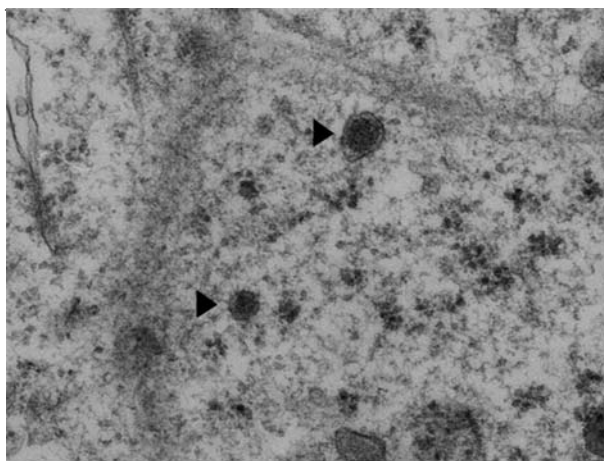


Fig. 2. a. Photomicrographs of H&E and immunohistochemical stainings. 1: A cellular tumor composed of small cells and exhibiting a diffuse pattern is recognized. The tumor cells are round with a spherical chromatin rich nucleus and a sparse chromophobic, slightly acidophilic cytoplasm. Note the anuclear areas (arrow) suggesting the gathering of cellular processes. (H&E, original magnification $\times 200$). 2: In some areas spindle-shaped cells arrange as a perivascular pseudo-rosettes. (H&E, original magnification $\times 200$). b. Electron micrographs. 1: Low-power view of a representative area from the tumor. The individual tumor cells have round nuclei, relatively scanty cytoplasm and few intracellular components. There are several cellular junctions between the tumor cells (original magnification $\times 2000$). 2: High-power view of the intercellular junctions showing that they are composed of tightly packed neurites filled with dense-core vesicles measuring 90 to 110 nm (arrow head)(original magnification $\times 15000$).



b-1



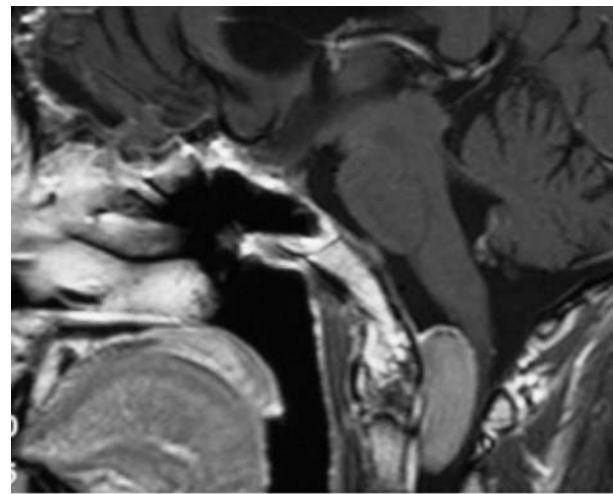
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Fig. 2 (Continued).

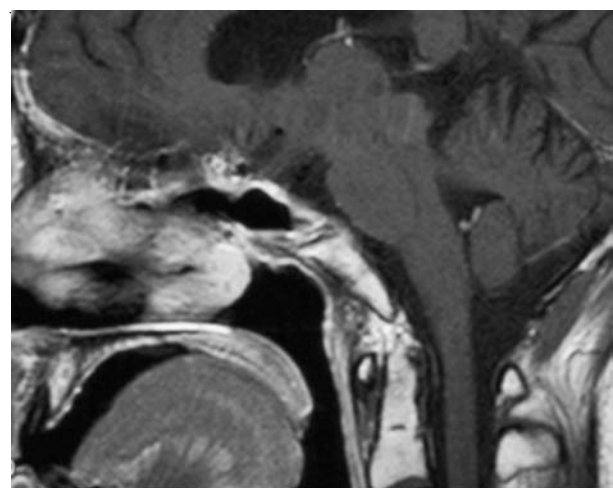
cles measuring 90 to 110 nm (Fig. 2b-2). These findings are consistent with the diagnosis of neuroblastoma. A careful search revealed no primary tumor in either nasal cavity or anywhere else in his body. His urine was negative for vanillylmandelic acid (VMA), and his blood pressure level was within normal limits.

Postoperative course

Postoperatively, he underwent conventional local radiation therapy (50.0 Gy in 25 installment) to the sellar region. Follow-up MRI, obtained at the end of the irradiation treatment, revealed a remarkable shrinkage of the sellar tumor (Fig. 3); his bitemporal hemianopsia and left oculomotor nerve paralysis improved within a few months. However, he developed severe neck pain due to an enlarged cervical mass 3 months after the completion of radiation therapy, local radiation was administered to the cervical region (50.0 Gy in 25 installments). Post-irradiation MRI revealed the disappearance of the



a



b

Fig. 3 a. MRI, obtained after local radiation to the sellar and parasellar region, revealed a reduction in the volume of the sellar tumor. b. MRI, obtained after additional radiation to the cervical region, shows the almost complete disappearance of the cervical mass.

cervical mass and he reported improvement of his cervical pain (Fig. 3). At his most recent outpatient follow-up visit he manifested no signs of tumor regrowth and he was free of any symptoms.

Discussion

Esthesioneuroblastomas were first described as being of neural crest origin with pathological features similar to those of neuroblastoma of sympathetic origin [8]. These tumors, also known as olfactory neuroblastoma, usually arise in the nasal or paranasal cavity and result in epistaxis and nasal obstruction [1, 2]. The even more rare primary intracranial neuroblastomas tend to arise in the supratentorial parenchyma or paraventricular

Table 1 Clinical summary of sellar neuroblastomas reported in the literature

Case no. Series [ref no.]	Age/ Sex	Symptom	Endocrinological exam	Neuroimaging	Metastasis	Operation	Irradiation	Follow-up result
1 Sarwar, 1979 [24]	31/F	Hypesthesia in lt.V2,V3 Bitemporal hemianopsia	NM	Calcified lesion (X-P) Siphon closing (angio)	NM	TCS	CRT	No tumor regrowth (5 years)
2 Lach et al., 1996 [4]	40/F	Irregular mense Bitemporal hemianopsia	Hyperprolactinemia	Suprasellar extension (CT)	NM	TCS	Not done	NM
3 Roy et al., 2000 [23]	44/F	Bitemporal hemianopsia	Hyperprolactinemia	Suprasellar extension (MRI) Inhomogeneous enhancement	None	TSS	CRT	No recurrence (1.5 years)
4 present case, 2003	33/M	Bitemporal hemianopsia Left oculomotor nerve palsy	Panhypopituitarism	Suprasellar extension (MRI) Inhomogeneous enhancement	Cervical mass	TCS TSS (5 times)	GKS CRT	No recurrence (1 year)

NM: not mentioned in the literature, TCS: transcranial surgery, TSS: transsphenoidal surgery, CRT: conventional radiation therapy, GKS: gamma-knife radio-surgery.

region [3, 4]. Primary sellar neuroblastomas are extremely rare and to the best of our knowledge, only 3 cases have been reported to date [5–7] (Table 1). The patients' age at presentation ranged from 31 to 44 years (mean 37 years). Primary cerebral neuroblastomas, on the other hand, tend to be found in children [3, 4]; the age at presentation of patients with olfactory neuroblastomas exhibited a bimodal peak in the 2nd and 5th decade of life [9]. All previously reported patients experienced bitemporal visual field loss; 3 manifested endocrine disorders. On neuroimaging studies, these tumors were recognized as sellar tumors with suprasellar extension. Based on their neuroimaging appearance and their symptomatology, sellar neuroblastomas are similar to nonfunctioning pituitary adenomas. Neuroblastomas arising in the sellar region are rare, and the decision elsewhere to diagnose this tumor based on H&E staining results alone resulted in a misdiagnosis of pituitary adenoma and iterative surgical interventions. The earlier pathological diagnosis should have been confirmed by immunohistochemical and ultrastructural studies when the tumor recurred within only 16 months, which reflected its malignant potential.

Intrasellar neuronal neoplasms are very uncommon, they usually are well-differentiated gangliocytomas or ganglioneuromas [10–16], in the middle of a spectrum of tumors between neuronal hamartomas and rare malignant gangliogliomas [17]. In our patients, histological study returned a diagnosis of neuroblastoma; the tumor exhibited no features of gangliocytoma such as binucleated ganglial cells, glial stroma, or calcospherites.

Extracranial neuroblastomas are known for their spread and metastasis; in autopsy studies, the inci-

dence of metastasis or dissemination in patients with primary cerebral neuroblastomas was at least 38% [4]. Our patient developed leptomeningeal dissemination to the cervical region. This was suggestive of a malignant neuroblastoma associated with tumor dissemination to the cervical region mimicking a pituitary carcinoma (Table 1).

In urine and blood of patients with peripheral neuroblastoma, catecholamine metabolites are usually elevated [18, 19]. On the other hand, in the presence of primary cerebral neuroblastoma, the plasma and urine level of catecholamine metabolites is normal [3, 4, 20]. If the tumor is truly intrasellar, it is located outside the blood-brain-barrier and catecholamine metabolites may be measurable. As in the presence of primary cerebral neuroblastomas, the VMA level in our patient was in the normal range, suggesting that this tumor primarily arose in the supradiaphragmatic region and extended into the sella turcica.

The origin of primary cerebral neuroblastomas remains controversial. Berger et al. [3] claim that the original cells are neuroblasts that derive from the division of primitive neuroepithelial matrix cells in the 2nd stage of neurocytogenesis. Two hypotheses have been proposed regarding the origin of pituitary neuroblastomas [5–7]. Lach et al. [5], who performed ultrastructural studies for a differentiating neuroblastoma of the pituitary in a 40-year-old woman, speculated that the tumor was attributable to transformation of the pituitary epithelium into neuronal cells. They based their hypothesis on the co-localization of prolactin-immunopositive granules in the neuronal cells. Neuronal transformation from pituitary epithelium was also reported in patients with neuronal choristoma or gangliocytoma associated

with pituitary adenoma [13, 16]. Genetic experiments and tissue culture studies have demonstrated the generations of neuronal cells from epithelial cells derived from pituitary adenomas [21, 22]. Roy et al. [6] and Sarwar [7], on the other hand, pointed out that the 2 pituitary neuroblastomas they reported arose primarily from the part of the ganglion of Lacy that grows between the olfactory fossa and the telencephalic vesicle. In our case, there was no evidence supporting neuronal transformation from pituitary epithelium. We postulate that its origin was the locus proposed by the latter investigators [23, 24].

At present, there is no consensus regarding the treatment of primary cerebral neuroblastomas. The effectiveness of irradiation in both primary cerebral and olfactory neuroblastomas has been documented [3, 4, 9, 25]. Conventional radiation therapy effectively reduced the tumor volume in our case. Similarly, 2 of 3 reported patients with sellar neuroblastoma (cases 1 and 3, Table 1) also achieved good clinical outcomes following radiotherapy although the follow-up periods after irradiation were not long (5 years, 1.5 years and 1 year, respectively). We plan to follow our patient for the long term to monitor the tumor for recurrence.

GKS may be useful for both primary cerebral- and olfactory neuroblastomas; at marginal irradiation doses ranging from 16 to 34 Gy. GKS was effective in the treatment of olfactory neuroblastomas [23, 24]. This was not true in our case, possibly because the administered dose (marginal dose 15 Gy) was too small to control tumor growth. Conventional fractionated irradiation may be more effective than a large amount of radiation delivered all at once in this type of tumor. Conventional radiotherapy may be more reliable, safe, and effective in pituitary neuroblastomas because the avoidance of optic nerve radiation damage can render the administration of an appropriate radiation dose difficult in patients with large sellar tumors.

The efficacy of adjuvant chemotherapy remains also controversial in primary neuroblastomas. Berger et al. [3] recommended that patients with subtotally resected solid primary neuroblastomas and patients with tumor recurrence should receive adjuvant chemotherapy. Further studies are needed to identify the optimal chemotherapeutic regimens for primary neuroblastomas.

In summary, we report a patient with an extremely rare sellar neuroblastoma that recurred despite iterative surgical resection and GKS. A detailed pathological study returned a diagnosis of neuroblastoma that based on the results of MRI- and histological studies, mimicked a pituitary adenoma. Although sellar neuroblastomas are extremely rare, they should be considered in the differential diagnosis of patients with pituitary lesions. Extensive investigation, including pathological-, immunohistochemical-, and ultrastructured studies are needed for the differentiation of these tumors from pituitary adenomas and for the selection of the appropriate therapy.

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