

## Atypical Granular Cell Tumor of the Sellar Region

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We report a very rare case of atypical granular cell tumor arising in the neurohypophysis of a 56-year-old woman. The tumor was seen on radiology to be lobulated, soft and diffusely enhanced, the same as pituitary macroadenoma, but it was anatomically localized within the posterior part of the hypophysis. We partially removed the tumor via the transsphenoidal approach. The pathology showed nuclear pleomorphism, spindling features, and lymphoplasmacytic infiltration. Ki-67 and S-100 protein were focally positive in tumor cells. Histological diagnosis confirmed an atypical granular cell tumor in the sellar region, which is a rare tumor that often has the clinical appearance of a pituitary adenoma. Ophthalmologic symptoms are the most common, followed by endocrinologic manifestations. Here we describe its symptoms and radiological and pathological features.

**KEY WORDS :** Atypical granular cell tumor · Suprasellar · Neurohypophysis · Central nervous system.

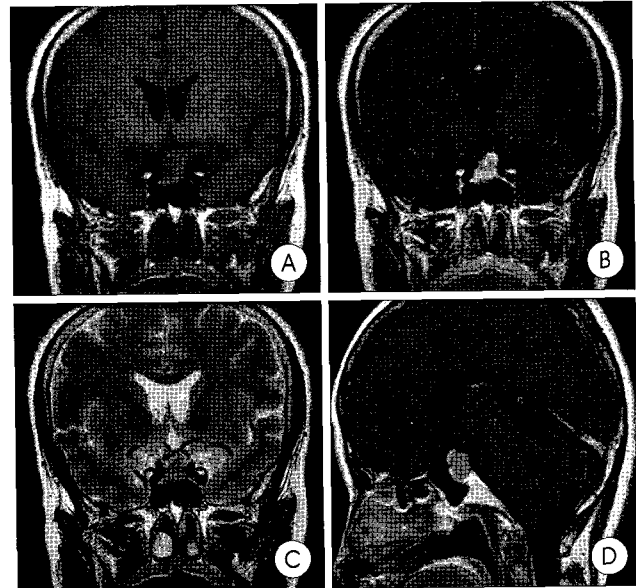
### Introduction

Granular cell tumor (GCT) can arise in a variety of sites, and they are most commonly seen in the dermis or subcutaneous soft tissue of the head and neck. Symptomatic granular cell tumors of the neurohypophysis and pituitary stalk are rare findings<sup>3,9-11,22,30</sup>. They comprise less than 0.1% of the primary brain tumors, which themselves account for approximately 1.5~2% of all the adult neoplasms<sup>31</sup>. Small GCTs or tumorlettes were found incidentally on 6.5% to 17% of autopsies when serial section of the posterior pituitary gland and stalk were examined<sup>3</sup>. Most reported cases have shown biologically benign behavior and this tumor's malignant counterpart, i.e., atypical GCT of the neurohypophysis, is extremely rare with only 8 cases having been reported in the literature<sup>14</sup>. We demonstrate a case of neurohypophysial GCT with atypical nuclei and increased mitotic activity and discuss the pathohistological, radiological and clinical features.

### Case Report

A 56-year-old woman first presented with a one year history of intermittent headache. She had no significant neurological and ophthalmologic deficits. We performed magnetic resonance imaging (MRI) on her brain. MRI demonstrated

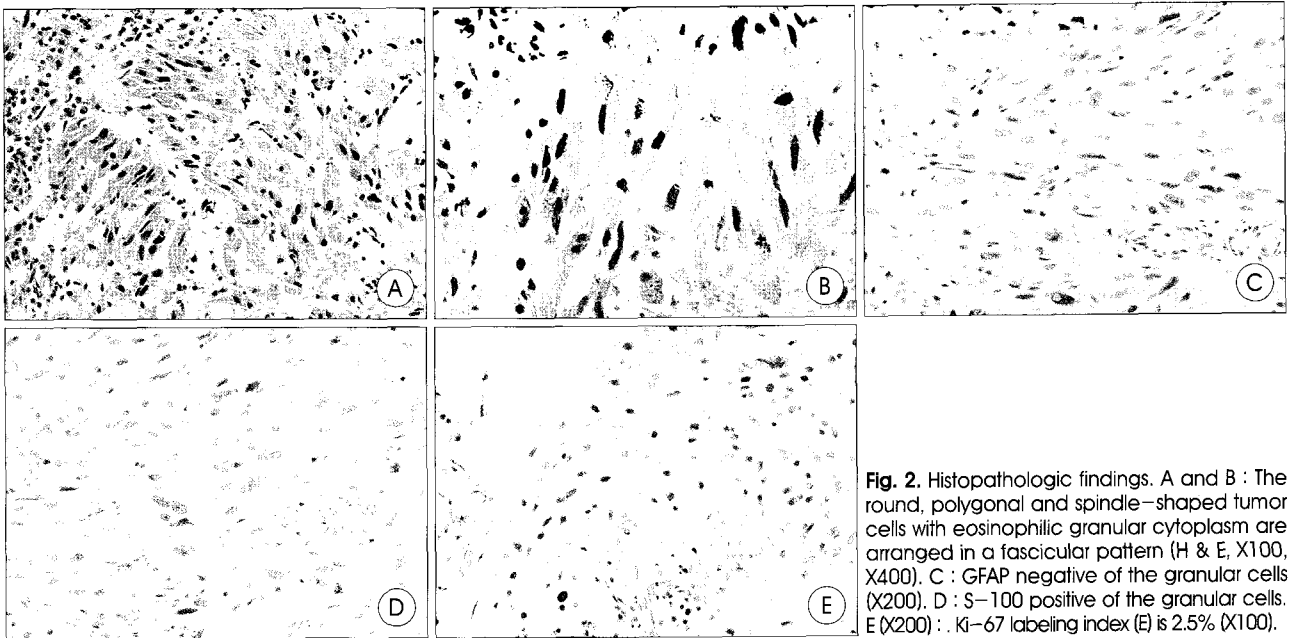
a lobulated mass about 1.5 × 1.3 cm in size on the sellar turcica. This mass was bulging into suprasellar cistern and compressing the left optic chiasm. The normal pituitary gland was com-



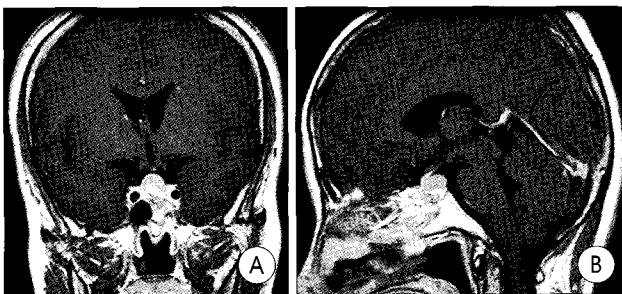
**Fig. 1.** Preoperative magnetic resonance images. T1 weighted coronal (A), Gd-enhanced T1 weighted coronal (B), T2 weighted coronal (C), and Gd-enhanced T1 sagittal (D) images show a lobulated soft tissue mass at sellar turcica. Note the tumoral enhancement is intense and homogeneous and the mass is localized at the posterior part of the pituitary gland.

• Received : May 3, 2006 • Accepted : July 18, 2006

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**Fig. 2.** Histopathologic findings. A and B : The round, polygonal and spindle-shaped tumor cells with eosinophilic granular cytoplasm are arranged in a fascicular pattern (H & E, X100, X400). C : GFAP negative of the granular cells (X200). D : S-100 positive of the granular cells (X200). E : Ki-67 labeling index (E) is 2.5% (X100).



**Fig. 3.** Postoperative magnetic resonance images. Gd-enhanced T1 weighted coronal (A) and sagittal (B) images. Small amount of tumor is removed.

pressed to the anterior-superior aspect by the tumor. There was no associated bony erosion or destruction. The tumor was isointense on both T1- and T2-weighted images. It also showed diffuse enhancement after intravenous administration of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) (Fig. 1). The laboratory studies, including a complete blood count (CBC), electrolyte studies, chemistry profiles and urinalysis, were all within normal limits. The preoperative hormone levels were all within normal limit except moderate elevation of prolactin level : a morning serum cortisol level of 5.9  $\mu\text{g/dL}$ , a serum adrenocorticotrophic hormone (ACTH) level 20.0 of pg/mL, a prolactin level of 74.7 ng/mL, a free thyroxine (T4) level of 7.5 pg/mL, a free triiodothyronine (T3) level of 1.2 pg/mL, a thyroid-stimulating hormone (TSA) level of 2.29  $\mu\text{IU/mL}$  and a growth hormone (GH) level of 0.15 ng/mL.

On February 2004, the tumor was partially removed through the transsphenoidal approach. The tumor was softer in consistency than the usual meningioma, but firmer than the usual pituitary adenoma. It was encapsulated, gray-reddish in color

and it easily bled. The tumor was partially removed in a piecemeal fashion. On frozen biopsy, the tissues were not meningioma nor pituitary adenoma, but rather, seemed to be a granular cell tumor. In hematoxylin and eosin staining, most of the tumor cells were round or polygonal in shape with abundant granular eosinophilic cytoplasm and they were infiltrated with lymphoplasmacytes. The granular cytoplasm was focally stained with PAS and the cell borders were sharply demarcated. The tumor cells formed large sheets, trabecules or small lobules. There were some spindle-shaped cells with a fascicular arrangement and nuclear pleomorphism was observed. Immunohistochemically, some of the tumor cells were positive for S-100, but not for GFAP. The positivity rate for Ki-67 was 2.5% (Fig. 2).

The patient's immediate postoperative course was uneventful. The serum hormones levels were within normal ranges. Postoperative MRI revealed a small focus of tumor removal on the tuberculum sellae (Fig. 3), and the patient has been followed up every 6 months via the outpatient department.

## Discussion

Due to this tumor's uncertain cellular origin and histogenesis, various terms have been used to designate this tumor since its first description by Boyce and Beadles in 1893. They initially believed it to be an aberrant growth of ectopic embryological tissue and so it was called 'choristoma'. Later, the term 'granular cell myoblastoma' was used because of the histological similarity of this tumor to the granular cell tumors of the tongue, which were originally considered to be derived from embryonic muscle cells. However, there is no evidence

**Table 1.** Summary of the reported cases of neurohypophysial granular cell tumors with histologically atypical features

Reference	Age (years)/Sex	Tumor size (cm)	Spindling	NPM	NHC	Large nucleoli	Mitosis	Necrosis	Local recurrence
Doron et al. (5)	47/F	N	N	+	N	N	N	N	-
Kasashima et al. (14)	63/F	2.8	+	+	+	N	+	-	-
Lima et al. (17)	27/F	3	+	+	N	+	+	-	+
Satyamuri et al. (25)	42/F	N	N	+	+	N	-	+	-
Schlachter et al. (26)	62/F	1.2	N	+	+	N	-	-	-
Shuangshoti et al. (27)	76/M	3.9	+	+	N	N	+	-	+
Symon et al. (28)	49/M	N	N	+	+	N	-	-	-
Symon et al. (28)	56/M	N	N	+	N	N	-	-	-
Present case	56/F	1.5	+	+	+	+	+	-	-

NPM : nuclear pleomorphism, NHC : nuclear hyperchromatism, F : female, M : male, N : not mentioned, '+' : present, '-' : absent

that this neurohypophysial tumor originates from muscle cells. Other researchers have suggested that these tumors originate from the neuroparenchymal cellular elements of the neurohypophysis or 'pituicytes'; thus, they have used the term 'pituicytoma' for these tumors<sup>1,6,9,19</sup>. However, there are several different kinds of pituicytes such as 'granular', 'astrocyte-like', 'ependymal' or 'oncocyctic' pituicytes, and so the term 'pituicytoma' has been used not only for granular cell tumors, but also for a variety of other intrinsic neurohypophysial tumors<sup>13,21,29</sup>.

Light microscopy revealed that the tumor cells had abundant granular eosinophilic cytoplasm with a lot of coarse diastase-resistant PAS granules. Electron microscopy indicated that the granules were lysosomes and apparently different from the neuroendocrine secretory granules. The negative staining of such endocrine markers as chromogranin A (CGA), GH and ACTH was helpful to distinguish this tumor from pituitary adenoma. Although the spindle-shaped tumor cells were somewhat similar to pilocytic astrocytoma, this possibility could be discounted because of the lack of any fibrillar cytoplasm and the strong positivity for both S-100 and GFAP<sup>20,24</sup>. The malignant counterparts of these tumors are exceedingly rare, i.e., 1~2% of all cases. Because of the rarity of malignant GCTs, the reliable histological criteria for malignancy have not been fully established. Fanburg-Smith et al.<sup>7</sup> studied 73 cases of malignant, atypical and multicentric GCTs of the soft tissue and they proposed six histological criteria to define malignant GCT : necrosis, spindling, vesicular nuclei with larger nucleoli, increased mitotic activity (>2 mitosis/10 h.p.f. at ×200 magnification), a high N/C ratio and pleomorphism.

They classified the neoplasms that satisfied three or more of these criteria as being histologically malignant GCT, or if only two criteria were satisfied, then they were classified as atypical GCT; those that displayed only focal pleomorphism, but fulfill none of the other criteria were classified as benign GCT. Positivity for Ki67 and p53 was correlated with malignancy.

There are a small number of reports on GCT in the neurohypophysis. To the best of our knowledge, about 50 cases of symptomatic neurohypophysial GCT have been reported on the literature<sup>1-5,8-10,12-23,25-31</sup>. All the cases were clinically benign; none showed distant metastases and no patients died from the tumors. Yet among

them, eight cases<sup>5,14,17,25-28</sup> showed histologically atypical features such as spindling of tumor cells, nuclear pleomorphism or nuclear hyperchromatism. Two cases displayed occasional mitosis (Table 1)<sup>17,27</sup>. Mitotic activity was observed in both the cerebral malignant GCT and the neurohypophysial GCT with local recurrence. Thus, the mitotic activity seems to be particularly related to the prognosis for intracranial GCT. Applying the histological criteria of Fanburg-Smith et al.<sup>7</sup> to the neurohypophysial GCTs, these previously reported tumors and our case could be classified as atypical or malignant GCT. Our case showed atypical histological features such as spindling of tumor cells, nuclear pleomorphism and the Ki-67 positivity.

The clinical pictures on CT and MRI do not reveal any specific findings for this tumor, and these diagnostic modalities usually only indicate an expanding lesion in the sellar or suprasellar region. CT scans usually show a more or less hyperdense tumor with enhancement after the administration of contrast medium<sup>12,16,31</sup>. The T1-weighted MRIs usually demonstrate an isointense tumor with non-homogeneous enhancement after the administration of Gd-DTPA. The proton density images demonstrate a tumor with an iso- or increased signal intensity and the T2-weighted images also show an iso- or hypo-signal intensity<sup>11,12,16</sup>. For our patient, the T1-weighted as well as the T2-weighted MRIs showed a suprasellar isointense tumor that became hyperintense with contrast enhancement. Such CT and MR imaging features are also observed in the other neoplasms of this region, including pituitary adenomas and germ cell tumors.

The clinical manifestations of granular cell tumors of the neurohypophysis are non-specific. In most cases, these tumors are small and show no space-occupying effect. Actually, asymptomatic minute granular cell nests or pinhead-sized granular cell tumorlettes are observed in 6.4%~17% of autopsy cases with almost the same frequency in the pituitary stalk and in the posterior hypophysis<sup>3</sup>. In some rare cases, however, these granular cell nodules become large and so they cause headaches, visual disturbances and endocrine disorders. Sudden-onset diplopia or visual loss, and short-term histories of confusion, headache and vomiting have been described. Cone et al.<sup>4</sup> have described one case of suprasellar GCT that became symptomatic due to tumor hemorrhage 4 years after subtotal removal and irradiation. Some of the reported GCT presentations include acromegaly that is secondary to hypersecretion of a growth hormone-releasing substance<sup>18</sup>, and other cases have shown a history of a reduced growth rate of facial and body hair, decreased libido and impotence<sup>12</sup>.

The natural history of a GCT is poorly understood. Although no systematic studies of GCTs have been undertaken to date, these tumors seem to be typically benign and indolent despite reports of occasional invasion and recurrence<sup>27</sup>. Relapse, although infrequent, has been attributed to incomplete excisions, and it usually manifests several years later<sup>4</sup>. Complete surgical excision appears to be the treatment of choice. However, in view of the location, high vascularity and the benign, slow-growth nature of the tumor, a partial removal that adequately decompresses the optic chiasm is usually all that is recommended<sup>1</sup>. The role of radiation therapy for these lesions remains controversial, especially in light of their slow growth.

## Conclusion

We experienced an extremely rare case of the atypical GCT of sellar region. As in this case, we suggest considering the diagnosis of GCT when a mass is located posteriorly within the gland, it is isointense on all sequences of MRIs and is strongly enhanced after contrast administration. Because the prognosis and treatment of an atypical GCT are not clear, long term follow-up should be done.

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