Atypical Granular Cell Tumor of the Neurohypophysis: A Case Report with Review of the Literature

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Abstract

A 76-year-old man had an atypical granular cell tumor of the neurohypophysis which showed pleomorphic nuclei, mitotic figures, and spindle-shaped cells, extremely rare findings to be encountered. Review of 45 patients with neurohypophyseal granular cell tumor revealed a ratio of 1 : 2 between male and female with the peak occurrence (31%) in the fifth decade, and with the mean age of 50 years. There were no patients below 20 years of age. The common clinical presentations included visual disturbances and endocrinopathies relating to sex hormones. Surgical removal was the treatment of choice. If it is possible, total extirpation should be attempted. Because of uncertain cellular origin, the lesion should be descriptively diagnosed as granular cell tumor although multiple terms have been proposed.

Granular cell nests (tumorettes) in the posterior pituitary gland and stalk are a fairly common incidental postmortem finding[1]. However, symptomatic neurohypophyseal granular cell tumors (GCT) are exceedingly rare[2]. To our knowledge, only 44 cases have been published[2-25]. The purpose of this communication is to report another example of a large intrasellar GCT with atypical histologic features and suprasellar extension. The related literature is also reviewed.

Patient

A 76-year-old man developed headache with blurred vision of both eyes 5 months before hospitalization. Physical examination revealed bitemporal hemianopia, bilateral impairment of visual acuity, and intact extraocular movement. Funduscopy showed no papilledema.

Hormonal profiles were as follows: morning cortisol 4.84 μg% (normal 7-25 μg%), free T4 0.5 ng/dl (normal 1-2.2 ng/dl), TSH 2.2 uIU/ml

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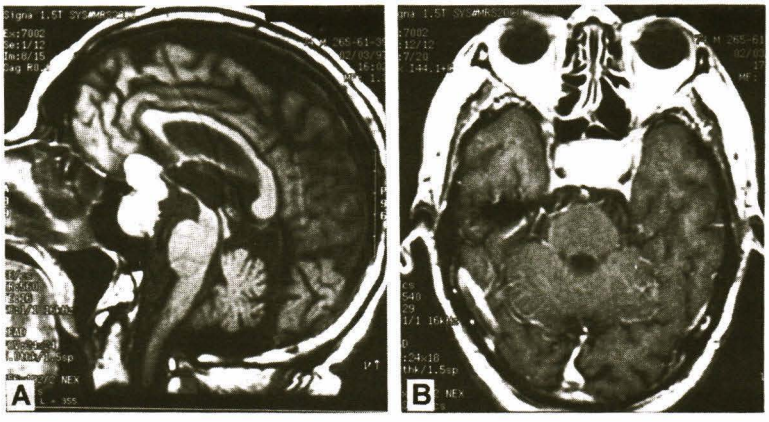

Fig. 1. MRI of the brain and pituitary fossa.
A. A sagittal T1W image reveals a hypersignal intensity mass in the pituitary fossa with supra-sellar extension.
B. An axial T1W image after intravenous gadolinium DTPA shows the mass with moderately homogeneous enhancement.

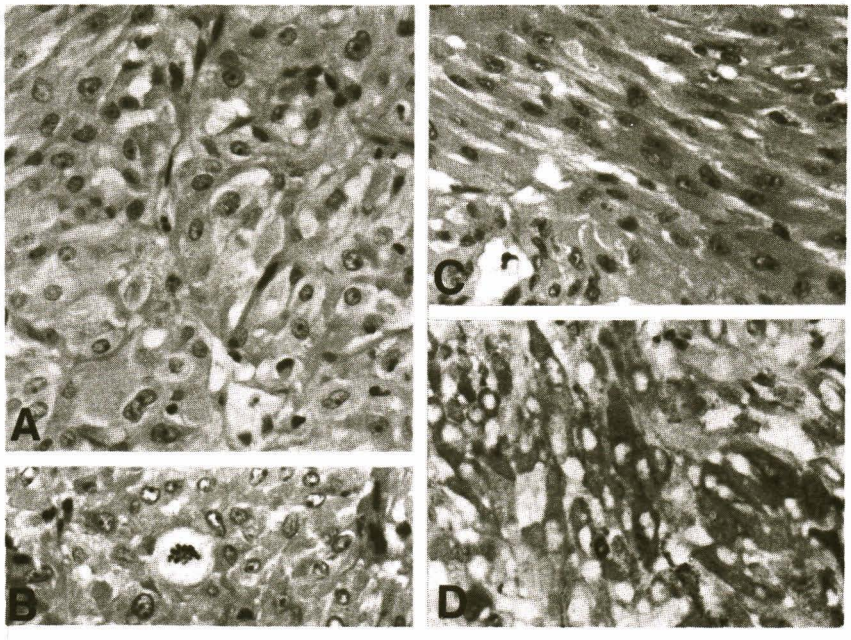

Fig. 2. Histopathological and immunohistochemical features of neurohypophyseal granular cell tumor.
A. Bizarre tumor cells with granular cytoplasm and pleomorphic nuclei with distinct nucleoli are shown. H & E, x 400.
B. A mitotic figure lies among granular tumor cell having pleomorphic nuclei. H & E, x 400.
C. Spindle-shaped granular neoplastic cells are arranged on stream. H & E, x 400.
D. Strong cytoplasmic positivity to alpha-1-antichymotrypsin is demonstrated in tumor cells. Immunostain, x 400.

(normal 0.5-4 uIU/ml), and prolactin 26 ng/ml (normal 1-20 ng/ml).

Magnetic resonance imagine (MRI) disclosed a 3.9 x 2.8 x 2- cm hypervascular enhancing mass in the pituitary fossa with suprasellar extension (Fig.1). The lesion displaced the prechiasmal part of the optic nerve, especially the right one, and invaded the left carvernous sinus.

The patient underwent sublabial rhinoseptal transphenoidal hypophysectomy on April 17, 1997. A gray, firm, and highly vascular tumor was subtotally resected because of intraoperative bleeding. Postopertive radiotherapy was not given.

Microscopically, the lesion consisted of tumor cells with fine eosinophilic granular cytoplasm and distinct cell membrane. The nuclei showed considerable pleomorphism with prominent nucleoli (Fig. 2A). Mitotic figures and spindle-shaped tumor cells were observed (Fig. 2B & C). Hemorrhagic foci and thin-walled small blood vessels were scattered in the lesion. Periodic acid-Schiff (PAS) stain with and without diastase digestion disclosed fine pink cytoplasmic granules in many tumor cells.

Immunohistochemical study demonstrated positivity to alpha-1-antichymotrypsin (ACT) (Fig. 2D), alpha-1-antitrypsin (AAT), S-100 protein, and vimentin. Chromogranin A, all pituitary hormones, neurofilament, and glial fibrillary acidic protein (GFAP) were negative. The pathological diagnosis was atypical granular cell tumor of the neurohypophysis.

Postoperatively, the patient did well. However, the visual symptom was not improved. A follow-up MRI 3 months later revealed a sizable residual mass. A right pterional craniotomy, then, was performed and complete removal of the tumor was achieved. At this reporting, 7 months after the second operation, the patient is still in the hospital and has respiratory difficulty from chronic obstructive pulmonary disease. He can respond to verbal command but can not speak. Hence, the visual symptom could not be evaluated.

DISCUSSION

Table 1 demonstrates 45 cases of neurohypophyseal granular cell tumor (GCT), including the current instance (No 44)[2-25]. There were 15 men and 30 women. Thirty-one per cent (14 cases) were encountered in the fifth decade of life. No patients were under 20 years of age. The oldest one was a 78-year-old female. The mean age of both genders was 50 years.

Common clinical presentations were visual disturbances, including visual field defect and/or impaired visual acuity, endocrinopathies such as secondary amenorrhea, oligomenorrhea, loss of hair, decreased libido, infertility, panpituitarism, diabetes inspidus and galactorrhea[2-7,9-12,14-16, 18,19,21,22-25]. The latter symptom was related to compression of the pituitary stalk resulting in hyperprolactinemia. The duration of symptoms ranged from sudden onset to 11 years. Eighteen patients received postoperative irradiation. The survival rate was 0 to 22 years.

Diagnosis of the granular cell tumor (GCT) in our case was based on the morphology of tumor cells which contained fine diastase-resistant PAS positive cytoplasmic granules. Because of the rarity of the tumor, its immunoprofile remains to be established[26]. Most neurohypophyseal GCTs show immunoreactivity to penut lectin agglutinin[20]. S-100 protein, vimentin, AAT, ACT, and cathepsin B are variably expressed[20,26,27]. GFAP is usually negative[20]. Therefore, the immunohistochemical study also supported our diagnosis. Generally, neurohypophyseal GCT consists of monotonous population of polygonal tumor cells with fine eosinophilic granular cytoplasm, bland eccentric nuclei, and devoid of mitoses[26,27]. In contrast, our GCT exhibited nuclear pleomorphism, some of which possessed prominent nucleoli, spindle-shaped tumor cells, and a few mitoses. Such histologic findings are in accord with the clinical aggressive behavior of the tumor as implied by its recurrence of the lesion within 3 months after the first operation. We, thus, prefer to descriptively diagnose our case as an atypical granular cell tumor.

Although GCT of the infundibulum has been described for more than a century, the cell origin of the tumor remains enigmatic as reflected by several diagnostic terms used for this lesion such as choristoma, granular cell myoblastoma, and pituicytoma[2]. The term "choristoma" was coined by Sternberg in 1921 indicating a hamartomatous lesion originating during the development of the pituitary gland[18]. However, this term seems to be inappropriate since most tumors occur in elderly patients, usually beyond 40 years of age, and are not found under the age of 20[20].

Granular cell myoblastoma is a name firstly used to describe a tumor taking place in the

Table 1. Summary of neurohypophyseal granular cell tumors arranging in relation to increasing age of 45 patients.

No	Age (yr)	Sex	Visual impairment	Endocrinopathy	Duration of symptom	No. of surgery	Rx	Survival	Ref No.
1	23	M	na	na	na	na	na	na	20
2	26	F	+	+ amen	3 yrs	3	+	8 yrs	2
3	27	F	+	+ amen	2 yrs	1	+	5 yrs *	6
4	30	F	+	+	1.5 yrs	1	-	8.5 yrs *	2
5	31	F	+	-	3 yrs	1	+	7 mos	4
6	34	M	+	+	few mos	1	+	22 yrs *	2
7	35	F	+	+	2 yrs	1	-	3 mos	2
8	36	F	+	+ galact , oligomen	4 mos	1	+	2 mos *	18
9	37	F	+	-	2 yrs	0	-	1 mo	3
10	38	F	-	-	na	0	+	2 yrs	8
11	39	M	+	-	2 yrs	1	+	4 mos *	16
12	40	F	-	+ amen	8 yrs	1	-	2 mos *	22
13	42	F	+	-	3 mos	2 (18 mos later)	+	2.5 yrs *	11
14	42	M	+	+ pan	1 yr	1	+	1 yr	16
15	43	F	+	-	1 yr	1	na	na	24
16	44	F	+	+ amen	9 yrs	1	-	6 mos *	12
17	45	F	+	+	6 mos	4	-	14 yrs	2
18	46	F	-	-	2 mos	0	-	0	13
19	46	M	-	-	0	1	-	0	17
20	47	F	+	+	na	1	-	2 yrs *	2
21	47	F	+	-	4 yrs	1	+	16 yrs *	9
22	47	F	+	+ amen ↓hair ↓libido	12 yrs	2 (10 yrs later)	+	10 yrs	5
23	48	F	+	+	4 yrs	1	+	2 yrs *	2
24	49	M	+	+ ↓libido	1.5 yrs	1	-	6 yrs *	10
25	49	M	+	+ ↓libido	1.5 yrs	1	-	4 mos	7
26	50	M	-	+	na	1	-	na	14
27	53	F	+	-	2 yrs	1	-	na	16
28	53	F	na	na	na	na	na	na	20
29	54	M	+	+ ↓hair ↓libido	24 yrs	2 (5 yrs later)	-	10 yrs	15
30	56	F	+	+ ↑prolactin ↓LH	several mos	2	+	4 yrs *	19
31	56	M	+	+ Infertility	2 yrs	1	-	1.5 yrs *	10
32	58	M	+	-	2 yrs	1	+	2 yrs	16
33	62	F	na	na	na	na	na	na	20
34	62	F	-	+ DI	8 mos	1	-	na	23
35	62	M	+	-	sudden diplopia	1	+	4 yrs *	19
36	65	F	na	na	na	na	na	na	20
37	68	F	-	-	sudden disorientation	1	-	2 yrs *	21
38	68	M	na	na	na	na	na	na	20
39	69	F	+	+	na	1	+	2 mos *	21
40	69	M	-	+	11 yrs	0	-	0	2
41	70	F	+	-	na	na	na	na	2
42	73	F	na	na	na	na	na	na	20
43	75	F	+	+ ↓FSH ↓Ins	2 yrs	1	+	10 mos*	25
44	76	M	+	+	5 mos	2 (3 mos later)	-	10 mos*	current case
45	78	F	+	-	na	1	+	5 yrs *	16

Rx = radiotherapy, Ref = reference, M = male, F = female, amen = secondary amenorrhea, oligomen = oligomenorrhea, galac = galactorrhea, pan = panpituitarism, DI = diabetes inspidus, LH = lutinizing hormone, FSH = follicle-stimulating hormone, Ins = insulin-like growth factor-1, d = day, mo = month, yr = year, na = not available, * alive at the last follow up

subcutaneous soft tissue and oral cavity; the term designated the origin from skeletal muscle[18]. Because of the morphological similarity, the term "granular cell myoblastoma" was also used by many authors in pertaining to the neurohypophyseal GCT[3,7,9-13]. Nevertheless, the concept of striated muscle being a cellular origin of extracranial granular cell myoblastoma is no longer maintained[28]. On the other hand, the expression of S-100 protein, myelin basic protein, and ultrastructural finding of a continuous basal lamina in the peripheral GCT point to the possibility of Schwann cell in origin[20,27,28]. Therefore, the term "granular cell myoblastoma" should not be used in both extracranial and intracranial GCTs. Additionally, the different results in immunohistochemical study between the neurohypophyseal GCT and extracranial GCT, and the fact that myelin and myelin forming cells are extremely rare in the neurohypophysis suggest that they are unlikely to be the same entity[20].

Identification of transitional change among pituicytes, modified astrocytes in the pituitary gland and its stalk, and neurohypophyseal GCT suggests that these native cells may be the progenitor of the tumor, rendering the diagnostic term of "pituicytoma"[29]. However, this term is sometimes erroneously used to describe astrocytoma of this region; therefore, it has lost specific meaning[26,29]. Moreover, granular cells in GCT usually lack GFAP expression which is normally found in pituicytes[26].

Currently, the term "granular cell tumor" appears to be suitable for this uncommon neurohypophyseal tumor because it describes the morphologic feature rather than the uncertain cellular origin of the lesion.

As a rule, total resection results in a satisfactory outcome. However, it cannot be done in all cases because of intraoperative bleeding from hypervascularity of the tumor[27]. Subtotal resection usually provides a long-term survival[30]. The role of postoperative irradiation is controversial [19]. Some authors suggests that it should be rendered when surgical removal cannot be accomplished[21(see comment), (25)].

It should be noted that GCT not only arises in the infundibulum but also occurs in other areas of the nervous system such as cerebral hemisphere and thalamus[31]. Moreover, a focus of granular cells can be encountered as well in some brain tumors including astrocytoma, glioblastoma maltiforme, and meningioma[29,31]. The divergent immunoexpression but consistent ubiquitin, a heat shock protein, positivity suggests that granular cells in nonhypophyseal GCTs may develop from different precursor cells under stress condition[31].

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เอทิพิคัล แกรนูลาร์ เซลล์ ทูเมอร์ ของกลีบหลังของต่อมใต้สมอง

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ได้รายงานผู้ป่วยชาย อายุ 76 ปี มี เอทิพิคัล แกรนูลาร์ เซลล์ ทูเมอร์ เกิดที่กลีบหลังของต่อมใต้สมอง เซลล์ของเนื้องอกมีนิวเคลียสใหญ่ บางตัวเห็นนิวคลีโอไลชัดเจนและมีการแบ่งตัวให้เห็นได้บ้าง กับทั้งมีเซลล์เนื้องอกรูปกระสวยอยู่ด้วย ผิดแบบไปจาก แกรนูลาร์ เซลล์ ทูเมอร์ ของกลีบหลังของต่อมใต้สมองที่เคยพบกัน จากการทบทวนวารสารพบมีเนื้องอกชนิดนี้ 45 ราย อัตราส่วนระหว่าง ชาย : หญิง เท่ากับ 1 : 2 ร้อยละ 31 ของเนื้องอกเกิดในทศวรรษที่ 5 แห่งอายุ ไม่พบเกิดในคนอายุน้อยกว่า 20 ปีเลย เซลล์ต้นกำเนิดของเนื้องอกชนิดนี้ยังไม่เป็นที่ทราบแน่ชัด อาการแสดงทางคลินิกที่สำคัญคือ ความผิดปกติเกี่ยวกับการมองเห็นและระบบฮอร์โมนอันเนื่องมาจากประสาทตา ก้านต่อมใต้สมอง หรือ ฮัยโปธาลามัส ถูกกด การรักษาทำได้โดยการผ่าตัด

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