Chordoid Glioma

Clinicopathologic Profile and Differential Diagnosis of an Uncommon Tumor

Anna Maria Buccoliero, MD; Adele Caldarella, MD; Pasquale Gallina, MD; Nicola Di Lorenzo, MD; Antonio Taddei, MD; Gian Luigi Taddei, MD

• Chordoid glioma is an uncommon low-grade brain neoplasm arising in the third ventricular region, predominantly in middle-aged women. It characteristically shows chordoma-like histologic features and glial fibrillary acidic protein immunoreactivity. We present a case of chordoid glioma in a previously healthy 56-year-old woman admitted to our hospital because of a cranial trauma subsequent to an incidental fall. Radiologic examinations revealed a well-demarcated, partially cystic, enhancing mass at the level of the lamina terminalis. The lesion was surgically removed. The patient remained alive and well 8 months after the surgery. Histologically, the tumor consisted of clusters and cords of epithelioid cells embedded in a mucinous matrix. Lymphoplasmacytic infiltrates and Russell bodies were prominent. Immunohistochemically, the tumor cells were positive for glial fibrillary acidic protein, neurofilaments, and neuron-specific enolase, suggesting a divergent neuronal and glial differentiation. The Ki-67 index was low. The clinicopathologic profile and the differential diagnosis of this tumor are discussed.

(*Arch Pathol Lab Med.* 2004;128:e141–e145)

Chordoid glioma is an infrequent low-grade primary brain neoplasm typically arising in the third ventricular–hypothalamic region. It was described by Brat and colleagues[1] in 1998 as a novel and distinct clinicopathologic entity. Nevertheless, the first report of this tumor probably dates to 1995, when Wanschitz and colleagues[2] reported a third ventricular lesion interpreted as chordoid meningioma with a peculiar expression of glial fibrillary acidic protein (GFAP). Chordoid glioma was so named because of its histologic features resembling a chordoma and because of its immunoreactivity to GFAP.

The histogenesis of chordoid glioma is uncertain. Ultrastructural data have indicated a possible derivation from the subcommissural organ, a specialized form of ependyma present in embryonic life and regressing after birth.[3] Recently, a tanycytic origin of this tumor has also been suggested.[4]

We describe the clinical, morphologic, and immunohistochemical features of a new case of chordoid glioma affecting an adult woman and discuss its differential diagnosis.

REPORT OF A CASE

The patient, a previously healthy 56-year-old woman, was admitted to our hospital because of a cranial trauma subsequent to an incidental fall. Cerebral computed tomography and magnetic resonance imaging (Figure 1) revealed a well-demarcated and partially cystic mass in the third ventricular region at the lamina terminalis level, measuring about 2 cm in diameter and enhancing after the administration of the contrast medium. The lesion was surgically removed. Surgical excision was pronounced as gross total resection by the surgeon. The patient's postoperative course was uneventful. No further therapy was recommended. The patient remained alive and well 8 months after the surgery and showed no clinical and radiological signs of recurrence.

MATERIALS AND METHODS

Surgical specimens were fixed in 10% buffered formalin and embedded in paraffin. Some 5-μm sections were stained with hematoxylin-eosin, periodic acid–Schiff, and Alcian blue for the morphologic evaluation, whereas other 5-μm sections were mounted on electrostatic slides and used for the immunohistochemical study (standard avidin-biotin-peroxidase method). The primary antibodies used were monoclonal antibody directed against Ki-67 (clone MIB-1, 1:80 dilution; Immunotech, Marseille, France), cytokeratins (clone AE1/AE3, 1:200 dilution; BioGenex, San Ramon, Calif), GFAP (clone ZCG29, prediluted; Zymed Laboratories, San Francisco, Calif), neuron-specific enolase (NSE; clone MIG-N3, prediluted; BioGenex), synaptophysin (clone Snp 88, prediluted; BioGenex), vimentin (clone V9, 1:2000 dilution; BioGenex), CD45 (clone 2B11; PD7/26, 1:400 dilution; Dako, Glostrup, Denmark), CD20 (clone L26, 1:400 dilution; Dako), CD138 (clone 5F7, 1:10 dilution; Novocastra, Newcastle upon Tyne, United Kingdom), κ (clone Hp6054, 1:300 dilution; BioGenex) and λ (clone L1C1, 1:2000 dilution; BioGenex) light chains, CD34 (clone QBEnd710, 1:20 dilution; BioGenex), and epithelial membrane antigen (EMA; clone E29, 1:50 dilution; Dako); multiclonal antibody against neurofilaments (NF; clone DA2, FNP7, RMb020.11, 1:20 dilution; Zymed); and polyclonal antibody against CD3 (1:50 dilution; Dako) and S100 protein (1:2000 dilution; Dako). Microwave antigen enhancement was used for the following antibodies: Ki-67, cytokeratins, GFAP, NSE, synaptophysin, vimentin, CD45, CD20, CD138, CD34, EMA, NF, and CD3; protease treatment (0.05%) was used for λ light chains.

Immunohistochemical staining was performed on a NEXES automated immunostainer (Ventana Medical Systems Inc, Tucson,

Accepted for publication July 8, 2004.

From the Departments of Human Pathology and Oncology (Drs Buccoliero, Caldarella, and G. L. Taddei), Neurosurgery (Drs Gallina and Di Lorenzo), and General Surgery (Dr A. Taddei), Medical School, University of Florence, Florence, Italy.

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Anna Maria Buccoliero, MD, Department of Human Pathology and Oncology, Medical School, University of Florence, viale G. B. Morgagni, 85, 50134 Florence, Italy (e-mail: ambuccoliero@unifi.it).

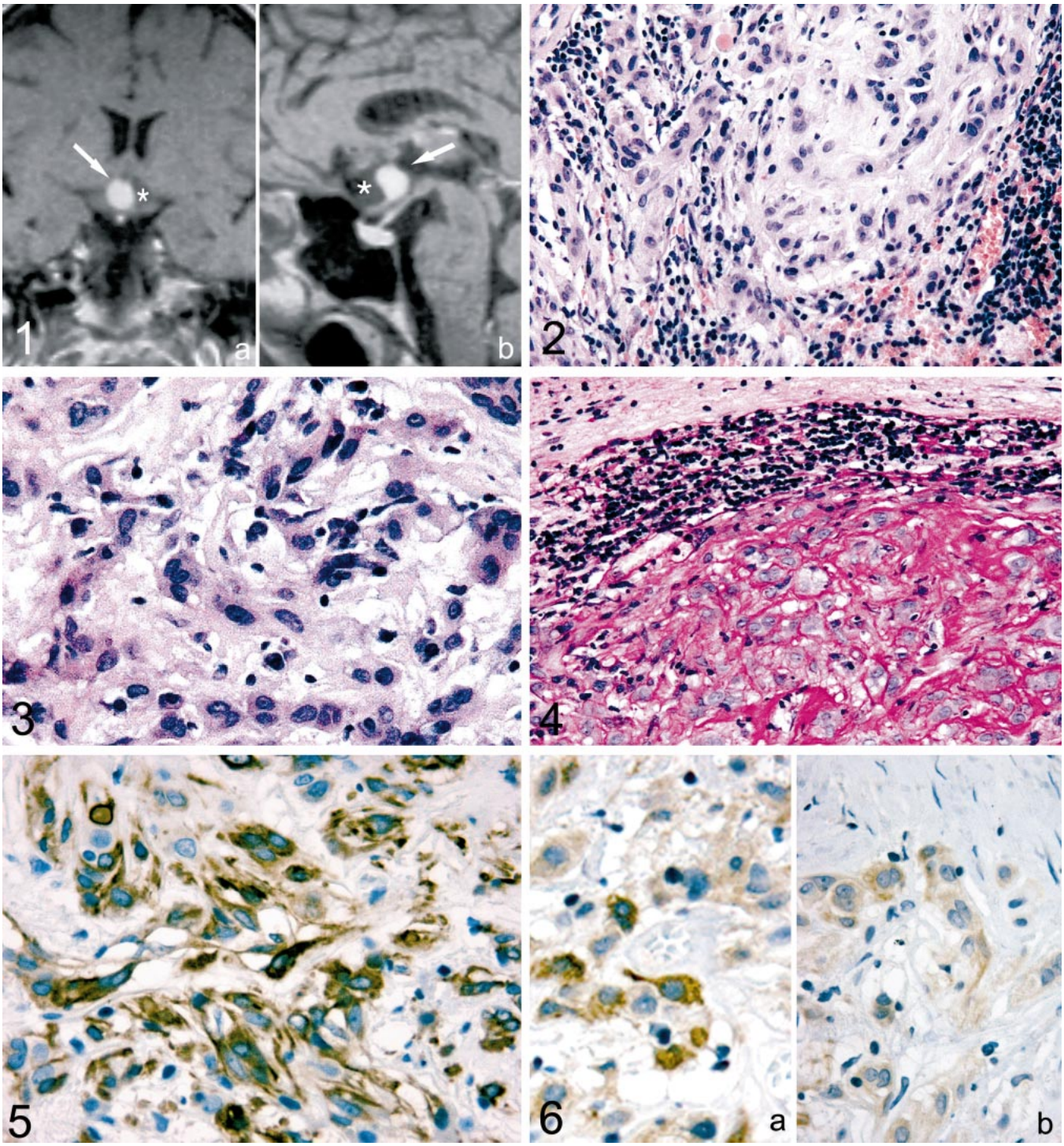

Figure 1. *Well-demarcated and partially cystic mass (asterisk) homogeneously enhancing in its solid area (arrows) (coronal [a] and sagittal [b] contrast-enhanced magnetic resonance images).*

Figure 2. *The tumor was moderately cellular; lymphoplasmacytic infiltrates with Russell bodies (top) were prominent (hematoxylin-eosin, original magnification ×200).*

Figure 3. *Oval-polygonal epithelioid cells with abundant eosinophilic cytoplasm, isomorphous nuclei, fine chromatin, and inconspicuous nucleoli (hematoxylin-eosin, original magnification ×400).*

Figure 4. *Periodic acid-Schiff–positive intercellular matrix; lymphoplasmacytic infiltrate often formed a well-defined and thick rim at the tumor-brain parenchymal interface (top) (original magnification ×200).*

Figure 5. *Glial fibrillary acidic protein–positive immunoreaction (original magnification ×400).*

Figure 6. *Neurofilament-positive immunoreaction (a, b); negative internal control: vascular structures (a, center), fibrous tissue focally surrounding the tumor (b, top) (original magnifications ×400).*

Ariz) (Ki-67, GFAP, NSE, vimentin, synaptophysin, CD45, CD20, CD3, EMA, NF, and S100) and on a GENOMIX automated immunostainer (BioGenex) (cytokeratins, CD34, and κ and λ light chains). No automated immunostainer was used for CD138. Negative controls were performed by omission of the primary antibody and its substitution with either an irrelevant mouse monoclonal IgG antibody or an irrelevant rabbit polyclonal antibody. Moreover, lymphocytes, plasma cells, endothelial cells, and fibrocytes were used as negative internal controls when we evaluated the GFAP, NF, and NSE immunoreactions.

The proliferation index was determined by estimating the percentage of Ki-67–positive neoplastic cells in the total number of tumor cells in the more positive areas.

RESULTS

Histologically, the tumor showed a sharp interface with the adjacent nervous tissue parenchyma and focally appeared encapsulated by fibrous tissue. It was moderately cellular and consisted of clusters and cords of oval to polygonal epithelioid cells with abundant eosinophilic cytoplasm, isomorphous nuclei, fine chromatin, and inconspicuous nucleoli (Figures 2 and 3). Tumor cells were embedded in a mucinous, often vacuolated and microcystic periodic acid-Schiff–positive (Figure 4) and Alcian blue–positive matrix. Prominent lymphoplasmacytic infiltrates were appreciable particularly at the tumor-brain parenchymal interface, where they focally formed a well-defined and thick rim (Figures 2 and 4). Numerous Russell bodies were seen (Figure 2). The lesion did not show necrosis, and mitoses were exceedingly rare. Vascularization was moderate.

Immunohistochemically, tumor cells showed diffuse expression of GFAP (Figure 5), NF (Figure 6), vimentin, and CD34 and weaker expression of NSE. A small subset of neoplastic cells were cytokeratin and EMA positive. CD45-, CD20-, CD3-, CD138-, EMA-, and κ and λ light chain–positive cells were seen in the inflammatory infiltrates, documenting the presence of B and T lymphocytes and of polyclonal plasma cells. No tumor labeling was observed for S100 protein or synaptophysin. The Ki-67 index was very low (about 1%).

COMMENT

Chordoid glioma is an uncommon tumor and was first incorporated into the World Health Organization classification of tumors of the nervous system in the recently revised edition (2000) under the category of glial tumor of uncertain origin. To our knowledge, 32 cases (including the present case) of chordoid glioma have been reported to date (Table).

The lesion typically arises in the third ventricular region with frequent attachment to hypothalamic and suprasellar structures (63% of the reported cases) and affects adults (median age, 45 years; range, 12–70 years) with a female predominance (female, 63%; male, 37%). Radiologically, chordoid glioma typically is a well-circumscribed, solid, enhancing mass, which occasionally shows a cystic component (19% of the reported cases).

Surgical resection of the lesion is considered the therapy of choice (97% of patients), even if it may result in an incomplete resection (50% of reported cases). Only 3 patients were treated postoperatively with radiotherapy, 2 with γ-knife radiosurgery and 1 with radiosurgery.[1,5–7]

Three (16%) of 19 previously described cases in which follow-up was available (excluding the patients who died because of surgical complications) recurred. In these 3 patients, the tumor was subtotally excised; 2 of 3 were treated with adjuvant radiotherapy, and 1 of 3 died of recurrence 3 years after the initial diagnosis.[1]

On the basis of these experiences, chordoid glioma is thought to be a third ventricular tumor, preferentially affecting middle-aged women and characteristically presenting solid enhancing radiological features; it has a relatively indolent prognosis.

Nevertheless, the scarcity of reported cases and their short follow-up periods (mean, 18 months; range, 0–68 months), as well as their location within the third ventricle with frequent attachment to hypothalamic and suprasellar structures, make it difficult to reliably predict prognosis. Moreover, the benefit of radiotherapy, of γ-knife radiosurgery, and of chemotherapy in the treatment of the partially excised chordoid gliomas is uncertain because of the small number of patients treated.[1,5–7]

Histopathologic features of chordoid glioma have been similar in all reported cases, namely, clusters and cords of epithelioid cells embedded in a mucinous matrix with prominent lymphoplasmacytic infiltrates. Chondroid metaplasia and papillary formations were additional focal features in a 12-year-old boy and in a 57-year-old woman, respectively.[8,9]

Common immunohistochemical results include a low Ki-67 index; diffuse GFAP, vimentin, and CD34 positivity; focal cytokeratin and EMA positivity; inconsistent S100 protein positivity; and negativity for neuronal markers (synaptophysin, NF, and NSE). Our case surprisingly showed positive NS and NSE immunoreactivity. These results could indicate a divergent neuronal and glial differentiation and at the same time could suggest that the immunohistochemical positivity to NF and NSE should not exclude chordoid glioma in the differential diagnosis of a third ventricular lesion.

Numerous tumors, including pituitary adenoma, craniopharyngioma, choroid plexus papilloma, neurocytoma, metastases, and pilocytic astrocytoma have been included in the differential diagnosis of chordoid glioma at the radiologic or morphologic level. However, from a histologic point of view, the most difficult differential diagnosis is between chordoid glioma and chordoma and chordoid meningioma. The absence of bone infiltration and of physaliphorous cells (typical features of chordoma) and the lack of psammoma bodies, cellular whorls, and nuclear pseudoinclusions (common in meningioma) can help in the diagnosis. The inflammatory infiltrates are not distinctive of chordoid glioma. Reactive lymphocytes and plasma cells with Russell bodies may also be numerous in chordoid meningioma.

Immunohistochemistry may be decisive. Meningioma is almost always EMA positive and GFAP negative, and chordoma is almost always positive for EMA, cytokeratins, and S100 and negative for GFAP. Chordoid glioma, on the other hand, is typically immunopositive with GFAP and, in some cases, focally positive with EMA, cytokeratins, and S100.

Moreover, Reifenberger et al[6] suggested immunohistochemistry together with molecular genetic analyses could be particularly useful to differentiate chordoid glioma from meningioma (strong immunohistochemical expression of schwannomin/merlin; absence of deletions on chromosome arm 22q), as well as from other types of gliomas (weak immunohistochemical expression of epidermal growth factor receptor; absence of pathologic accu-

Choroid Glioma Cases Reported in the Literature				
Source, y	**Age, y/Sex**	**Localization**	**Treatment**	**Follow-up**
Brat et al,[1] 1998	50/F	Third ventricle	GTR	NA
	70/M	Solid/cystic third ventricle	STR	Alive; 1 y
	59/F	Solid/cystic third ventricle–suprasellar	STR-RT	Died of recurrence; 3 y
	47/F	Third ventricle–suprasellar	STR	Died unrelated causes; recurrence; 8 mo
	31/F	Third ventricle–suprasellar–hypothalamic	GTR	Alive; 6 mo
	56/F	Third ventricle–suprasellar	STR	Alive; 1 y
	31/F	Third ventricle–suprasellar–hypothalamic	STR-RT	Alive; recurrence; 4 y
	35/F	Third ventricle–hypothalamus compressing	STR	Died postoperative pulmonary embolism
Reifenberger et al,[6] 1999	56/F	Third ventricle–suprasellar	STR-GKRS	Alive; 3.5 y
	53/F	Suprasellar	GTR	NA
	65/M	Third ventricle–suprasellar	GTR	Died postoperative pulmonary embolism
	35/M	Third ventricle	GTR	Died postoperative pulmonary embolism
Vajtai et al,[12] 1999	60/F	Third ventricle	STR	Died postoperative hyponatremia and tracheobronchitis
Tonami et al,[5] 2000	42/F	Solid/cystic third ventricle	STR-RT-RS	Alive; 9 mo
Ricoy et al,[10] 2000	41/F	Third ventricle–suprasellar	GTR	Alive; 13 mo
Castellano-Sanchez et al,[8] 2001	36/M	Supracellar	STR (successive second resecton)	NA
Pomper et al,[13] 2001	59/M	Solid/cystic third ventricle–hypothalamic	STR	NA
	41/F	Third ventricle–hypothalmic	STR	NA
	36/M	Third ventricle–hypothalmic	Biopsy	NA
	40/F	Third ventricle–hypothalmic	STR	NA
Cenacchi et al,[3] 2001	34/M	Third ventricle	GTR	Alive; 2 y
	40/M	Third ventricle	GTR	Alive; 3 y
	43/F	Third ventricle	GTR	Died postoperative pulmonary embolism
Galloway et al,[14] 2001	54/M	Suprasellar–hypothalamic	GTR	Alive; 9 mo
Castellano–Sanchez et al,[8] 2001	12/M	Hypothalamic	STR (?)	NA
Oda et al,[15] 2002	25/M	Solid/cystic third ventricle	GTR	Alive; 17 mo
Pasquier et al,[11] 2002	35/M	Third ventricle	GTR	Alive; 68 mo
	39/F	Solid/cystic third ventricle	GTR	Alive; 16 mo
Raizer et al,[9] 2003	57/F	Third ventricle–suprasellar	GTR	Alive; 16 mo
Nakajima et al,[7] 2003	49/F	Third ventricle	STR-GKRS	Alive, 24 mo
Sato et al,[4] 2003	65/F	Third ventricle	STR	Alive; 2.5 y
Present case	56/F	Solid/cystic third ventricle	GTR	Alive; 8 mo

* GTR indicates gross total resection; STR, subtotal resection; RT, radiation therapy; GKRS, γ-knife radiosurgery; RS, radiosurgery; and NA, not available.

mulation of p53; no evidence for amplification of epidermal growth factor receptor, CDK4, and of MDM2; and mutations of neither *TP53* nor *CDKN2A*).

Ultrastructural studies may certainly provide interesting data, particularly regarding the possible histogenesis of chordoid glioma. Common features are the presence of abundant intermediate cytoplasmic filaments, microvilli, intermediate junctions, and (at least focally) of the basal lamina. Nevertheless, the small number of cases studied ultrastructurally (9 of 32), some conflicting results (ie, clear cell body zonation in 3 of 9 cases and normal and/or abnormal cilia in 3 of 9 cases), and the possible difficulty in performing electron microscopy on routinely treated surgical specimens (formalin-fixed and paraffin-embedded) could reduce its definitive utility in the diagnosis.[3,4,7,9–11]

In conclusion, we believe that if precise clinical data, for example, the localization, are available, morphologic and immunohistochemical studies may be sufficient for a correct diagnosis. In addition, owing to the rarity of chordoid glioma, each new case should be recorded to produce a better characterization of this lesion.

References

1. Brat DJ, Scheithauer BW, Staugaitis SM, Cortez SC, Brecher K, Burgher PC. Third ventricular chordoid glioma: a distinct clinicopathologic entity. *J Neuropathol Exp Neurol.* 1998;57:283–290.
2. Wanschitz J, Schmidbauer M, Maier H, Rossler K, Vorkapic P, Budka H. Suprasellar meningioma with expression of glial fibrillary acidic protein: a peculiar variant. *Acta Neuropathol.* 1995;90:539–544.
3. Cenacchi G, Roncaroli F, Cerasoli S, Ficarra G, Merli GA, Giangaspero F. Chordoid glioma of the third ventricle: an ultrastructural study of three cases with a histogenetic hypothesis. *Am J Surg Pathol.* 2001;25:401–405.
4. Sato K, Kubota T, Yoshida K, Takeuchi H, Handa Y. Immunohistochemical and ultrastructural study of chordoid glioma of the third ventricle: its tanycytic differentiation. *Acta Neuropathol (Berl).* 2003;106:176–180.
5. Tonami H, Kamehiro M, Oguchi M, et al. Chordoid glioma of the third ventricle: CT and MR findings. *J Comput Assist Tomogr.* 2000;24:336–338.
6. Reifenberger G, Weber T, Weber RG, et al. Chordoid glioma of the third ventricle: immunohistochemical and molecular genetic characterization of a novel tumor entity. *Brain Pathol.* 1999;9:617–626.
7. Nakajima M, Nakasu S, Hatsuda N, Takeichi Y, Watanabe K, Matsuda M. Third ventricular chordoid glioma: case report and review of the literature. *Surg Neurol.* 2003;59:424–428.

8. Castellano-Sanchez AA, Schemankewitz E, Mazewski C, Brat DJ. Pediatric chordoid glioma with chondroid metaplasia. *Pediatr Dev Pathol*. 2001;4:564–567.

9. Raizer JJ, Shetty T, Gutin PH, et al. Chordoid glioma: report of a case with unusual histologic features, ultrastructural study and review of the literature. *J Neurooncol*. 2003;63:39–47.

10. Ricoy JR, Lobato RD, Baez B, Cabello A, Martinez MA, Rodriguez G. Suprasellar chordoid glioma. *Acta Neuropathol (Berl)*. 2000;99:699–703.

11. Pasquier B, Peoc'h M, Morrison AL, et al. Chordoid glioma of the third ventricle: a report of two new cases, with further evidence supporting an ependymal differentiation, and review of the literature. *Am J Surg Pathol*. 2002;1330–1342.

12. Vajtai I, Varga Z, Scheithauer BW, Bodosi M. Chordoid glioma of the third ventricle: confirmatory report of a new entity. *Hum Pathol*. 1999;30:723–726.

13. Pomper MG, Passe TJ, Burger PC, Scheithauer BW, Brat DJ. Chordoid glioma: a neoplasm unique to the hypothalamus and anterior third ventricle. *AJNR Am J Neuroradiol*. 2001;22:464–469.

14. Galloway M, Afshar F, Geddes JF. Chordoid glioma: an uncommon tumor of the third ventricle. *Br J Neurosurg*. 2001;15:147–150.

15. Oda M, Sasajima T, Kinouchi H, Sageshima M, Mizoi K. Third ventricular chordoid glioma: report of a surgical case. *No Shinkei Geka*. 2002;30:973–979.