A 57-year-old man presented with a history of several months of general fatigue. In the 2 months prior to admission, the patient experienced severe headaches, malaise, and anorexia. He also complained of recent loss of his sense of smell and increased sweating. His past medical history was significant for diabetes mellitus, hypertension, myocardial infarction, and nephrolithiasis. The family history was significant for colon cancer. A magnetic resonance scan of the brain showed a midline suprasellar mass with the greatest diameter, 1.8 cm, in the dorsal-ventral plane (Figure 1). Dense homogeneous enhancement was seen following gadolinium administration.

A stereotactic biopsy was performed. Tissue sections showed a neoplasm composed of tumor cells arranged in cords and clusters surrounded by a prominent basophilic myxoid matrix (Figure 2, A). The tumor cells exhibited an epithelioid appearance with eosinophilic cytoplasm and uniform round-to-oval nuclei that occasionally displayed small nucleoli. Mitotic figures were rare. Immunohistochemistry performed with the monoclonal antibody MIB-1 (Ki-67 antigen) showed a tumor labeling index of 3.7%. Tumor necrosis and microvascular proliferation were not seen. Scattered chronic inflammatory cell infiltrates with a prominent plasma cell component were present.

Immunohistochemical studies revealed strong diffuse cytoplasmic reactivity for glial fibrillary acidic protein (Figure 2, B) and vimentin. Focal positivity was seen for cytokeratins and epithelial membrane antigen (not illustrated).

The anatomic location, the morphologic features seen on hematoxylin-eosin sections, and the immunophenotypic profile are characteristic of chordoid glioma of the third ventricle.

**COMMENT**

In 1995, Wanschitz et al reported a tumor localized to the third ventricle of a 24-year-old woman; the tumor resembled chordoid meningioma but exhibited immunopositivity for glial fibrillary acidic protein. The authors classified the tumor as a variant of meningioma. Three years later, Brat and colleagues determined that the tumor was of glial derivation and, based on a series of 8 cases, described chordoid glioma as a novel clinicopathologic entity. Additional reported cases confirmed a glial immunophenotype and showed ultrastructural features of endymal differentiation. The literature relative to chordoid glioma has recently been summarized by Buccoliero and colleagues.

Chordoid glioma of the third ventricle is provisionally assigned grade II (of IV) in the World Health Organization 2000 classification, and is viewed as a relatively uncommon low-grade circumscribed glioma arising in the region of the third ventricle that exhibits unique clinical, neuro-
radiologic, and histopathologic features. Both the anatomic localization and the microscopic and ultrastructural features that characterize chordoid glioma point to many shared features with the specialized ependyma covering the lamina terminalis and the circumventricular organs in this anatomic vicinity, the organum vasculosum of the lamina terminalis and the subfornical organ.

**Clinical and Radiologic Features of Chordoid Glioma**

Most of the patients with chordoid glioma are in the fourth or fifth decades of life (mean age, 46; range, 12–70 years). There is a female predominance with a female-to-male ratio of approximately 2:1. The most common clinical manifestations of chordoid glioma are obstructive hydrocephalus and headache. The clinical symptoms, however, vary and can include headache, weight loss, endocrine disturbances (hypothyroidism, diabetes insipidus, amenorrhea), neurologic symptoms (ataxia, urinary incontinence, loss of olfactory sense), psychotic disorders, and, as seen in the present case, autonomic disturbances (in particular, hyperhidrosis).

Although chordoid glioma is considered to be a low-grade tumor, the anatomic origin in the rostral third ventricular region in close juxtaposition to hypothalamic structures increases the risk of surgical morbidity and mortality. Incompletely resected tumors continue to enlarge slowly, and some patients experience a poor outcome. In one recent report, there were 7 documented cases of death secondary to recurrent tumor in a series of 19 patients. Gross total surgical resection, when possible, appears to be the treatment of choice, although, as noted, the proximity to vital central nervous system structures increases the possibility of significant morbidity. The role of radiation therapy and/or chemotherapy for incompletely resected and recurrent tumors remains under investigation. Stereotactic radiosurgery has been performed and may offer a therapeutic alternative.

The appearance of chordoid glioma on neuroimaging studies is consistent and stereotypical. All documented cases have shown a well-circumscribed, uniformly contrast-enhancing, suprasellar mass. A cystic component can be seen in some instances. Chordoid gliomas exhibit a fusiform gross morphology, with narrow superior and inferior poles and a broad central axis in both the sagittal and coronal planes. This stereotypical configuration is best visualized and accentuated in smaller examples, such as in the present case (Figure 1), in which surrounding morphologic landmarks are least effaced and the anatomic relationships can best be appreciated.

**Histologic, Immunohistochemical, Ultrastructural, and Molecular Features of Chordoid Glioma**

The light microscopic appearance of chordoid glioma is characterized by cords and clusters of epithelioid cells set in a prominent basophilic myxoid background. Because these histologic features are reminiscent of chordoma, the term “chordoid glioma” was coined by Brat and colleagues. Tumor cells exhibit abundant eosinophilic cytoplasm and uniform round-to-oval nuclei. Prominent lymphoplasmacytic infiltrates are highly characteristic, and Russell bodies may be seen. Nuclear hyperchromasia and pleomorphism, microvascular proliferation, and necrosis...
are not generally present. Occasional mitotic figures can be present (less than 1 per 10 high-power fields). Other histologic variations are rarely observed, such as the papillary and alveolar growth patterns reported by Raizer and colleagues.7 Similar to other gliomas, osseous or chordoid metaplasia may occur.14 The surrounding brain parenchyma shows the typical hallmarks of chronic neuropil compression secondary to a slowly expanding mass: reactive astrocytosis, Rosenthal fiber formation, and chronic inflammatory cell infiltrates. Diffuse infiltration into surrounding brain tissue is not a feature of chordoid glioma.

Immunohistochemical studies show strong diffuse tumor cell cytoplasmic positivity for glial fibrillary acidic protein and vimentin. In addition, positivity for epithelial membrane antigen, cytokeratins, CD34, and S100 protein can also be present.

Molecular genetic abnormalities have been investigated in a series of 5 cases.15 No chromosomal imbalances or molecular genetic alterations seen in the diffuse astrocytomas, such as aberrations of the TP53 and CDKN2A tumor suppressor genes or amplifications of the EGFR, CDK4, and MDM2 proto-oncogenes, were observed in this
series. These molecular data argue against an astrocytic lineage of chordoid glioma.

Ultrastructural examination has been critical in the evolution of thinking about the derivation and nature of chordoid glioma. Characteristic features include abundant cytoplasmic intermediate filaments, microvilli, and focal basal lamina material. Scattered hemidesmosomes and zonula adherens-like junctions have been observed in several cases. Intracytoplasmic cilia and subplasmalemmal pinoctytic vesicles were seen in 1 case. In the 3 cases studied by Cenacchi et al, features of ependymal differentiation were seen in conjunction with cell body zonation (perinuclear, intermediate, subapical, and apical regions) and secretory granules, leading the authors to propose that chordoid glioma may be a subtype of ependymoma, with a possible origin from the specialized secretary ependyma of the subcomissural organ, which is vestigial in adult humans but prominent during embryologic development (Figure 3, upper panel). The argument against the origin being in the subcomissural organ is that it is present in the posterior dorsal third ventricle, whereas chordoid gliomas arise more rostrally, closer to the lamina terminalis (Figure 3, upper panel).

Although many chordoid gliomas reach a large size, essentially filling the third ventricle, the rostral origin is evident in smaller tumors, such as in the present case. The ultrastructural features and anatomic localization led Pasquier and colleagues to propose that the term chordoid glioma of the third ventricle could be further refined both anatomically and histogenetically to chordoid ependymoma of the lamina terminalis. Sato and colleagues also applied transmission electron microscopy to the study of chordoid glioma and pointed out that, among the cellular constituents that comprise the developing and adult ependymal lining, the ultrastructural features of chordoid glioma most closely resemble those of tanyocytes. Embryonic tanyocytes are the common progenitor cells of both astrocytes and ependymal cells, and a subpopulation of tanyocytes remains in the adult brain at specific sites of the ventricular system, most commonly in association with the circumventricular organs, including the organum vasculosum of the lamina terminalis. A putative lineage link to the tanyocyte has been previously proposed for several different types of central nervous system tumors, including astroblastoma and tanyctic ependymoma.

### Histogenetic Hypothesis

In all cases of chordoid glioma reported to date, the anatomic site of origin can be traced to the vicinity of the lamina terminalis. Origin from this structure would account for a number of the tumor's observed properties, including (1) the circumscribed gross morphology, (2) the fusiform shape (this geometry exactly would be predicted for a low-grade, noninvasive tumor originating from the lamina terminalis), and (3) certain specific endocrinologic disturbances, such as hyperhidrosis, that have been noted in even relatively small tumors, such as the present case, that are regulated by the organum vasculosum of the lamina terminalis. An additional circumventricular organ, located in the superior region of the lamina terminalis at its junction with the fornix, is the subfornical organ. The vasculature of these circumventricular organs lacks the properties of the blood-brain barrier, and this would correlate with the typical uniform contrast-enhancement of chordoid gliomas seen on neuroimaging studies. In addition, similar to other circumventricular organs, the organum vasculosum lamina terminalis and subfornical organ are covered by a specialized ependyma containing tanyocytes, which, like the cells of chordoid glioma and undifferentiated ependymoma, are strongly positive for glial fibrillary acidic protein.

Thus, there is a growing consensus among investigators that the characteristic clinical, neuroimaging, histopathologic, and ultrastructural features reported to date for chordoid glioma strongly point to an origin of the tumor in the vicinity of the lamina terminalis in association with the specialized ependymal lining that covers the lamina and the circumventricular organs of this region.

### SUMMARY

Chordoid glioma is a unique glial neoplasm that has been formally recognized and codified by the World Health Organization. The precise anatomic origin of chordoid glioma has been the subject of debate. Several different lines of available clinical and scientific evidence provide support for an origin of chordoid glioma from the lamina terminalis in association with the specialized ependyma that covers the lamina and its associated circumventricular organs. Further study of chordoid glioma, the lamina terminalis, the specialized ependymal lining of this region of the third ventricle, and the 2 circumventricular organs of the region may provide additional insight.

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### References


