DIABETES INSIPIDUS, PANHYPOPITUITARISM, AND SEVERE MENTAL STATUS DETERIORATION IN A PATIENT WITH CHORDOID GLIOMA: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Objective: To describe a rare progressive case of chordoid glioma clinically masquerading as idiopathic diabetes insipidus (DI).

Methods: We describe the clinical, radiographic, and laboratory findings of the study patient and briefly review the relevant literature.

Results: A 41-year-old woman was referred to our center for evaluation of worsening mental status changes, a newly diagnosed suprasellar mass, and possible endocrine dysfunction. Three years earlier, a physician at another institution diagnosed idiopathic DI and prescribed desmopressin. At that time, laboratory workup and magnetic resonance imaging (MRI) revealed no brain lesions or other hormonal irregularities. Slow, progressive symptomatology in the following 3 years included mental status changes, nonhealing skin lesions, recurrent infections, temperature dysregulation, and midsection weight gain. She became withdrawn and emotionally labile and developed a flat affect, short-term memory loss, poor concentration, and sleep disturbance. MRI revealed a 2.2×2.1 × 1.9-cm suprasellar region lesion. Biopsy samples from the third ventricular lesion revealed a circumscribed glial tumor. Chordoid glioma is a rare tumor, and the 50 previously reported cases have been located in the suprasellar region. This is the third reported case of a chordoid glioma positive for neurofilament protein, which brings into question the hypothesis of a single phenotype for glial tumors.

Accepted for publication February 12, 2009

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Tumors in this region frequently result in endocrine dysfunction that prompts patients to seek medical attention.

Conclusions: There is no formally recognized treatment protocol for chordoid glioma, and postoperative mortality and morbidity is high. Our report emphasizes the necessity of close follow-up of patients after a diagnosis of idiopathic DI. Early detection of any evolving occult hypothalamic-pituitary stalk lesion may improve outcome. (Endocr Pract. 2009;15:240-245)

Abbreviations:

DI = diabetes insipidus; **MRI** = magnetic resonance imaging

INTRODUCTION

We describe a rare and interesting progressive case of chordoid glioma clinically masquerading as idiopathic diabetes insipidus (DI). Chordoid gliomas are rare tumors located in the suprasellar region; 50 cases have been previously reported in the literature (1). Chordoid gliomas are generally negative for neuronal markers, and to our knowledge, this is the third reported case of a chordoid glioma positive for neurofilament protein (2,3), a finding that prompts us to question the hypothesis of a single phenotype for glial tumors.

CASE REPORT

A 41-year-old woman was referred to the pituitary center at Oregon Health & Science University for evaluation of worsening mental status changes, a newly diagnosed suprasellar mass, and possible endocrine dysfunction. Interestingly, 3 years earlier a physician at another institution diagnosed idiopathic DI and prescribed desmopressin (2 intranasal puffs twice a day). At that time, laboratory and radiographic workup (magnetic resonance imaging [MRI]) revealed no brain lesions or other hormonal irregularities. Her clinical course was followed yearly without

Submitted for publication December 31, 2008

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repeated imaging or hormonal testing, but with refilling of the desmopressin prescription (in the form of desmopressin acetate tablets). Slow, progressive symptomatology in the following 3 years included mental status changes, nonhealing skin lesions, recurrent infections, temperature dysregulation, and midsection weight gain. She became withdrawn and emotionally labile and developed a flat affect. She developed short-term memory loss, poor concentration, and sleep disturbance. Duloxetine had been prescribed, with mild effect. In the months before presentation to our clinic, she reported a 50-pound weight gain, fatigue, confusion, personality changes, and generalized pain. All symptoms were attributed to deepening depression, and she was referred to a psychiatric provider. She had several hospital admissions with fever (temperature greater than 100°F) of unknown etiology and negative blood cultures. One incident was attributed to a recurrent urinary tract infection. Furthermore, she experienced severe hot flashes and profuse night sweats, as well as rapid and generalized hair loss in the axilla, extremities, and pubic area. A partial hysterectomy had been performed 5 years previously for menorrhagia. Before hysterectomy she had had regular menstrual cycles and 2 normal pregnancies. In the months before presentation to our clinic, she was diagnosed with presumed central hypothyroidism (on the basis of low free thyroxine concentration and normal thyrotropin concentration in the past) and diabetes mellitus. She began treatment with levothyroxine, 112 mcg daily, and a sulfonylurea. Other medications included duloxetine for depression as previously mentioned. Periodic laboratory results consistent with hypercalcemia were left unexplained. Further progressive mental state deterioration and difficulty with ataxia prompted her family to pursue a more aggressive care plan that included additional MRI and subsequent referral to us by another endocrinologist.

The patient was seen in consultation at our multidisciplinary pituitary clinic by an endocrinologist and neurosurgeon. History as detailed in the preceding text was provided by the family and outside records. In addition to severe memory loss and profound personality changes, a shuffling gait was noted. On digital confrontation, a visual field examination yielded normal results; however, patient cooperation was limited. Physical examination revealed a patient who looked much older than her stated age with several traits of panhypopituitarism including pallor; parchment-like, cool, dry skin with fine wrinkles; decreased pubic and axillary hair; midsection weight; and decreased breast size. The patient did not have galactorrhea on expression. No other neurologic deficits were identified on examination. Laboratory testing revealed the following values: mildly elevated prolactin (81 ng/mL), undetectable corticotropin and cortisol, hypernatremia, normal calcium and parathyroid hormone concentrations, and low luteinizing hormone and follicle-stimulating hormone concen-

trations. Previously documented hypercalcemia (calcium, 12.3 mg/dL) resolved after high-dose dexamethasone treatment prescribed 2 days earlier by the referring endocrinologist (Table 1), and hypernatremia also resolved after doubling the daily dosage of desmopressin, excluding reset osmostat as an etiology. In the presence of a normal parathyroid hormone level, this suggested adrenal insufficiency as a contributing factor. The patient had been treated with desmopressin before presentation. Serum or urine osmolality were not evaluated at the time of presentation with anticipation of postoperative review. MRI revealed a 2.2 × 2.1×1.9 -cm suprasellar region lesion. The mass was posterior to the stalk, and a normal-appearing pituitary gland was identified within the sella. The lesion incorporated and protruded into the anterior wall of the third ventricle. Hydrocephalus was not present (Figs. 1A and 1B).

The patient underwent a right-sided orbitozygomatic craniotomy for lesion resection. Intraoperatively, the tumor was grayish in appearance and tenacious with a rubbery consistency adherent to all surrounding structures, with dense adherence to the hypothalamus and anterior wall of the third ventricle.

Biopsy samples from the third ventricular lesion revealed a circumscribed glial tumor, World Health Organization grade 2, with a background of fibrillary processes, focal myxoid degeneration, stromal collagen, hyalinized blood vessels, and prominent lymphoid and plasma cell infiltrates (Figs. 2A and 2B). Russel bodies were not readily identified. Tumor cells stained with glial fibrillary acidic protein, vimentin, synaptophysin, and neurofilament protein. Epithelial membrane antigen was not expressed in tumor cells. Tumor cells also stained with keratin AE1. However, there was no tumor cell labeling with keratin CAM 5.2, CD34, or p53. Individual glial cells with prominent nucleoli, cells with gemistocytic morphology, and areas with cells wrapped around blood vessels (Fig. 2C) were visible. There were also more solid areas with polygonal or round cells with truncated or no processes (Fig. 2D). No mitoses, vascular endothelial proliferation, or necrosis were identified. Ki-67 index was approximately 1% to 2%. Ganglion cells, granulomas, and ependymal features were absent. Germ cell tumor, eosinophilic granuloma, and lymphoma were ruled out by specific immunohistochemical staining.

The postoperative period was uneventful, and the patient's level of alertness immediately improved. She remained disoriented to time, place, and person throughout hospitalization; was without motor deficit; and maintained reactive bilateral pupils. High-dose steroids were subsequently tapered and switched to hydrocortisone, 20 mg daily. As expected, she continued to have central DI and central hypothyroidism and was adequately treated (Table 1) with desmopressin, 0.1 mg orally twice daily, and levo-thyroxine, 150 mcg orally daily. History revealed polyuria

Table 1 Laboratory Test Results of the Study Patient				
Analyte (reference range)	10 Months before surgery	1 Week before surgery (before dexamethasone)	2 Days before surgery	2 Months after surgery
Glucose (60-99 mg/dL)	127	142	89	93
Serum urea nitrogen (6-20 mg/dL)	13	27	20	26
Plasma creatinine (0.6-1.1 mg/dL)	1.2	1.6	0.9	1
Total protein (6.1-7.9 g/dL)			6.9	
Albumin (3.5-4.7 g/dL)	4		4.2	
Calcium (8.5-10.5 mg/dL)	10.8	11.3	9.6	9
Total bilirubin (0.3-1.2 mg/dL)			0.4	
Alkaline phosphatase (42-98 U/L)		 107 (high)	103 (high)	
Aspartate aminotransferase	40		105 (iligh) 18	
(15-41 U/L)	10		10	•••
Sodium (136-145 mEq/L)	141	153 (high)	149 (high)	143
Potassium (3.5-5.1 mEq/L)	4.5		3.6	4
Chloride (98-107 mEq/L)			113 (high)	107
Total carbon dioxide			27	29
(23-29 mEq/L)	•••		21	2)
Alanine aminotransferase (13-48 U/L)	64		23	
Direct bilirubin (low: <0.4 mg/dL)			<0.1	
Plasma adrenocorticotropic hormone (low: <46 pg/mL)			<5	<5
Prolactin (3-20 ng/mL)		121 (high)	81 (high)	68 (high)
Luteinizing hormone (follicular, <11; midcycle, 9-113; luteal, <13 IU/L)			<1	<1
Thyrotropin (0.34-5.60 mIU/L)	N/A	0.02 (low)	0.02 (low)	0.02 (low)
Free thyroxine (0.6-1.6 ng/dL)	0.45		0.8	1.2
Follicle-stimulating hormone (4-9 follicular; 5-23 midcycle; 2-5 luteal IU/L)			1	<1
Total serum cortisol (morning: 7.0-23 μg/dL)			<1.0	<1.0
Parathyroid hormone (15-75 pg/mL)		24		
Insulinlike growth factor 1 (101-267 ng/mL)				119
Serum estradiol (adult females: follicular, 20-75; midcycle, 62- 534; luteal, 80-273 pg/mL)				<20
Abbreviation: NA, not available.				

and polydipsia while desmopressin was held to evaluate persistent DI. Serum sodium rose to 156 mEq/L with a serum osmolality of 324 mOsm/kg H_2O and an inappropriately low urine specific gravity of 0.003 (reference range, 0.002-0.03). Thus, a water-deprivation test was not

required. She had a low-normal insulinlike growth factor 1 concentration, most likely consistent with growth hormone deficiency, but in the presence of chordoid glioma, we did not pursue growth hormone-stimulation testing or replacement. Prolactin continued to be mildly elevated

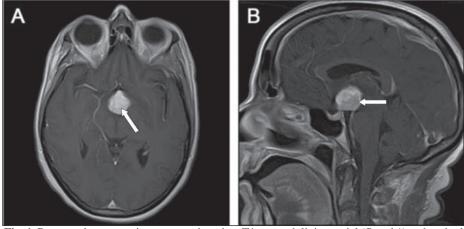


Fig. 1. Preoperative magnetic resonance imaging. T1 postgadolinium axial (*Panel A*) and sagittal (*Panel B*) images demonstrating a well-circumscribed lesion (*arrow*) in the suprasellar region that incorporates the hypothalamus and anterior wall of the third ventricle.

without galactorrhea. Postoperatively, a neuro-oncologist recommended observation with serial imaging, but no chemotherapy or radiation therapy.

Three months after surgery, the patient's clinical status had greatly improved. She was more awake, alert, and interactive. She was able to sustain short conversations that were limited by her persistent short-term memory deficits. She was oriented to month and day, but not to year, and was able to perform complex tasks. Her greatest difficulty was orientation to time. Motor strength was symmetric in both extremities, pupils were reactive, and extraocular movements were intact. Postoperative MRI revealed interval debulking of tumor, with residual tumor remaining in the hypothalamus and anterior wall of the third ventricle (Figs. 3A and 3B). Hydrocephalus did not develop. Clinically and biochemically, hormonal replacement was adequate:

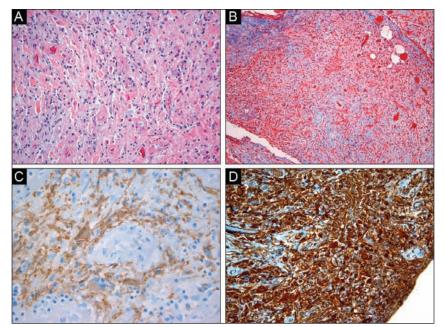


Fig. 2. Immunohistochemical labeling. *Panel A*, Moderately cellular glioma with scattered round cell and gemistocytic elements, lymphoplasmacytic infiltrates, and prominent blood vessels (hematoxylin-eosin stain; original magnification ×200). *Panel B*, Stromal collagen and mural hyalinization of blood vessel walls are evident, as well as circumscribed architecture (Masson trichrome stain; original magnification ×100). *Panel C*, Tumor cells wrapping around blood vessels (glial fibrillary acidic protein immunostain; original magnification ×400). *Panel D*, Solid areas with round cells are also present (vimentin immunostain; original magnification ×200).

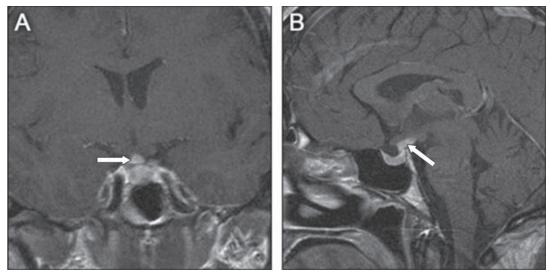


Fig. 3. Postoperative magnetic resonance imaging. T1 postgadolinium coronal (*Panel A*) and sagittal (*Panel B*) images revealing residual tumor (*arrow*) in the hypothalamus and third ventricle.

hydrocortisone, 20 mg daily in the morning; levothyroxine, 150 mcg daily; and desmopressin, 0.1 mg twice a day. Hypercalcemia was not evident in follow-up testing, and because hypercalcemia resolved preoperatively with glucocorticoid treatment and hydration, the hypercalcemia was therefore most likely related to adrenal insufficiency and dehydration. The patient was referred for an obstetrics and gynecology consultation for discussion of estrogen replacement. One year after surgery, disorientation to time of unclear origin persisted. Metabolic and hormonal etiologies are unlikely given the patient's replacement therapies. MRI 1 year after operation revealed no further growth of residual tumor.

DISCUSSION

DI may be familial or secondary to injury of the hypothalamic-infundibular-neurohypophyseal system (4-6). Frequently, an organic lesion in this region may be due to inflammatory diseases, such as Langerhans cell histiocytosis, sarcoidosis, tuberculosis, or autoimmune processes (4-6). In the absence of the above etiologies, DI is usually classified as idiopathic.

DI is rarely associated with primary pituitary adenomas, especially in the absence of pituitary surgical history or gross suprasellar extension of the tumor. Even large intrasellar masses usually grow slowly over long periods of time, and this allows an adaptation of neurohypophyseal function to occur. Hence, DI in patients with normal initial MRI and subsequent anterior pituitary dysfunction should raise one's suspicion of possible hypothalamic or stalk involvement. The lethargy and somnolence that developed in the patient we describe were unlikely to have been caused by central nervous system effects of the moderate hypernatremia. Her presumed idiopathic DI was found more than 3 years later to be caused by a rare suprasellar chordoid glioma. Although in the presence of elevated calcium levels, nephrogenic DI could have been considered on presentation, the patient had documented central DI post operatively after normalization of the calcium concentration. She continued to require higher doses of desmopressin 1 year after surgery, making a nephrogenic component unlikely.

Chordoid glioma is classified by the World Health Organization (7) as a neuroepithelial tumor of uncertain origin. Histologically, they consist of clusters, chords, and streams of eosinophilic, rather epithelioid cells in a mucinous stroma often containing a lymphoplasmacytic infiltrate replete with Russell bodies. Immunoreactivity for glial fibrillary acidic protein is widespread, while S100 immunoreactivity is variable. Focal epithelial membrane antigen reactivity may also be observed, and MIB-1 labeling indices are low. In general, chordoid gliomas are negative for neuronal markers, with the exception of our patient and 2 other reported cases of positive neurofilament immunoreactivity (2,3). This suggests that if tumor neurofilament immunoreactivity is detected, presence of a chordoid glioma should not be ruled out (2). Chordoid gliomas are located in the suprasellar region with involvement of the hypothalamus and third ventricle. On MRI, they appear as a primarily solid mass, and cystic components have been described. They homogeneously enhance upon administration of gadolinium, and as a result, local involvement of the hypothalamic-pituitary axis is expected. In retrospect, closer review of initial magnetic resonance images in our patient revealed slight enhancement of the hypothalamus with contrast administration, but no definite tumor.

To date, there is no published, universally accepted protocol for chordoid glioma treatment. In general, it is left to the discretion of the treating physician(s). Available literature is limited primarily to case reports and descriptive studies (8). In 2003, Raizer et al published an extensive review of the literature including clinical and pathologic features of 32 case reports (9). The review of 44 cases later published by Iwami et al (3) noted a predilection in middleaged to older women. Symptoms due to mass effect of the optic apparatus and hypothalamic-pituitary axis included headaches, visual changes, and endocrine disturbances. There was little variation in radiographic appearance, and homogeneously enhancing masses were predominately located in the suprasellar region. Pathology consistently demonstrated chords and nests of epithelioid cells in a stromal matrix, along with "lymphoplasmocellular infiltrates with Russell bodies as a rule."

Of the 50 cases reported to date (1), gross total resection was achieved in 23 patients (46%), subtotal resection in 22 (44%), and iridium implantation followed by subtotal resection in 2 (4%). In our patient, subtotal resection was expected because of hypothalamic involvement. Mortality as a result of postoperative complications is high (12 of 38 patients for whom follow-up data were available). Interestingly, weight gain was reported in 2 patients, memory disturbances and psychotic changes were reported in 7 patients, and DI was reported in 4 patients. Seven of the patients who underwent subtotal resection also underwent radiation treatment (standard or gamma knife) with variable results (2). The role of postoperative radiotherapy is unknown. One review (2) suggests that radiosurgery with or without conventional irradiation is superior to conventional radiation alone. There were no reports of chemotherapy administration. The patient we describe did not undergo radiation or chemotherapy, and tumor radiographic appearance remains stable 1 year after surgery, an encouraging result considering most tumors recur within a year (2).

CONCLUSION

Space-occupying lesions in the pituitary causing DI include tumors derived from neural or endocrine tissues, cystic lesions, chronic inflammatory processes, and meta-static malignancies. Chordoid gliomas are rare tumors of reported glial phenotypic origin. However, our patient is the third reported case with positive neurofilament immunoreactivity suggestive of a neuronal differentiation or stem cell origin (3). Treatment currently involves surgical resection and/or radiation therapy coupled with appropriate hormone replacement. Chordoid gliomas should be

included in the differential diagnosis of suprasellar masses, particularly when a homogenously enhancing lesion is noted to involve the hypothalamus or third ventricle.

In summary, so-called idiopathic central DI warrants close investigation to determine a precise etiology, especially if anterior pituitary hormone deficiencies are detected. A search for extrapituitary involvement is essential. Normal brain MRI should be followed by serial contrast-enhanced brain MRI to detect any early onset of an evolving occult hypothalamic-stalk lesion.

ACKNOWLEDGMENT

We are indebted to Shirley McCartney, PhD, for editorial assistance.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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