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Epithelioid Pituicytoma

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Abstract

Background—Pituicytomas are rare tumors of the sellar region that are derived from specialized glial cells called pituicytes. They characteristically exhibit spindle cell features and fascicular or storiform patterns of growth. No other histological variants of this tumor have been described.

Case Description—Here we report a diagnostically challenging case of pituicytoma in a 42 year-old man with a sellar mass arising from the pituitary stalk. On histological examination, the tumor displayed an epithelioid histoarchitecture with no characteristic spindle cell or fascicular growth features. Strong immunopositivity for the pituicyte marker thyroid transcription factor-1 (TTF-1) within tumor cells proved essential for diagnosing this unusual pituicytoma variant.

Conclusion—Pituicytomas may display epithelioid rather than fascicular or storiform histoarchitecture. Epithelioid pituicytoma variants may be diagnosed in cases such as ours where both the clinical findings and immunohistochemical analysis suggest a tumor derived from pituicytes.

Keywords

brain tumor; low grade glioma; neurohypophysis; pituicytoma; thyroid transcription factor-1 (TTF-1)

Introduction

Pituicytomas are uncommon low-grade (WHO grade I) glial tumors of the sellar region that originate within the neurohypophysis or infundibulum and are thought to derive from specialized glial cells within the neurohypophysis called pituicytes [1]. Fewer than 60 cases of pituicytoma meeting World Health Organization (WHO) criteria have been reported (Table 1). Previous reports describe the histopathology of pituicytomas as spindle cells arranged in fascicles or in a storiform pattern. Here we present the case of a patient with a

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pituicytoma that departed from this usual appearance, instead displaying a more epithelioid histoarchitecture. This represents the first report of this unique histological pituicytoma variant.

Case Report

Presentation and Clinical Evaluation

The patient is a 42-year-old man with a previously unremarkable medical history who presented with a one year history of decreased libido and sexual dysfunction. His physical examination was normal and initial laboratory workup was significant only for a low testosterone level of 66 ng/dl. Other endocrine studies including follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin, and adrenocorticotrophic (ACTH) were normal. MRI of the brain showed a homogenously enhancing 1.7 X 2.5 cm suprasellar mass with extension into the sella and inferior third ventricle (Figure 1). Formal visual fields were normal and serum levels of the germ cell tumor markers alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (hCG) were not elevated.

Surgery

The tumor was approached through a right frontal-orbital craniotomy. At surgery, the tumor was soft, moderately vascular, and appeared to be arising from the pituitary stalk. The intraoperative frozen section and squash preparation (Figure 2) were consistent with a low grade glial neoplasm. A gross total resection of the tumor was accomplished.

Pathology

Microscopic examination revealed a hypercellular neoplasm, composed of small and medium sized, mildly pleomorphic cells in vague trabeculated and perivascular arrangements (Figure 3A). The neoplastic cells had an epithelioid morphological appearance with plump ovoid or irregular vesiculated nuclei, distinct nucleoli, and pale eosinophilic and occasional vacuolated cytoplasm (Figure 3B). Granular cell features were not observed. Rare mitotic figures were noted with no more than 1 found in 10 consecutive high power (400X) fields. Areas of necrosis and vascular proliferation were absent.

Immunohistochemical analysis confirmed the glial origin of the neoplasm, with a subset of tumor cells displaying strong immunopositivity for glial fibrillary acidic protein (GFAP) and S-100 (Figure 4A–B). The majority of tumor cells showed nuclear staining for thyroid transcription factor-1 (TTF-1) (Figure 4C). The neoplastic cells were negative for pancytokeratin (CK), growth hormone (GH), prolactin, adrenocorticotrophic hormone (ACTH), epithelial membrane antigen (EMA), progesterone receptor (PR), synaptophysin, chromogranin, Neu-N, phosphorylated neurofilament (NF), CD31, and CD34. Only very rare scattered cells showed weak immunopositivity for nuclear protein p53 (less than 1%). Reticulin fibers were limited to the walls of blood vessels. The Ki-67 (MIB1) cell proliferation index was 4% on average with focal elevation to 8% (Figure 4D). Based on these histological and immunohistochemical findings a diagnosis of epithelioid pituicytoma (WHO grade I) was rendered.

Post-operative course

Postoperatively the patient transiently developed diabetes insipidus which was successfully treated with desmopressin (DDAVP) followed by syndrome of inappropriate antidiuretic hormone (SIADH) which responded to fluid restriction. At the time of discharge he was neurologically intact with plans for outpatient treatment of his secondary hypogonadism.

Follow-up brain MRI 3 months postoperatively showed no evidence of tumor recurrence (Figure 5).

Discussion

Historically the term pituicytoma has been applied to a hodgepodge of sellar/suprasellar tumors including pilocytic astrocytoma and granular cell tumor. Although case reports of posterior pituitary lobe gliomas appeared in the literature as early as the 1950s it is unclear if these tumors conform to the World Health Organization (WHO) formulation [2, 3]. A review of 54 cases in the modern literature (Table 1) reveals that pituicytomas, as currently defined by the WHO, present during adulthood (median age 48 years) and have a slight male preponderance (1.3:1).

Typically, patients present with complaints of headache, visual impairment, or sexual dysfunction over a period of several months, however, acute presentation secondary to intratumoral hemorrhage can occur [4]. Brain MRI with contrast is the diagnostic imaging modality of choice and generally shows a homogeneously enhancing sellar/suprasellar mass. Gross total resection (GTR) is the preferred therapeutic strategy as subtotally resected tumors commonly recur. Some practitioners advocate radiation to residual tumor, however, the efficacy of adjuvant therapy for pituicytomas is unknown.

The tumors reported in the modern literature as pituicytomas are generally described as having a spindle cell architecture with cells arranged in fascicles or in a storiform pattern [3–33]. In contrast to this classical description, the tumor we describe was a diagnostic challenge owing to its epithelioid morphology. Based on the clinical and preliminary histological findings, the differential diagnosis included several glial neoplasms namely pituicytoma, chordoid glioma, and ependymoma, as well as other neoplasms of epithelioid appearance such as meningioma and pituitary adenoma.

With increasing reports of pituicytomas in the literature, the immunohistochemical profile of this tumor has become better defined and useful in the clinical setting (Table 2). In our case, immunohistochemistry proved very useful for narrowing the differential diagnosis. The glial nature of the tumor was supported by positive staining for GFAP and S100 (Figure 4A–B). As in previous reports of pituicytoma, GFAP expression was exhibited by only a limited subset of tumor cells. Pituitary adenoma was excluded based on negative staining for synaptophysin, chromogranin, ACTH, GH, and prolactin. Meningioma was thought less likely based on negativity for EMA, PR, and lack of characteristic features. Likewise, chordoid glioma was excluded due to the absence of EMA, CK, and CD34 staining.

To further distinguish among the possible glioma subtypes TTF-1 immunostaining was utilized. In addition to expression in lung and thyroid tissue, TTF-1 is expressed in the developing ventral forebrain and pituitary gland [34, 35]. Additionally, TTF-1 immunopositivity has been recently reported in fetal and adult human pituicytes as well as in pituicytoma, infundibular granular cell tumors, and spindle cell oncocytoomas of the adenohypophysis [18]. In our case, strong nuclear TTF-1 immunopositivity was seen in the majority of neoplastic cells further pointing toward a glioma originating from pituicytes (Figure 4C). While the labeling of glioblastoma cells by the SPT24 clone TTF-1 antibody has been reported to be a common finding [36], the 8G7G3/1 clone TTF-1 antibody used in our case has not been reported to label central neuroepithelial neoplasms arising outside the hypophysis [36, 37] except for two tumors interpreted as ependymomas of the third ventricle [37]. Again, the lesion we report did not evidence any pattern of EMA expression that would suggest ependymal differentiation.

Conclusion

The clinical presentation, neuroimaging findings, gross tumor location, and immunohistochemistry of the tumor we describe support the diagnosis of an epithelioid pituicytoma variant. Diagnostic consideration of such a variant should be given in cases of sellar region lesions that fail to display the expected spindle cell morphology. Further studies will be necessary to elucidate the clinical significance of pituicytoma variants.

Acknowledgments

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Glossary

TTF-1	Thyroid transcription factor-1
WHO	World Health Organization
FSH	follicle-stimulating hormone
LH	luteinizing hormone
TSH	thyroid-stimulating hormone
ACTH	adrenocorticotrophic
AFP	alpha-fetoprotein
hCG	beta-human chorionic gonadotropin
EMA	epithelial membrane antigen
PR	progesterone receptor
DDAVP	desmopressin

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Figure 1. Preoperative brain imaging

Contrast MR in axial (A), sagittal (B), and coronal (C) views show a homogenously enhancing suprasellar lesion with mass effect within the inferior third ventricle.

Figure 2. Intraoperative diagnosis

Squash preparation of fresh tissue during intraoperative consultation shows loosely-cohesive clusters of cells with occasional small cytoplasmic processes (400X).

Figure 3. Histological features

Hematoxylin and eosin (H&E) stained sections at low (A, 100X) and high (B, 400X) power magnification shows a hypercellular neoplasm with vague trabecular architecture and epithelioid morphology. Tumor cells have plump ovoid or irregular vesiculated nuclei, distinct nucleoli, and pale eosinophilic cytoplasm with occasional vacuolation.

Figure 4. Immunohistochemical analysis

Focal, strong immunopositivity for GFAP (A), cytoplasmic immunopositivity for S-100 (B), and widespread nuclear immunopositivity for TTF-1 (C) is evident within the tumor (100X). Ki-67 immunoreactivity (D, 40X) is demonstrated in 4% of cells on average and in up to 8% of cells focally (inset, lower right, 100X).

Figure 5. Postoperative brain imaging

Contrast MR in axial (A), sagittal (B), and coronal (C) views show no evidence of tumor recurrence 3 months postoperatively.

Table 1

Clinical Characteristics of Reported Pituitaryomas

Author (Year)	Year	Age (yrs)	Sex	Presenting Symptoms	Duration of Symptoms (mo)	Extent of Surgical Resection	Adjuvant Therapy	Time to Recurrence (mo)/Treatment
Hurley et al.	1994	26	F	dizziness, imbalance, headaches, visual disturbances, hemianopsia	4	STR	RT (5040 cGy total)	
Brat et al.	2000	55	F	visual disturbances	n/a	GTR	none	
		30	M	headaches	several	GTR	none	
		39	M	headaches		GTR	none	
		42	M	fatigue, hy popituitarism, hemianopsia	24	STR	none	26/repeat STR
Cenacchi et al.	2001	42	M	visual distur decreased libido	bances, n/a	STR	none	20/repeat STR
		46	M	hypopituitarism	n/a	GTR	none	
		83	F	headaches, visual disturbance	n/a	GTR	none	
		48	M	hypogonadism	n/a	STR	none	
Schultz et al.	2001	51	F	headaches, visual disturbance	n/a	GTR	none	
		79	F	panhypopituitarism, visual disturbances	n/a	GTR	none	
		66	M	lassitude, weakness, imbalance, headaches, visual disturbances	n/a	GTR	none	
Figarella-Branger et al.	2002	59	M	fatigue, hypopituitarism, decreased libido	36	STR	none	
		46	M	fatigue, decreased libido, gynecomastia, hypogonadism	n/a	GTR	none	
		58	M	memory disturbances, fatigue, decreased libido, diabetes insipidus, visual disturbances	60	GTR	none	
Uesaka et al.	2002	34	M	bitemporal hemianopsia	4	STR	none	
		32	F	amenorrhea, visual disturbances	12	GTR	none	
		52	M	panhypopituitarism, gynecomastia, decreased libido	180	STR	RT (to recurrent tumor)	11/RT
Ulm et al.	2004	45	M	decreased libido	60	STR	fractionated stereotactic RT	
		26	M	decreased libido, hypopituitarism, visual disturbances	n/a	STR	fractionated stereotactic RT after second recurrence	60/repeat STR, then 24/RT
		54	M	headache	7	STR	none	60/repeat STR
Shah et al.	2005	36	F	headache, amenorrhea	n/a	STR	none	
		45	F	headache, visual disturbance	n/a	n/a		
		54	F	incidental autopsy finding	n/a			
Takei et al.	2005	54	F					

Author (Year)	Year	Age (yrs)	Sex	Presenting Symptoms	Duration of Symptoms (mo)	Extent of Surgical Resection	Adjuvant Therapy	Time to Recurrence (mo)/ Treatment
Benveniste et al.	2006	47	M	severe headache	1 day	STR	none	
Gibbs et al.	2006	64	M	bitemporal hemianopsia, headache, memory loss	24	GTR	none	
Nakasu et al.	2006	42	F	amenorrhea, vertigo	72	STR	none	
		62	F	headache, fatigue	n/a	STR	none	
Thirayayi et al.	2007	77	M	hypogonadism, bitemporal quadrantanopia, decreased gonadotrophins, decreased testosterone	n/a	STR		
Newnham et al.	2008	43	M	lethargy, weakness, headaches, loss of body hair, declining libido, hypopituitarism, hypogonadism	24	GTR	none	
Wolfe et al.	2008	71	F	impaired visual acuity, bitemporal hemianopsia	12	STR	none	
Lee et al.	2009	58	F	weight loss, fatigue	several	GTR	none	
		54	M	panhypopituitarism, diabetes insipidus	12	STR	none	12/repeat resection
		62	M	headaches, visual changes	24	GTR	none	
		77	M	bitemporal hemianopsia, lethargy, somnolence	n/a	STR	none	4/observation
		59	F	bitemporal hemianopsia, weight loss	12	STR	RT and chemo after second recurrence	repeat STR then RT and chemo
Orrego et al.	2009	55	M	hyponatremia, fatigue, weight loss, decreased libido, ACTH deficiency, bitemporal hemianopsia	4	STR	none	
Zhi et al.	2009	46	F	headache, vertigo, impaired visual acuity	several	STR	none	
		45	F	impaired visual acuity	12	STR	none	
Brandao et al.	2010	17	M	headache, bitemporal hemianopsia	n/a	STR	none	
Furtado et al.	2010	23	F	headache, visual disturbance, 3rd nerve palsy, seizures	12	STR	none	
		45	F	headache, vertigo, tiredness	24	GTR	none	
Hammoud et al.	2010	71	M	bitemporal hemianopsia	n/a	n/a	n/a	
		69	F	hyponatremia	n/a	n/a	n/a	
		45	M	visual changes	n/a	n/a	n/a	
		67	F		n/a	n/a	n/a	
		52	M	hypopituitarism, visual disturbances	n/a	n/a	n/a	
		47	F	seizure, elevated prolactin	n/a	n/a	n/a	
		39	M	incidental	n/a	n/a	n/a	
Phillips et al.	2010	48	F	weight loss, fatigue	several	STR	none	
		54	M	panhypopituitarism, diabetes insipidus	120	STR	none	12/repeat resection

Author (Year)	Year	Age (yrs)	Sex	Presenting Symptoms	Duration of Symptoms (mo)	Extent of Surgical Resection	Adjuvant Therapy	Time to Recurrence (mo)/ Treatment
Grote et al.	2010	45	M	incidental, headaches, decreased libido	6	STR	none	
Schmalisch et al.	2010	48	M	Cushing syndrome, secondary hypogonadism	48	GTR	none	
Chu et al.	2011	45	F	bitemporal hemianopsia headaches, diabetes insipidus	12	GTR	none	
Prayesh	2011	51	F	headaches, bitemporal	n/a	STR	none	
Islamian et al.				superior quadrantanopia				
Zunarelli et al.	2011	63	M	hypopituitarism	3	GTR	RT to residual tumor after STR of recurrence	31/STR then RT
Ellis et al. (Present Case)	2011	42	M	decreased libido and sexual dysfunction	12	GTR	none	

Gy- gray; STR- subtotal resection; GTR- gross total resection; n/a- not available; RT- radiotherapy; chemo- chemotherapy

Table 2

Immunohistochemical Profile of Reported Pituicytomas

Ki67 index (range)	Vimentin	S100	EMA	GFAP	PAS	TTF1	BCL2	Synaptophysin	Neuro-filament	Chromogranin A	Anterior pituitary hormones	Cytokeratin
Typical 0–5% ; Atypical 5–12%	27/28	45/46	9/35	38/45	0/8	8/8	10/11	1/28	1/24	0/14	0/13	1/10