Intrasellar chordomas mimicking pituitary adenoma

Report of three cases

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Whereas chordomas involving the sellar region are uncommon, largely or entirely intrasellar chordomas are rare. The authors report three cases in which the chordomas filled the pituitary fossa and presented as nonfunctioning pituitary adenomas. All lesions exhibited the typical histological patterns and immunophenotype of chordoma. One tumor, studied ultrastructurally and subjected to DNA analysis, was shown to have a diploid histogram. The authors present a clinicopathological study of these three cases and review the literature on intrasellar chordomas.

KEY WORDS • chordoma • electron microscopy • DNA ploidy • immunohistochemistry • pituitary • sella turcica

Chordomas are rare, slow-growing malignant tumors of the midline, representing approximately 1% of all malignant tumors of the bone and 0.1 to 0.2% of intracranial neoplasms.^{10,20} They are thought to arise from cell rests, particularly of the proximal and distal extremes of the notochord. Approximately 50% develop in the sacrococcygeal region, 35% in the sphenoccipital region, and 15% in vertebrae.⁴⁸ Most chordomas involving the sellar region are parasellar or suprasellar, and largely or entirely intrasellar lesions are very rare.^{31,38} In terms of their characteristics demonstrated on neuroimaging studies and their clinical presentation, intrasellar chordomas may mimic pituitary adenomas.⁴³

In this report we describe the clinical and operative features of three examples of intrasellar chordomas mimicking nonfunctioning pituitary adenoma. All lesions were subjected to immunocytochemistry and one to electron microscopy and DNA image analysis.

MORPHOLOGICAL METHODS

For light microscopic examination, 4 to 6- μ m formalin-fixed, paraffin-embedded tissue samples were stained

with hematoxylin and eosin and by the periodic acid-Schiff method. For immunocytochemical analysis, the avidin-biotin-peroxidase complex technique was used. Primary antisera were directed against EMA, S-100 protein α 1-FP CEA, NSE, vimentin, pan-keratin cocktail, HMW cytokeratins 1, 5, 10, and 14, cytokeratins 5 and 8, and LMW cytokeratins 8, 18, and 19. Sections were incubated overnight with primary antibodies at 4°C. Before the application of cytokeratin antibodies, sections were treated with 0.25% pronase at 37°C for 10 minutes. For examination by electron microscopy, 1-mm tissue fragments were fixed in 2.5% glutaraldehyde, postfixed in osmium tetroxide, routinely processed, and embedded in a Epon-Araldite mixture. Ultrathin sections stained with uranyl acetate and lead citrate were studied using an electron microscope. To determine DNA content, fresh touch preparations fixed in 4% buffered formaldehyde were stained using the standard Feulgen method. A total of 512 nuclei were examined using the CAS 200 image analyzer.

CASE REPORTS

Case 1

This 61-year-old man presented with complaints of retroorbital headache, diplopia, and progressive loss of vision, which was more severe in the left eye, over the past 3 months. Visual field examination disclosed bitemporal hemianopsia. Radiography of the skull revealed enlarge-

Abbreviations used in this paper: CEA = carcinoembryonic antigen; CT = computerized tomography; EMA = epithelial membrane antigen; HMW = high-molecular weight; LMW = low-molecular weight; MR = magnetic resonance; NSE = neuron-specified enolase; α 1-FP = α 1-fetoprotein.

Fig. 1. Case 1. Sagittal (*left*) and coronal (*right*) MR images revealing a large, intrasellar tumor elevating and stretching the optic chiasm. Note infiltration of the left cavernous sinus and protrusion of tumor into the sphenoid sinus.

ment and distortion of the sella, with osteolysis of its floor and invasion of the sphenoid bone. A high-resolution CT scan revealed a large, partly calcified intrasellar tumor showing suprasellar extension and erosion of the sphenoid bone. An MR imaging study demonstrated that the lesion measured 3.6 cm in its greatest diameter and that it elevated and stretched the optic chiasm, infiltrated the left cavernous sinus, and protruded into the sphenoid sinus (Fig. 1). No endocrinopathy was noted, and serum pituitary hormone levels were normal. Initially, the lesion was considered to be a nonfunctioning pituitary adenoma (Grade IVB according to the Hardy classification¹⁶). During transsphenoidal surgery, intrasellar and suprasellar portions of the tumor were resected, the optic chiasm was decompressed, and the intracavernous part of the lesion was subtotally removed. A small portion of the tumor remained attached to the left carotid artery. The patient underwent conventional fractionated radiotherapy, receiving a total dose of 6000 cGy. At 4-year follow-up examination he was asymptomatic.

Pathological Findings. The multiple tan-to-red tumor fragments were composed of large epithelioid and physaliphorous cells arranged in lobules and embedded in a mucoid stroma. The nuclei were round and uniform with

Fig. 2. Case 1. Photomicrograph demonstrating the typical histological appearance of one physaliphorous cell-rich chordoma composed of lobular cell clusters embedded in a mucoid stroma. The tumor invades the submucosa of sphenoid sinus. H & E, original magnification $\times 160$.

no mitotic figures (Fig. 2). Examination of the specimen by using the period-acid-Schiff method demonstrated abundant cytoplasmic glycogen. Fragments of adenohypophyseal parenchyma adjacent to chordoma elements appeared to be histologically normal. Immunocytochemical analysis of the chordoma cells showed focal positivity for EMA, S-100 protein, $\alpha 1$ -FP, and vimentin. In addition, the cells were immunoreactive for pan-keratin but negative for the HMW keratins 1, 5, 10, and 14 (Fig. 3). Scant immunoreactivity for CEA was also noted, whereas NSE stains were negative. Ultrastructurally, the tumor was composed of large cells containing irregular nuclei with multiple indentations and prominent nucleoli. The latter scattered profiles of rough endoplasmic reticulum, occasional mitochondria, beta particles of glycogen intermediate filaments, and vacuoles. Cytoplasmic vacuoles were smaller than those in the intercellular matrix. Analysis of DNA revealed a diploid histogram.

Case 2

This 80-year-old woman presented with a 1-month history of right ptosis, which had been followed within days by the occurrence of ipsilateral orbital pain. Her medical history was noncontributory. A CT scan revealed a contrast-enhancing intrasellar mass that was eroding the sell-

Fig. 3. Case 1. Photomicrographs of physaliphorous cell-rich chordoma showing strong, diffuse cytoplasmic reactivity for cytokeratins (*upper*) and characteristic membranous staining for EMA (*lower*). Avid-biotin-peroxide complex, original magnification $\times 160$.

Fig. 4. Case 2. Magnetic resonance imaging studies. Sagittal (A) and coronal (B and C) MR images revealing a large mass occupying the pituitary fossa, elevating the pituitary gland and optic chiasm, and invading the right cavernous sinus. D: Horizontal MR image demonstrating invasion of the right cavernous sinus and the sphenoid sinus, with protrusion into the sphenoid sinus cavity.

ar floor and a small portion of the clivus. In addition, MR imaging demonstrated that the mass measured 2.5 cm in diameter and that it occupied the pituitary fossa, invaded the right cavernous sinus, and protruded into the sphenoid sinus (Fig. 4). Its upward growth elevated the pituitary gland and the optic chiasm. Moderate tumoral contrast enhancement was noted, mainly at its periphery. Despite a slightly elevated basal prolactin level (36 ng/ml; normal range 5–20 ng/ml) the endocrinological assessment demonstrated normal findings. On opening the dura at transsphenoidal surgery, the tumor was seen to protrude into the sphenoid sinus. The rather hard and moderately hemorrhagic tumor was partially removed.

Pathological Findings. Microscopically, the tumor was composed of lobules of large cells with uniform nuclei, mostly embedded in a chondroid stroma. Small numbers of vacuolated (physaliphorous) cells were arranged in a syncytial manner (Fig. 5). In addition, lobules of tumor cells were occasionally separated by bundles of fibrous tissue. The tumor cells contained abundant glycogen. Immunostains were positive for EMA, S-100 protein, vimentin, and for cytokeratins 5, 8, 18, and 19. The CEA preparations showed only mild focal immunoreactivity.

Case 3

A 63-year-old woman was referred to the Mayo Clinic for resection of an incidentally discovered sellar mass. While undergoing chemotherapy for local recurrence of a previously resected ovarian carcinoma, she was noted to have developed a right scotoma. Ophthalmological evaluation demonstrated a right-sided pupillary defect, and visual field examination revealed an ipsilateral asymmetric bitemporal hemianopsia. On subsequent radiological evaluation, a large asymmetric intrasellar mass was seen to be eroding the right anterior clinoid artery. A CT scan revealed suprasellar extension on the right side. The sellar floor and clivus appeared normal. Basal serum prolactin levels were elevated at 97.5 ng/ml, whereas follicle-stimulating hormone and luteinizing hormone levels were low at 15.2 mIU/ml and 3.3 mIU/ml, respectively (normal range 20–138 mIU/ml and 15–62 mIU/ml, respectively). Both clinical and neuroimaging findings suggested a non-secreting pituitary adenoma with chiasmal compression (Hardy Grade IIIB).¹⁶ During transsphenoidal surgery, the sphenoid bone was destroyed, the sinus itself being filled

with a multinodular tumor of rubbery consistency. The lesion had greatly expanded the dura. The entire tumor, both intrasellar and intracranial, was removed. The post-operative course was uneventful, with significant improvement of right-sided vision. Four months later, the patient died of the underlining ovarian cancer. No autopsy was performed.

Pathological Findings. On light microscopic examination, the tumor was shown to be composed primarily of physaliphorous cells forming sheets that were separated by broad fibrous bands. Focal hemorrhage and hemosiderin deposits were observed (Fig. 6). One tissue fragment showed bone invasion.

Sources of Supplies and Equipment

The Elite Vectastain kit (Vector Laboratories Inc., Burlingame, CA) was used in the cytochemical analysis. We obtained the following supplies from Dako A/S (Copenhagen, Denmark): monoclonal (1:1000) EMA, polyclonal (1:1000) S-100 protein, polyclonal (1:2000) α 1-FP, polyclonal (1:1000) CEA, and monoclonal (1:1000) NSE. The monoclonal (1:1500) vimentin is manufactured by Sigma Chemical Co. (St. Louis, MO). We acquired the pan-keratin cocktail CK22 from Biomedica (Foster City, CA). The HMW cytokeratins 1, 5, 10, and 14 (monoclonal, clone 34 β 12, prediluted) were purchased from Enzo

Fig. 5. Case 2. Photomicrograph demonstrating the typical histological appearance of chordoid chordoma composed of lobules of large cells with uniform nuclei, mostly embedded in chondroid stroma. H & E, original magnification $\times$ 400.

Fig. 6. Case 3. Photomicrograph depicting a physaliphorous cell-rich chordoma composed of large vacuolated cells forming sheets that are separated by broad fibrous bands. H & E, original magnification $\times 100$.

Diagnostics Inc. (Farmingdale, NY). The cytokeratins 5 and 8 (monoclonal, clone RCK102, prediluted) and the LMW cytokeratins 8, 18, and 19 (monoclonal, clone NC L5D3, prediluted) were acquired from Monosan (Uden, The Netherlands). Serve, Feinbiochemica (Heidelberg, Germany) manufactures the Epon and Araldite.

The image analyzer (CAS 200) is manufactured by CAS Inc. (Elmhurst, IL), and the electron microscope (JEM-100CX2) is produced by JEOL Ltd. (Tokyo, Japan).

DISCUSSION

The genesis of chordomas has been linked to notochordal rests, which found are embedded in the dorsum sellae in 4 to 5% of adult autopsies.⁵¹ Despite initial skepticism,³⁹ many researchers now believe that such rests appear to represent sites at which sellar chordomas develop. Similarities in immunohistochemical, ultrastructural, and in vitro features between chordoma and notochordal elements provide support for the notochordal theory.⁶ To date, only one case has been reported in which there was an entirely intrasellar chordoma unassociated with sphenoid bone involvement.³¹

The incidence of endocranial chordomas shows a slight male predilection (6:5),⁵⁰ whereas chordomas occurring at other sites exhibit a 2:1 male/female ratio.¹⁹ The incidence of skull base chordomas is also higher in younger-age patients, often appearing in the second to fifth decades.^{17,19,20} Based on anatomical location and clinical features,¹⁴ chordomas of the skull base can be classified into three categories: 1) sellar chordomas associated with chiasmal compression and hypopituitarism; 2) parasellar tumors characterized by oculomotor nerve palsy, optic tract compression, and hypopituitarism; and 3) tumors involving the clival region and presenting with bilateral sixth cranial nerve paresis and brainstem compression. Accordingly, our three cases are classified as having chordoma defined in the first classification.

As previously stated, chordomas involving the sellar region are uncommon. Including of our three cases, only 21 tumors with a primarily intrasellar component have

been reported since 1966 (Table 1).^{2,4,7,9,12,14,22,23,31,32,37,38,46,47} No sex predilection was noted, and patients' ages were within the expected range. Fifteen patients experienced visual deficits (71.4%). In nine cases (43%) a pituitary adenoma was suspected.

The neuroimaging features of Falconer Type 1 and 2 lesions,¹⁴ particularly when accompanied by endocrinological signs, can easily prompt an erroneous diagnosis of pituitary adenoma. Hyperprolactinemia and hypopituitarism commonly result from compression of the pituitary stalk ("stalk section effect") and of the pituitary.^{12,14,22,23,38} As a result, sellar chordomas may mimic prolactinomas or nonfunctioning pituitary adenomas.

Some authors advocate obtaining a preliminary transsphenoidal biopsy sample to establish a histological diagnosis that aids in the design of surgical therapy.^{7,11} Dynamic MR imaging may also contribute to the differentiation of sellar chordoma from meningioma, schwannoma, and metastatic tumor.²¹ Magnetic resonance spectroscopy may provide additional information for the preoperative diagnosis of brain tumors. Based on differences in their metabolic profile, MR spectroscopy may differentiate pituitary adenomas from other sellar-region masses that originate outside the pituitary gland. With regard to sellar chordomas, however, it is of note that the technique failed to diagnose one recently reported patient with chondroid chordoma involving the sellar region and left jugular foramen.²⁴ In addition to pituitary adenoma,²² craniopharyngioma,²³ and a small number of rare tumors affecting the sellar region,⁴² the differential diagnosis of chordoma also includes cartilaginous tumors of the skull base.³⁴ These include primarily chondrosarcoma and cartilage-containing chordomas ("chondroid chordoma"). The latter, long considered a special prognostically favorable variant of chordoma,¹⁷ was the subject of a recent clinicopathological study,³⁴ in which the authors found no inherent difference in the survival of such chordomas as compared with conventional chordoma and chondrosarcoma. Instead, the more favorable prognosis in patients with chondroid chordoma was attributed to their occurrence in younger patients.

Evident in the immunoprofile of chordoma cells is reactivity for LMW cytokeratins 7, 8, 18, and 19 (simple epithelium), as well as HMW 4, 5, and 6 (mucosal epithelia),^{18,34,40} vimentin and EMA.^{1,5,8,32,33} The results of our immunocytochemical analyses are in accordance with these findings. In both Cases 1 and 2 EMA and vimentin were expressed. Examination demonstrated immunopositivity for a panepithelial cytokeratin cocktail in Case 1 and positivity for both LMW and HMW cytokeratins in Case 2. Approximately 50% of chordomas are S-100-protein immunoreactive.³⁴ Inconsistent staining results for CEA have also been reported.^{5,32,33,40} Immunostaining for NSE and α 1-FP yield positive results in the majority of tumors.^{1,5,8,32,34} Focal immunopositivity for S-100 and CEA was apparent in our two cases tested (Cases 1 and 2). In addition to immunocytochemistry, electron microscopy has significantly contributed to the characterization of chordomas.^{6,20,34}

Although total resection of chordomas is the theoretical goal, as in cases of extraosseous chordoma,³¹ this is only infrequently achieved. Adjuvant radiotherapy has been recommended to prolong the disease-free survival, but its

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TABLE 1
Cases of chordomas of the sellar region obtained from review of the literature & present report

Case No	Authors & Year	Age (yrs), Sex	Symptom Duration (mos)	Clinical Findings	Sellar Relation	Endocrine Signs & Possible Diagnosis	No. of Ops	Radiation Dose (cGy)	Survival (mos)
1	Belza, 1966	53, M	UN	incomplete lt IIIrd CN palsy	intra-	UN	2	6000	20
2	Falconer, et al., 1968	51, M	60	chiasmal compression, rhinorrhea, meningitis	intra-, supra-, & infra-	hypopituitarism	3	UN	48
3		42, F	72	headaches, temporal hemianopsia	intra-, supra-, & para-	amenorrhea	1	5000	50
4		47, M	4	optic track compression, unilat IIIrd CN palsy	intra-, supra-, & para-	pituitary adenoma	2	3500	36
5	Steimlé, et al., 1969	52, F	180	migranous headaches	intra-	amenorrhea 13 yrs ago		NO	>18
6	Chaddock, 1973	63, F	UN	signs from lt II, III, IV, V, and VI CNs	intra-, supra-, & infra-	pituitary adenoma	UN	UN	96
7	Mathews & Wilson, 1974	41, M	24	rt visual impairment, bitemporal hemianopsia	intra- & supra-	hypothyroidism, acromegaly	2	UN	UN
8	de Cremoux, et al., 1980	66, M	1/2	disorientation, mental defects	intra-, supra-, & para-	UN	1	6000	UN
9		39, F	7		intra-, supra-, & para-	amenorrhea, galactorrhea, prolactinoma	1	UN	UN
10	Pluot, et al., 1980	48, M	17	lt visual impairment, exophthalmos	intra- & supra-	UN	1	6100	>84
11		53, F	60	diplopia, lt visual impairment	intra- & para-	UN	1	5000	>11
12	Tan, et al., 1982	26, M	8	lt eye pain, lt temporal blindness	intra- & supra-	pituitary adenoma or craniopharyngioma	1	NO	UN
13	Elias & Pavers, 1985	34, M	6	diplopia	intra- & para-	increased prolactin	1	UN	UN
14	Raffel, et al., 1985	42, M	27	headaches, visual loss	intra-	UN	1	6000	>14
15	Arnold & Hermann, 1986	37, F	3	lt blindness	intra-, supra-, & para-	UN	2	UN	>54
16	Kagawa, et al., 1993	67, F	UN	visual impairment	intra- & supra-	hypopituitarism	2	UN	>120
17	Pinzer, et al., 1993	58, F	12	decreased visual acuity (lt eye) congenital blindness (rt eye)	intra-, supra-, & para-	craniopharyngioma or pituitary adenoma	2	UN	>24
18	Kikuchi & Watanabe, 1994	56, M	3	bilateral visual impairment	intra- & supra-	increased prolactin, craniopharyngioma	1	UN	UN
19	present cases	61, M	3	diplopia, bilateral visual impairment, headaches	intra-, supra-, & para-	nonfunctioning pituitary adenoma	1	6000	>48
20		80, F	1	rt upper lid ptosis	intra- & para-	nonfunctioning pituitary adenoma	1	UN	>15
21		63, F	UN	rt eye scotoma	intra-, supra-, & para-	increased prolactin, nonfunctioning pituitary adenoma	1	NO	UN

* CN = cranial nerve; NO = no radiation; UN = unknown.

effect on prolonging overall survival has not been established.¹⁵ Transsphenoidal surgery followed by radiotherapy is the generally accepted therapy.^{2,15,17,41} The develop-

ment of a postirradiation sarcoma is a rare but serious complication²⁰ that should be distinguished from sarcomatous transformation of chordoma.⁴⁹

In terms of the surgery, the goal of initial management of sellar chordomas is a gross-total resection.^{26,29} Because of the distinct tendency of chordomas to invade surrounding bone, it is true that total removal is generally not possible. Specifically when extensive skull base procedures and large scale resections are performed, minute residua that have permeated bone are often left behind at the resection margins. In addition, chordomas also have the ability to invade and perforate nearby dura. A variety of strategies have been developed to achieve maximum tumor removal, including bifrontal, transsphenoidal, transpalatal, and transmandibular approaches.^{27,30} In most cases, a transsphenoidal approach permits very satisfactory resection of chordomas primarily involving the sella, and it offers the surgeon an opportunity to decompress the suprasellar compartment and optic chiasm, as well as cavernous sinus in which nerves subserving ocular movement may be affected. The transsphenoidal approach also permits one to treat midline tumor involvement of the clivus and of the clival dura. However, the surgeon should consider the limitations of the transsphenoidal approach, particularly when manipulating very hard tumors.

Because the majority of chordoma resections are, by nature incomplete, adjunctive therapy is usually recommended. In our review of pediatric chordomas, it was interesting to note that all long-term survivors had undergone radiotherapy.⁵² Conventional fractionated radiotherapy has been the most commonly used; however, stereotactically delivered "radiosurgery," either linear accelerator or gamma knife, has recently become vogue.^{3,13,25,35} In the future, these modalities may play a significant role in the treatment of patients with chordomas; at present, it is too early to assess their efficacy. The Harvard group, which administered fractionated stereotactic proton-beam radiosurgery, has treated a large number of patients harboring chordomas and chondrochordomas of the skull base,²⁸ and their results have been outstanding. Their technique clearly permits the delivery of an effective radiation dose while protecting vital structures. Once a chordoma has been successfully resected, one ordinarily recommends annual follow up in which the patient undergoes high-quality imaging studies to assess for tumor recurrence.

The malignant behavior of skull base chordomas is primarily a function of their location, tendency to osseous permeation, and high rate of recurrence, and not their capacity for metastasis.^{17,38} The metastatic potential of chordomas cannot be estimated by histological examination, except in cases in which the lesion exhibits a high-grade, spindle cell sarcomatous component.^{19,49} In recent clinicopathological studies the authors have claimed that longer survival times are demonstrated in patients younger than 40 years of age^{15,34} as well as in those presenting with diplopia.¹⁵ The overall survival rate in the study conducted by Forsyth, et al.,¹⁵ was estimated to be 51% and 35% at 10 years and 20 years, respectively. With regard to DNA analysis of chordomas, analysis of recent findings has shown a statistical trend in the relationship of diploidy and a favorable prognosis.^{44,45} The long recurrence-free period observed in one patient (Case 19, Table 1) in our series may be related to the diploid DNA histogram of the tumor.

In summary, sellar chordomas are rare. Their occasional favorable prognosis no doubt relates to the limited

extent of disease and the aggressiveness of the surgical resection. The effect of radiation therapy on disease-free and overall survival rates remains unsettled.

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Manuscript received October 14, 1999.

Accepted in final form January 5, 2000.

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