Intrasellar chordomas mimicking pituitary adenoma

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Object. Whereas chordomas involving the sellar region are uncommon, largely or entirely intrasellar examples are rare. The goal in this study was to present examples of these rare tumors as a guide to their proper diagnosis and treatment.

Methods. 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.

Conclusions. Although these tumors are easily misdiagnosed and therefore may not receive optimal treatment, aggressive surgical resection can yield a favorable prognosis in lesions with a limited extent.

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. 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. Most chordomas involving the sellar region are parasellar or suprasellar, and largely or entirely intrasellar lesions are very rare. In terms of their imaging characteristics and clinical presentation, intrasellar chordomas may mimic pituitary adenomas.

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–μm sections of 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; α1-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 osium tetroxide, routinely processed, and embedded in an 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 3 months. Visual field examination disclosed bitemporal hemianopsia. Radiography of the skull revealed enlargement and distortion of the sella, with osteolysis of its floor.
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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 the 4-year follow-up 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 no mitotic figures (Fig. 2). Examination of the specimen by using the periodic-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, α1-FP, and vimentin. In addition, the cells were immunoreactive for pan-keratin but negative for immunoreactivity for the HMW keratins 1, 5, 10, and 14 (Fig. 3). Scant immunoreactivity for CEA was also noted, whereas NSE stains were negative for immunoreactivity. Ultrastructurally, the tumor was composed of large cells containing irregular nuclei with multiple indentations and prominent nucleoli. The cytoplasm contained 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 was admitted with a 1-month history of right ptosis, which had been followed within days by ipsilateral orbital pain. Her medical history was noncontributory. A CT scan revealed a contrast-enhancing intrasellar mass that was eroding the sellar 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 (Figs. 4 and 5). 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 endocrine 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. 6). 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**

This 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). 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 postoperative course was uneventful, with significant improvement of right-sided vision. Four months later, the patient died of the underlying 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. 7). 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) α1 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 Biomeda (Foster City, CA). The HMW cytokeratins 1, 3, 10, and 14 (monoclonal, clone 34β12, prediluted) were purchased from Enzo Diagnostics, Inc. (Farmingdale, NY). The cytokeratins 5 and 8 (monoclonal, clone RCK102, prediluted) and the LMW cytokeratins 8, 18, and 19 (monoclonal, clone NCL5D3, prediluted) were acquired from Monosan (Uden, The Netherlands). Serva Feinbiochemica (Heidelberg, Germany) manufactures the Epon–Araldite mixture. 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 are found embedded in the dorsum sellae in 4 to 5% of autopsies conducted in adults. Despite initial skepticism, 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 noto-

Fig. 3. Case 1. Photomicrographs of physaliphorous cell–rich chordoma showing strong, diffuse cytoplasmic reactivity for cytokeratins (right) and characteristic membranous staining for EMA (left). Avidin-biotin-peroxidase complex, original magnification × 160.

Fig. 4. Case 2. Magnetic resonance imaging studies. Sagittal (left) and coronal (center and right) MR images revealing a large mass occupying the pituitary fossa, elevating the pituitary gland and optic chiasm, and invading the right cavernous sinus.
chordal elements provide support for the notochordal theory. To date, only one case has been reported in which there was an entirely intrasellar chordoma unassociated with sphenoid bone involvement.

The incidence of endocranial chordomas shows a slight male predilection (6:5), whereas chordomas occurring at other sites exhibit a 2:1 male/female ratio. The incidence of skull base chordomas is also higher in younger patients, often appearing in the second to fifth decades of life. Based on anatomical location and clinical features, chordomas of the skull base can be classified into three categories: 1) sellar chordomas associated with chiasmatic 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 patients are classified as having chordoma defined in the first classification.

As previously stated, chordomas involving the sellar region are uncommon. Including our three cases, only 21 tumors with a primarily intrasellar component have been reported since 1966 (Table 1). No tumor predilection for either sex 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 presentation of Falconer Type 1 and 2 lesions, 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. 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. Dynamic MR imaging may also contribute to the differentiation of sellar chordoma from meningioma, schwannoma, and metastatic tumor. 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 chondroid chordoma involving the sellar region and left jugular foramen. In addition to pituitary adenoma, craniopharyngioma, and a small number of rare tumors affecting the sellar region, the differential diagnosis of chordoma also includes cartilaginous tumors of the skull base. These include primarily chondrosarcoma and cartilage-containing chordomas ("chondroid chordoma"). The latter, long considered a special prognostically favorable variant of chordoma, was the subject of a recent clinicopathological study, in which the authors found no inherent difference in the survival of patients with such chordomas compared with conventional chordoma and chondrosarcoma.
Instead, the more favorable prognosis in patients with chondroid chordoma was attributed to the tumors’ occurrence in younger patients.

Evident in the immunoprofile of chordoma cells is reactivity for LMW cytokeratins 7, 8, 18, and 19 (simple epithelia), as well as HMW 4, 5, and 6 (mucosal epithelia), vimentin, and EMA. 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 immunoposi-

### TABLE 1

Review of the literature on cases of chordomas of the sellar region*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Duration (mos)</th>
<th>Clinical Findings</th>
<th>Sellar Relation</th>
<th>Endocrine Signs &amp; Possible Diagnosis</th>
<th>No. of Ops</th>
<th>Radiation Dose (cGy)</th>
<th>Survival (mos)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Belza, 1966</td>
<td>53, M</td>
<td>UN</td>
<td>incomplete lt third CN palsy, chiasmal compression, rhinorrhea, meningitis, headaches, temporal hemianopsia, optic tract compression, unilat third CN palsy</td>
<td>intra-</td>
<td>UN</td>
<td>2</td>
<td>6000</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Falconer, et al., 1968</td>
<td>51, M</td>
<td>60</td>
<td>chiasmal compression, rhinorrhea, meningitis, headaches, temporal hemianopsia</td>
<td>intra-, supra-, &amp; para-</td>
<td>hypopituitarism</td>
<td>3</td>
<td>UN</td>
<td>48</td>
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<td>3</td>
<td>42, F</td>
<td>72</td>
<td>intra-, supra-, &amp; para-</td>
<td>amenorrhea</td>
<td>1</td>
<td>5000</td>
<td>50</td>
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<td></td>
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<td>4</td>
<td>47, M</td>
<td>4</td>
<td>intra-, supra- &amp; para-</td>
<td>pituitary adenoma</td>
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<td>3500</td>
<td>36</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>Steimlè, et al., 1969</td>
<td>52, F</td>
<td>180</td>
<td>migrainous headaches signs from lt CNs II–VI</td>
<td>intra-</td>
<td>amenorrhea</td>
<td>UN</td>
<td>NO</td>
<td>&gt;18</td>
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<td>6</td>
<td>Chadduck, 1973</td>
<td>63, F</td>
<td>UN</td>
<td>left visual impairment, exophthalmos, diplopia, lt temporal blindness</td>
<td>intra- &amp; para-</td>
<td>pituitary adenoma</td>
<td>UN</td>
<td>UN</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>Mathews &amp; Wilson, 1974</td>
<td>41, M</td>
<td>24</td>
<td>decreased visual acuity (lt eye)</td>
<td>intra- &amp; supra-</td>
<td>hypothyroidism, acromegaly</td>
<td>2</td>
<td>UN</td>
<td>UN</td>
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<tr>
<td>8</td>
<td>de Cremoux, et al., 1980</td>
<td>66, F</td>
<td>0.5</td>
<td>disorientation, mental defects</td>
<td>intra- &amp; supra- &amp; para-</td>
<td>amenorrhea, galactorrhea, prolactinoma</td>
<td>UN</td>
<td>1</td>
<td>6000</td>
</tr>
<tr>
<td>9</td>
<td>39, F</td>
<td>7</td>
<td>UN</td>
<td>UN</td>
<td>1</td>
<td>6000</td>
<td>UN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Phout, et al., 1980</td>
<td>48, M</td>
<td>17</td>
<td>left visual impairment, exophthalmos, left temporal blindness, diplopia, left visual impairment</td>
<td>intra- &amp; supra-</td>
<td>pituitary adenoma or craniopharyngioma</td>
<td>2</td>
<td>UN</td>
<td>&gt;84</td>
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<tr>
<td>11</td>
<td>53, F</td>
<td>60</td>
<td>intra- &amp; para-</td>
<td>pituitary adenoma</td>
<td>1</td>
<td>5000</td>
<td>&gt;11</td>
<td></td>
<td></td>
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<tr>
<td>12</td>
<td>Tan, et al., 1982</td>
<td>26, M</td>
<td>8</td>
<td>left eye pain, lt temporal blindness</td>
<td>intra- &amp; supra-</td>
<td>pituitary adenoma or craniopharyngioma</td>
<td>UN</td>
<td>1</td>
<td>NO</td>
</tr>
<tr>
<td>13</td>
<td>Elias &amp; Powers, 1985</td>
<td>34, M</td>
<td>6</td>
<td>bilateral visual impairment</td>
<td>intra- &amp; para-</td>
<td>increased prolactin</td>
<td>1</td>
<td>UN</td>
<td>UN</td>
</tr>
<tr>
<td>14</td>
<td>Raffel, et al., 1985</td>
<td>42, M</td>
<td>27</td>
<td>headaches, visual loss</td>
<td>intra-</td>
<td>UN</td>
<td>1</td>
<td>6000</td>
<td>&gt;14</td>
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<tr>
<td>15</td>
<td>Arnold &amp; Herrmann, 1986</td>
<td>37, F</td>
<td>3</td>
<td>lt blindness</td>
<td>intra-</td>
<td>UN</td>
<td>2</td>
<td>UN</td>
<td>&gt;54</td>
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<td>16</td>
<td>Kagawa, et al., 1993</td>
<td>67, F</td>
<td>UN</td>
<td>decreased visual acuity (lt eye)</td>
<td>intra- &amp; supra-</td>
<td>hypopituitarism</td>
<td>2</td>
<td>UN</td>
<td>&gt;120</td>
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<tr>
<td>17</td>
<td>Pinzer, et al., 1993</td>
<td>58, F</td>
<td>12</td>
<td>bilateral visual impairment</td>
<td>intra- &amp; supra- &amp; para-</td>
<td>craniopharyngioma or pituitary adenoma</td>
<td>2</td>
<td>UN</td>
<td>&gt;24</td>
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<tr>
<td>18</td>
<td>Kikuchi &amp; Watanabe, 1994</td>
<td>56, M</td>
<td>3</td>
<td>bilateral visual impairment</td>
<td>intra- &amp; supra- &amp; para-</td>
<td>increased prolactin, craniopharyngioma</td>
<td>1</td>
<td>UN</td>
<td>UN</td>
</tr>
<tr>
<td>19</td>
<td>present study</td>
<td>61, M</td>
<td>3</td>
<td>diplopia, bilateral visual impairment, headaches</td>
<td>intra- &amp; supra- &amp; para-</td>
<td>nonfunctioning pituitary adenoma</td>
<td>1</td>
<td>6000</td>
<td>&gt;48</td>
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<tr>
<td>20</td>
<td>80, F</td>
<td>1</td>
<td>intra- &amp; para-</td>
<td>nonfunctioning pituitary adenoma</td>
<td>1</td>
<td>UN</td>
<td>&gt;15</td>
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<tr>
<td>21</td>
<td>63, F</td>
<td>UN</td>
<td>intra- &amp; supra- &amp; para-</td>
<td>increased prolactin, nonfunctioning pituitary adenoma</td>
<td>1</td>
<td>NO</td>
<td>UN</td>
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</table>

* CN = cranial nerve; NO = no radiation; UN = unknown.
Intrasellar chordomas mimicking pituitary adenoma

Intracranial chordomas mimicking pituitary adenoma have also been reported. 5,32,33,41 Immunostaining for NSE

mas and chondrochordomas of the skull base,28 and their
tered fractionated stereotactic proton-beam radiosurgery,
the treatment of chordomas; at present, it is too early to
the future, these modalities may play a significant role in
or gamma knife, has recently come into vogue.3,13,25,35 In
py has been the most commonly used; however, stereo-

of sellar chordomas is a gross-total resection. 26,29 Because

Livingston,19–20 that should be distinguished from sarcoma-

tous transformation of chordoma. 49

Although total removal of chordomas is the theoretical
goal, as in cases of extraosseous chordoma,44 this is only
infrequently achieved. Adjuvant radiotherapy has been
recommended to prolong disease-free survival, but its
effect on prolonging overall survival has not been estab-
lished.15 Transsphenoidal surgery followed by radiother-
apy is the generally accepted treatment.2,15,17,39 The devel-


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Manuscript received July 29, 1999. Accepted in final form February 8, 2000.

An earlier version of this manuscript appeared in Neurosurg Focus 8(2):Clinical Pearl, 2000.

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