Atypical pituitary adenomas: incidence, clinical characteristics, and implications

Clinical article

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Object. The 2004 WHO classification of pituitary adenomas now includes an “atypical” variant, defined as follows: MIB-1 proliferative index greater than 3%, excessive p53 immunoreactivity, and increased mitotic activity. The authors review the incidence of this atypical histopathological subtype and its correlation with tumor subtype, invasion, and surgical features.

Methods. The records of 121 consecutive patients who underwent transsphenoidal surgery for pituitary adenomas during an 18-month period were retrospectively reviewed for evidence of atypical adenomas.

Results. Eighteen adenomas (15%) met the criteria for atypical lesions; 17 (94%) of the 18 were macroadenomas. On imaging, 15 (83%) demonstrated imaging evidence of surrounding invasion, compared with 45% of typical adenomas (p = 0.004). Atypical tumors occurred in 12 female (67%) and 6 male (33%) patients. Patient age ranged from 16 to 70 years (mean 48 years). Nine patients (50%) had hormonally active tumors, and 9 had nonfunctional lesions. Four (22%) of the 18 patients presented to us with recurrent tumors. Immunohistochemical analysis demonstrated the following tumor subtypes: GH-secreting adenoma with plurihormonal staining (5 patients [28%]); null-cell adenoma (5 patients [28%]); silent ACTH tumor (3 patients [17%]), ACTH-staining tumor with Cushing’s disease (2 patients [11%]), prolactinoma (2 patients [11%]), and silent FSH-staining tumor (1 patient [6%]). The MIB-1 labeling index ranged from 3% to 20% (mean 7%).

Conclusions. Atypical tumors were identified in 15% of resected pituitary adenomas, and they tended to be aggressive, invasive macroadenomas. More longitudinal follow-up is required to determine whether surgical outcomes, potential for recurrence, or metastasis of atypical adenomas vary significantly from their typical counterparts.

Key Words • pituitary adenoma • transsphenoidal • atypical • tumor biology • Ki 67 • MIB-1 • p53 • carcinoma

Over the past few decades, attempts have been made to develop markers that correlate with the behavior of pituitary adenomas to identify lesions with an increased potential for malignancy (metastasis), invasion, or recurrence following treatment. As a result, numerous molecular and immunohistochemical markers have been correlated to aggressive behavior in pituitary adenomas. In 2004, the WHO developed a new classification for atypical adenomas, based on tumor markers thought to correlate with more aggressive pituitary tumor biology, including pituitary carcinomas characterized by cerebrospinal and/or systemic metastasis. The new designation serves as an intermediary between typical pituitary adenomas and pituitary carcinomas (malignant), the latter of which are rarely encountered, comprising less than 1% of all primary pituitary tumors. According to the recent WHO classification, diagnostic criteria for an atypical adenoma include excessive p53 immunoreactivity, MIB-1 proliferative index greater than 3%, and increased mitotic activity. Questions regarding the legitimacy and utility of this new classification invoked some controversy following its initial description. Since that time, few studies have reported clinical experience with the new WHO classification of atypical pituitary adenomas, with regard to incidence, tumor subtype, and clinicopathological characteristics. In the current study, the institutional experience at the Brigham and Women’s Hospital following surgical treatment for 121 pituitary adenomas over an 18-month period was reviewed. The aim of this study was to characterize the clinical, neuroimaging, and histopathological features correlating with the WHO designation of atypical pituitary adenomas.
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Methods

Patient Population

A retrospective review of the Brigham and Women’s Hospital Pituitary Center database was performed to identify all patients who underwent transsphenoidal surgery performed by the senior author (E.R.L.) between April 2008 and October 2009. Approval for the study was granted by the Brigham and Women’s Hospital institutional review board. Of the 188 transsphenoidal cases performed for all sellar lesions during this time period, pathology was consistent with a pituitary adenoma in 121 patients. The pathology reports of all patients with pituitary adenomas were reviewed to identify cases meeting the criteria for atypical pituitary adenoma. The neuroimaging and clinical features of patients with atypical adenomas were subsequently reviewed to identify characteristics associated with this designation.

Imaging Analysis

Based on MR imaging, a macroadenoma was defined by a maximal tumor diameter of greater than or equal to 10 mm, whereas microadenomas were defined by a maximal tumor diameter of less than 10 mm. Cavernous sinus invasion was determined by extension beyond the line corresponding to the lateral tangents of the 2 components of the intracavernous ICA, as defined by Knosp et al.12 Suprasellar invasion was defined by clear tumor growth through the diaphragma sella or above the plane of the inferior optic chiasm. Finally, infrasellar invasion was determined by clear tumor growth into the sphenoid sinus or clivus.

Immunohistochemical Techniques

Immunohistochemical studies, reticulin, and H & E staining were performed on formalin-fixed, paraffin-embedded sections. Five-micron sections were deparaffinized, subjected to antigen retrieval, and incubated with individual antibodies raised against specific pituitary hormones or cellular proteins as follows: PRL (1:750, DAKO, Inc.), GH (1:250, Vector Laboratories, Inc.), alpha–subunit (1:50, Biogenex Laboratories, Inc.), TSH (1:500, DAKO, Inc.), LH (1:500, DAKO, Inc.), FSH (1:50, DAKO, Inc.), ACTH (1:4,000, DAKO, Inc.), and p53 (1:80, Immuno-tech S.A.). Following incubation with primary antibodies, slides were washed and detected using the DAKO EnVision system (DAKO, Inc.). The MIB-1 proliferation index is determined by anti–Ki 67 immunohistochemical analysis (MIB-1, 1:200; DAKO, Inc.) with subsequent manual counting of positive and negative nuclear fractions (> 300 nuclei counted). The MIB-1 immunohistochemical analysis is routinely performed in all pituitary adenoma specimens, whereas p53 immunohistochemical analysis is performed in selected lesions that have excessive MIB-1 immunoreactivity and mitotic features.

Definition of Atypical Pituitary Adenoma

The current International Classification of Diseases codes for pituitary tumors include the following: typical pituitary adenoma (8272/0), atypical pituitary adenoma (8272/1), and pituitary carcinoma (8272/3). As per the 2004 WHO classification of CNS tumors, diagnostic criteria for atypical adenoma include: excessive p53 immunoreactivity, elevated MIB-1 proliferative index (> 3%), increased mitotic activity, and atypical morphological features.1 All pathological specimens were reviewed by a staff neuropathologist to ensure that all WHO criteria were met prior to the designation of an atypical adenoma.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism (GraphPad Software, Inc.). A 2-tailed Fisher exact test was used to compare categorical data, whereas an unpaired t-test was used to compare subgroup means. Statistical significance was defined as a p value < 0.05.

Results

Clinical Characteristics

Of the 121 consecutive patients with pituitary adenomas who underwent transsphenoidal surgery over an 18-month period, 18 patients (15%) with atypical adenomas were identified (Table 1). The clinical and imaging characteristics of the 18 patients with atypical adenomas are presented in Table 2. Of these patients, there were 12 female (67%) and 6 male (33%) patients. The mean age was 48 years (range 16–70 years). Four (22%) of the 18 patients had undergone previous transsphenoidal surgery, compared with 19 (18%) of 103 patients with typical adenomas. Nine patients (50%) had hormonally active tumors (5 with acromegaly, 2 with Cushing’s disease, and 2 with prolactinomas), whereas the other 9 had nonfunctional lesions. Histopathological analysis demonstrated the following: GH-secreting adenoma with plurihormonal staining (5 patients [28%]); null-cell adenoma (5 patients [28%]); silent ACTH tumor (3 patients [17%]), ACTH-staining tumor associated with Cushing’s disease (2 patients [11%]), prolactinoma (2 patients [11%]), and silent FSH-staining tumor (1 patient [6%]). The incidence of tumor recurrence in the atypical group was 22%, compared with 18% in the typical adenoma group (difference not significant). The mean time interval until postsurgical recurrence was 4 years. One patient underwent previous Gamma Knife surgery and proton-beam radiotherapy for a recurrent tumor. One patient had a tumor that was resistant to medication (prolactinoma resistant to dopamine agonist therapy).

The only preoperative factor that correlated with atypical lesions was evidence of surrounding invasion on imaging studies (83% [atypical] vs 45% [typical]; p = 0.004, Fisher exact test). Analysis of patient age, sex, reoperation status, and tumor size (microadenoma vs macroadenoma) did not demonstrate significant differences between the atypical and typical tumor groups. However, patients with atypical tumors were more likely to have silent ACTH tumors (17% [atypical] vs 2% [typical], p = 0.02) and less likely to have gonadotropin-staining nonfunctional adenomas (6% [atypical] vs 28% [typical], p = 0.04), than patients with typical adenomas.
Imaging Characteristics of Atypical Adenomas

Of the 18 atypical tumors identified, 17 (94%) were macroadenomas. Fifteen (83%) of the 18 lesions were noted to be invasive on MR imaging, compared with 45% in the group of typical adenomas (p = 0.004). Ten lesions (56%) demonstrated infrasellar invasion with clival or sellar floor erosion, 9 (50%) had suprasellar invasion, and 6 (33%) invaded at least one cavernous sinus. In 5 patients (28%), invasion of all 3 regions was noted. Infrasellar extension was identified in all 5 patients with atypical GH-secreting adenomas (Fig. 1) and was noted to occur in the absence of suprasellar or cavernous sinus invasion in 4 (80%) of these patients. Of the 5 patients with atypical null-cell adenomas (Fig. 2), all had suprasellar and infrasellar extension, and 3 had cavernous sinus involvement. One patient had an atypical giant null-cell adenoma that invaded the right temporal lobe, sphenoid sinus, and bilateral cavernous sinuses. Of the 3 patients with atypical silent ACTH tumors (Fig. 3), all demonstrated suprasellar and infrasellar extension, and 2 tumors invaded the bilateral cavernous sinuses. Another patient, a 16-year-old boy with headaches, had a hemorrhagic and cystic-appearing PRL-secreting macroadenoma.

Histopathological Features

The mean MIB-1 labeling index of all atypical lesions was 7% (median 6%), and ranged from 3% to 20%. The MIB-1 labeling index ranged from 3% to 5% in 7 patients, 5% to 10% in 8 patients, 10% to 15% in 1 patient, and 15% to 20% in 2 patients. All lesions demonstrated positive p53 immunoreactivity and increased mitotic activity. Examples of the morphological and immunohistochemical findings of 4 patients are shown in Figs. 4–7. Figure 4 shows a typical prolactinoma characterized by densely cellular sheets of monomorphic adenoma cells with round-to-ovoid nuclei, prominent nucleoli, and moderate-to-abundant amounts of eosinophilic cytoplasm. A reticulin stain demonstrates effacement of the normal anterior pituitary acinar architecture. A prolactin immunostain shows a strong paranuclear (“Golgi pattern”) pattern of staining. Weak nuclear p53 is detected in rare cells and the MIB-1 proliferative index is low (<1%). Figure 5 demonstrates an atypical ACTH-producing adenoma composed of a monomorphous population of cells with ACTH immunoreactivity, scattered p53-positive cells, and an elevated MIB-1 proliferative index (7.2%). Figure 6 shows an atypical prolactin and GH-secreting adenoma with strong cytoplasmic immunoreactivity for HGH and prolactin, diffuse p53 positivity, and elevated MIB-1 proliferative index (7.5%). Figure 7 highlights an atypical silent-ACTH adenoma with marked nuclear pleomorphism, effacement of acinar architecture, ACTH immunoreactivity, diffuse p53 nuclear staining, and elevated MIB-1 proliferative index (7%).

Intraoperative Characteristics and Early Patient Outcomes

All patients underwent transsphenoidal tumor resection. Intraoperatively, 16 (89%) of the 18 tumors were noted to be locally invasive, with extension into a parasellar region or clear dural invasion. One patient with Cushing’s disease (Case 11) was noted to have significant local cavernous sinus dural invasion intraoperatively, de-
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TABLE 2: Clinical, imaging, operative, and pathological characteristics of 18 patients with atypical pituitary adenomas*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Clinical Presentation</th>
<th>Hormonal Function†</th>
<th>Previous Treatment(s)</th>
<th>Degree of Extension on Imaging</th>
<th>Pathology</th>
<th>MIB-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72, M</td>
<td>headache, fatigue,</td>
<td>hypothyroid, hypocortisol, hypogonadism, low IGF-I, hyperprolactinemia,</td>
<td>none</td>
<td>suprasellar, infrasellar, cavernous sinus</td>
<td>null-cell adenoma</td>
<td>4%</td>
</tr>
<tr>
<td>2</td>
<td>53, F</td>
<td>visual loss, fatigue,</td>
<td>hypothyroid, hypocortisol, low IGF-I, hyperprolactinemia, hypogonadism,</td>
<td>none</td>
<td>suprasellar, infrasellar, cavernous sinus</td>
<td>null-cell adenoma</td>
<td>4%</td>
</tr>
<tr>
<td>3</td>
<td>67, F</td>
<td>visual loss</td>
<td>hyperprolactinemia</td>
<td>none</td>
<td>suprasellar, infrasellar, cavernous sinus</td>
<td>null-cell adenoma</td>
<td>17.5%</td>
</tr>
<tr>
<td>4</td>
<td>49, F</td>
<td>visual loss, headache</td>
<td>low IGF-I, hypogonadism, hyperprolactinemia</td>
<td>none</td>
<td>suprasellar, infrasellar, cavernous sinus</td>
<td>null-cell adenoma</td>
<td>4%</td>
</tr>
<tr>
<td>5</td>
<td>69, F</td>
<td>visual loss</td>
<td>hypothyroid, hyperprolactinemia</td>
<td>none</td>
<td>suprasellar, infrasellar</td>
<td>null-cell adenoma</td>
<td>6.6%</td>
</tr>
<tr>
<td>6</td>
<td>36, F</td>
<td>history of ovarian hyperstimulation syndrome, hypopituitarism</td>
<td>hypothyroid, hypocortisol, hyperprolactinemia</td>
<td>op</td>
<td>suprasellar</td>
<td>FSH-positive adenoma</td>
<td>3%</td>
</tr>
<tr>
<td>7</td>
<td>53, F</td>
<td>previous Cushing's disease, recurrent tumor</td>
<td>low GH, IGF-I</td>
<td>op × 2, GKS, PBRT</td>
<td>infrasellar, cavernous sinus</td>
<td>silent ACTH</td>
<td>3.4%</td>
</tr>
<tr>
<td>8</td>
<td>57, F</td>
<td>early menopause, cognitive dysfunction</td>
<td>hyperprolactinemia</td>
<td>none</td>
<td>suprasellar, infrasellar, cavernous sinus</td>
<td>silent ACTH</td>
<td>7%</td>
</tr>
<tr>
<td>9</td>
<td>61, M</td>
<td>vertigo, visual loss, hypopituitarism</td>
<td>hypothyroid, hypocortisol, hypogonadism, low IGF-I, hyperprolactinemia</td>
<td>none</td>
<td>suprasellar</td>
<td>silent ACTH</td>
<td>7%</td>
</tr>
<tr>
<td>10</td>
<td>31, F</td>
<td>Cushing's disease, headache, amenorrhea</td>
<td>hypercortisolemia, hypogonadism</td>
<td>op</td>
<td>intrasellar</td>
<td>ACTH, pluri (GH, LH, &amp; PRL positivity)</td>
<td>7.2%</td>
</tr>
<tr>
<td>11</td>
<td>28, F</td>
<td>Cushing's disease</td>
<td>hypercortisolemia</td>
<td>none</td>
<td>intrasellar, microadenoma</td>
<td>ACTH</td>
<td>20%</td>
</tr>
<tr>
<td>12</td>
<td>42, F</td>
<td>acromegaly, visual loss</td>
<td>increased GH, IGF-I, hypogonadism</td>
<td>none</td>
<td>suprasellar, infrasellar</td>
<td>GH, pluri (PRL, FSH, &amp; LH positivity)</td>
<td>3.2%</td>
</tr>
<tr>
<td>13</td>
<td>32, M</td>
<td>acromegaly</td>
<td>increased GH, IGF-I, hypogonadism</td>
<td>none</td>
<td>infrasellar</td>
<td>GH, pluri (TSH, LH, FSH, &amp; ACTH positivity)</td>
<td>8%</td>
</tr>
<tr>
<td>14</td>
<td>51, F</td>
<td>acromegaly</td>
<td>increased GH, IGF-I, hypogonadism</td>
<td>none</td>
<td>infrasellar</td>
<td>GH, pluri (PRL, TSH, FSH, &amp; LH positivity)</td>
<td>3%</td>
</tr>
<tr>
<td>15</td>
<td>51, M</td>
<td>acromegaly</td>
<td>increased GH, IGF-I</td>
<td>none</td>
<td>infrasellar</td>
<td>GH w/ PRL positivity</td>
<td>5.3%</td>
</tr>
<tr>
<td>16</td>
<td>38, M</td>
<td>acromegaly</td>
<td>increased GH, IGF-I, hyperprolactinemia</td>
<td>none</td>
<td>infrasellar</td>
<td>GH w/ PRL positivity</td>
<td>7.5%</td>
</tr>
<tr>
<td>17</td>
<td>16, M</td>
<td>headache, fatigue</td>
<td>hypogonadism, low IGF-I, hyperprolactinemia</td>
<td>none</td>
<td>suprasellar</td>
<td>prolactinoma</td>
<td>5.5%</td>
</tr>
<tr>
<td>18</td>
<td>54, F</td>
<td>amenorrhea/galactorrhea</td>
<td>hyperprolactinemia, hypogonadism</td>
<td>op, cabergoline</td>
<td>suprasellar, infrasellar, cavernous sinus</td>
<td>prolactinoma</td>
<td>10.6%</td>
</tr>
</tbody>
</table>

* GKS = Gamma Knife surgery; IGF-I = insulin-like growth factor–I; PBRT = proton-beam radiotherapy; pluri = plurihormonal.
† Full dynamic testing of the GH axis was not performed.

spite having a microadenoma. Intraoperatively, a gross-total resection was thought to have been achieved in 13 patients (72%), whereas a subtotal resection was assumed in 5 patients (28%). Eleven of 18 patients had early postoperative imaging available for review with a median follow-up time of 3.5 months. Of the 11 patients with early follow-up imaging available, residual tumor was noted in 4 (36%). Postoperative imaging was available in 5 of 9 patients with nonfunctional adenomas; a gross-total resection was noted in 3 of 5 of these patients (60%). Post-
Operative hormonal data were available in 7 of 9 patients with hormonally active tumors, of which 4 (57%) had evidence of an early endocrinological remission.

Discussion

The aim of the current study was to identify the incidence as well as clinical, imaging, and histopathological characteristics of tumors satisfying the 2004 WHO criteria for atypical pituitary adenomas. The incidence of atypical adenomas in 121 patients undergoing transsphenoidal surgery for pituitary adenomas was 15%, with half demonstrating evidence of hormonally functional adenomas. Five patients had acromegaly, 2 had Cushing’s disease, and 2 had PRL-secreting adenomas. Ninety-four percent of patients had macroadenomas, with the majority demonstrating evidence of tumor invasion into surrounding structures. The most common atypical tumor subtypes were GH-secreting, null-cell, and silent ACTH adenomas, which together accounted for greater than 70% of atypical adenomas. Interestingly, all GH-secreting adenomas also demonstrated immunoreactivity for other cell lines, mostly PRL. Furthermore, the majority of nonfunctional tumors (8 of 9) were either null-cell or silent ACTH adenomas, with only one tumor expressing immunoreactivity for gonadotropin markers (silent FSH adenoma). The MIB-1 labeling index ranged from 3% to 20%, with a mean value of 7%.

In the past, pituitary tumors with atypical behavior have been referred to as invasive, aggressive, or prema-
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In a recent review of the role of the Ki 67 protein in defining the invasion of adenomas, Salehi et al. noted several variations in the definition of invasion among previous studies reviewed, ranging from assessment based on imaging studies, to histopathological evidence of dural invasion, to intraoperative observations. The authors further discussed the conflicting data reported in several studies analyzing Ki 67 and its relationship with invasion in pituitary adenomas, noting that variations in the definition of invasion and differing techniques in Ki 67 immunostaining are likely to in part account for the wide spectrum of observed results. In the current study, invasion was based on MR imaging features, and all tumors (typical and atypical adenomas) were subject to the same criteria. Furthermore, many clinical characteristics of patients with typical and atypical adenomas were similar to each other, including patient age, proportion of recurrent tumors undergoing reoperation, and overall proportion of functional versus nonfunctional tumors. Nevertheless, a clear difference in the proportion of invasive tumors was noted, with 83% of atypical tumors demonstrating invasion on MR imaging, compared with 45% in typical tumors (p = 0.004).

The patterns of extra- and intrasellar invasion of the atypical tumors in this series demonstrate the inherently invasive nature of these lesions. Patients with atypical GH-secreting adenomas had a predisposition for infrasellar extension, with 80% of these tumors demonstrating isolated infrasellar extension into the sellar floor and/or clivus, without evidence of suprasellar or cavernous sinus involvement. Atypical null-cell adenomas tended to be very large tumors with suprasellar and infrasellar extension in all cases, and cavernous sinus extension in 60% of these cases. The silent ACTH adenomas, which are known to be aggressive, invasive tumors, all had suprasellar and infrasellar extension, with 2 of 3 also involving the bilateral cavernous sinuses.

In 2007, Saeger et al. reported their series of 4122 cases from the German Pituitary Tumor Registry. In 2005, this registry reported 12 of 451 cases of atypical pituitary tumors for an overall incidence of 2.7%. As in our series, the most common tumor subtypes demonstrating atypical features in this study were GH-secreting adenomas, null-cell adenomas, and silent ACTH adenomas. However, in the current series, the incidence of atypical adenomas was noted to be several times higher (15% [atypical] vs 2.7% [typical]). One potential explanation for this is that the current series may contain some degree of selection bias and over-represent the true incidence of atypical tumors, because our institution is a tertiary referral center for challenging pituitary tumors. In a study by Scheithauer et al., which had available follow-up on 78 patients with adenomas, the criteria for atypical lesions were met in 6 cases (14.7%), of which 5 were recurrent tumors. Our study demonstrates a similar incidence of atypical lesions yet a lower rate of tumors undergoing reoperation within this group.

Fig. 3. Preoperative sagittal (upper) and coronal (lower) Gd-enhanced MR images obtained in the 3 patients with atypical silent ACTH adenomas.

Diagnostic criteria (2004 WHO classification) of atypical adenomas include elevated MIB-1 proliferative index (3%), excess p53 immunoreactivity, increased mitotic activity, and pleomorphism. Although each of these factors has been independently associated with more aggressive and invasive neoplastic lesions, the accuracy of these diagnostic features taken collectively has not been assessed to date, particularly in regard to the degree of surrounding invasion and tumor recurrence rates. The MIB-1 labeling index, which stains for the Ki 67 antigen, has been correlated with the velocity of tumor growth, tumor invasion, responsiveness to pharmacological treatment, and tumor remission, and tumor recur-
rence. On the other hand, several other studies did not demonstrate a correlation between positive MIB-1 immunoreactivity and recurrence or invasion. In 1996, Thapar et al. studied the Ki 67 labeling index in pituitary adenomas and carcinomas. The mean Ki 67 growth fraction in noninvasive adenomas, invasive adenomas, and carcinomas was 1.37%, 4.66%, and 11.91%, respectively. These authors suggested a labeling index of 3% as a useful marker of distinguishing invasive from noninvasive adenomas, and this threshold level has been carried over to the WHO criteria.

Expression of p53 has also been shown to correlate with the aggressiveness of pituitary adenomas and numerous other neoplastic lesions in selected studies. Another study by Thapar et al. analyzed p53 expression in pituitary adenomas and carcinomas, reporting the proportion of p53 expression in noninvasive adenomas, invasive adenomas, and carcinomas to be 0%, 15.2%, and 100%, respectively. As in the case with MIB-1, however, the evidence for p53 as a diagnostic marker in pituitary adenomas remains to be fully determined, as some studies did not demonstrate a correlation between p53 expression and pituitary adenoma aggressiveness or recurrence.

The goal of the current study was to assess the incidence rates, preoperative and intraoperative characteristics, and histological characteristics that correspond to the designation of atypical pituitary adenoma. To our knowledge, the current study makes up the first and largest series of atypical pituitary adenomas to date, and it provides some characterization regarding the common

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**Fig. 4.** Photomicrographs of a typical prolactinoma. Densely cellular sheets of monomorphic adenoma cells with round-to-ovoid nuclei, prominent nucleoli, and moderate-to-abundant amounts of eosinophilic cytoplasm are present (A and B). A reticulin stain demonstrates effacement of the normal anterior pituitary acinar architecture (C). A PRL immunostain (D) shows a strong paranuclear (“Golgi pattern”) pattern of staining. Weak nuclear p53 is detected in rare cells (E), and the MIB-1 proliferative index is low (<1%, F). H & E (A and B); original magnification × 20 (A); × 40 (B–F).

**Fig. 5.** Photomicrographs of an atypical ACTH-producing adenoma. The tumor is composed of a monomorphous population of cells (A) with ACTH immunoreactivity (B), scattered p53-positive cells (C), and an elevated MIB-1 proliferative index (7.2%, D). H & E (A); original magnification × 40.

**Fig. 6.** Photomicrographs of an atypical GH-PRL–positive adenoma. Image of a moderate-to-densely cellular adenoma composed of cells with large, occasionally pleomorphic nuclei, prominent nucleoli, and moderate amounts of pale eosinophilic cytoplasm. Scattered mitotic figures are seen (A and B). The adenoma demonstrates strong cytoplasmic immunoreactivity for HGH (C) and prolactin (D), diffuse p53-positivity (E), and elevated MIB-1 proliferative index (7.5%, F). H & E (A and B); original magnification × 20 (A); × 40 (B–F).
A

Fig. 7. Photomicrographs of an atypical silent ACTH adenoma. A smear preparation showing adenoma cells with marked nuclear pleomorphism and occasional multinucleated forms (A). A densely cellular adenoma composed of cells with large, markedly atypical nuclei, occasional prominent nucleoli, and scattered mitotic figures (B). The tumor demonstrates marked nuclear pleomorphism, effacement of acinar architecture (C), ACTH immunoreactivity (D), diffuse p53 nuclear staining (E), and elevated MIB-1 proliferative index (7%, F). H&E (A and B), reticulin (C); original magnification \( \times 40 \).

histological subtypes and degree of invasiveness associated with these tumors. Our study, however, does not provide the longitudinal outcome data that will eventually be required to assess the long-term predictive utility of this designation. To date, there has not been any definitive evidence that atypical pituitary adenomas have lower rates of surgical remission, are more likely to undergo malignant transformation, or demonstrate higher rates of recurrence. Whether a difference exists in the rates of long-term recurrence or metastatic potential (carcinomas) between typical and atypical adenomas remains to be determined.

Conclusions

Atypical tumors were identified in 15% of resected pituitary adenomas and tended to be aggressive, invasive macroadenomas. The majority of tumors were null-cell adenomas, GH adenomas, and silent ACTH adenomas. While these tumors do correlate with an increased degree of surrounding invasion over their typical adenoma counterparts, more longitudinal follow-up is required to determine whether surgical outcomes, potential for recurrence, or metastasis of atypical adenomas will vary.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Zada, Woodmansee, Laws. Acquisition of data: Zada, Ramktsoo, Amadio, Nose. Analysis and interpretation of data: all authors. Drafting the article: Zada, Woodmansee, Ramktsoo, Amadio, Laws. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Zada. Administrative/technical/material support: Nose. Study supervision: Laws.

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