Review Article

Pathology of invasive pituitary tumors with special reference to functional classification

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Pituitary adenomas may remain intrasellar or infiltrate dura and bone. Invasive adenomas are not considered to be malignant; in biological behavior they are between non-infiltrative adenomas and pituitary carcinomas. The latter are defined as tumors with subarachnoid, brain, or systemic metastasis. Invasion may be defined radiologically, operatively, or histologically. On the basis of operatively assessed tumor size and gross invasion of dura and bone as well as immunocytochemical and ultrastructural analysis of 365 pituitary adenomas, the following data were obtained. There were 23 growth hormone (GH)-cell adenomas: 14% microadenomas and 86% macroadenomas; their overall frequency of invasion was 50%. There were 24 prolactin (PRL)-cell adenomas: 33% microadenomas and 67% macroadenomas, with an overall frequency of invasion of 52%. Mixed GH-cell and PRL-cell adenomas were found in 35 cases; 26% were microadenomas and 74% were macroadenomas, and the overall frequency of invasion was 31%. Sixty patients had adrenocorticotropic hormone (ACTH)-cell adenomas (Cushing's disease): 87% microadenomas and 13% macroadenomas; the overall frequency of invasion was 25% (in 8% of microadenomas and 62% of macroadenomas). Twenty patients had ACTH-cell adenomas (Nelson's syndrome): 30% microadenomas and 70% macroadenomas; the overall frequency of invasion in these cases was 50% (in 17% of microadenomas and 64% of macroadenomas). Silent ACTH-cell adenomas, 100% macroadenomas, were found in 11 patients, with an 82% frequency of invasion. There were 32 follicle-stimulating and luteinizing hormone adenomas, all macroadenomas, with a frequency of invasion of 21%. Four patients had thyroid-stimulating hormone adenomas, all macroadenomas, with a 75% frequency of invasion. Null-cell adenomas were found in 93 cases: 2% microadenomas and 98% macroadenomas, with a frequency of invasion of 42%. There were 63 plurihormonal adenomas (GH, PRL, glycoprotein): 25% microadenomas and 75% macroadenomas, with a 50% overall frequency of invasion.

Based on this study, and on their usual frequency of occurrence, the estimated rate of gross invasion by pituitary adenomas of all types is approximately 35%. It is concluded that immunocytochemical and ultrastructural characteristics of pituitary adenomas reflect the tendency of these tumors to infiltrate and hence may be of prognostic significance.

Key Words • invasive adenoma • pituitary adenoma • Cushing's disease • acromegaly • prolactinoma
clinical significance. Invasive pituitary neoplasms have been the subject of numerous previous reports and have usually represented isolated cases or limited series. The references emphasize reports concerning the morphological aspects of pituitary adenomas with extrasellar spread. 7-9,11,12,14,15,18,24,25,27-31,33,35,37-45,50,54,56,59-64,66,67,69,70

Terminology and Classification

Pituitary Adenomas

Pituitary adenomas are the most common tumors of the sellar region and are histologically benign neo-
Invasive pituitary adenomas

### TABLE 1

**Classification and incidence of surgically removed pituitary adenomas**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH-cell adenoma</td>
<td>10</td>
</tr>
<tr>
<td>densely granulated</td>
<td>5</td>
</tr>
<tr>
<td>sparsely granulated</td>
<td>5</td>
</tr>
<tr>
<td>PRL-cell adenoma</td>
<td>29</td>
</tr>
<tr>
<td>densely granulated</td>
<td>1</td>
</tr>
<tr>
<td>sparsely granulated</td>
<td>28</td>
</tr>
<tr>
<td>mixed GH-cell/PRL-cell adenoma</td>
<td>5</td>
</tr>
<tr>
<td>acidophil stem-cell adenoma</td>
<td>3</td>
</tr>
<tr>
<td>mammosomatotroph-cell adenoma</td>
<td>1</td>
</tr>
<tr>
<td>ACTH-cell adenoma</td>
<td>14</td>
</tr>
<tr>
<td>endocrinologically active</td>
<td>11</td>
</tr>
<tr>
<td>endocrinologically silent</td>
<td>3</td>
</tr>
<tr>
<td>FSH/LH-cell adenoma</td>
<td>74</td>
</tr>
<tr>
<td>TSH-cell adenoma</td>
<td>1</td>
</tr>
<tr>
<td>null-cell adenoma</td>
<td>19</td>
</tr>
<tr>
<td>non-oncocytic</td>
<td>13</td>
</tr>
<tr>
<td>oncocytic</td>
<td>6</td>
</tr>
<tr>
<td>plurihormonal adenoma (largely GH/PRL/glycoprotein)</td>
<td>10</td>
</tr>
<tr>
<td>unclassified adenoma</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>100</td>
</tr>
</tbody>
</table>

* Based on a study of approximately 1500 adenomas classified according to the scheme of Kovacs and Horvath. Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone (folitropin); GH = growth hormone (somatotropin); LH = luteinizing hormone (lutropin); PRL = prolactin; TSH = thyroid-stimulating hormone (thyrotropin).

† Incidence in the Mayo Clinic experience approaches 15%.


tinct, adenomas are not truly encapsulated — they have a “pseudocapsule” consisting of compressed adenohypophyseal cells and the condensed reticulin fiber network of the adjacent nontumorous anterior lobe (Fig. 2). The interface with the surrounding dura is usually discrete (Fig. 3).

Pituitary adenomas can be classified in various ways. Early schemes were based on the staining affinity of tumor cells and categorized them into acidophilic, basophilic, and chromophobic adenomas. Although simple, this classification is of little value because it contributes nothing to our knowledge of the hormone content, cellular derivation, or structure-function relationships of the tumor. Recently, a new classification has been developed that separates adenomas on the basis of their immunocytological and ultrastructural features. This functional classification, which requires application of sophisticated methods including the immunoperoxidase technique and transmission electron microscopy, has led to substantial progress. In providing information regarding hormone content and cellular differentiation, this system permits correlations between morphology and endocrinological activity. Table 1 summarizes this new classification system and gives the frequencies of the adenoma types based on the combined surgical and pathological experience at St. Michael’s Hospital and the Mayo Clinic.

**Pituitary Carcinomas**

Representing the opposite end of the behavioral spectrum, pituitary carcinomas are the malignant counterparts of pituitary adenomas. Like the benign variants, they originate from and are composed of adenohypophyseal cells. The malignant nature of an adenohypophyseal tumor is not reliably indicated by its microscopic appearance; hence, distinction between carcinoma and adenoma is difficult or impossible on the basis of histological criteria alone. Hypercellularity, nuclear pleomorphism, occasional mitotic figures, necrosis, hemorrhage, and even invasion are not reliable indicators that a tumor is malignant (Fig. 4). In our view, a necessary criterion for the diagnosis is metastasis to remote areas of the cerebrospinal subarachnoid space, the brain parenchyma, or extraneural sites including lymph nodes, lungs, liver, or bone (Figs. 5 and 6). Application of such strict criteria necessarily means that pituitary carcinomas are rare.

Pituitary carcinomas characteristically grow rapidly and may invade surrounding tissues, including cranial
nerves and the brain. In addition, they may infiltrate the sphenoid bone and either spread into the cavernous sinus or protrude into the nasopharynx. Pituitary carcinomas may produce growth hormone (GH), prolactin (PRL), or adrenocorticotropic hormone (ACTH), with resultant endocrinological abnormalities and biochemical alterations. In contrast, some are silent: there is no clinical or biochemical evidence of increased hormone secretion.

Attempts should be made to determine the type of cell constituting the tumor by immunocytochemical or electron microscopic examination. In many instances, the immunoperoxidase technique demonstrates the presence of pituitary hormones and thereby indicates functional differentiation of the tumor, a potentially useful piece of information in guiding therapy. It also provides presumptive evidence of the origin of the tumor. In some cases of pituitary adenoma or carcinoma, the technique fails to provide positive or conclusive results. In such instances: 1) no hormone is present; 2) an abnormal hormone is produced but is not recognized by the antibody; 3) hormone is released without storage and thus is not demonstrable; or 4) technical errors in tissue fixation and processing have resulted in loss of antigenicity. Hence, a negative immunoreaction does not necessarily indicate lack of hormone production.

Electron microscopy may reveal subcellular features, thus confirming the adenohypophyseal origin of adenomas or carcinomas. Although in most instances fine-structure features are sufficiently characteristic to define the functional differentiation and presumed cytogenesis of a tumor, in some cases the tumor cells are poorly differentiated and ultrastructural studies are not contributory.

Invasive Pituitary Adenomas

Invasive pituitary adenomas are tumors of adenohypophyseal origin representing biologically intermediate forms between the sharply demarcated benign adenomas and the metastasizing pituitary carcinomas. Despite the fact that they infiltrate surrounding tissues, including dura, bone, venous structures, cranial nerves, and sinuses, invasive adenomas are classified as benign and behave as such. Invasion may take the form of individual cell infiltration or of tongue-like dissection between dural connective tissue planes (Fig. 7). Histologically, such tumors more often are cellular and pleomorphic and may show more abundant mitotic activity than noninvasive adenomas. Nonetheless, there are no major histological differences between benign and malignant pituitary neoplasms, and thus no conclusions regarding their biological behavior may be drawn on the basis of microscopy alone. The same limitation is applicable to microscopic or gross invasion, although rates of recurrence after therapy may be higher with invasive tumors compared to noninvasive adenomas.

Other Diagnostic Terms

Terms such as "malignant," "fetal," "embryonal," "precursor cell," "undifferentiated," "pleomorphic," "massive," "florid," "expanding," "extending adenoma," and "adenocarcinoma" serve no real purpose and should be discarded. The contradictory term "malignant adenoma" makes no sense; adenomas are either noninvasive or invasive benign tumors. Only if cerebrospinal or systemic metastasis has occurred should the designation "malignant" or "carcinoma" be applied.

Use of the terms "fetal," "embryonal," and "precursor cell" adenoma is not justified because it is not
known whether the tumors derive from fetal, embryonal, or precursor cells. The term "undifferentiated adenoma" likewise should be discarded in that, despite the lack of clinical function or immunoreactivity in many adenomas, ultrastructural studies uniformly demonstrate the presence of both organelles characteristic of cells engaged in hormone synthesis and secretory granules. The other terms mentioned above illustrate only one characteristic of the tumor and lend nothing to our understanding of it. The designation "adenocarcinoma" is misleading in that adenohypophyseal carcinomas most often show a diffuse or organoid growth pattern and do not form gland-like structures.

Microadenomas and Macroadenomas

Microadenomas are arbitrarily defined as adenohypophyseal tumors having a diameter of 10 mm or less; the diameter of macroadenomas exceeds 10 mm (Figs. 1 and 8). These designations are popular among endocrinologists, neurosurgeons, and neuroradiologists. Although conceptually and prognostically the distinction of small from large tumors is important, there are no appreciable differences in the histological appearance of microadenomas and macroadenomas. More importantly, a prediction cannot be made as to whether a given microadenoma will enlarge to be a macroadenoma or whether it will remain small.

From the standpoint of the clinical endocrinologist or neurosurgeon, the distinction of microadenomas from macroadenomas is important because the outcomes of surgical treatment are different, a long-lasting "cure" being more frequent in patients with microadenomas. Incomplete tumor removal and recurrence of clinical symptoms are more common in patients with large pituitary tumors. Because the size of the surgical specimen rarely approximates that of the tumor in situ, the pathologist cannot accurately assess the diameter of the tumor. Hence, from the standpoint of the pathologist, the distinction between microadenomas and macroadenomas is of little diagnostic significance. However, macroadenomas are more likely than microadenomas to be associated with dural invasion, and macroadenomas are generally associated with higher levels of hormone production in instances of hyperfunctioning pituitary adenomas.

Invasion

A large number of tumors in the region of the sella are capable of invasion and thus are part of the differential diagnosis of pituitary adenoma. Many of these tumors arise from nonadenohypophyseal cells (Table 2). Such processes may infiltrate the pituitary gland, destroy large portions of the sella, interfere with hypophyseal blood supply, and cause pituitary infarction as well as various degrees of hypopituitarism. The pathology of these tumors will not be discussed here.

Three main questions regarding invasive adenohypophyseal neoplasms require discussion: 1) What is the incidence of invasive tumors? 2) What are the usual pathways of invasion? and 3) What correlations exist between the pattern of invasion and the functional (hormonal) classification of various adenomas?

Incidence of Invasion

The estimated incidence of invasion by pituitary adenomas of all types varies considerably, ranging from
5% to 20%. The validity of these numbers remains uncertain in that the incidence of invasion cannot be evaluated reliably by histological methods alone. Invasiveness as defined by the pathologist is undoubtedly more frequent than is reported, primarily because it is easily overlooked unless numerous microsections including dura or bone are examined. Because histological confirmation of invasion is often missing, its presence is more consistently established by direct observation through the operating microscope during surgery or, less frequently, by sophisticated neuroradiological techniques. The tendency of various authors to use different terminology further adds to the confusion.

Large pituitary tumors are rarely encountered at autopsy, and only one series has been reported in which invasion has been systematically evaluated: the study by Selman, et al., of the incidence of surgically apparent invasion as well as microscopic invasion by 60 pituitary adenomas of all types (13 microadenomas, 16 macroadenomas, and 31 adenomas with suprasellar extension). A positive correlation was reported between tumor size and the frequency of microscopic dural invasion, the latter being present in 66% of microadenomas, 87% of intrasellar macroadenomas, and 94% of tumors with suprasellar extension. The significance of the microscopic demonstration of invasion remains to be seen; it was more than twice as common (85%) as surgically observed invasion of bone or dura (40%) in the cases studied.

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**FIG. 8.** Gross photograph of a macroadenoma (Ad) of the pituitary. Note total replacement of the adenohypophysis as well as encroachment upon the neurohypophysis (N).

**FIG. 9.** Pituitary adenoma with suprasellar extension (A) and posterior displacement and marked attenuation of the overlying optic chiasm (C).

**FIG. 10.** Left: Pituitary adenoma with marked suprasellar extension and deep indentation of the third ventricle by the tumor. Right: Invasive pituitary adenoma demonstrating growth on the brain surface and within the leptomeninges. Parenchymal invasion is uncommon and is more often observed in association with frank pituitary carcinoma.
Direction of Invasion

The direction of growth of pituitary adenomas may be upward, downward, or lateral. However, in view of decreased resistance across the roof of the sella, upward extension of the tumor is most frequent. The diaphragma sellae, the firm dural covering of the sella, is composed of connective tissue and forms a relative barrier against tumor expansion. Nonetheless, the sellar contents are incompletely separated from the suprasellar space because an opening is present in the diaphragm. The hypophyseal stalk, with its vascular channels and unmyelinated nerve fibers, enters the sella through this aperture. The size of the opening varies considerably; most frequently it is small. In some cases, however, it can be large, creating an easy path for bulging of the superior aspect of the tumor into the suprasellar areas. In a strict sense, this process represents extension rather than invasion. Nevertheless, it is of practical significance because a large tumor mass may project into the suprasellar space via an incompetent, relaxed, or stretched diaphragma sellae. In cases of true invasion, the tumor penetrates and destroys the covering diaphragm sellae, gains free access to the suprasellar space, and may infiltrate surrounding tissues. An expanded diaphragm may also be invaded by adenoma cells.

Upward-growing tumors may compress and damage the optic nerves and chiasm (Fig. 9) or the hypothalamus, and can deeply indent the floor of the third ventricle (Fig. 10 left). Parenchymal brain invasion is less common than leptomeningeal infiltration; brain displacement is the rule (Fig. 10 right). The resulting clinical symptoms include disturbances of vision or cranial nerve palsies, headache, nausea or dizziness due to increased intracranial pressure, loss of consciousness, epilepsy, hydrocephalus, and dysfunction of the hypothalamus along with resultant endocrine abnormalities.

Downward growth of an adenoma involves the sphenoid dura, bone, and sinus. The proliferating tumor causes an increase in intrasellar pressure, with resultant attenuation of the sellar floor (Fig. 11) and remodeling of bone over time to produce sellar enlargement. If the expanding tumor is not treated, the bordering bone may be extensively eroded (producing a “ghost” sella) or be completely resorbed, leaving a free path for the spread of tumor to the sphenoid sinus (Fig. 12). More aggressive adenomas directly penetrate the substance of the sphenoid bone; in advanced cases, the entire sphenoid sinus may be filled with tumor tissue (Fig. 13). With further growth, such neoplasms may extend into the nasopharynx or nasal cavity.

Lateral growth of an adenoma into the parasellar region is least common because the lateral boundaries of the sella, composed of bone and firm connective

TABLE 2

<table>
<thead>
<tr>
<th>Invasive tumors of the sellar region</th>
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<tbody>
<tr>
<td>chordoma</td>
</tr>
<tr>
<td>choristoma</td>
</tr>
<tr>
<td>craniopharyngioma</td>
</tr>
<tr>
<td>germ-cell tumors: germinoma, teratoma, etc.</td>
</tr>
<tr>
<td>glioma</td>
</tr>
<tr>
<td>hemopoietic neoplasms: leukemia, lymphoma, plasmacytoma</td>
</tr>
<tr>
<td>lymphoma</td>
</tr>
<tr>
<td>meningioma (meningothelial &amp; angioblastic variants)</td>
</tr>
<tr>
<td>metastatic neoplasms: carcinoma, melanoma, etc.</td>
</tr>
<tr>
<td>pituitary adenoma</td>
</tr>
<tr>
<td>pituitary carcinoma</td>
</tr>
<tr>
<td>carcinoma of the sphenoid sinus or nasopharynx</td>
</tr>
<tr>
<td>sarcomas of the skull base</td>
</tr>
</tbody>
</table>
tissue, provide a substantial barrier. Most often the cavernous sinus and its contents are simply indented and displaced laterally by the pituitary tumor. In some instances, however, adenomas invade the wall of the cavernous sinus and the sinus itself, compressing or infiltrating the cranial nerves within (Figs. 7 and 14). Mass effect on the adjacent temporal lobe may produce seizures.

Correlation Between Invasiveness and Adenoma Type

Only one morphological study dealing with the correlation between invasiveness and adenoma type has been published previously. Based on a study of 365 surgically removed pituitary adenomas treated in our laboratories between 1980 and 1985, we attempted to clarify the relationship among the clinical, radiological, and surgical frequencies of occurrence of invasion and the functional classification of pituitary adenomas. We investigated 284 tumors by immunocytological and, in many instances, by electron microscopic techniques as well as by conventional histological methods. Because the resected tumor specimens were obtained in fragments and adjacent nontumorous tissue and dura were not systematically available for histological examination, serial sections were not generally made and histopathological confirmation of invasion was lacking in the majority of cases.

Although the presence of invasion may sometimes be assumed on the grounds of clinical signs and symptoms and may be suggested by sophisticated neuroradiological techniques or direct surgical inspection, histological demonstration of invasion provides unequivocal evidence of tumor spread. The twofold greater frequency of infiltration that is observed by systematic histopathological evaluation is evident in the series of Selman, et al. This raises the question of which method of examination is more relevant clinically. We favor the concept that the operative or neuroradiological demonstration of invasion may be a more important factor affecting therapeutic decision-making than the isolated finding of microscopic dural infiltration. From our study of the Mayo Clinic experience, it appears that a correlation does exist between the frequency and nature of invasiveness and the functional adenoma type (Table 3).

GH-Cell Adenomas

Tumors that produce GH represent approximately 10% of the pituitary adenomas treated. Their clinicopathological characteristics are well known. Of 23 GH-cell adenomas recently encountered at the Mayo Clinic, 14% were microadenomas and 86% were macroadenomas. Invasion was noted only with macroadenomas, half being grossly infiltrative at operation.

Two types of GH-cell adenomas are recognized on the basis of light microscopic and ultrastructural characteristics: acidophilic (densely granulated) and chromophobic (sparsely granulated); they occur with about equal frequency. In a study of 95 GH-cell adenomas, Robert compared the behavior of densely and sparsely granulated tumors. All the latter were larger than microadenomas and were three times more likely to show invasive behavior than were densely granulated lesions. Of the densely granulated forms, nearly 40% were...
Invasive pituitary adenomas

TABLE 3

<table>
<thead>
<tr>
<th>Types of Pituitary Adenoma</th>
<th>Microadenoma</th>
<th>Macroadenoma</th>
<th>Overall Invasion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>% of Total Invasion</td>
<td>% of Total Invasion</td>
<td></td>
</tr>
<tr>
<td>GH-cell</td>
<td>23</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>PRL-cell</td>
<td>24</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>mixed GH-cell/PRL-cell</td>
<td>35</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>ACTH-cell (Cushing's syndrome)</td>
<td>60</td>
<td>87</td>
<td>8</td>
</tr>
<tr>
<td>ACTH-cell ( Nelson's syndrome)</td>
<td>20</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>silent ACTH-cell</td>
<td>11</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>FSH/LH-cell</td>
<td>32</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>TSH-cell*</td>
<td>4</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>null-cell</td>
<td>93</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>plurihormonal</td>
<td>63</td>
<td>25</td>
<td>31</td>
</tr>
</tbody>
</table>

* These cases were treated at the Mayo Clinic. GH = growth hormone; PRL = prolactin; ACTH = adrenocorticotropic hormone; FSH/LH = follicle-stimulating hormone/luteinizing hormone; TSH = thyroid-stimulating hormone; --- = no data available.
† Nonconsecutive cases; the number of tumors studied does not reflect their relative frequency.
‡ Note the small sample size.

Microadenomas and only 10% showed invasive activities, all local rather than diffuse. Adenomas containing both cell types seem to behave like sparsely granulated tumors. Similar observations were reported by Young, et al. Pituitary adenomas that produce only GH are less common than plurihormonal tumors, most of which also produce glycoprotein hormones and PRL (see below).

Prolactin-Cell Adenomas

Tumors that produce only PRL are common, and they occur in both sparsely and densely granulated forms. Densely granulated PRL-cell adenomas are rare, and their growth pattern has not been well explored. Sparsely granulated PRL-cell adenomas, the most common PRL-producing type, often show significant dural infiltration. The overall frequency of surgically observed invasion in the series of Selman, et al. included 24 PRL-cell adenomas, was 52%. In contrast, microscopic dural infiltration was noted in 91% (five of eight microadenomas and all 16 macroadenomas, including all tumors with suprasellar extension). Prolactin-cell adenomas exhibit considerable differences in clinical presentation depending on the sex of the patient. In women of reproductive age, the onset of amenorrhea and galactorrhea with associated infertility are obvious signs; hence, the diagnosis of a PRL-producing adenoma is established early in the course. Most such patients have a microadenoma confined to the sella. In men, however, the clinical endocrine symptoms, which include decreased libido and impotence, are not as conspicuous and initially may be disregarded by the patient. As a result, male patients frequently do not come to medical attention until their tumors are large and have spread beyond the confines of the sella. In the series of Selman, et al. which was composed in large part of PRL-cell adenomas (40%), tumors of all types occurred later among men (age range 40 to 69 years) than among women (age range 20 to 39 years). Tumors in men were also associated with microscopic dural invasion more often (91%) than tumors in women (62%).

Because there are no histological, immunocytochemical, or ultrastructural differences between PRL-cell adenomas of women and of men, the increased frequency of invasion in male patients is attributed to delayed diagnosis. It remains to be seen, however, whether this interpretation is valid. More work is required to exclude the possibility that the pace of tumor growth and tendency to invasiveness differ between the two sexes.

Although large, sparsely granulated PRL-cell adenomas can spread in any direction, their preferential path is infrasellar. They often invade the sphenoid bone and, on occasion, they may grow farther downward, to appear in the nasopharynx or nasal cavity as a circumscribed mass.

GH- and PRL-Producing Adenomas

Mixed GH-cell/PRL-cell adenomas, first described by Corenblum, et al. are associated with acromegaly or gigantism and, in some cases, with hyperprolactinemia. In the 35 examples in the Mayo Clinic experience, such tumors presented as microadenomas (26%) or macroadenomas (74%). A few spread into neighboring tissue, showing variably directed patterns of growth. We observed invasive features at surgery in 31%, all macroadenomas.

The acidophilic stem-cell adenoma, clinically characterized by Horvath, et al., is a monomorphous tumor ultrastructurally. The cells show features of GH and PRL cells. This rapidly growing neoplasm is associated with varying degrees of hyperprolactinemia and, rarely, acromegaly. Acidophilic stem-cell adenomas showed a very high frequency of invasion. In general, the pattern of growth is downward. Penetration into the sphenoid sinus is approximately twice as common as for invasive adenomas of all types in unselected surgical material.

Mammosomatotroph-cell adenoma, first described by Horvath, et al. is the least common form of GH-cell/PRL-cell adenoma. Such tumors are benign, stationary, or slow-growing. They are associated regularly with acromegaly and often with hyperprolactinemia. Confined to the sella turcica, this rare adenoma is usually sharply demarcated and shows little tendency to invade adjacent structures.

ACTH-Producing Adenomas

Especially when associated with Cushing's disease, ACTH-cell adenomas are small, well-demarcated, intra-
pituitary tumors. On occasion, such adenomas may become large and invasive. The ratio of microadenomas to macroadenomas in the 60 examples at the Mayo Clinic was 8:1. Gross features of invasion were noted in 8% of the microadenomas and in 62% of the macroadenomas. The basophilic type usually remains small; the chromophobic, sparsely granulated variant more often demonstrates aggressive behavior and infiltration of neighboring structures. Adenomas producing ACTH tend to grow upward. Such tumors may show perineural infiltration when they invade the cavernous sinus.

Nelson's syndrome represented approximately 25% of functional ACTH-secreting adenomas in the Mayo Clinic experience. In the 20 examples studied, the mean duration from adrenalectomy to hypophysectomy was approximately 10 years (range 6 to 18 years). The ratio of microadenomas to macroadenomas was 1:2.3. Gross invasion was noted in 17% of microadenomas and in 64% of macroadenomas.

Silent ACTH-Cell Adenomas

Silent ACTH-producing adenomas have been recognized only recently, and the data available are insufficient to characterize their behavior fully. These unusual tumors contain immunoreactive ACTH and related peptides but are not associated with clinical or biochemical evidence of hormonal hypersecretion. In the Mayo Clinic experience with 11 such tumors, they tended toward a rapid rate of growth and frequently showed suprasellar extension. All 11 tumors were macroadenomas, and nine of them were grossly invasive.

Glycoprotein Hormone-Producing Adenomas

Until recently, follicle-stimulating hormone/luteinizing hormone (FSH/LH)-cell adenomas have been considered rare. Recent publications have shown that they are relatively common, representing 5% to 10% of all adenomas. A preliminary review of nonfunctioning adenomas (exclusive of GH-, PRL-, or ACTH-containing tumors) at the Mayo Clinic showed more than one-third to be FSH/LH-cell adenomas. The growth pattern of FSH/LH-cell tumors has not been studied definitively, but in our experience they frequently are large circumscribed lesions that spread by compression rather than by gross invasion.

Among eight FSH/LH-cell adenomas in the series of Selman, et al., microscopic invasion was present in seven; only one of these showed gross features of infiltration at surgery. In the Mayo Clinic experience with 32 FSH/LH-cell adenomas, none was associated with clinical hyperfunction, all were macroadenomas, 88% showed suprasellar extension, 21% showed invasion surgically, and the rate of short-term (<5 years) recurrence was 6%. The adenomas occurred most often in elderly patients, displayed a 2:1 male:female ratio, and were often associated with gonadal failure.

Thyrotropin-Cell Adenomas

Adenomas secreting thyroid-stimulating hormone (TSH) are rare; the majority of reported examples are associated with either hypo- or hyperthyroidism. In our experience with four such tumors, all were macroadenomas and three were grossly invasive. Hence, their clinical behavior appears to be similar to that of gonadotropinomas.

A role for end-organ insufficiency and preexisting TSH-cell hyperplasia in the pathogenesis of TSH-cell adenomas is suggested by experimental animal studies, by reports of TSH-cell adenomas in the setting of hypothyroidism, and by a recent clinicopathological and immunocytochemical study of the pituitary gland in humans with long-standing hypothyroidism. It is noteworthy that hyperplasia of TSH cells due to long-standing primary hypothyroidism, which may lead to significant enlargement of the pituitary with resultant suprasellar extension and visual symptoms, is reversible by appropriate thyroid hormone replacement therapy.

Null-Cell Adenomas

Null-cell adenomas of the non-oncocytic and oncocytic type are usually large neoplasms at the time of clinical diagnosis. Late presentation is attributable to the fact that they produce no hormones and thus do not cause endocrinological abnormalities. Such tumors are usually diagnosed only when they reach a considerable size and produce symptoms such as headache or visual defects. A modest degree of hyperprolactinemia due to stalk compression is relatively common, and various degrees of hypopituitarism may occur. Null-cell adenomas characteristically become manifest in older patients; the mean age was 57 years in the Mayo Clinic experience. Although it is not known when the neoplastic transformation occurs, it is likely that the tumors begin many years prior to presentation but, because of slow growth, they take years or decades to produce clinical symptoms.

When recognized clinically, most null-cell adenomas have spread outside the sella or have invaded neighboring tissues. Among 12 null-cell tumors in the series of Selman, et al., four (33%) showed gross surgical infiltration whereas 11 (92%) showed microscopic invasion. In our review of 93 null-cell adenomas operated on at the Mayo Clinic, 98% were macroadenomas. Grossly apparent invasion was present in 42%. They have no preference in regard to direction of invasion. There usually are no signs of abrupt growth in these cases, the tumors being more likely to exhibit slow expansile enlargement. In a review of 100 nonfunctioning pituitary adenomas at the Mayo Clinic, the combined rate of clinical and radiographic recurrence after surgical treatment of null-cell adenomas was approximately 17% over a 10-year follow-up period.

Plurihormonal Adenomas

Tumors that produce unusual combinations of ade-
Invasive pituitary adenomas

nohypophyseal hormones have been considered uncommon until recently. 17-27 Few examples studied by modern methods have been reported. Our review of 63 cases showed that the majority occurred in the setting of acromegaly and were composed of cells producing GH, PRL, and one or more glycoprotein hormones. 28 For such adenomas the frequency of gross surgical invasion was 50%; the ratio of microadenomas to macroadenomas was 1:3. Less common plurihormonal tumors composed of other unusual combinations of cell types remain clinicopathological curiosities; too few have been studied to characterize their behavior. The variants of GH- and PRL-producing tumors, as well as adenomas that produce both FSH and LH, are not considered truly plurihormonal.

The estimated rate of gross invasion by pituitary adenomas of all types, based upon their usual frequency of occurrence and upon our observed frequency of invasion, is approximately 35%.

Acknowledgments

The authors thank Dr. E. Horvath, Mrs. Gezina Ilse, Mrs. Noemi Losinski, and Mrs. Nancy Ryan for their contributions to this study and Mrs. Jill A. Johnson and Mrs. Wanda Wlodarski for excellent secretarial work.

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