Aggressive Pituitary Tumors

Although almost all pituitary tumors are benign adenomas, a surprisingly large number of these tumors invade tissues outside of the pituitary gland. Such invasion, by itself, is not diagnostic of pituitary carcinomas, which are

Aggressive pituitary adenomas are important in clinical practice. Analysis of their molecular mechanisms and genetic underpinnings also provides important lessons relevant to the fundamental biology of pituitary neoplasia. All too often, however, the proliferative and invasive features of pituitary tumors are downplayed, and such tumors are assumed, even by endocrinologists and oncologists (who should know better), to be benign, slow to enlarge, easy to treat with drugs or transsphenoidal microsurgery, and harmful mainly in the perturbations of hormonal homeostasis that they induce. Patients, on the other hand, often fear rapid growth, metastasis, and worse. As usual, the truth lies somewhere between these two extremes.

"Invasive" Does Not Necessarily Mean "Aggressive"

As Blevins et al show in their systematic, thorough review of the different subtypes of pituitary tumors, invasion is a frequent event. It usually occurs at the interface with the dura of the sellar floor or medial wall of the adjacent cavernous sinus, which form the first barriers to egress from the sella turcica. The authors focus on this attribute, rather than on rapid growth, which is less common by far but more clinically significant.

The most frequently cited study, by Selman et al, found microscopic invasion of the dura in 85% of patients, with a slightly lower incidence in individuals with small tumors and a slightly higher one in those with larger tumors.[1] Perhaps this number is actually an underestimate, as it comes from operative biopsies, which, practically speaking, can be done only on the portion of the sellar floor exposed at surgery, not the entire lining of the pituitary fossa.

The problem in extrapolating from these data to the clinical arena is that the majority of such "invasive" tumors are histologically benign and actually quite sluggish in their growth. Even those that grossly invade the cavernous sinus and skull base, as judged by modern scanning techniques, need not enlarge quickly, do not generally invade the brain or cranial nerves, and (usually) offer no external clinical clues that predict their identity as invasive tumors. We really have no defined criteria for determining what denotes clinically significant invasion, or for predicting which tumors will grow quickly.

What Constitutes a Truly Aggressive Pituitary Tumor?

What, then, constitutes a truly aggressive pituitary tumor? And which tumors should be called pituitary carcinomas? Much confusion and argument are evident in the literature through the late 1980s, with the most cogent statement being that put forward over 40 years ago by Sir Geoffrey Jefferson.[2] He suggested that although rapid progression, an invasive pattern of growth, and an anaplastic histology were helpful features, metastasis should be required for the diagnosis of a pituitary carcinoma. The current consensus in the pathologic literature holds that spread by either blood (extraneurally) or cerebrospinal fluid (within the central nervous system) qualifies a pituitary tumor as a carcinoma.

However, such malignant tumors may exhibit a bland histology indistinguishable from that of their benign counterparts, and may follow a variable clinical course that may allow long survival. Indeed, most "aggressive" pituitary adenomas do not metastasize: Only 100 such tumors have been reported.[3-5] This number is somewhat higher than the figure quoted by Blevins et al but still low enough to make such behavior distinctly unusual. Thus, pinning down the elusive sine qua non, the defining element of such tumors, demands something beyond the clinical criteria applied to other neoplasms.

Molecular Correlates of Aggressive Pituitary Tumor Behavior

In an effort to find that defining element, Blevins et al review some of the molecular correlates of
aggressive behavior in pituitary tumors. Many of these studies have used immunohistochemistry to define the relative abundance or absence of protein products known to be significant in other, more classically malignant tumors.

Indices of proliferation, calculated by counting the proportion of cells staining for various cell-cycle antigens, do correlate with aggressiveness when adenomas are divided into noninvasive, invasive, and (in some studies) metastatic groups. However, conflicting reports that both support[6-8] and reject[9,10] a correlation with clinical invasiveness and recurrence make it difficult to interpret MIB-1 labeling, the most popular index, in individual tumors. Because such labeling indices do not account for apoptosis in tumors and are subject to sampling error, they are better used as predictors of behavior for a population of tumors rather than for any one tumor.

The surface has only been scratched in the hunt for relevant markers of proliferation and invasion. Hormonal secretion has been adduced as a correlate of invasion, particularly in prolactinomas, but represents more of an epiphenomenon than an underlying cause.

The products of such tumor-suppressor genes as p53 or retinoblastoma or of such oncogenes as ras or epidermal growth factor receptor have been studied, although usually by fairly simple techniques that can only demonstrate gross changes in volume of the gene product, usually at the protein level. Although alterations in p53 have been linked most convincingly with invasive behavior in pituitary adenomas,[5,11] a role for other genes has not been excluded, given the absence of studies that examine gene regulation on a deeper level for each candidate locus.

In addition, apart from the study of nm23 mentioned by Blevins et al, no molecular studies relevant to the effectors of invasion (eg, studies measuring proteases, protease inhibitors, adhesion molecules, and so on) have been published to date.

**Prevalence of Invasive Behavior in Adenoma Subtypes**

In this review, the authors offer a careful catalogue of the relative prevalence of invasive behavior in each of the subtypes of adenoma. The results are interesting, and bear comment. Clinically silent corticotroph adenomas are more likely to be invasive than their more "noisy" adrenocorticotropic hormone (ACTH)-secreting counterparts, possibly because the profound hormonal derangement caused by even small functional corticotrophic tumors results in earlier detection and treatment. Although the figures quoted in the authors’ Table 1 for invasive macroadenomas in patients with Nelson’s syndrome do not differ significantly from those for patients without prior adrenalectomy, pituitary adenomas do seem to grow faster (when present) after adrenalectomy than when the adrenal is intact. Such excess tumor growth in Nelson’s syndrome, along with the tendency of patients with thyroid-stimulating hormone (TSH)-secreting tumors who have undergone inappropriate thyroid ablation to harbor relatively large, invasive tumors, suggests that interference with negative feedback from the target organ may induce the onset of the aggressive phenotype.

The induction of thyrotropic tumors in mice subjected to thyroid ablation also argues in favor of this hypothesis.[12] However, such musings fail to explain fully why some macroadenoma subtypes are more likely than others to invade: Gonadotroph adenomas, for example, are half as likely to display this one facet of aggressive behavior as are somatotroph adenomas. Why would hormonal silence from growth hormone or ACTH-producing tumors imply more aggressive activity than other "silent" adenomas of the gonadotropic or null cell varieties? Only when such questions have answers can we claim to understand in a meaningful way the process of malignancy in pituitary tumors.

**A New Way of Classifying Pituitary Tumors?**

For that is what one must grasp—malignancy and the spectrum that defines the poorly understood slide of both genotype and phenotype toward outright anaplasia. In the absence of a perfectly sensitive and specific marker of malignancy in pituitary tumors, it is probably best to classify them, not as noninvasive vs invasive, but by some sort of scale that creates separate scores for proliferation, invasion, hormone secretion, and, perhaps, angiogenesis. Such a scale might bring together labeling index, rate of apoptosis, degree of histologic anaplasia, markers of the invasive phenotype, p53 status, and other relevant factors yet to be discovered to give an overall index of aggression useful in formulating treatment strategies.

As Blevins et al have convincingly shown, pituitary tumors that would score high on such an instrument remain a significant challenge for the clinician and a relatively untapped area for the tumor biologist.

**References:**


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