Phenotypic And Evolutionary Characteristics Of Aggressive Pituitary Adenomas: About 14 Cases

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Summary: Pituitary adenomas define a group of slowly growing tumors, developed at the expense of the anterior pituitary. They account for 10-15% of all intracranial neoplasms. Mostly benign, processing and its attendant monitoring are part of a surgical resection and / or specific medical treatment, which generally pose few problems in current practice. A significant number of pituitary tumors, 25-55% depending on the criteria used, can show signs of invasion of dura, bone and/or surrounding anatomical structures. However, these so-called 'invasive' pituitary adenomas display benign behavior even in the presence of marked dural invasion and are not considered malignant by current definition. Truly malignant pituitary tumors (pituitary carcinomas) are only defined by the presence of cerebrospinal or systemic metastases and are exceedingly rare, with an incidence of 0.2% of symptomatic pituitary tumors. The so-called 'aggressive' adenomas lie between benign adenomas and malignant pituitary carcinomas and display a rather distinct clinical behavior with marked/gross invasion of nearby anatomical structures and a tendency towards resistance to conventional treatments and early postoperative recurrence.

The objective of our study is to report the clinical, paraclinical and evolutionary characteristics of atypical pituitary adenomas observed in our practice.

Keywords: Indices of proliferation, atypical pituitary adenomas, temozolomide, chemotherapy, surgical resection

I. Introduction

Pituitary adenomas define a group of slowly growing tumors, developed at the expense of the anterior pituitary. They account for 10-15% of all intracranial neoplasms. Their prevalence based on recent cross-sectional community-based studies is estimated at 80-90 per 100,000 (1). Mostly benign, processing and its attendant monitoring are part of a surgical resection and / or specific medical treatment, which generally pose few problems in current practice. A significant number of pituitary tumors, 25-55% depending on the criteria used, can show signs of invasion of dura, bone and/or surrounding anatomical structures (2) (3). However, these so-called 'invasive' pituitary adenomas display benign behavior even in the presence of marked dural invasion and are not considered malignant by current definition. Truly malignant pituitary tumors (pituitary carcinomas) are only defined by the presence of cerebrospinal or systemic metastases and are exceedingly rare, with an incidence of 0.2% of symptomatic pituitary tumors (4). The so-called 'aggressive' adenomas lie between benign adenomas and malignant pituitary carcinomas and display a rather distinct clinical behavior with marked/gross invasion of nearby anatomical structures and a tendency towards resistance to conventional treatments and early postoperative recurrence (3).

The objective of our study is to report the clinical, paraclinical and evolutionary characteristics of atypical pituitary adenomas observed in our practice.

II. Population, Methodology

This is a retrospective study of atypical adenomas observed in 6 years (2010-2016). All patients underwent complete clinical examination and an hormonal (hypophysiogram) and neuroradiological assessment. After neurosurgical treatment, a histological study in particular of Indices of proliferation and immunohistochemistry of surgical specimens was performed. Reassessments were regularly performed and additional treatment and / or surveillance was decided according to the surgical outcome: Neurosurgical recovery ± radiotherapy ± medical treatment (dopaminergic and somatostatinergic agonists) ± chemotherapy ± TEMOZOLOMIDE.

III. Results

10 cases were identified. The mean age is 34.5 ± 0.1 (21-44). The sex ratio is 7 H / 3F. The pattern of consultation was dominated by tumor syndrome (100%, Table II)
Adenomas were hypersecreting in 80% (Table II). They were aggressive and giant in all cases with an average size of 64 ± 0.5mm (55-78).

### Table II: Distribution of pituitary adenomas

<table>
<thead>
<tr>
<th>Adenoma</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactinoma</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Cushing Disease</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>Gonadotropic</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Somatotropic</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Non-Functioning</td>
<td>4</td>
<td>28.6</td>
</tr>
</tbody>
</table>

Histologically, the association of a high mitotic index, a Ki-67> 3% and a diffuse detection of p53 was noted in 100%. Surgery was partial in all cases (100%), which necessitated a neurosurgical recovery, medical treatment (dopaminergic agonists ± somatostatinergic agonists) and radiotherapy. In view of the resistance to conventional treatments, chemotherapy and or treatment with testis lomide is undertaken. A tumor reduction of 32% (20-45) on average was noted in 68% of the cases. Tumor stability was observed in the other cases. The evolution was marked by a death in two cases by cerebral herniation. The revaluations did not show any secondary metastases after a mean of 4 years (1,5-6).

### IV. Discussion

Atypical pituitary adenomas are aggressive pituitary adenomas. ¼ are large and grow rapidly; The majority have a suprasellar, parasellar extension and an invasion of the dura mater, the cranial nerves, the bone, the cavernous sinuses, the wall of the internal carotid arteries and the cerebral parenchyma. They are characterized by multiple recurrences and resistance to conventional treatments including radiotherapy which requires more aggressive therapeutic options and often a combination of therapies. An evolution which makes evoke the possibility of pituitary carcinomas (5) (6). There are, however, indicators that differentiate them from benign pituitary adenomas; Generally, pituitary carcinomas have high mitotic activity, a Ki-67> 2% proliferation index, a positive p53 expression and a microvascular density; The majority of carcinomas are prolactinomas, corticotrophic adenomas and non-secreting. The presence of metastasis confirms the diagnosis when they are present in the CNS (35%): Spinal cord, cerebral and at the systemic level: Bones, lymph nodes, liver and lung (7) (8).

Atypical pituitary adenomas require multiple surgical procedures Transsphenoidal, transcranial or both, pharmacological treatments: Dopamine agonists (DA), somatostatin analogues (SSA), GH receptor antagonists and Radiotherapy: Fractional external radiotherapy, Stereotactic radiosurgery. The lack of response and tumor control necessitates the use of chemotherapy and temozolomide (6) however, due to the rarity of these tumors, no randomized prospective studies of systemic chemotherapy have been conducted. Different cytotoxic chemotherapy protocols including procarbazine-etoposide-lomustine (cyelo-hexyl-chloroethyl-nitrosourea or CCNU) and lomustine-doxorubicin have been used in individuals with aggressive pituitary tumors, achieving mostly transient tumor growth and hormonal responses. In a small series of 7 patients, of whom 3 had aggressive pituitary tumors and 4 carcinomas, combination therapy with lomustine and 5-fluorouracil showed an overall poor response rate in terms of tumor shrinkage, although temporary clinical responses were noticed in some patients (9)(10). Furthermore, observational data suggest that prolonged survival in some patients with pituitary carcinomas is associated with chemotherapy received prior to the appearance of distant metastases (1).

Since 2006, temozolomide (TMZ), originally approved for use in refractory glioblastoma multiforme, has been used to successfully treat pituitary carcinomas and aggressive pituitary adenomas (table 4). TMZ is an orally administered second-generation alkylating agent, an imidazotetrazine derivative that is rapidly converted at physiological pH to methyl-tryazeno-imidazole-carboxamide, which is the active drug. It exerts its action by attaching a methyl group to the O6 position of guanine bases causing mispair with thymine bases, DNA damage, proliferation arrest and cell (11)death (apoptosis). O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that counteracts the effects of TMZ by removing alkylating adducts from DNA. TMZ can readily cross the blood-brain barrier, and its
action is not cell cycle specific, thus inhibiting all stages of tumor cell growth, even in slow-growing tumors, such as pituitary tumors(12)(13).

Concerning the results about Aggressive pituitary tumors and pituitary carcinomas treated with TMZ in the literature, the overall clinical and radiological response rate was initially reported to be approximately 69% in carcinomas and 60% in aggressive adenomas (14). Combined data from 4 studies of small cohorts reveal a mean tumorural response (partial response) in 55.5% of patients with carcinomas and 41% with aggressive adenomas. If stabilization of the tumor (stable disease) is also considered as a favorable outcome, TMZ efficacy rises up to 72% for carcinomas and 70.5% for aggressive adenomas. Nevertheless, responses were frequently short lasting, and subsequent progression developed following an initial response to treatment(15).

Novel targeted therapies (mTOR inhibitors, anti-VEGF agents) may be warranted for further investigation following a case report of a patient showing disease control for 26 months after administration of the angiogenesis inhibitor bevacizumab and data showing the in vitro effect of everolimus on cell viability in cell cultures from NFPAs. The previously highlighted importance of EGFR and its receptor EGFR has also prompted research concerning the use of tyrosine kinase inhibitors, especially the EGFR inhibitor gefitinib, as a targeted medical therapy for ACTH adenomas, demonstrating promising in vitro results. There have also been some promising surgical techniques such as the implantation of Gliadel (carmustine) wafers in patients with aggressive pituitary adenomas showing stabilization or even objective responses in the majority of cases (16)(17).

Some authors have also reported changes in histopathological and morphological features of tumors after TMZ treatment based on findings from reoperated patients. Tumor softening and friability were noticed, facilitating easier resection at reoperation, while TMZ-treated tumors exhibited fewer mitoses, lower Ki67 LI, hemorrhage, necrosis, focal fibrosis and absent MGMT in IHC (18).

The DNA repair enzyme MGMT reverses the methylation caused by TMZ, being the major mechanism of resistance to TMZ treatment. A significant inverse correlation was found between IHC MGMT expression and response to TMZ; however, the absence of MGMT expression was not always predictive of tumor response (19). On the contrary, studies examining MGMT promoter methylation in pituitary tumors confirmed its poor prognostic value since methylated MGMT promoter was found only in 60% of TMZ-sensitive tumors and 50% of TMZ-resistant tumors. It appears that MGMT IHC but not MGMT promoter methylation status can be used to predict response to treatment in pituitary tumors. A clinically meaningful suggestion has been mad(20).

V. Conclusion

Atypical adenomas are aggressive tumors which are assimilated to pituitary carcinomas. They must be recognized and treated with aggressively.

Bibliographie


