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Clinico-Pathological Study

Clinical and histological correlations in prolactinomas, with special reference to bromocriptine resistance

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Summary

Background. Prolactinomas usually exhibit a benign course and can be safely and effectively managed by dopamine agonists (DA). However, some are locally invasive and may show resistance to DA therapy, and the management of such cases remains controversial. The aim of the present study was to determine whether histological features and markers of cell proliferation correlated to the clinical behaviour of prolactinomas and with DA resistance.

Method. This retrospective study included 74 cases (36 men and 38 women) who had monohormonal prolactinomas removed by transsphenoidal surgery. The prolactinomas were categorized on the basis of tumour size (48 macroadenomas), invasion of the cavernous sinus ($n = 31$), and resistance to bromocriptine (BRC) therapy ($n = 14$). Group 1 consisted of non-invasive microprolactinomas ($n = 24$), group 2 of non-invasive macroprolactinomas ($n = 19$), group 3 of invasive non-BRC-resistant tumours ($n = 19$), and group 4 of invasive BRC-resistant tumours ($n = 12$). The later group included one case of carcinoma with bone and lung metastases. Seven additional parameters were studied, these being age, sex, basal prolactin (PRL) levels, the Ki-67 and PCNA labelling indices (LI), mitotic count, and cellular atypia.

Findings. Age and preoperative PRL levels did not correlate to the histological parameters studied. Tumour size and invasion were related to cellular atypia and the Ki-67 LI. BRC-resistant tumours were more frequently invasive (12/14) than BRC-responsive tumours (11/30; $p = 0.002$) and were more frequent in men than in women (33 versus 5%; $p = 0.003$). BRC-resistant tumours had a higher Ki-67 LI and mitotic count ($4.2 \pm 2.0\%$ and 4 ± 1, respectively) than other tumours ($0.7 \pm 0.2\%$ and 1 ± 0, respectively; $p < 0.05$). The strongest correlations with tumoural staging were seen with male sex and high mitotic activity. Six out of the 12 invasive BRC-resistant macroprolactinomas, including the PRL secreting carcinoma, exhibited histological features of aggressiveness (a mitotic count ≥ 3 [i.e. in the fourth quartile] and/or a high Ki-67 LI and cellular atypia).

Conclusions. In this surgical retrospective series, histological signs of aggressiveness are present in 50% of invasive and BRC-resistant prolactinomas, which are more frequent in men than in women. This fits with the behaviour of BRC-resistant prolactinomas, which can continue to grow despite DA treatment. These findings justify the long-term follow up of these tumours, and the use of surgery and/or radiotherapy if there is concern about the control of tumour growth.

Keywords: Dopamine agonist resistance; Ki-67; mitotic activity; neurosurgery; pituitary; prolactinoma.

Introduction

Tumours arising from the anterior lobe of the pituitary gland tend to grow slowly and are generally regarded as benign. However, a minority exhibit a more aggressive growth, invading surrounding structures and, rarely, metastasising to extracranial sites. Currently, the behaviour of a pituitary tumour cannot be predicted from its histological appearance, and the most reliable feature of aggressiveness, recognised more than 50 years ago [6], remains invasion of the cavernous sinus space.

We decided to search for histological prognostic factors in a particular type of pituitary tumour, i.e. prolactinomas, because their tumoural behaviour is highly variable, with microprolactinomas having a benign course and rarely increasing in size with time, while macroprolactinomas can behave as highly invasive tumours, especially in men. In addition to cavernous sinus invasion, another parameter is associated with prolactinoma behaviour: their response to dopamine agonist (DA) therapy. Prolactinomas resistant to the DA, bromocriptine (BRC), have been shown to exhibit a more severe clinical course both in humans [1]

and in animal models [16]. Their management remains controversial, especially regarding indications for surgical removal. In the present retrospective study, to examine whether markers of cell proliferation and/or cellular atypia suggest aggressive behaviour, the clinical data were correlated with the histological features in a surgical series of 74 prolactinomas, classified by increasing aggressiveness on the basis of tumour size, invasiveness and response to DA therapy.

Subjects

We selected 74 patients with monohormonal prolactinoma removed by transsphenoidal surgery by two neurosurgeons in Lyon and Tours. These consisted of 36 male patients, who underwent surgery between 1987 and 1996, and 38 female patients, who underwent surgery between 1993 and 1996; during this period, BRC was the only DA used. Pretreatment MRI data were available for all patients. Fifty-three of these patients have been included in two previous studies [3, 4]. Medical records were reviewed for the clinical data of age, basal prolactin (PRL) levels, tumour size at the time of diagnosis, response to BRC, peri-operative data, and follow-up information. Serum PRL levels were measured using standard RIA or immunoradiometric assay methods, the upper limit of the normal range being taken as less than 15 μg/l in males and less than 20 μg/l in females. Biochemical cure was defined as a normalisation in serum PRL levels at the end of the follow-up period (mean follow-up 23 months, range 3–120 months). BRC-resistance was defined as an absence of normalisation of serum PRL values, despite increasing the daily dose of BRC to 15 mg (i.e. twice the usually effective dose) for at least 3 months [1]. Tumour size was determined using the maximal craniocaudal diameter in coronal sections of the pretreatment MRI scan. Invasion of the cavernous sinus space was defined according to pre-operative radiological criteria and peri-operative findings as previously described [3]. Both surgeons evaluated the cavernous sinus during surgery, invasion being defined as perforation of the medial wall of the cavernous sinus, with direct visualisation of and/or contact with the intracavernous internal carotid artery and/or intracavernous trabeculae, both of which were surrounded by tumour.

At initial presentation, 48 of the 74 patients (35 men and 13 women) presented with macroadenomas (diameter $\geq$ 10 mm), while 26 (one man and 25 women) presented with microadenomas (<10 mm). Surgery was performed as the primary treatment modality in 44 patients (24 men and 20 women), resulting in normal postoperative PRL levels in 17 (4 men and 13 women) (Fig. 1). Fifty-seven patients received BRC therapy before (n = 30) or after (n = 27) surgery. Of the 30 receiving BRC therapy before surgery, 18 were referred for surgery when found to be intolerant of (2 men and 8 women), or resistant to (7 men and 1 woman), medical treatment, while the indication for surgery in the other 12 patients (3 men and 9 women) was poor compliance with treatment or personal choice. In the 8 BRC-resistant patients

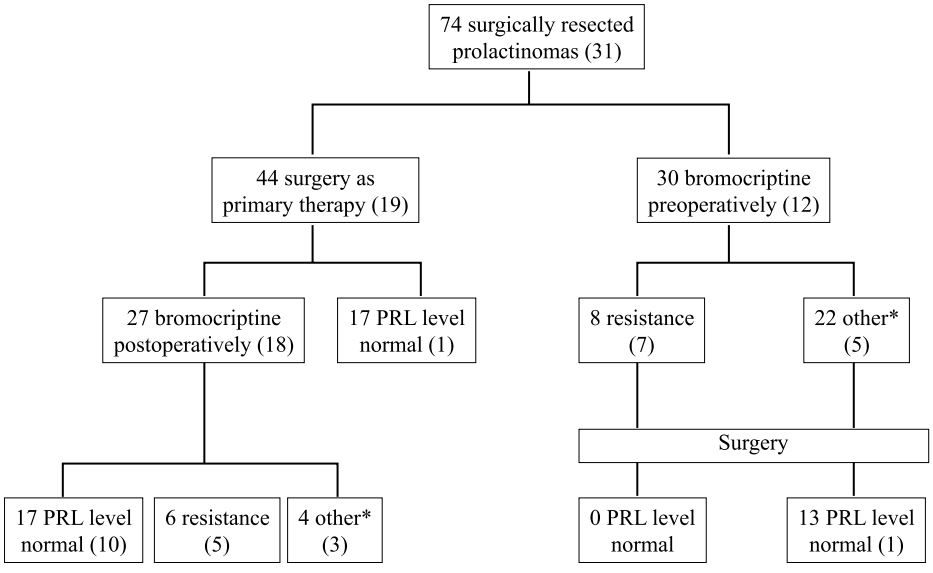

Fig. 1. Flow diagram of the patient population. The figures in parenthesis indicate the number with cavernous sinus invasion. * Other represents mainly patients intolerant to bromocriptine or not compliant to treatment

and 6 of the non-BRC-resistant patients (3 men and 3 women), treatment was continued up to pituitary surgery, whereas the other 16 patients had themselves discontinued treatment for more than 3 months before surgery.

One of the patients studied developed multiple systemic metastases. This man first presented at the age of 35 years with headaches and loss of libido. The serum PRL was 600 μg/l. A 40 mm height tumour invading the cavernous sinuses was partially removed by transsphenoidal surgery. Because of persistent hyperprolactinaemia, BRC was started and subsequently increased to 20 mg daily without normalisation of serum PRL level. Five years later, because of visual impairment and evidence of a large recurrent tumour on MRI, he was re-operated on, twice.

At the age of 43, multiple vertebral and lung metastases were discovered. The vertebral metastasis were proved to be related to the prolactinoma by anti-hPRL immunoreactivity. He died from his PRL secreting carcinoma soon after.

Classification of prolactinomas

Tumours were classified into four groups according to tumoural behaviour; these groups were: 1) non-invasive microprolactinomas (<10 mm), 2) non-invasive macroprolactinomas (≥10 mm), 3) invasive non-BRC-resistant prolactinomas (the term "invasive" being restricted to tumours presenting with cavernous sinus extension), 4) aggressive (i.e. invasive BRC-resistant) prolactinomas. The carcinoma was included in group 4 because the tumour was not metastatic at the time of the histological examination.

Histological parameters

All tumours were referred to the same pathologist. The tissues were fixed in Bouin-Hollande solution for 4 days and embedded in paraffin. Five micrometer sections were stained with Herlant's tetrachrome and periodic acid-Schiff-orange G methods. The diagnosis of monohormonal prolactinoma was established in all cases by immunocytochemistry using the indirect immunoperoxidase method and a streptavidin-biotin-complex (Dako A/S, Copenhagen, Denmark), as previously described [15]. The following monoclonal (m) and polyclonal (p) antibodies were used: anti-h PRL (m) (164-22-12), anti-βhFSH (m) (300-10-E-14-3), anti-αh subunit (m) (326-2-1; lot f 1079) and anti-Cytokeratin (m) (19-18; clone: KL1) (Immunotech, Marseille, France); anti-hGH (p) and anti-βhLH (p) (donated by Dr AF Parlow, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK)); anti-βhTSH (m) (M3503; clone: 0042) (Dako A/S, Copenhagen, Denmark); anti-17-39 ACTH (p) (donated by Dr. PA Dubois, France). The dilutions used were 1/100 to 1/10000 for the monoclonal antibodies and 1/8000 to 1/10000 for the polyclonal antibodies.

The proliferative behaviour of the tumours was evaluated using the Ki-67 and proliferating cell nuclear antigen (PCNA) labelling indices (LI) and the mitotic count. Immunocytochemical detection of Ki-67 and PCNA was performed using monoclonal antibodies specific for Ki 67 (MIB1, Immunotech; dilution 1/400) or PCNA (Tebu Novocastra, Newcastle upon Tyne, UK; dilution 1/400). To detect Ki-67, paraffin sections were heated in 10 mM citric acid, pH 6.0, for three 5-min cycles at 750 W in a microwave oven, then blocked in 0.5% H_2O_2/methanol for 10 min. To determine the LIs for Ki-67 and PCNA, cells were counted at high power (×400 magnification) in five fields per tumour, an average of 1000 nuclei being evaluated in each specimen. The Ki-67 and PCNA LIs were defined as the percentage of labelled nuclei. For the mitotic count, all the available sections of tumoural tissue were carefully observed at ×400 magnification; Ki-67 immunostaining facilitated this count, as the immunopositive interphasic and mitotic nuclei appear brown on the white background. The results were expressed as the absolute number of mitoses seen on examination of more than ten high power fields.

Cellular atypia consisting of large multinucleated cells or irregular nuclei and/or nuclear atypia (nuclear pleomorphism) was also recorded on a scale of 0 to 3. Moreover, in 6 tumours in group 4 which showed histological signs of aggressiveness, neo-angiogenesis was evaluated by immunostaining of the vascular basal membrane with an anti-collagen IV monoclonal antibody (clone CIV22, diluted 1/50, Dako A/S, Copenhagen, Denmark).

All the tumours were reviewed together by the pathologist and the histological data were subsequently correlated with the clinical parameters in a blinded manner.

Statistical analysis

Ten factors were studied, these being tumour size, invasiveness, BRC resistance, age, gender, preoperative PRL levels, the Ki-67 and PCNA LIs, mitotic count, and cellular atypia. The group data were expressed as the mean ± SEM [median]. Medians were compared using the non-parametric Mann-Whitney U or Kruskal-Wallis H tests. Frequencies were compared using the X^2 test. For correlations,

Table 1. *Relationships between clinical and pathological parameters in prolactinomas*

	Ki-67 LI (%)	PCNA LI (%)	Mitotic count (nb)	Cellular atypia[1] (n)
Gender				
– Females	0.7 ± 0.3 [0.0]	3.2 ± 0.3 [2.6]	1 ± 0 [0]	3/37
– Males	2.1 ± 0.8 [0.9]*	6.9 ± 1.6 [4.6]	2 ± 1 [1]	12/36**
Age	r = 0.22	r = 0.09	r = 0.13	r = 0.04
Prolactin	r = 0.07	r = −0.08	r = −0.10	r = 0.09
Tumour diameter	r = 0.27*	r = 0.22	r = 0.17	r = 0.50**
Invasion of cavernous sinus				
– No	0.7 ± 0.2 [0.0]	3.9 ± 1.0 [2.8]	1 ± 0 [0]	4/42
– Yes	2.3 ± 0.9 [0.9]*	6.4 ± 1.5 [4.5]	2 ± 1 [1]	11/31**
Bromocriptine resistance				
– No	0.7 ± 0.2 [0.0]	3.8 ± 0.8 [2.6]	1 ± 0 [0]	8/59
– Yes	4.2 ± 2.0 [1.9]**	10.0 ± 2.7 [8.3]*	4 ± 1 [3]**	7/14**
Tumour staging	r = 0.29*	r = 0.25*	r = 0.30**	r = 0.36**

LI Labelling index; *nb* number.
For proliferation markers (Ki-67, PCNA and mitotic count), the results are expressed as the mean ± SEM [median].
* $p < 0.05$; ** $p < 0.01$ (r = Spearman's correlation; for dichotomous variables [invasiveness, bromocriptine-resistance and gender], groups were compared using the Mann-Whitney U test and X^2 test).
[1] For correlations, cellular atypia was entered as a continuous variable, ranging from 0 to 3.

a score of 1 (microprolactinomas) to 4 (aggressive prolactinomas) was established. Tumour size and cellular atypia (range 0 to 3) were also recorded as continuous variables. The level of significance was set at $p < 0.05$.

Results

Invasion of the cavernous sinus space was seen in 31 cases. All invasive tumours, except two, were macroadenomas. Fourteen out of the 57 BRC-treated patients (24%) were BRC-resistant and, in 12 of these, the tumour was also invasive and was defined as aggressive (group 4). The remaining invasive tumours (n = 19) were classified as group 3. There were 19 non-invasive macroprolactinomas (group 2) and 24 non-invasive microprolactinomas (group 1). Thirty patients (including 2 women with invasive micro-adenomas and 6 men with non-invasive tumours) showed post-operative normalisation of serum PRL levels without further DA therapy. None of the 30 cured by surgery had a BRC-resistant prolactinoma. Biochemical cure was never obtained in patients with aggressive prolactinomas. BRC-resistant tumours were more frequently invasive (12 out of 14) than BRC-responsive tumours (11 out of 30; p = 0.002) and were more frequent in males than in females (33 versus 5%; p = 0.003).

The correlations between the various clinical and histological parameters studied are summarised in Table 1. All the tumours were monohormonal (Fig. 2) and none showed histological signs of DA treatment, such as small cells with hyperchromatic nuclei and slight perivascular fibrosis [10]. Cellular atypia and the Ki-67 LI, but not the PCNA LI or the mitotic count, correlated with invasiveness, tumour diameter, and male sex. Levels of all markers of histological aggressiveness were significantly higher in BRC-resistant tumours than in BRC-responsive tumours. In contrast, no correlation was found between age or preoperative PRL levels and the histological parameters studied.

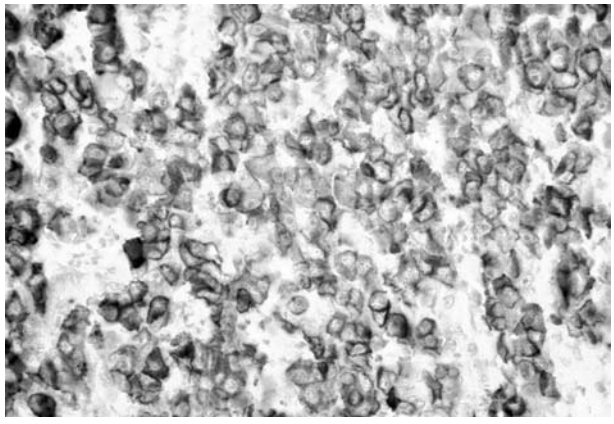

Fig. 2. Monohormonal aggressive prolactinoma. Almost all the cells are stained with anti-PRL antibodies. Immunoperoxidase technique. Original magnification ×400

As shown in Table 2, the strongest correlations with tumoural staging were seen with male sex and a high mitotic count. Men had a greater than ten-fold increased risk of harbouring an aggressive prolactinoma than women (odds ratio 16.3; 95% CI, 2.0 to 134.2). Both

Table 2. *Clinical and pathological characteristics of prolactinomas, as a function of tumoral behavior*

Characteristic	Stage				P value*
	Non-invasive microadenomas	Non-invasive macroadenomas	Invasive tumours	Aggressive tumours	
N	24	19	19	12	
Male sex, n	1 (4%)	9 (47%)	15 (79%)	11 (92%)	<0.001
Ki67 LI (%)	0.8 ± 0.4 [0.0]	0.6 ± 0.3 [0.0]	0.8 ± 0.2 [0.4]	4.8 ± 2.3 [1.9]	0.034
PCNA LI (%)	2.6 ± 0.7 [0.0]	5.6 ± 1.9 [3.5]	3.8 ± 1.1 [2.5]	10.6 ± 3.2 [8.3]	0.071
Mitotic count (nb)	1 ± 0 [0]	1 ± 0 [0]	1 ± 0 [0]	5 ± 2 [3]	0.001
Cellular atypia, n	1/23 (4%)	3/19 (16%)	5/19 (26%)	6/12 (50%)	0.013

LI Labelling index; *nb* number.
For proliferation markers (KI-67, PCNA, mitotic count), the results are expressed as the mean ± SEM [median].
* P values calculated using the Kruskal-Wallis and X^2 tests.

the Ki-67 LI and the mitotic count were significantly increased in aggressive prolactinomas. A Ki-67 LI ≥3% was found in 3 of the 12 aggressive prolactinomas but also in 4 of the 62 remaining tumours, including 3 microprolactinomas (sensitivity 25% and positive predictive value 43%). Fourteen of the 74 tumours studied had a mitotic count ≥3 (i.e. in the fourth quartile); these included 7 of the 12 aggressive tumours (sensitivity 58% and positive predictive value 50%). When patients with macroprolactinomas were stratified in quartiles according to the mitotic count, the odds ratio for tumour aggressiveness in the patients in the fourth quartile (≥3) compared to those in either the first or second quartile (both showing absence of mitosis) was 18.4 (95% CI, 2.7 to 12.30). The prevalence of cellular atypia also increased with tumour aggressiveness.

In six tumours, all belonging to group 4, the pathologist pointed out the association between mitoses (from 3 to 25 mitoses) (Fig. 3) and/or a high Ki-67 LI (up to 16% in one tumour), nuclear atypia (Fig. 4), and neoangiogenesis. Two tumours were composed of compact cords of cells, with a low percentage of PRL-immunoreactive (20%) in the carcinoma. These features, which are very unusual in prolactinomas, were underlined by the pathologist before the development of bone and lung metastases.

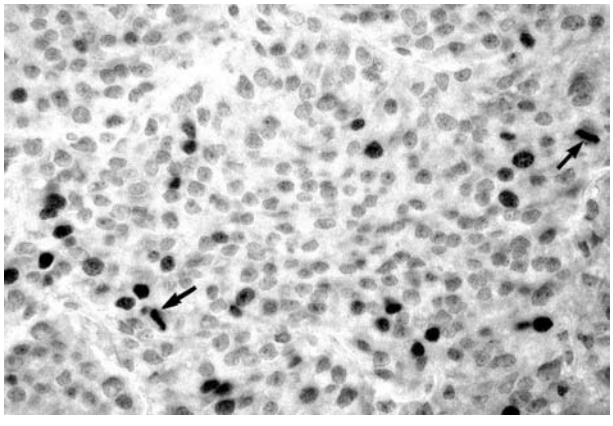

Fig. 3. The immunocytochemistry detection of Ki-67 facilitates the mitotic count. The positive interphasic and mitotic nuclei (arrows) appear dark. Original magnification ×400

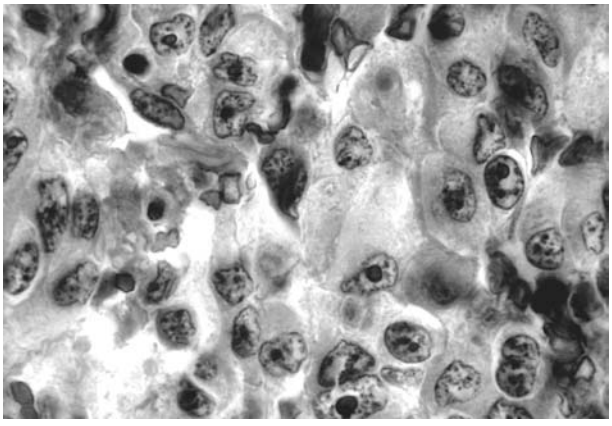

Fig. 4. In this invasive and BRC resistant prolactinoma in a man (group 4), many features of cellular atypia (binucleate cells and nuclear monstrosities) were observed. Original magnification ×400

Discussion

Clinicopathological correlations in prolactinomas

Attempts to correlate clinical and histological data for prolactinomas have been relatively rare [2, 12], probably because surgery for these tumours is seldom performed in the era of DA therapy. In this large retrospective surgical series, we focused on the invasiveness and DA resistance of prolactinomas and correlated tumoural behaviour with the histological data. The high proportion of aggressive tumours (12 out of 74:16%) is not typical of prolactinomas, but was due to a selection bias related to both

surgical recruitment, partly based on DA resistance, and the selection of a similar number of male and female patients.

In this series of prolactinomas, the Ki-67 LI, but not the PCNA LI, correlated to tumour size and invasion. However, in contrast to a previous study involving all adenoma subtypes [14], we found that a threshold Ki-67 LI value of 3% did not reliably distinguish between invasive and non-invasive prolactinomas. This is due to an important overlap in the distribution of individual values, as already outlined by some authors [5]. In our opinion, the Ki-67 LI is a very useful marker for assessing the histological aggressiveness of pituitary tumours, but, on its own, is not sufficient to distinguish between invasive and non-invasive tumours. Like in previous studies [13], the PCNA LI seems less reliable, because some arrested cells can still be positive for this antigen, leading to an overestimation of the growth rate of tumours.

Resistance to dopamine agonists

BRC-resistant tumours were found to more frequently express cell proliferation markers and present cellular atypia than responsive tumours. To the best of our knowledge, histological features, including the study of proliferative markers, have only been examined in isolated cases with DA resistance [7]. In the study by Calle-Rodrigue *et al.* [2], no correlation between DA responsiveness and histological features was possible, as none of the patients included had been treated with DA. In the present study, DA therapy, which is known to inhibit the proliferation of lactotroph cells, was generally discontinued at least 3 months before surgery, except in BRC-resistant patients. In this subgroup of patients, despite continuing the DA treatment up to pituitary surgery, the tumours did not exhibit cytological signs of DA treatment and had high proliferating cells LIs. This observation is in agreement with the behaviour of these tumours, which can continue to grow despite DA treatment. This resistance to BRC therapy can be overcome in some cases by cabergoline, a well-tolerated selective D2 dopamine receptor with a long-lasting action. This compound, introduced in France in 1998, was not available at the time of our study, but its use would probably have resulted in a reduction in the number of patients classified as resistant to DA therapy and in an even better selection of the most aggressive tumours, which would probably have further improved the correlations between the clinical and histological data. In our series, surgery did not normalise PRL levels in any of the invasive and BRC-resistant prolactinomas. In such cases, long-term follow up is mandatory because resistance to DA therapy may be a sign of malignancy. Indeed, the carcinoma in our series as almost all previously described PRL carcinomas have been DA-resistant and, in our rat transplantable prolactinoma model, the malignant cell line, SMtTW4, which is DA-resistant, was found to lack DA receptors [16].

Aggressive prolactinomas

Half of the aggressive prolactinomas (i.e., invasive BRC-resistant tumours) exhibited histological signs (nuclear atypia and mitotic activity) considered as reflecting a poor prognosis or malignancy in other endocrine gland tumours. However, these conventional pathological signs of tumour behaviour, especially the mitotic figures count, are considered unreliable in the case of pituitary tumours, even though high mitotic indices have been described in the majority of pituitary carcinomas [9]. This seems to be mainly due to the fact that, in these tumours, mitoses are very rare and difficult to see. The immunocytochemical detection of Ki-67, which is expressed in the G1, S, G2 and M phases of the cell cycle, makes the mitotic count easier, as the immunopositive interphasic and mitotic nuclei appear brown on the white background. In the present series, the six invasive BRC-resistant tumours with histological signs of aggressiveness (all removed from males) recurred, and one patient died with metastases.

Sex-related differences

When prolactinomas were classified by increasing aggressiveness on the basis of tumour size, invasiveness, and response to DA therapy, the tumoural staging showed a strong correlation with the mitotic count and also with male sex, males having a greater than tenfold increased risk of harbouring an aggressive prolactinoma than females. This is in agreement with our previous study [4] which demontrasted that the higher frequency of large prolactinomas in men is due not only to a longer delay in diagnosis in males, but also to a greater proliferative potential. In this first series, although higher amounts of Ki-67 nuclear antigen were seen in tumours from males, the difference did not reach statistical significance, whereas, in the present larger series, it did. Cellular atypia was also found to be significantly more frequent in prolactinomas from males, something already noted by Robert twenty years ago [12]. This simply reflects the fact that the large, often invasive tumours

seen in men have a greater propensity for cellular proliferation compared to smaller tumours, but does not really shed light on fundamental pathogenic differences. This sex-related difference in prolactinoma growth may be due to differences in blood supply, since prolactinomas in men are often highly vascularised, whereas, in women, they frequently present as haemorrhagic tumours (personal morphological data, not quantified). This hypothesis fits with the recent observation that macroprolactinomas, especially invasive ones, are significantly more vascular than microprolactinomas [18], and suggests that size- and/or sex-related difference in the expression of growth factor stimulating angiogenesis, such as vascular endothelial growth factor or fibroblast growth factor, should be examined.

Conclusions

Histological markers of cell proliferation are more often expressed in aggressive prolactinomas, especially in BRC-resistant tumours. Mitotic activity appears to be especially related to the behaviour of prolactinomas. Nevertheless, it should be born in mind that, until now histological features alone cannot distinguish between aggressive and non-aggressive prolactinomas, and should probably be integrated into a score of aggressiveness, similar to that established by Weiss for adrenal cortical neoplasms [8]. Long-term follow-up studies should establish the prognostic value of parameters, such as male sex, tumour size, cavernous space invasion, response to DA therapy, mitotic activity, and the Ki-67 LI. In addition, new histological prognostic factors, such as expression of cell adhesion molecules, are currently being evaluated [11, 17]. Meanwhile, the fact that BRC-resistant tumours exhibit mitotic activity and a high Ki-67 LI fits with the risk of tumour growth observed in these tumours despite DA treatment, and justifies their long-term follow up. If control of tumour growth becomes a matter of concern, surgery and/or radiotherapy should be considered.

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Comments

This paper documents the clinicopathological correlations in a series of prolactinomas, examining the relationships between histological signs

of aggressiveness and clinical evidence of invasion or resistance to the dopamine agonist, bromocriptine (BRC). The authors draw the conclusions that histological signs of aggressiveness (high proliferative rate and atypia) are more common in invasive and BRC resistant tumours.

The study seems to have been performed appropriately and the data support the conclusions.

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The authors have investigated clinical and histological correlates, including markers of cell proliferation, in a group of 74 patients undergoing surgery for prolactinoma. Not surprisingly, they found that tumour size and invasiveness, and bromocriptine resistance, were correlated with histological markers of aggressiveness. This is a carefully conducted study in a large surgical series, and the manuscript is well written although perhaps a little long. The authors conclude that ''these findings justify the long-term follow up of these tumours and the use of surgery and/or radiotherapy if there is concern about the control of tumour growth''.

The results are very interesting but, unfortunately, are of limited clinical utility, partly because surgery is now undertaken only infrequently for prolactinomas. It is interesting to note, in this regard, that none of the patients in this series had surgery after 1996. Also, surgery tends to be reserved for patients who are known to have aggressive or dopamine agonist-resistant tumours – these patients will already have been identified as being in the group requiring close follow-up and histological markers will therefore add relatively little. The authors concede that histological markers of aggressiveness, such as Ki-67, are of relatively little predictive value, and do not reliably distinguish between invasive and non-invasive adenomas. Overall, therefore, the findings of the study are of significant academic interest but of limited practical value in the clinical setting.

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