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Commentary

Initial pathology in aggressive pituitary tumours and carcinomas: 2b or not 2b?—that is the question

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Abstract

From a cohort of 171 patients comprising 121 aggressive pituitary tumours (APT) and 50 pituitary carcinomas (PC), the clinicopathological or five-tiered classification based on tumour invasion and proliferation evaluated by at least 2 proliferative markers over the cut-offs (Ki-67 ≥3% or ≥10%, p53 positive or expressed in %, mitotic count >2%), could be applied on 43 tumours: 20 PC and 23 APT. At the initial surgery, 29/43 tumours (67.4%) were grade 2b (invasive and proliferative) of which 44.8% developed metastases during follow-up (PC, grade 3). Out of these 29 tumours, 55.1% had a Ki-67 ≥10%, and were classified grade 2b* (invasive and highly proliferative). There was one tumour grade 1b* (non-invasive and highly proliferative) which metastazed. Out of the 43 tumours, 30.2 % were grade 2a (invasive and non-proliferative). The sensitivity and the specificity of grade 2b for the diagnosis of APT at the initial surgery, were 68% and 90% respectively. The comparison of the high percentage (67.4%) of grade 2b tumours in this selected cohort of APT/PC with the low percentage (8.8%) in a surgical cohort of unselected tumours shows that the initial pathological diagnosis of grade 2b tumour may be considered, in the clinic, as representing a diagnosis of APT. In addition, a significant subgroup of tumours, which will develop metastases supports the proposal that an aggressive grade 2b tumour is "a tumour with malignant potential" or "a malignant tumour without metastases". So, the clinician may take into account the pathological diagnosis, at the initial surgery, to propose a strict follow-up and to consider earlier use of radiotherapy and/or of temozolomide in the presence of tumours with aggressive behaviour.

Keywords: Pituitary carcinoma, aggressive pituitary tumour, pituitary tumour classification, pathology, ki67, p53

Introduction

Pituitary tumours of adenohypophyseal origin are the third most frequent (12%-15%) of central nervous system tumours in adults. These tumours are mostly benign, but many are invasive (around 50%). Historically, in the absence of clear pathological signs of malignancy, only the rare pituitary tumours with confirmed metastases (0.2%) were considered malignant and termed pituitary carcinoma (PC). Tumours with a clinically aggressive behaviour may be three to four times more common than PC.[1]

The pathologist's quest has been to find pathological criteria of malignancy that may alert clinicians, before metastases occur. In 2004, the WHO classification introduced the term "atypical adenoma" defined by morphological features (Ki-67 ≥ 3%, extensive p53 staining, and numerous mitoses) that are usually lacking in benign tumours.[2] Given the lack of clinical validation, this grading system was abandoned in the 2017 WHO classification. Moreover, in the recent WHO 2022 classification, no prognostic criteria have been mentioned.[3]

In 2006, a French collaborative study was initiated to develop a clinicopathological classification. The prognostic value of this clinicopathological classification, which is divided into five grades was first validated in two surgical cohorts: one multicentric retrospective cohort[4] and subsequently a monocentric prospective study.[5]

Meanwhile, a large European Society of Endocrinology (ESE) survey on aggressive pituitary tumour (APT) and PC was performed in 2015-2016. The data contributed to the definition of APT and was instrumental in the development of the ESE clinical management guideline establishing temozolomide as the first-line chemotherapy in these aggressive tumours.[6] The survey also highlighted the clinical and pathological similarities between APT and PC.[7,8] In the recently published second and more extensive ESE survey performed 5 years later, data on 171 patients (121 APTs and 50 PCs) were obtained.[9] In addition, the outcome of treatment with radiotherapy, temozolomide and targeted therapies, clinical and pathological characteristics of the tumours at the initial surgery, and the evolution over time were collated. In the present

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brief report, complementary to the second ESE survey publication, we have applied the clinicopathological or five-tiered classification in a subgroup of patients in which sufficient data on invasion and proliferative markers (Ki-67, p53, and mitotic count) were provided to answer the question: What is the role of pathology in the early diagnosis and the management of APT and PC?

Selection of patients and design of the study

The principle aim of this study was to analyse pathological markers of APT and PC at time of initial surgery. According to the ESE criteria, APT diagnosis is based on a radiologically invasive tumour and unusually rapid tumour growth rate or clinically relevant tumour growth despite optimal standard therapies (surgery, radiotherapy, and conventional medical treatments). We used clinical, radiological, pathological data, follow-up, and treatment from a recent published cohort of 171 tumours (121 APT and 40 PC).[9] Proliferative markers were available in about half of the 171 tumours; Ki-67 index had been evaluated in 93 tumours, p53 expression in 33 and mitotic count in 32 tumours. The five-tiered classification,[4,5] taking into account invasion and proliferation, could be applied in only 43 tumours. In this cohort of 20 PC and 23 APT, all tumours, except one PC, were invasive and at least two proliferative markers were provided. The tumours were considered as proliferative (designated "b" tumours), if two out of these three markers were above predefined cut-offs (Ki-67 ≥ 3%, mitotic count >2, or p53 positive or expressed in percentage) or highly proliferative (designated "b*; Ki-67 ≥ 10%, and mitotic count >2 and/or p53 positive or expressed in percentage). Invasion was defined as radiological

Table 1. Pathological characteristics and grading, at the initial surgery, in 43 tumours (20 PC and 23 APT).

Case	Sex	PC/ APT	Tumour types	Invasion	Ki-67 (%)	p53 (%)	Mitotic count	Grades	Follow-up Nb surg/duration/status at the last visit
1	F	PC	PRL	Invasive	>3	ND	>2	2b	4/8 yrs/deceased
2	F	PC	Pit1-Sil	Invasive	6	1	0	2b	2/10 yrs/alive
3	M	PC	ACTH-GH	Invasive	5	20	1	2b	1/6 yrs/alive
4	M	PC	ACTH-Sil	Invasive	5	60	ND	2b	3/8 yrs/deceased
5	M	PC	ACTH-LH	Giant invasive	7	7	2	2b	1/ND/alive
6	F	PC	ACTH	Invasive	8	3	ND	2b	4/ND/alive
7	F	PC	PRL	Invasive	12	1	11	2b*	1/7 yrs/alive
8	M	PC	PRL	Invasive	30	Negative	>2	2b*	3/5 yrs/alive
9	M	PC	PRL	Giant invasive	12	ND	4	2b*	2/9 yrs/deceased
10	M	PC	PRL	Invasive	20	2	9	2b*	4/5 yrs/deceased
11	M	PC	ACTH	Invasive	40	50	12	2b*	3/2 yrs/deceased
12	M	PC	ACTH	Invasive	30	30	16	2b*	2/8 yrs/alive
13	M	PC	GH-Sil	Invasive	10	Positive	ND	2b*	3/5 yrs/alive
14	F	PC	PRL	Non invasive	10	15	5	1b*	1/6 yrs/alive
15	M	PC	PRL	Invasive	15	Negative	ND	2a	2/6 yrs/deceased
16	F	PC	GH	Invasive	8	Negative	0	2a	3/15 yrs/alive
17	M	PC	PRL	Invasive	2	ND	5	2a	1/ND/deceased
18	M	PC	Pit1-Sil	Invasive	10	Negative	0	2a	3/8 yrs/alive
19	M	PC	ACTH	Invasive	0	ND	2	2a	2/ND/deceased
20	F	PC	ACTH	Invasive	2	ND	0	2a	3/11 yrs/deceased
21	F	APT	GH	Invasive	5	7	ND	2b	1/ND/alive
22	F	APT	GH	Giant invasive	8	2	1	2b	3/6 yrs/alive
23	F	APT	PRL	Invasive	6	10	2	2b	2/4 yrs/alive
24	M	APT	PRL	Giant invasive	9	9	5	2b	1/3 yrs/alive
25	F	APT	PRL	Invasive	4	Positive	1	2b	2/5 yrs/alive
26	M	APT	ACTH	Invasive	7	ND	2	2b	5/9 yrs/deceased
27	M	APT	ACTH-Sil	Invasive	6	ND	3	2b	3/14 yrs/alive
28	M	APT	ACTH	Invasive	10	30	5	2b*	1/8 yrs/deceased
29	M	APT	ACTH	Invasive	10	Positive	1	2b*	2/ND/alive
30	F	APT	ACTH	Invasive	20	4	0	2b*	2/10 yrs/alive
31	F	APT	PRL	Invasive	25	ND	13	2b*	2/7 yrs/deceased
32	M	APT	PRL	Invasive	40	15	ND	2b*	1/12 yr/deceased
33	F	APT	PRL	Invasive	10	10	ND	2b*	4/9 yrs/alive
34	F	APT	PRL	Giant invasive	23	1	1	2b*	1/7 yrs/alive
35	F	APT	ACTH-GH	Giant invasive	10	Negative	>2	2b*	3/12 yrs/ND
36	F	APT	GH	Invasive	20	30	4	2b*	1/12 yrs/alive
37	M	APT	ACTH	Invasive	3	Negative	2	2a	2/18 yrs/alive
38	F	APT	ACTH	Invasive	4	Negative	ND	2a	4/14 yrs/alive
39	M	APT	ACTH	Giant invasive	2	1	ND	2a	2/4 yrs/alive
40	M	APT	ACTH	Invasive	3	ND	0	2a	2/12 yrs/alive
41	M	APT	PRL	Invasive	18	Negative	ND	2a	1/14 yrs/alive
42	M	APT	PRL	Invasive	1	ND	0	2a	3/9 yrs/alive
43	M	APT	PRL	Invasive	8	Negative	2	2a	2/11 yrs/alive

Five-tired classification of the tumours: Grade 1b*, non-invasive and highly proliferative (Ki-67 ≥ 10%; p53 in %; mitotic count >2); Grade 2a, invasive and non-proliferative (Ki-67 < 3%; p53 negative; or mitotic count <2); Grade 2b, invasive and proliferative (Ki-67 ≥ 3%; p53 positive or in %, or mitotic count >2); Grade 2b*, invasive and highly proliferative (Ki-67 ≥ 10%; p53 positive or in %; or mitotic count >2).
Abbreviations: APT, aggressive pituitary tumour; ND, not determined; PC, pituitary carcinoma; Sil, silent.

Table 2. Comparison of the grades, at the initial surgery, in two surgical cohorts: 365 unselected tumours (cohort 1) and 43 selected APT/PC (cohort 2).

Grades	Cohort 1 of unselected tumours	Cohort 2 of selected tumours**		
		APT + PC	APT	PC
Patients (*n*)	365	43	23	20
Grades *n* (%)				
1a	187 (51.2)	0	0	0
1b	28 (7.7)	0	0	0
1b*	3 (0.8)	1 (2.3)	0	1 (5)
2a	118 (32.3)	13 (30.2)	7 (30.4)	6 (30)
2b	32 (8.8)	29 (67.4)	16 (69.5)	13 (65)
2b*	6 (1.6)	16 (37.2)	9 (39.1)	7 (36)

Grading adapted to (Trouillas et al.[4]), in the surgical cohort 2 of 43 APT/PC and in a surgical cohort 1 of 365 unselected tumours (Raverot et al.[5]). Grade 1a, non-invasive and non-proliferative (Ki-67 < 3%; p53 negative; or mitotic count <2; Grade 1b, non-invasive and proliferative (Ki-67 ≥ 3%, p53 positive or expressed in %, or mitotic count >2); Grade 1b*, non-invasive and highly proliferative (Ki-67 ≥ 10%, p53 expressed in %, or mitotic count >2) and included in grade 1b; Grade 2a, invasive and non-proliferative (Ki-67 < 3%; p53 negative; or mitotic count <2); Grade 2b, invasive and proliferative (Ki-67 ≥ 3%, p53 positive or expressed in %; or mitotic count >2); Grade 2b*, invasive and highly proliferative (Ki-67 ≥ 10%, p53 positive or expressed in %, or mitotic count >2) and included in grade 2b. In cohort 1, three markers were tested and at least two markers, in cohort 2. ** The tumours in cohort 2 were further subdivided according to the status at last follow-up into APT and PC.
Abbreviations: APT, aggressive pituitary tumour; PC, pituitary carcinoma.

signs of cavernous or sphenoid sinus invasion. According to these criteria, the tumours were classified into the following grading system: grade 1a (non-invasive and non-proliferative), grade 1b (non-invasive and proliferative), or grade 1b* (non-invasive and highly proliferative: Ki-67 ≥ 10%), grade 2a (invasive and non-proliferative), grade 2b (invasive and proliferative: Ki-67 ≥ 3%, or grade 2b*, invasive and highly proliferative: Ki-67 ≥ 10%),[10,11] and grade 3: malignant tumour with metastases.

Immunohistochemistry classified these tumours as lactotroph ($n = 18$), corticotroph ($n = 18$, including 2 silent and 3 rare plurihormonal), somatotroph ($n = 5$ including 1 silent), and 2 silent Pit1.

Results

In total, 29/43 tumours (67.4%) were grade 2b, at initial surgery, and 44.8% of them (13/29) developed metastases during follow-up. Of the 20 PCs, 13 (65%) were classified grade 2b at initial surgery, 6 tumours grade 2a, and one tumour grade 1b*. All these tumours were reclassified as grade 3 at the end of the follow-up, following development of metastases. Out of the 23 APT, 16 tumours were grade 2b (69.5%) and 7 grade 2a, at initial surgery.

Among the grade 2b tumours in the cohort, there were 7/13 PC and 9/16 APT in which Ki-67 index was ≥10% and thus classified as grade 2b*. They represented 55.1% of all grade 2b tumours (16/29). One tumour grade 1b*with Ki-67 ≥ 10% at initial surgery developed metastases. Out of the 43 tumours, 30.2% were grade 2a. No tumour was classified grade 1a or 3 at the initial surgery.

The duration of the follow-up after the first surgery varied from 1 to 14 years and was not different for patients with PC and APT. By the end of follow-up, 33/43 (77%) of patients had more than 1 surgery, and 14 patients were deceased as a direct consequence of the tumour. Pathological and key follow-up data, for each tumour, are presented in Table 1.

This selective cohort of 43 tumours (APT/PC) (cohort 2) was compared with a surgical cohort of 365 unselected tumours (cohort 1).[5] As shown in Table 2, the percentages of grade 2b tumours were different (67.4% and 8.8%, respectively), as were the percentages of grade 2b* (37.2% and 1.6%, respectively). Notably, the percentages of grade 2a tumours were similar in the two cohorts. The sensitivity of grade 2b for the diagnosis of APT, at the initial surgery, was 68% and the specificity 90% (90% CI 88%-94%).

Discussion

The prognostic value of the five-tiered classification has now been confirmed in six independent cohorts, comprising a total of 2565 patients.[4,5,12-15] The risk of recurrence/progression of grade 2b tumours was 3.5-fold higher when compared to grade 1a (non-invasive and non-proliferative) tumours, 3.5 years after surgery, and 12-fold higher at 8 years post-operatively.[4,5] Grade 2b represented 8.8%, 7.4%, 5.4%, and 8% of the tumours in four surgical cohorts of unselected tumours.[5,13-15] The % of grade 2b tumours which recurred or progressed were 68.7%, 61.9%, and 63.2%.[5,13,15] Among the 16 carcinomas included in 3 cohorts,[4,14,15] 13 were grade 2b tumour at diagnosis.

In the first ESE survey, the pathological features and the clinical outcomes of the 125 APT were very similar to those of the 40 PC.[7,8] When this cohort of APT/PC was compared with a reference surgical cohort of unselected tumours,[10] these two cohorts differed greatly, especially the percentage of tumours with a Ki-67 index ≥10% which was higher in the APT/PC cohort (35%) than in the unselected surgical cohort (3%).

In the second survey,[9] it is important to underline that no proliferative marker was provided in about half of the tumours, highlighting that better pathological evaluation of pituitary tumours is needed. Interestingly, 40.9% of the tumours tested (38/93) had a Ki-67 ≥ 10%, and at the first surgery, Ki-67 ≥ 10% was associated with a shorter survival.[9] Since 1996, Thapar et al.[16] reported that a Ki-67 index ≥10% was frequently observed in PC. Moreover, 35%-60% of APT and PC previously published had a Ki-67 index ≥10%.[10] Therefore, we can conclude that a Ki-67 ≥ 10% may be considered as a marker of aggressiveness or malignancy. However, since not all PC have a Ki-67 ≥ 10%, prognosis cannot be based only on this marker. P53 was not performed in 10 of 43 tumours. However, a study on 37 non-invasive, 33 invasive adenomas, and 7 carcinomas reported p53 expression in 0%, 15.2% and 100% of cases, respectively.[17] The authors concluded that "p53 expression may be of some diagnostic usefulness as a marker of biologically aggressive behaviour". Recently, *TP53* mutations were reported in 20%-30% of *USP8* wild type corticotroph macroadenoma cohorts,[18] characterized by recurrence after surgery and in corticotroph APT and carcinomas with ATRX mutations.[19] A large multicentre study on 86 functional corticotroph tumours revealed *TP53* mutations in 24% of invasive cases and association with more aggressive tumour features (Ki-67, invasion) and difficult-to-manage disease.[20] It should be noted that although somatic TP53 mutations are often found in invasive and aggressive corticotroph tumours, they are very rarely reported in APT of other histological subtypes.[18-21] In addition,

in pituitary tumours, p53 immunoreactivity does not reflect the TP53 mutational status. Nevertheless, we suggest testing systematically all three markers (Ki-67, mitotic count and p53) would facilitate tumour grading.

Out of these 43 APT/PC, more than a third of tumours (37.2%) were grade 2b* (Ki-67 ≥ 10%) and considered "invasive and highly proliferative" tumours. These results confirm the potential interest of this subgroup which may have a worse prognosis than the grade 2b tumour with a Ki-67 < 10%.[9,10,11] The comparison of the high percentage (67.4%) of grade 2b tumours in this selected cohort of APT/PC with the low percentage (8.8%) of a surgical cohort of unselected tumours shows that the initial pathological diagnosis of grade 2b tumour may be considered, in the clinic, as representing a diagnosis of APT. Moreover, a substantial subgroup of these tumours developed metastases supporting the proposal that an aggressive grade 2b tumour is "a tumour with malignant potential" or "a malignant tumour without metastases".[10,11] Therefore, the clinician should take note of the pathological diagnosis, at initial surgery and consider a strict follow-up and earlier use of radiation therapy and/or temozolomide treatment in the presence of unusual tumour growth and resistance to medical treatment. Early treatment of grade 2b tumours in some case may block or delay the tumoural progression.[15,22] It must be underlined that in unselected tumours, the percentage of grade 2b tumours which will become clinically aggressive or malignant remains unknown.

Limitations of this study

The absence of standardized techniques and the absence of review of the pathological reports by two independent pathologists, which was impossible by way of the nature of the survey-based study, were the main limitations. The Ki-67 evaluation is now standardized and the cut-off ≥3% accepted by the great majority of pituitary pathologists. In this retrospective study, in the absence of standardized quantification, expression of p53 varied (positive or negative or in %). Whatever the technical problems, p53 was taken into account in the grading in 33 tumours of this cohort of APT/PC. This cohort of 43 tumours is highly selective. Although small, this is the largest published cohort of APT/PC, tested with at least two proliferative markers.

Conclusion

We recommend that the pathological assessment of pituitary tumours includes the three markers (Ki-67, p53, and mitotic count). This study highlights the clinical utility of the 5-tiered classification and supports the proposal that grade 2b tumours may be "tumours with malignant potential". The pathological diagnosis, considered in the clinical context of aggressive behaviour could help the clinician in the difficult management of these pituitary tumours. Collaborative studies with large cohorts allow progress in the knowledge of rare pathologies, such as APT.

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