Aggressive pituitary tumours and carcinomas: two sides of the same coin?

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Abstract

The European Society of Endocrinology (ESE) survey reported on the largest cohort of 125 aggressive pituitary tumours (APT) and 40 pituitary carcinomas (PC). Whilst the survey focused on treatment effectiveness, all pathological data were not explored in detail. Here, we comment on some interesting pathological findings, notably the difference between APT and PC.

European Journal of Endocrinology
(2018) **178**, C7–C9

Introduction

For a pituitary pathologist, the cohort of 125 aggressive pituitary tumours (APTs) and 40 pituitary carcinomas (PCs) of the European Society of Endocrinology (ESE) survey is clearly a 'gold mine', by far the largest series thus far. As this study, recently published in EJE (1), mainly focused on treatment effectiveness, not all pathological data were explored in full detail. Here, we would like to comment on some interesting pathological findings, especially regarding the difference between APT and PC.

Comment

The ESE collaborative study demonstrated a high degree of similarity between the 125 APTs, defined as 'an invasive tumour with rapid growth, multiple recurrences and resistance to standard therapies' and the 40 PCs with metastatic disease. Clinically, the sex ratio, percentage of corticotroph tumours, percentage of tumours with Ki-67 index $\geq 3\%$, percentage with elevated mitotic count $n \geq 2/10\text{HPF}$ and p53 expression, respectively, as well as

time-to-death after the diagnosis were similar between the two groups (APT means 11 years, range 4–31; PC 12 years, range 1–26). However, mortality was higher in PC than APT patients, Fig. 1.

Here, we explore whether our survey cohort of aggressive pituitary tumours (henceforth APT+PC cohort) differed from series of pituitary tumours unselected for their aggressive behaviour. We compare the survey's results with two large series of surgically treated pituitary tumours, recently published (2, 3). In those series, gonadotroph or non-functioning tumours were the most frequent subtypes (47–50%) but were uncommon in the APT+PC cohort (18%). In contrast, corticotroph tumours were rare in surgical series (about 15%), but common (45%) in the APT+PC cohort. More importantly, in the Lyon cohort (2) in whom the two proliferative markers were systematically tested in 365 tumours, the Ki-67 index was $\geq 3\%$ in only 23.5% of all tumours compared to 82.5% in the APT+PC cohort. A Ki-67 index $\geq 10\%$, considered a sign of malignancy, was found in 46% of the APT+PC cohort, without distinction between APT or PC,

but is exceptional in other series. Furthermore, tumours displaying positivity for all three markers (Ki67 $\geq$ 3%, positive P53, mitotic rate $>$ 2/10 HPF) represent about 2% of all types (2) and 56% in the APT+PC cohort. In short, surgically treated, but otherwise unselected, pituitary tumours have clinically and pathologically distinct features.

Are malignant pituitary tumours rare? If only tumours with metastasis are considered they are very rare, accounting for just 0.2% of all pituitary tumours. The prevalence of APT is not well known. The frequency of Grade 2b pituitary tumours (invasive with high proliferation) is around 10% (4). However, not all Grade 2b tumours will develop clinically aggressive behaviour. Nevertheless, as has been demonstrated, APT and PC are clinically and histologically similar, so we suggest that APTs are ‘tumours with malignant potential without metastasis’. It is one of the reasons why it has been proposed to change the term pituitary adenomas to Pituitary NeuroEndocrine Tumours (PitNET) (5). However, it must be underlined that the majority of pituitary tumours (50–60%) are benign (adenomas) and that the great majority of malignant tumours remain well differentiated. We propose the following diagram (Fig. 2) of pituitary tumour behaviour, knowing that hyperplasia was never observed before or associated with tumour formation and assuming that the great majority of patients are cured or controlled by surgery, with or without radiotherapy or standard medical therapies.

Conclusion

In conclusion, the diagnosis of a malignant pituitary tumour remains difficult. Given that both APT and PC result

Figure 1

Similarities between the 125 aggressive pituitary tumors (APT) and the 40 pituitary carcinomas (PC).

Figure 2

Diagram representing potential pituitary neuroendocrine tumour (PitNET) behaviours.

in premature death as a result of tumour progression, we propose that an aggressive pituitary tumour is considered a tumour with malignant potential. The management of these patients must be multidisciplinary, with a dialogue between the endocrinologist, the neurosurgeon and the pathologist.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this commentary.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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Received 25 March 2018

Accepted 26 March 2018