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LETTER TO THE EDITOR

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Cellular markers in corticotroph adenomas correlate with hormones–concerns on interpretation

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Dear Editor,

We read with great interest the article written by Lim et al. [1]. (Hormonal aggressiveness according to the expression of cellular markers in corticotroph adenomas; *Endocrine*, 24 Nov 2018. https://doi.org/10.1007/s12020-018-1815-x.). Since the associations between the expressions of cellular markers of corticotroph adenomas and the hormone levels in patients with Cushing's Disease (CD) were not clear, the authors investigated the associations between these indices and found that although pituitary tumor-transforming gene 1 (PTTG1) and Ki-67 were highly expressed compared with other markers in tumor tissue, they did not reflect hormone levels. On the contrary, the expressions of cyclin D1, p27, and brahma related-gene 1 (Brg1) had better correlations with hormone levels. This article gives us a fresh view of the predictive function of tumor cellular markers to hormone levels in patients with CD, but some points need to be addressed.

First, the audience of this article, including neurosurgeons, neuropathologists, neurooncologists, endocrinologists, etc., need to correctively interpret the results and fully understand the meaning of "hormonal aggressiveness". To the best of our knowledge, "hormonal aggressiveness" has not been used in patients with CD or other pituitary adenomas. It was raised for the first time in this article. The term "hormonal aggressiveness" was defined by the authors as high levels of hormones, including plasma adrenocorticotropic hormone, serum cortisol, and 24 h urinary free cortisol, but the relationship between these hormones and aggressiveness were not studied. Even though the authors found the expressions of tumor cellular markers including cyclin D1, p27, and Brg1 were related to hormone levels, it was not proper to use "hormonal aggressiveness". Tumor aggressiveness generally represented the invasion of pituitary adenomas to the surrounding structures, i.e., cavernous sinus, carotid artery, and cranial nerves, and the Knosp system was used for aggressiveness classification. Adenomas were graded into 5 categories (from grade 0 to grade 4) based on the magnetic resonance imaging, with grade 4 the most aggressive. The biological aggressiveness of pituitary adenomas was characterized by the tumor proliferation potential according to pathology (by mitotic count and Ki-67 labeling index), and patients' resistance to treatments [2]. Although patients with CD had increased mortality and morbidity, this article did not directly investigate the relationship between hormone levels and the post-treatment consequences. In a recently published nationwide study with more than 500 patients with CD, cardiovascular disease, infections, and suicides were reported to be the commonest causes of death, and bilateral adrenalectomy and glucocorticoid replacement therapy were independent risk factors [3]. Therefore, the correlations between cellular expressions and hormone levels in this article could not be over-interpreted as disease aggressiveness and could not reflect patients' prognosis, until it was investigated and confirmed.

Second, the utility of "hormone activity" also blurred the relationships between hormone levels and their effects on patients with CD, resulting in potential over-interpretation. The "hormone activity" the authors used in this study did not reflect the actual effects of hormones in this article; instead, it reflected the levels of hormones. So, the utilization of "hormone activity" was also improper, and the authors need to use a more appropriate term to present their findings and make reasonable but not excessive interpretations.

In conclusion, readers should definitely and only learn from this study that the initial hormone levels of patients with CD were correlated with the expressions of tumor cellular markers, including cyclin D1, p27, and Brg1.

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Relationships between hormone levels and tumor aggressiveness or patients' clinical outcomes were not investigated in this article. Further studies on these relationships in patients with CD need to be validated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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References

1. J. S. Lim, M. K. Lee, E. Choi, N. Hong, I. Jee S, S. H. Kim, E. J. Lee, Hormonal aggressiveness according to the expression of cellular markers in corticotroph adenomas. Endocrine (2018). https://doi.org/10.1007/s12020-018-1815-x.
2. E. Chatzellis, K.I. Alexandraki, I.I. Androulakis, G. Kaltsas, Aggressive Pituitary Tumors. Neuroendocrinology **101**(2), 87–104 (2015). https://doi.org/10.1159/000371806.
3. O. Ragnarsson, D. S. Olsson, E. Papakokkinou, D. Chantzichristos, P. Dahlqvist, E. Segerstedt, T. Olsson, M. Petersson, K. Berinder, S. Bensing, C. Höybye, B. Edén-Engström, P. Burman, L. Bonelli, C. Follin, D. Petranek, E. M. Erfurth, J. Wahlberg, B. Ekman, A. K. Åkerman, E. Schwarcz, I. L. Bryngelsson, G. Johannsson, Overall and disease-specific mortality in patients with Cushing's disease: a Swedish nationwide study. J. Clin. Endocrinol. Metab. (2019). https://doi.org/10.1210/jc.2018-02524.