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LETTER TO THE EDITOR

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Response to Letter to the Editor: "Hormonal aggressiveness according to the expression of cellular markers in corticotroph adenomas"

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This communication is in response to the letter of Dr. Guo et al. regarding our recent publication titled "Hormonal aggressiveness according to the expression of cellular markers in corticotroph adenomas".

The aim of our study was to investigate the association between cellular markers regarding cell proliferation or tumor progression and hormonal activity in patients with Cushing's disease (CD); we reported that cyclin D1, p27, and Brg1 may be better biomarkers to show hormonal aggressiveness of the corticotroph adenoma [1]. Dr. Guo et al. commented on two major findings in our study. One was about the concept of "hormonal aggressiveness", which may be first proposed in our manuscript. And the other was about the interpretation of "hormonal activity". They stated that "hormonal activity" used in this study reflected hormone levels, but not the actual effects of hormones.

As Dr. Guo et al. mentioned, tumor aggressiveness is generally associated with the invasion of pituitary adenomas to the surrounding structures such as cavernous sinus. However, tumor size and invasiveness cannot fully explain tumor aggressiveness of ACTH-secreting pituitary adenomas, indicating that corticotroph adenomas may have distinctive characteristics, unlike other types of pituitary tumors that present as macroadenomas. The Knosp system can be used in invasive ACTH-secreting pituitary macroadenomas [2]. However, it seems difficult to apply in all of the pituitary tumors, because macroadenoma in our research accounted for only 28.6% [1]. Furthermore, Ki-67 labeling index (LI) may not be enough to determine the aggressiveness of corticotroph adenomas; half of the tumors showed Ki-67 LI with zero %, whereas only 10.7% had Ki-67 LI of more than 1.5%, as described in the Supplemental Table [1]. In this regard, neither of them can necessarily represent the aggressiveness of ACTH-secreting pituitary tumors. Hence, tumor aggressiveness in CD may be divided into two categories as follows: tumor proliferation accompanied by the invasiveness and the severity of clinical presentation caused by high hormonal activity, which indicates "hormonal aggressiveness" in this study.

Currently, none of diagnostic tests predict hormonal activity or recurrence in CD when used alone. Although preoperative hormone level itself could not completely reflect clinical outcome of patients with CD, it has been well known that prolonged exposure to hypercortisolism is associated with increased mortality of CD due to cardiovascular, metabolic, psychiatric disorders, and infections, as well as the significant clinical burden caused by comorbidities [3], suggesting that initial hormone level can be an important factor in predicting the hormonal activity of corticotroph adenomas.

We agree that the association between the expression of cellular markers and hormone activity could not be overinterpreted, because the sample size in our study was too small to determine how these cellular markers can affect the prognosis of those with CD. Nevertheless, when interpreting our findings, another point we should think about is surgical successful rate that can differ between hospitals or neurosurgeons. Surgical outcome also depends on surgeon's skill and experience. In this study, most of patients are on remission status, in spite of the long-term follow-up (mean duration: 88 months). That may be the reason why we could not find the statistical significance between these cellular markers and postoperative hormone levels,

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especially in terms of recurrence. Therefore, further study using larger sample size and long-term investigations are required to clarify the usefulness of each cellular marker in predicting clinical outcome in CD patients.

We would like to thank Dr. Guo et al. for providing insightful and valuable comments on our research.

Compliance with ethical standards

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

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