Reviewer’s report

Title: Endothelial Cell-Specific Molecule-1 as an Invasiveness Marker for Pituitary Null Cell Adenoma

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Reviewer: Takatoshi Anno

Reviewer’s report:

In this manuscript, the authors reported it is possible that ESM-1 expression would become an invasiveness marker for pituitary NCA. In NCA, ESM-1 expression was association tumor invasion and tumor size in vascular endothelial tissues but only tumor size in adenoma cells, thus concluded that pituitary NCA progression occurs through ESM-1 associated angiogenesis. However, this report includes several problems that should be addressed.

1. For new WHO classification of pituitary adenoma, "null cell adenoma requires the demonstration of immunonegativity for pituitary transcription factors and adenohypophyseal hormones". The authors are necessary to use 4th edition of the WHO classification even if the data of sample collection was before 2017. In addition, "the term of atypical pituitary adenoma is no longer recommended". In histologically it is difficult to diagnosis of malignancy for pituitary adenoma, therefor invasion on pituitary adenoma was reflected of tumor size and/or associated with angiogenesis.

2. The authors concluded that "NCA progression occurs through ESM-1 associated angiogenesis". ESM-1 expression regulated by VEGF and FGF and VEGF is a key regulator of angiogenesis which was the process of building new blood vessels. It is possibility ESM-1 expression was occurred by VEGF expression for angiogenesis of tumor.

Authors should describe more details of expression or amounts of another angiogenesis or invasive marker on sample collection. If angiogenesis marker, such as VEGF, were expression, it is possibility that ESM-1 expression was resulted for angiogenesis and VEGF expression. Please describe more details for availability of ESM-1 rather than VEGF and another markers.

3. In addition, it is not clear for conclusion of this report. Did the authors suggest that "ESM-1 expression would become an invasiveness marker for pituitary NCA"? NCA was nonfunctional pituitary tumors and asymptomatic, therefor NCA was detected it size were large and progression. If the NCA tumor was detected at small size, did the ESM-1 expression in vascular endothelial tissues become the marker of enlargement of tumors? It was difficult to understand how ESM-1 expression in vascular endothelial tissues was became the marker of invasiveness. Please describe the definition of invasion on pituitary NCA and which marker ESM-1 expression was became, for example invasion, angiogenesis or enlargement of tumors.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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No

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