

Peer Review File

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Reviewer A

The authors report a case of primary neuroendocrine breast carcinoma in a patient with a markedly elevated level of AFP. The patient was operated for a tumor of the left breast with modified radical mastectomy. It was assumed that the occurrence of neuroendocrine breast carcinoma promoted AFP secretion, because there was no reduction in AFP levels after mastectomy. There are several points to be considered.

Note: Dear reviewers, the red text in the manuscript is the modified part.

Comment 1: The WHO classification of breast tumors of 2012 is no longer used. There is a new classification in the 4th WHO edition. They do not even quote this reference, but the older one instead (Tavassoli FA, Devilee P, Pathology and genetics [M]//Tumors of the breast and female genital organs. WHO Classification of Tumors Series. Lyon, France: IARC Press, 2003: 32—34).

Reply 1: We have added the latest classification criteria for primary breast neuroendocrine carcinoma and modified it in accordance with expert opinions.

Changes in the text: In 2019, the World Health Organization redefined neuroendocrine tumors as aggressive tumors, and their characteristics are low/intermediate grade (see Page 1, line38 and Page 2, line39-40). In 2019, however, there was a radical change in the WHO classification of neuroendocrine tumors/carcinomas, neuroendocrine carcinoma was defined as an aggressive tumor, which is characterized by: low/intermediate grade, neuroendocrine morphology, and supports the presence and supported by the presence of neurosecretory granule and diffuse, uniform immunoreactivity for neuroendocrine markers (see Page 5, line127-131).

Comment 2: No immunohistochemistry for AFP was performed in the surgical material of the breast carcinoma to exclude the possibility primary AFP production.

Reply 2: We performed AFP immunohistochemical staining on the resected breast cancer tissue and the results were strongly positive.

Changes in the text: We have added a picture of AFP immunohistochemistry (see Page3, line89).

Comment 3: There are many papers reporting AFP in breast cancer, as a maker of poor prognosis. None of them is included in the reference list.

Reply 3: We have added relevant documents based on the opinions of experts.

Changes in the text: Previous research has also suggested AFP as a risk factor for breast cancer (see Page6, line153-154).

Comment 4: H&E illustrations are of low magnification, so the reader cannot rely on carcinoma morphology.

Reply 4: We have uploaded high-definition pictures.

Changes in the text: See Page3, line77 and Page4, line113-114.

Comment 5: In general, the quality of illustrations is sub-optimal.

Reply 5: We have replaced poor quality images.

Changes in the text: See Page4, line117.

Reviewer B

Authors describe a case of neuroendocrine carcinoma of the breast with markedly elevated alpha-fetoprotein.

The manuscript is well thought and interesting.

As the authors write, the invariability of AFP levels after surgery is perplexing.

Comment 1: It is not clear in the diagnostic process whether any primary origins of the tumor have been excluded for certain.

Reply 1: There were no obvious abnormalities in the related examinations of other parts of the patient after admission.

Changes in the text: And the patient had no past medical history of increased AFP, abnormal liver function, or gastrointestinal tumor (see Page1, line21-22). And the patient had no past medical history of increased AFP, abnormal liver function, or gastrointestinal tumor. Abdominal ultrasonography and enhanced computed tomography (CT) on admission indicated no obvious abnormalities either (see Page2, line68-71).

Comment 2: Furthermore, the observation period is too short to draw conclusions.

Reply 2: We followed up for 10 months and the patient has developed axillary lymph node metastasis, but no tumors in other parts have been found. Therefore, we think that the increase in AFP levels is related to the occurrence and poor prognosis of NEBC.

Changes in the text: At the time of submission, the patient has been followed up for 10 months and there has been axillary lymph node metastasis, but no tumors in other parts have been found (see Page1, line29-31 and Page4, line106-108).

Comment 3: It would be interesting to study the Immunohistochemical staining for anti-alpha1 fetoprotein in the tumor cells.

Reply 3: We performed AFP immunohistochemical staining on the resected breast cancer tissue and the results were strongly positive.

Changes in the text: We have added a picture of AFP immunohistochemistry (see Page3, line89).

Comment 4: References can be updated with: Irelli A et al. Neuroendocrine Cancer of the Breast: A Rare Entity. J Clin Med. 2020 May 13;9(5):1452. doi: 10.3390/jcm9051452.

Reply 4: We have added the above references to the text.

Changes in the text: See Page1, line38 and Page5, line131,138.