Peer Review File

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Reviewer Comments

Rare extra-mammary metastases of adenocarcinoma to the breast closely mimic primary invasive breast carcinoma (PBC) and, specifically without an aware of clinical history, pose a difficult diagnostic issue. In the manuscript "Metastatic adenocarcinoma to the breast from the lung simulates primary breast carcinoma-A clinicopathologic study", authors improved the differential diagnosis criteria of primary breast nodules and breast nodules metastasized from lung adenocarcinoma by retrieving and analyzing 41 cases of metastatic adenocarcinoma from the lung to breast.

Couple questions are required to be answered before it will be accepted.

Comment 1:

There were several similar reports (J Clin Pathol. 2007 Dec;60(12):1333-41) and (Ultrasound Q. 2013 Sep;29(3):205-9) about the differential diagnosis from lung adenocarcinoma metastasis and primary breast carcinoma in the breast in the PubMed. What is the novel idea in the paper? Please elaborate in the introduction.

Reply 1:

Thank you for your suggestion. We have modified our text as advised (see Page 4, line 89-93).

Changes in the text:

We made a comparative analysis from the perspective of the accuracy of the first diagnosis in order to explore which factors affect the accuracy of pathological diagnosis. A documented lung cancer history combined with the clinicoradiological assessment and pathological evaluation are essential to make a correct differential diagnosis.

Comment 2:

IHC was the key method in the methods. So please supplement the IHC method and the used antibodies in the methods.

Reply 2:

Thank you for your suggestion. We have modified our text as advised (see Page 4-5, line 111-115).

Changes in the text:

Immunohistochemical markers were also collected and analyzed in which lineage-specific stains for lung carcinoma (thyroid transcription factor-1, TTF-1 **(SP141, Roche Diagnostics, China)**) and those for the breast (gross cystic disease fluid protein, GCDFP-15 **(23A3, Maixin, China)** or transcription factor, GATA-3 **(EP368, Zhongshan, China)**)

as well as ER**(SP1, Roche Diagnostics, China)**, PR**(1E2, Roche Diagnostics, China)** and Her-2**(4B5, Roche Diagnostics, China)**.

Comment 3:

Please add a title each section in the part of results. It is easy to understand for reader.

Reply 3:

Thank you for your suggestion. We have added a title each section in the part of results.

Changes in the text:

Clinicopathological features of lung adenocarcinomas to the breast, retrieved from CHCAMS and literatures (see Page 5, line 123-124)

Clinicopathological features of initial diagnosis retrieved from CHCAMS and literatures (see Page 6, line 147)

IHC of initial diagnosis retrieved from CHCAMS and literatures (see Page 7, line 170)

Comment 4:

It is better to provide representative images of ultrasonography for PBC in supplementary figures.

Reply 4:

Thank you for your suggestion. We have **provided representative images of ultrasonography for PBC in supplementary figure S1.**

Changes in the text:

In supplementary figure S1.

Comment 5:

Please mark red arrow and black arrow in the figure 1 and 2. The figure 3 was not clearly enough. Please replace it with a new. Additionally, scale bar and more magnification images were also needed.

Reply 5:

Thank you for your suggestion. We have replaced figure 3 with new figure 3 and figure 4.

Changes in the text:

Comment 6:

The IHC images of GCDFP-15 and GATA-3 were missing the paper. It is more convincing to provide co-staining images of GCDFP-15 and TTF-1.

Reply 6:

Thank you for your suggestion. We have provided images of TTF-1(figure 3)and GCDFP-15(figure 4).

Changes in the text:

Comment 7:

Please supplement the discussion about main reason for misdiagnosis between metastatic adenocarcinoma to the breast from the lung and primary breast carcinoma in the discussion.

Reply 7:

Thank you for your suggestion. We have modified our text as advised. All of the 13 misdiagnosed cases from the enrolled 41 cases in this study were analyzed and compared in Table 2. It was found that history of prior non-mammary malignancy was of paramount importance in this context to be aware of by both clinicians and pathologists.

Changes in the text:

Unlike lung squamous cell carcinoma or small cell lung cancer, pulmonary adenocarcinoma metastasis to the breast is more difficult to be distinguished from primary breast cancer due to the similar morphological features they shared. Moreover, the inadequate sample size from the commonly applied fine needle biopsy may lead to lack of specific histological images such as comedo necrosis in breast carcinoma. Thus, there is a big challenge in differential diagnosis (see Page 7, line 190-195).

Comment 8:

How about the metastatic mechanisms about lung adenocarcinoma to breast? Please supplement in the discussion.

Reply 8:

Thank you for your suggestion. We have modified our text as advised.

Changes in the text:

The pathogenesis of lung cancer metastasis to breast has not been reported (see Page 11, line 281).

Comment 9:

It is an interesting topic. What are your advisements for different diagnosis in metastatic adenocarcinoma to the breast from the lung and primary breast carcinoma? Please supplement in the discussion.

Reply 9:

Thank you for your suggestion. We have modified our text as advised.

Changes in the text:

Histologically, some indicators may help to identify the metastatic adenocarcinomas and primary invasive breast carcinomas. First, elastosis is a consistent indicator of primary neoplasm but is rarely observed in secondary tumors [3]. Other studies described a sharp transition at the border of the lesion and the tumor

presence in the subcutaneous, rather than parenchymal breast tissue [30, 31]. Also noted in our series, metastatic tumors to the breast frequently showed irregular tumor borders and commonly present as a solitary (rather than multicentric) breast mass. The absence of in situ carcinoma strongly supports a metastatic tumor, although it may not occur in all primary invasive carcinomas [32, 33]. Most researchers agree that calcifications and micro-calcifications except for ovarian serous carcinoma are extremely rare and observed only in the patients with metastatic papillary carcinoma with psammoma bodies [32, 34, 35]. However, for samples from fine needle aspiration, a correct differential diagnosis is more challenging, especially for those patients without a documented history of lung cancer [34-36]. The authors experienced one such case (No.7 in table 1), which was a needle biopsy sample from a solitary mass in a 66-year-female patient. Microscopically, this patient exhibited a poorly differentiated adenocarcinoma, with scattered irregular adeno ducts in mammary parenchymal, which featured a diagnosis of primary breast cancer (seen in Fig.1). However, the patient subsequently came to consult the pathologist and provided a history of lung adenocarcinoma for 3 years and presented the original pulmonary biopsy for consultation (seen in Fig.2). Subsequently, this patient was corrected to a final diagnosis of metastatic lung adenocarcinoma to the breast by immunostaining of TTF-1 (seen in Fig.3). In this scenario, the documentation of a lung cancer history would have great importance for alerting the pathologist to exclude metastatic lesions

(Page 8-9, line 207-231).

Thank you for your suggestion.