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Reviewer A

Basis of each cancer treatment is the early diagnosis. In the most common breast cancer, it determines the success of the treatment. The authors of this publication take a very important problem of breast cancer treatment. Basic data characterizing invasive breast cancer are presented. With regard to the presented unique material describing a patient with breast cancer and thyroid metastases, a few questions arise. I am asking for an answer to them:

1. **Why was breast tumor puncture (FNA) performed and not the open biopsy with sentinel node biopsy?**

Reply1: I am very sorry for the mistake of this expression. The bilateral mammography showed an irregular hyperdense mass in the right retroareolar region. Ultrasonography revealed a 1.7 cm × 1.3 cm hypoechoic irregular mass with no blood flow at 6 o'clock direction of the right breast, and enlargement of multiple axillary lymph nodes. These results showed the lump inclined to be malignant. For further diagnosis, A preoperative Core needle biopsy of the mass was made. Besides, the reason why not to perform the open biopsy with sentinel node biopsy was the size and the location was not appropriate. We have carefully changed the expression.

Changes in text: "Core needle biopsy revealed that the cancer was IDC–NST, grade 2 (according to the Nottingham grading system)." (Page4, Line1-2).

2. What follow-up examinations were performed during the 3-year follow-up period after mastectomy?

Reply2: Thanks for your suggestion. Monitoring the patient's condition is of great significance, the metastatic breast cancer was found via laboratory tests and imagings. so, we have added follow-up examinations during 3-year follow-up.

Changes in text: "Periodic imaging and biochemical examinations were performed every 3 months." (Page4, Line13-14).

3. Please specify the breast cancer therapy conducted after surgery - medications...

Reply3: The reviewer's comment on this problem is very significant. I apologize for omissions of these important information. We have carefully added these information in text.

Changes in text: "The patient subsequently received adjuvant chemotherapy with 4 cycles of pirarubicin and cyclophosphamide regimens followed by docetaxel for 4 cycles, which was followed by toremifene therapy for 3 years" (Page4, Line11-13);

"She was started on additional radiation therapy and letrozole instead of toremifene to treat the breast cancer" (Page4, Line16-17;
"The patient was given the chemotherapy combined with targeted therapies, followed by nanoparticle albumin-bound paclitaxel, trastuzumab and Pertuzumab in January 2021." (Page5 , Line25 ; Page6, Line11).

4. Why did remove the cervical lymph nodes on both sides during thyroidectomy? Were they suspected of metastasis? If YES , on what basis?

Reply4: Yes, the cervical lymph nodes were suspected of metastasis. Blood tests showed increased carcinoembryonic antigen (CEA), CA199 and CA125, A positron emission tomography-computed tomography scan (PET-CT) revealed the elevated uptake in thyroid gland mass and multiple cervical lymph nodes on both metastasis. Besides, the patient has a history of breast cancer with involvement of axillary lymph nodes. Considering the possibility of breast cancer metastasis via lymph nodes, surgeons removed the cervical lymph nodes on both sides during thyroidectomy.(Page4, Line17-23)

5. Has primary thyroid cancer and its coexistence with breast cancer been taken into account in the diagnosis of thyroid metastases? Was CK19 determined and TG after treatment?

Reply5: The reviewer's consideration is very significant. Metastasis primary thyroid cancer and its coexistence with breast cancer had been taken into consideration. However, markers thyroglobulin (TG) and thyroid transcription factor-1 (TTF-1) ,expressed the majority of thyroid neoplasms and normal thyroid tissue, were negative in metastatic tumors and positive in normal thyroid gland. It showed that the tumor was not primary thyroid cancer. Markers GATA3 and Mammaglobin are the most commonly used markers to identify breast origin and they were positive in thyroid gland tumors. So we can make a definitive diagnosis：the origin of thyroid tumors is from breast. Cytokeratin 19 (CK19) longs to a family of keratins, used to confirm epithelial immunophenotype, which can be expressed in both thyroid tumors and breast cancers(1,2).It is not specific so the CK19 was not be determined.

6. What was the reassessment of paraffin preparations? Is pathological serial examination?

Reply6: I am very sorry for the mistake of this expression. The patient did thyroidectomy at the local hospital. The tumors were fixed and embedded in paraffin wax for specimen preparation. For further diagnosis, she took pathological HE-stained sections of thyroid gland to our pathology department for pathologists to review these sections and wax blocks for immunohistochemical staining.

Changes in text: "Wax blocks and HE-stained pathological sections of the thyroid

gland were sent to the pathology outpatient department for a definitive diagnosis." (Page5, Line5-6).

7. The discussion does not take into account the proposed recommendations – like: take the message to home.

Reply7: Thank you for giving us this significant suggestion. We have added these messages in the discussion section.

Changes in text: "In conclusion, apart from the possibility of metastatic IDC-NST to the thyroid, pathologists should take metastasis of IMPC of the breast into consideration, especially when the patient has a history of breast cancer and thyroid nodules. It is very important to make an accurate diagnosis of IMPC in primary breast cancers to promote therapy and improve prognosis of patients. Specific morphology, immunohistochemical characteristics, and gene detection are all helpful for diagnosis when IMPC of the breast has metastasized to the thyroid. In addition, HER2 FISH gene detection plays an important role and the HER2 positive patient is beneficial from trastuzumab and pertuzumab." (Page7, Line25；Page8,Line1-8).

Reviewer B

Yu and colleagues describe a rare and interesting case of an invasive micropapillary carcinoma metastasising into the thyroid gland.

There are a few issues I'd like the authors to consider.

The primary invasive breast cancer is not well characterised. It would add to the case presentation if there was information on:

1. **Radiological findings in mammogram and ultrasound including radiological tumour size in 2015.**

Reply1: I am very sorry for the omission of these results. We have carefully added these results in the case presentation.

Changes in text: "Bilateral mammography showed an irregular, hyperdense mass in the right retroareolar region (see Supplementary Fig. 1a). Ultrasonography revealed a 1.7 cm × 1.3 cm hypoechoic irregular mass with no blood flow at 6 o'clock direction of the right breast , and enlargement of multiple axillary lymph nodes (see Supplementary Fig. 1b)." (Page3, Line21-25).

2. **Histopathological tumour classification after mastectomy instead of a clinical TNM, including number of tumour involved lymph nodes.**

Reply2: Thanks for your meaningful suggestion**.** We have carefully changed these results and added the number of tumors involved lymph nodes.

Changes in text: "A right modified radical mastectomy was performed, and postoperative pathology confirmed both the histopathological tumor classification and the grade were same as the previous diagnosis, with involvement of 6 axillary lymph

nodes" (Page4, Line2-5).

3. **Histological grade of the primary tumour.**

Reply3: Thanks for your meaningful suggestion. We have carefully added this result.

Changes in text: "Core needle biopsy revealed that the cancer was IDC–NST, grade 2 (according to the Nottingham grading system). A right modified radical mastectomy was performed, and postoperative pathology confirmed both the histopathological tumor classification and the grade were same as the previous diagnosis, with involvement of 6 axillary lymph nodes." (Page4, Line1-5).

4. **Information on focality (uni vs multi) and DCIS size that could explain why mastectomy was performed instead of breast conserving surgery and which could also explain (at least in part) the clinical course.**

Reply4: According to the imaging findings, there was only a 1.7×1.3cm lump in the right breast, so this was a Unifocal breast cancer. Core needle biopsy showed the cancer was invasive ductal carcinoma with no component of DCIS. Breast conserving surgery had been taken into consideration. However, the patient was a 59-year-old woman, she had no willingness to choose breast conserving surgery, so the mastectomy was performed. We have added some important information in the paper.

Changes in text: "Bilateral mammography showed an irregular, hyperdense mass in the right retroareolar region (see Supplementary Fig. 1a). Ultrasonography revealed a 1.7 cm × 1.3 cm hypoechoic irregular mass with no blood flow at 6 o'clock direction of the right breast , and enlargement of multiple axillary lymph nodes." (Page3, Line21-25).

5. **Information on results of post-mastectomy staging in this HER2+ cancer.**

Reply5: Thanks for your significant suggestion. We have added these results in the paper.

Changes in text: "Fluorescence in-situ hybridization (FISH) results were negative for HER2 gene amplification, so the molecular subtype was identified as luminal A." (Page4, Line9-11).

"As HER2 amplification was detected, the metastatic breast cancer was classified as HER2-positive breast cancer." (Page5, Line13-14).

6. A last point is that the clinical course is probably due to both histological type and HER2 positivity in this case. Maybe the authors could add one sentence about biological behaviour of HER2+ breast cancers?

Reply6: Thanks for your suggestion. We have added some points for HER2+ breast cancers in our paper.

Changes in text: "In addition, the molecular subtype of this case should be considered. The cancer was identified as luminal A type (ER + and/or PR+, and HER2–) after breast

surgery, but 5 years later, the metastatic carcinoma was HER2+, which may be closely related to the biological behavior observed in this case." (Page7, Line14-18).

Reviewer C

This manuscript describes a case of breast cancer metastatic to the thyroid gland.

This reviewer believes that this case can be more aptly described as "a case of breast cancer metastatic to cervical region, including thyroid" rather than as "thyroid metastasis of breast cancer." With enlarged lymph nodes around thyroid, which were later histologically confirmed to harbor metastatic carcinoma, we doubt the meaningfulness of singling out thyroid lesion and discussing its significance. In many parts of the manuscript, the authors seem to consider the thyroid lesion as hematogenous spread of the breast cancer, but this reviewer believes that direct extension or spread via lymphatics from the nearby lymph nodes is more likely.

Reply: The reviewer's suggestion on this problem is of great significance. There were axillary lymph nodes involvement in the primary site. Five years later, a metastasis of IMPC breast cancer was detected in cervical region, including thyroid. It showed that the neoplasm spread via lymphatics from the axillary lymph nodes is more likely. We have changed our title and added some important results in the text.

Changes in text: "Invasive micropapillary carcinoma of mixed breast cancer metastasizing to the cervical region and thyroid: report of a rare case". (Page1, Line1-2).

"Histopathological examination revealed invasive tumor cells with lympho-vascular invasion (LVI) in both thyroid lobes……" (Page5, Line6-8).

The main point of this article seems to be pointing out the difference between "IBC-NST metastatic to the thyroid" and "IMPC metastatic to the thyroid" (page 2 line 15-16, page 6 line 15-20). This reviewer fail to see its significance. Why is this so important? This should be clearly stated in the text.

1. **Language editing recommended.**

Reply1: Thanks for your suggestion. We have improved the quality of language using the Language Editing Services from AME.

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2. Title: The word "faster" does not feel right to this reviewer.

Reply2: Thanks for your meaningful suggestion. We have changed a more appropriate title.

Changes in text: "Invasive micropapillary carcinoma of mixed breast cancer metastasizing to the cervical region and thyroid: report of a rare case". (Page1, Line1-2).

"This report presents a peculiar case in which the cervical region including thyroid gland was invaded much more easily by IMPC than by IDC-NST of the breast." (Page3, Line15-18).

"Our results suggest that IMPC metastasizes into distant organs much more easily than do other subtypes of invasive breast cancer." (Page7, Line13-14).

3. Page 2 line 7: "grade 2" The authors should specify the grading system used.

Reply3: Thanks for your meaningful suggestion. I am very sorry for the omission of it. We have added the grading system in the paper.

Changes in text: "Core needle biopsy revealed that the cancer was IDC–NST, grade 2 (according to the Nottingham grading system)". (page4, Line1-2)

4. Page 2 line 13: "TG" The full form should be provided before using abbreviation.

Reply4: I am very sorry for the omission of it. We have added the full form in the text.

Changes in text: "but negative for Thyroglobulin (TG) and thyroid transcription factor-1(TTF-1)." (page2, Line14-15).

5. Page 3 line 7: "Invasive breast cancer is recently divided into invasive ductal

carcinoma – no special type (IDC-NST) and other specific subtypes(5).” The reference does not seem to be appropriate.

Reply5: The authors would like to thank the reviewer for the suggestion. We have changed a more appropriate reference in the text. The title is: Rare Breast Cancer Subtypes. DOI: 10.1007/s11912-021-01048-4 .

Changes in text: “The most common form of invasive breast cancer, invasive ductal carcinoma, was recently divided into invasive ductal carcinoma–no special type (IDC-NST) and other specific subtypes(3)”(page3, Line5-7)

6. **Page 4, line 12-13: “Pathological biopsy revealed that thyroid gland nodules were inclined to metastatic cancer from breast.” Meaning unclear to this reviewer.**

Reply6: I am very sorry for the unclear expression. The patient only did HE-stained sections of thyroid gland with no immunohistochemistry stain at local hospital. It was difficult to differentiate the IMPC of breast from Papillary thyroid microcarcinoma. However, the patient had a history of breast cancer, and the morphological of the thyroid tumor cells were more likely to be IMPC of breast cancer (a subtype of invasive breast cancer), so the tumor of thyroid gland nodules was inclined to be metastatic cancer from breast. Then she came to our hospital for further diagnosis. We have carefully changed an appropriate expression in the text.

Changes in text: “The HE-stained sections of thyroid gland and the history of breast cancer showed the thyroid gland nodules were inclined to metastatic tumors from the breast.” (page5, Line1-4)

7. **Page 6, line 6: “metastasized in much more direct and immediate ways” Meaning unclear to this reviewer.**

Reply7: I am very sorry for the unclear expression. We have deleted the sentence and added an appropriate expression in the text.

Changes in text: “In this case, mixed components of breast cancer metastasized to the axillary lymph nodes, while only IMPC was discovered in the cervical region, including the thyroid gland.” (Page7, Line6-8)

8. **Page 6, line 14: “higher proportion” The authors should make clear what they are comparing to (pure IMPC? breast cancer without IMPC component? breast cancer in general?).**

Reply8: Thanks for your meaningful suggestion. We have added some messages to make clear the comparison.

Changes in text: “……, and that metastasis and death occur more often in these patients compared to pure IDC and IDC+DCIS” (Page7, Line22-24)

9. **Page 6, line 21: “gene detection” More elaborate description might be useful to the readers.**

Reply9: Thanks for your meaningful suggestion. We have added some important information about HER2 FISH gene detection.

Changes in text: "In addition, HER2 FISH gene detection plays an important role and the HER2 positive patient is beneficial from trastuzumab and pertuzumab." (Page8, Line6-8)

Reviewer D

Major point

1. **Authors showed this case on the assumption that two parts of IDC-NST and IMPC were different tumors, and they metastasize separately. It is just a speculation and authors told that "IPMC is easily mixed with other type of invasive neoplasm" in discussion part. We can think that this tumor is mainly IPMC and they showed different pathological form in the breast and axillary lymph nodes. This point should be considered.**

Reply1: Thanks for your meaningful consideration. Invasive micropapillary carcinoma (IMPC) is a subtype of invasive ductal carcinoma, characterized by small, hollow, or morule-like clusters of neoplastic cells without fibrovascular cores, and are situated in distinct empty spaces. IMPC differs from invasive ductal carcinoma (IDC) in its clinicopathological characteristics. Figure 3a-b showed both IDC-NST (arrow) and IMPC (triangle) in primary breast cancer and axillary lymph nodes. Besides, immunohistochemical staining revealed that characteristics of epithelial membrane antigen (EMA) expression exhibited reversed polarity, and E-cadherin was positive in most of the cell membrane for the tumor studies, which were the distinct characteristics of IMPC. In IDC-NST areas , immunohistochemical staining was not specific like Impacting expression. were 2 components, IDC-NST and IMPC in the primary site and only the IMPC had a metastasis into thyroid gland.

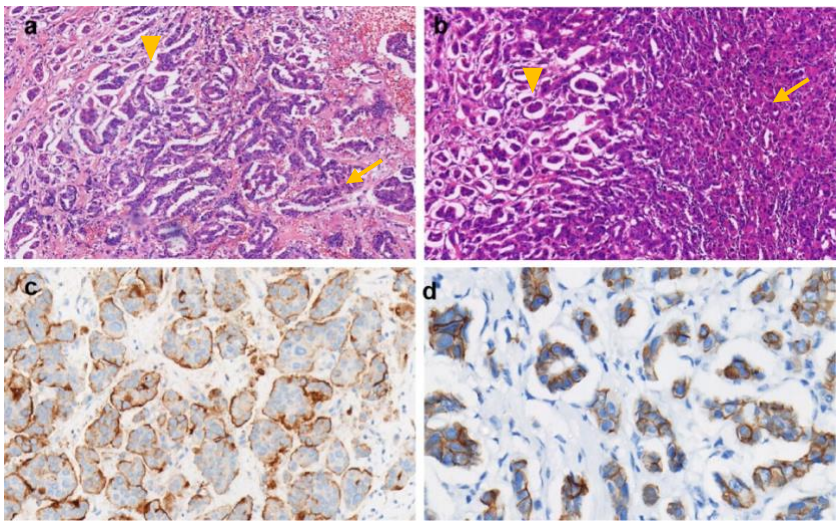

Figure 3

2. **Before the operation for thyroid, what was the diagnosis for thyroid tumors**

and cervical lymph nodes? Please clarify the clinical judgement.

Reply2 I am very sorry for the omission of it. Before the operation for thyroid, A fine-needle aspiration (FNA) was performed and it showed the thyroid nodules were malignant. Apart from the primary thyroid neoplasm, the metastasis of breast cancer had been taken into consideration. However, without morphology and immunohistochemistry, it was difficult to differentiate the IMPC of breast from Papillary thyroid microcarcinoma.

Changes in text: "Fine-needle aspiration (FNA) revealed the thyroid nodules were malignant." (Page4, Line25)

3. **Were all thyroid tumors and lymph nodes metastasis of breast cancer? Was it contained thyroid cancer?**

Reply3: The reviewer's consideration is very meaningful. Actually, the primary thyroid cancer had been taken into consideration. However, markers thyroglobulin (TG) and thyroid transcription factor-1 (TTF-1) ,expressed the majority of thyroid neoplasms and normal thyroid tissue, were negative in metastatic tumors and positive in normal thyroid gland and lymph nodes. It showed that the tumor was not primary thyroid cancer. Markers GATA3 and Mammaglobin are the most commonly used markers to identify breast origin and they were positive in thyroid gland tumors. Ultimately the patient was diagnosed with metastatic thyroid tumor.

4. **What was the diagnosis of mediastinal lymph nodes? And what was the treatment for them?**

Reply4: The reviewer's consideration is very meaningful**.** According to the PET-CT, it showed elevated uptakes in mediastinal lymph nodes. The metastasis of breast cancer could not be excluded. However, the location of mediastinal lymph nodes is not appropriate for an ultrasound-guided lymph node puncture biopsy. So, the patient received chemotherapy, and periodic PET-CT showed the decreased FDG uptake in mediastinal lymph nodes as follow up.

References

1. Cheung CC, Ezzat S, Freeman JL, et al. Immunohistochemical diagnosis of papillary thyroid carcinoma. Mod Pathol 2001;14:338-42.
2. Saloustros E, Mavroudis D. Cytokeratin 19-positive circulating tumor cells in early breast cancer prognosis. Future Oncol 2010;6:209-19.
3. Jenkins S, Kachur ME, Rechache K, et al. Rare Breast Cancer Subtypes. Curr Oncol Rep 2021;23:54.