How can we better distinguish metastatic tumors from primary tumors in the breast?

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1. Introduction

Breast cancer is the most common malignancy in women worldwide. However, metastases to the breast from extramammary solid tumors are rare and account for only 0.2–0.9% of all breast malignancies [1–3]. The most common primary tumors metastasizing to the breast vary depending on the specific patient population studied [4], but malignant melanoma, lung carcinoma, ovarian carcinoma, gastrointestinal carcinoma, and sarcoma have been repeatedly reported [4–7].

Accurate diagnosis of metastatic tumors in the breast is crucial because their staging, treatment, and prognosis are essentially different from primary breast tumors [6]. However, due to their rarity and uncharacteristic histology, it is sometimes challenging for pathologists to reach an accurate diagnosis. According to my experience as a breast pathologist [8] and a review of the literature [2–5,7,9,10], the following four points can be taken as diagnostic clues for metastatic tumors in the breast: (1) clinical history of extramammary malignancy, (2) unusual history for primary breast cancer, (3) absence of an in situ carcinoma component, and (4) lack of breast-related immunophenotype and presence of extramammary organ/tumor-specific immunophenotype. In this editorial, I present details of the clues to aid pathologists and oncologists with future diagnoses, and from my experience, I also present pathological images of four breast tumors that need a differential diagnosis between primary and metastatic tumors (Figure 1).

2. Diagnostic clues for metastatic tumors in the breast

2.1. Clinical history of extramammary malignancy

A clinical history of extramammary cancer is vital in making a diagnosis of metastasis to the breast [3,5,9]. Almost all breast cancer cases that pathologists diagnose in daily practice are primary carcinomas. Thus, suspicion of metastatic tumors may sometimes be raised only after a clinical history is provided. Therefore, clinicians should provide patients’ prior/concomitant cancer history along with tissue samples to pathologists. Similarly, pathologists should inquire of clinicians about the possibility of a metastatic tumor when they encounter cases with unusual histology or without an in situ carcinoma component.

The diagnosis may be straightforward when a patient has a prior history of extramammary malignancy, particularly if previous slides are available for comparison. However, approximately 12% of patients with a metastatic tumor of the breast have no prior cancer history [6]. In this situation, accurate pathological diagnosis of a metastatic tumor can be much more challenging. Pathologists may need to suspect a metastatic tumor based on a combination of the clinical presentation, histology, and the absence of an in situ carcinoma component. In addition, they should proactively perform immunohistochemical analysis if there are any suspicious findings, suggesting a metastatic tumor.

2.2. Unusual histology for primary breast cancer

The diagnosis of metastatic tumors is easier when the tumor has an unusual appearance for a breast primary lesion or distinct histology of its primary site of origin [10]. Two-thirds of metastases to the breast have been reported to have distinctive histological features, raising the possibility of a diagnosis [3]. The following examples can be unusual histology for primary breast tumors but are distinctive histology for metastatic tumors [3,5,10]: 1) typical nuclear features and cytoplasmic pigment in melanoma and clear cell sarcoma, 2) typical glandular appearance in colorectal adenocarcinoma, 3) typical (macro-)papillary architecture and psammoma bodies in serous carcinoma, and 4) typical clear cell morphology in renal cell carcinoma.

In the remaining one-third of cases, however, the histology could not be distinguished from primary breast tumors [3]. The following examples are histological features shared by both metastatic and primary tumors: 1) high-grade solid growth pattern in both metastatic poorly differentiated carcinoma and primary grade 3 invasive carcinoma of no special
Figure 1. Hematoxylin-and-eosin (H&E)-stained and immunohistochemical images (serial sections) of four breast tumors that needed to be distinguished between primary and metastatic (all images, magnification 100×).

Case 1 (a, b, c): Primary breast carcinoma with a prior history of metastatic lung adenocarcinoma to the bones. Presence of in situ carcinoma component (a, H&E, arrowhead) confirmed by myoepithelial markers (b, p63, arrowhead), presence of breast-related immunophenotype (c, GATA3), and lack of pulmonary immunophenotype helped to make the correct diagnosis. Case 2 (d, e, f): Metastatic clear cell sarcoma to the breast. The known prior history, distinct histology of its primary site of origin (d, H&E; arrowhead, melanin pigment), absence of in situ carcinoma component, and presence of melanoma/clear cell sarcoma-specific immunomarkers (e, HMB45; f, SOX10) helped the diagnosis. Pathologists should carefully note that SOX10, a triple-negative breast cancer-related marker, can be positive in other extramammary malignancies. Case 3 (g, h, i): Metastatic ALK-positive lung adenocarcinoma to the breast. This case was first diagnosed as primary breast cancer because the histology was uncharacteristic and clinical information on a concomitant lung tumor was missing (g, H&E). After the clinical information was provided, the absence of an in situ carcinoma component, the lack of breast-related immunophenotype, and the presence of lung adenocarcinoma-specific markers (h, TTF1; i, ALK) helped with the correct diagnosis, which resulted in systemic therapy with an ALK-inhibitor. Case 4 (j, k, l): Metastatic ovarian serous carcinoma to the breast [8]. Based on the prior history, micropapillary structures (j, H&E), and psammomatous calcifications (j, arrow), metastatic serous carcinoma was primarily suspected, but invasive micropapillary carcinoma of
the breast origin could not be ruled out considering the \textit{in situ}-like tubular foci (i, inset) surrounded by myoepithelium (j, arrowhead). The presence of a serous carcinoma-specific immunophenotype (k, WT1) and the lack of breast-related immunophenotype helped with the correct diagnosis. The histogenesis of the \textit{in situ}-like foci was explained by the spread of metastatic ovarian cancer cells into existing mammary ducts confirmed by immunohistochemistry of serous carcinoma-specific markers (k, inset, WT1) and myoepithelial markers (l, inset, p63, arrowhead).

2.3. Absence of an \textit{in situ} carcinoma component

One of the key morphological features for the diagnosis of metastatic tumors is their lack of an \textit{in situ} (intraductal and/or intralobular) carcinoma component [3,5,7]. In contrast, the presence of an \textit{in situ} component strongly supports the diagnosis of primary carcinoma. For cases with an indistinct \textit{in situ} component, immunohistochemical markers (e.g. p63, calponin, cytokeratin 14, and CD10) can be useful to demonstrate a continuous myoepithelial layer surrounding the ductal structures.

However, \textit{in situ}-like atypical ductal proliferations have been reported in metastatic tumors in the breast, and pathologists should be careful not to regard these \textit{in situ}-like structures as true \textit{in situ} carcinoma and not to exclude the possibility of metastatic tumors. My colleagues and I classified the \textit{in situ}-mimicking lesions in metastatic tumors into three categories based on their histogenesis [8]: (1) lymphovascular emboli from metastatic tumors [2,9], (2) metastatic tumors spreading into existing mammary duct units [2,8,11,12], and (3) \textit{true} \textit{in situ} carcinoma or atypical ductal/lobular hyperplasia of breast origin coexisting with metastatic tumors [10,11]. To distinguish the histogenesis of these \textit{in situ}-like architectures, we also proposed the use of an immunohistochemical panel using a combination of breast-related, extramammary organ/tumor-specific, myoepithelial, and endothelial markers (e.g. podoplanin and CD31) (Table 1).

2.4. Lack of breast-related immunophenotype and presence of extramammary organ/tumor-specific immunophenotype

Immunohistochemistry plays a major role in the accurate diagnosis of metastatic tumors in the breast. However, no marker is 100% sensitive or specific, and there is a possibility of false-negative results on small biopsy samples [3]. Thus, combined results of breast-related and extramammary organ/tumor-specific markers can be helpful to distinguish between primary and metastatic tumors and to indicate the possible primary site or tumor type of metastatic tumors. When a patient has a prior/concomitant cancer history or a breast tumor with distinct histology, a focused small panel would be enough to confirm the diagnosis. However, for a patient with no cancer history or a tumor with uncharacteristic histology, a broad panel should be used following the path of work-up of a tumor of unknown origin [4].

Lack of breast-related immunophenotype is helpful in ruling out primary breast tumors [5]. A panel of breast-related markers include some of: estrogen receptor, GATA3, mammaglobin, gross cystic disease fluid protein-15 (GCDFP15), androgen receptor, and SOX10. However, pathologists should be careful because each of the markers can also be positive in extramammary malignancies [5]: e.g. estrogen receptor for ovarian, uterine, and gastric cancers; GATA3 for urothelial cancers; mammaglobin and GCDFP15 for salivary gland tumors; androgen receptor for prostate cancers; and SOX10 for melanoma and clear cell sarcoma.

On the other hand, the presence of an extramammary organ/tumor-specific immunophenotype can suggest the primary site of metastasis [5]. Extramammary organ/tumor-specific markers include TTF1 and napsin A for lung adenocarcinoma; WT1 and PAX8 for serous carcinoma; HNF4a for gastrointestinal adenocarcinoma; and S100, HMB45, and melan A for melanoma.

3. Conclusions

Histologically correct and type-specific diagnosis of tumors metastasizing to the breast is crucial to ensure appropriate patient management. However, due to their rarity and uncharacteristic histology, it is sometimes challenging for pathologists to distinguish between primary and metastatic tumors in the breast. The prior/concomitant cancer history, histology, \textit{in situ} carcinoma component, and immunophenotype constitute four diagnostic clues to suspect and diagnose metastatic tumors. Regarding the \textit{in situ} carcinoma component, pathologists should be aware of \textit{in situ}-mimicking structures in
metastatic tumors and should not exclude the possibility of metastatic tumors.

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