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Non-Mammary Metastasis to Breast; a Diagnostic Challenge

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ABSTRACT

Background: Non-mammary metastasis to the breast poses a diagnostic challenge for the pathologists especially when no prior history of non-mammary malignancy is provided. Since non-mammary metastasis is not a very common occurrence, there is a chance that it can be easily missed especially with overlapping morphology and unknown prior history of any malignancy.

Methods: In total, 40 patients matching our inclusion criteria were identified through hospital information system in a 10-year period. Confirmatory stains were used to confirm the diagnosis.

Results: The most common primary malignancy site was gastrointestinal tract comprising 35% of the metastasis. This was followed by small cell carcinomas (17.5%). In addition, in 72.5% of the patients, there was a known history of primary malignancy but only in 18 (45%) of the cases, the clinicians mentioned it on the biopsy request form. For the remaining cases (27.5%), the clinician was contacted after the verification of the report and was asked to evaluate the possibility of metastasis from the known primary site.

Conclusion: Identifying the non-mammary metastasis is important at the time of initial diagnosis as it can prevent the patient from extensive surgery, which might not be needed, if it is not a primary breast tumor. Provision of prior history and use of immunohistochemical stains can aid in timely and accurate diagnosis.

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INTRODUCTION

Breast cancer is one of the most common cancers in the female population worldwide. However, metastasis to breast from other non-mammary primary malignancies is uncommon, varying between 0.2% and 1.3%.^{1,2,3} Since it is not a very common occurrence, there is a chance that it can be easily missed, especially with overlapping morphology and unknown prior history. Whilst the morphologically distinct tumors such as follicular carcinoma thyroid and papillary ovarian tumors are relatively easy to identify on initial

screening, the conventional adenocarcinomas from other sites are difficult to identify if no history is available. In the literature, there are very few case reports and case series of metastasis to the breast. The reports published so far show that melanoma and lung cancer are the most reported metastatic malignancy in the breast.^{1,4,5} However, to our knowledge, no such study has been published on the south-Asian population.

One of the hindrances that we face in our setup is that not all patients are registered in our own hospital for follow-up. Previous history and clinical findings are not readily available. In such instances, most of the time, if suspicion of metastasis is raised, this cannot be confirmed by radiological findings, as the patient's follow-up is not available. Clinically, metastasis represents a breast mass and can be easily missed and treated on lines of the primary breast site if the original

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primary site is not known. A multidisciplinary approach can identify such cases in time and spare the patient from the wrong line of treatment.

In this study, we aim to highlight the diagnostic challenges and role of optimal clinical information and immunohistochemistry in diagnosing non-mammary metastasis into the breast.

METHODS

The cases were selected from 2010 to 2020. The anatomical search engine in the hospital information system was used to identify metastatic tumors. Different keywords were used, including breast, metastasis, and sarcoma, in different fields of the reporting elements. Inclusion criteria were all non-mammary and non-hematolymphoid malignancies metastasizing to the breast. Exclusion criteria included cases where the sarcomatous component was part of phylloides tumor, small cell carcinomas with negative TTF1 and positive GATAIII immunohistochemical expression, and cases with ambiguous immunohistochemical results.

RESULTS.

In total, 40 patients who fulfilled our inclusion criteria were identified in a 10-year period. The ages of the patients ranged from 16 to 72 years. The laterality of the breast was right-sided in 20 patients, 17 were from the left breast, and in 3 cases, laterality was not known as the biopsy was performed outside the hospital. In 72.5% of the patients, there was a known history of primary malignancy, but out of those only in 18 (45%) cases, the clinicians mentioned

it on the history sheet submitted along with the biopsy. For the rest of the cases (27.5%), the clinicians was contacted after the verification of the report and was asked to evaluate the possibility of metastasis from the known primary site (Table 1).

Providing such information is very important as routinely no immunohistochemical stains are performed on invasive breast tumor unless there is a history of prior malignancy from other sites. If this information is provided beforehand, targeted immunohistochemistry is performed and there is less chance of misinterpreting the tumor as primary breast cancer.

Table 2 shows the variety of metastatic malignancies found in the breast in a 10-year period. All these were confirmed by the positivity of relevant confirmatory stains. The most common primary malignancy site was gastrointestinal tract comprising 35% of the metastasis. Among these, colorectal adenocarcinoma was the most common primary diagnosis. This was followed by small cell carcinomas of the lung (17.5%). The small cell carcinomas with GATA 3 (breast specific immunohistochemical stain) positivity were excluded from this study as they were considered primary breast small cell carcinomas. The next most common tumors were from ovarian serous carcinomas (10%), melanomas (12.5%), myeloid sarcoma (7.5%) and Ewing sarcoma (5%). There was one case of leiomyosarcoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma and clear cell renal carcinoma.

Table 1. Patients’ characteristics

Total number of patients	40
Age range	16 years – 72 years
Laterality	
Left	17
Right	20
Not known	3
Type of biopsy	
Core biopsy	28
Resections	7
Mastectomy	5
History of primary malignancy	29 (72.5%)
History provided beforehand	18 (45%)
History provided after reporting	11 (27.5%)
No known prior history	11 (27.5%)

DISCUSSION

Breast cancer remains one of the most common tumor in women worldwide, affecting at least 1 in 9 women in Pakistan.⁶ Metastasis to the breast is not a very common occurrence. This most often requires the provision of appropriate history.⁷ It is important to recognize this in reporting routine diagnostic biopsies

as the management plan is entirely different for metastatic disease, and patients can be spared unnecessary aggressive breast surgeries.⁸ This makes the provision of appropriate history at the time of slide examination more important.

**Table 2.** The primary malignancies metastasized to the breast.

Primary malignancies detected	Numbers
Gastrointestinal primary	
Upper gastrointestinal tract	7
Colorectal primary	7
Respiratory tract	
Small cell carcinoma	7
Lung adenocarcinoma	1
Gynecological tract	
Ovarian serous carcinoma	4
Melanoma	
Skin	4
Eye	1
Hematolymphoid	
Myeloid sarcoma	3
Soft tissue sarcoma	
Ewing sarcoma	2
Leiomyosarcoma	1
Endocrine	
Anaplastic thyroid carcinoma	1
Follicular thyroid carcinoma	1
Genitourinary tract	
Clear cell renal cell carcinoma	1
Total No	40

According to WHO guidelines of breast 2019,⁹ all invasive breast carcinomas are diagnosed on histological sections of Hematoxylin and eosin stain only. Routinely, immunohistochemistry is not performed unless there is a history of any other known primary malignancy or an ambiguous morphology. Our department is one of the busiest among the other tertiary care hospitals in the country. For reference, our annual workload for total histology cases for the year 2021 was 87406, and out of them, 14141(16.17%) were breast cases which is a significant number. There are eight pathologists in our department who share routine breast cases. For this study, data was collected from the last 10 years.

As discussed previously, we did not include hematolymphoid malignancies in this study, focusing on 40 cases for this study. Comparatively, Hadju² published the study of 50 cases of non-mammary breast tumors metastatic to the breast, including lymphomas.

The data collected showed that in 18 out of 40 cases, the history of prior malignancy was available at the time of reporting. In 11 cases, the history was provided after the verification of the report. Therefore, these cases were reviewed again with appropriate immunohistochemical stains to confirm the clinical suspicion of metastasis to the breast. Such cases included serous carcinomas from the ovarian origin, colorectal adenocarcinomas and squamous cell carcinomas of the esophagus. The immunohistochemical stains used to distinguish the serous tumors of the ovary were WT1, Pax8 and GATA3. The point

to be noted here is that some of the breast tumors can also show WT1 positivity,¹⁰ but prior history, GATA3 negativity and Pax8 positivity confirmed the diagnosis. Metastasis of ovarian tumors to the breast is apparently not an uncommon occurrence and a significant number of case reports have been published in the literature.^{11,12} Similarly, metastasis from colorectal primaries are adenocarcinomas, which morphologically can mimic the invasive ductal carcinoma of the breast with mucinous features on core biopsy. The only way to identify them was the presence of widespread necrosis and a history of known primary. Cytokeratin (CK)7, CK20, GATA 3, CK20 and CDX2 immunohistochemical stains were applied for confirmation.¹³

Interestingly, there was no known prior history of malignancy in 11 cases, and breast biopsy confirmed the primary malignancy. The bulk of these tumors were small cell carcinomas. In our study, we only included the small cell carcinomas, which were either GATA3 negative or showed positive TTF1 staining.¹³ GATA3 positive small cell carcinomas were considered primary breast tumor and were not included in our study.

Thyroid malignancies metastasizing to the breast are very rare.¹⁴ There was a female patient in her 30s with very well-differentiated thyroid tissue present in the lumpectomy specimen. This case required input from the treating physician because based on the morphology observed, the differential diagnosis included ectopic thyroid tissue and follicular carcinoma of the thyroid. TTF1 immunohistochemical stain was positive (Figure 1).

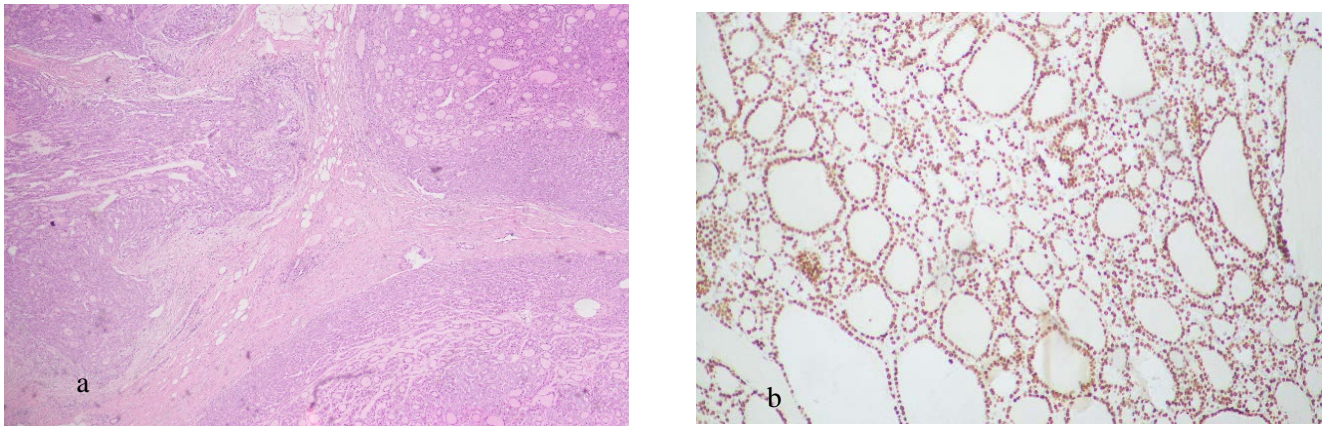


Figure 1. a) Metastatic follicular thyroid carcinoma to the breast. b) TTF1 immunohistochemical stain, which is diffusely positive.

After the verification of the report, the feedback from the primary physician confirmed this to be follicular thyroid carcinoma.

In other similar studies, melanoma was the most common tumor metastasizing in the breast.^{15,16,17,18} However, most of these studies focused on American or Asian populations. It is interesting that melanoma was not among the top tumors in our population. Similarly, one of the cases of melanomas was diagnosed after E-cadherin stain as well as hormone receptors turned out to be negative. This observation raised our suspicion, as invasive lobular carcinomas are usually positive for hormone receptors. This led to performing S100 and HMB45 staining, which were diffusely positive. The other 2 melanoma cases were morphologically suspicious for melanomas with a moderate amount of melanin pigmentation. In one of the cases, there was already a history of melanoma of orbit, which was confirmed immunohistochemically. Caution must be applied for SOX10 immunohistochemical stain, which is sometimes used for melanoma diagnosis, as it can also be positive in primary breast malignancy.

To diagnose such cases, a team-based approach is necessary.¹⁸ For example, one of the cases was initially reported as invasive mammary carcinoma with metaplastic features on the breast core biopsy, with a squamous differentiation. Later, in a multidisciplinary team (MDT) meeting, it turned out that the patient was a case of esophageal squamous cell carcinoma and had been treated for it 5 years back. The hormone receptors and HER2/neu were negative. So, based on the MDT information and lack of conventional ductal component, it was considered as a metastatic tumor rather than a primary breast malignancy.

The need for correct timely diagnosis cannot be emphasized enough as this saves the patient from overtreatment.¹⁹ Our study included five mastectomy specimens, 3 of which turned out to be small cell

carcinomas widespread in the whole body, including the lung, mediastinum and brain. This was confirmed by immunohistochemistry (Figure 2).

Upfront surgery in widespread small cell carcinoma is debatable.²⁰ In our study, one was ovarian serous carcinoma and one was signet ring cell adenocarcinoma from the gastrointestinal tract. In these cases, none of the primary core biopsies was reported in our institute. This again shows that knowledge of the prior history of malignancy and radiological findings at the time of primary diagnosis can lead to the correct diagnosis and save the patient from unnecessary surgeries.

To the best of our knowledge, this is the only study, which considered a population from Pakistan in particular, and South Asians in general. Compared to other studies on Asian or western populations, our results are quite different. For example, a study of 28 such cases by Shulin Zhou,²¹ showed that the most common non-mammary tumor site metastasizing to the breast was the lung. In our population, the most common primary site to metastasize to the breast was from the gastrointestinal origin, followed by the lung, melanoma and gynecological tract. However, other studies found that melanoma and gynecological primaries to constitute most of the metastases.^{15,16,17}

One of the difficulties we encountered was the absence of a central health record system in our country where the cases, which are not treated here usually, are lost to follow-up and obtaining the prior history becomes impossible. In the data collection period, all the patients identified with non-mammary metastasis to the breast were females. Immunohistochemistry is helpful as there are sensitive immunomarkers for specific malignancy, as shown in (Table 3), but this alone cannot unequivocally suggest metastasis without clinical input.²² Seven patients showed negative breast immunohistochemical marker (GATA3, mamoglobin or GCDFP15) with only CK7 positivity (Table 3).

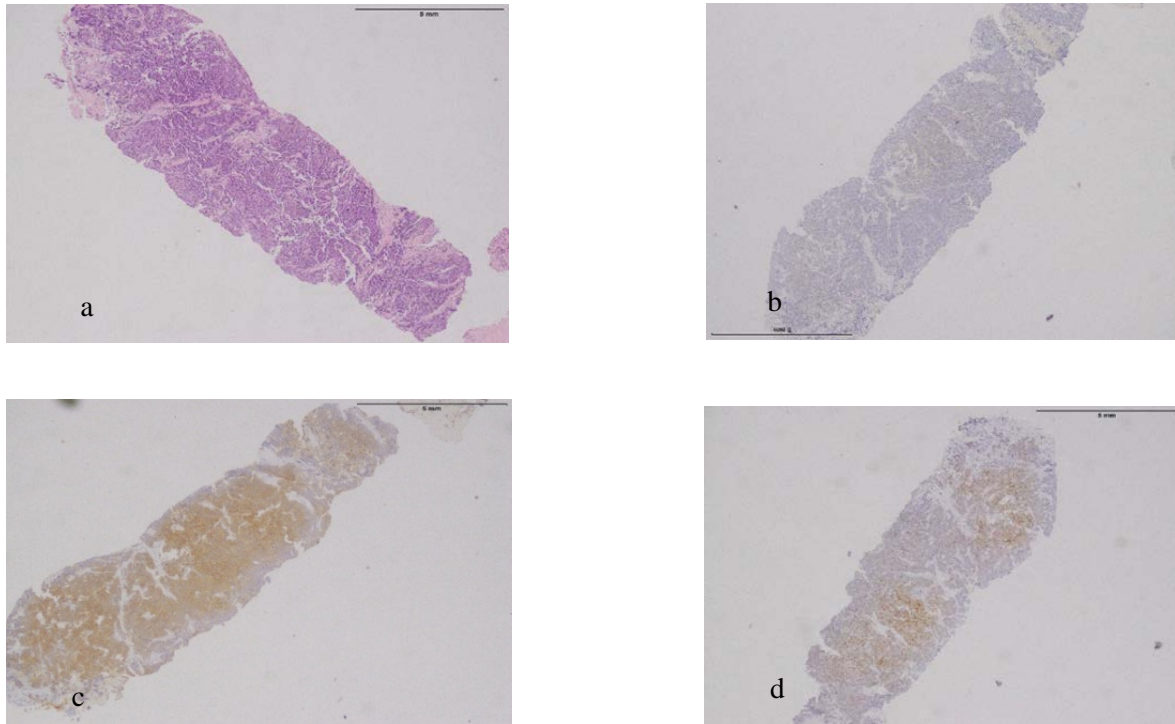


Figure 2. Small cell carcinoma metastasizing to the breast. a) Hematoxylin and eosin (H&E) b) GATA3 c) Synaptophysin d) TTF1

There was a suspicion raised for metastasis, but no follow-up was available and no organ-specific immunohistochemical marker was positive. Therefore, we had to exclude them from the study. Our results are

comparable with the results reported by DF Delair,⁸ and Peng Sun,⁹ (Table 4). However, in our population, the most common non-mammary malignancy was from the gastrointestinal tract.

Table 3. Important immunohistochemical markers for specific primary malignancies

Primary malignancy	Immunohistochemical stains used
Ovary	WT1, Pax8, Ck7
Upper gastrointestinal tract	CK7, CDX2,
Lower Gastrointestinal tract	CK20, SATB2
Respiratory tract	Synaptophysin, TTF1, CD56, CK7
Melanoma	HMB45, MelanA
Myeloid sarcoma	CD34, CD117, Myeloperoxidase
Ewing Sarcoma	CD99
Leiomyosarcoma	Desmin
Thyroid tumors	TTF1, Pax8
Renal tumors	Pax8, Carbonic anhydrase

Table 4. Comparison of our results with those reported by two already published studies

Our study	DF DeLair et al(2013)((16))	Peng Sun et al (2016)((17))
Gastrointestinal tract =14(35%)	Melanoma = 18(21.7%)	Lung and Nasopharynx = 9(41%)
Respiratory tract =8 (20%)	Sarcomas= 18(21.7%)	Ovary = 3(13.6%)
Melanoma= 5(12.5%)	Ovarian= 14(16.8%)	Melanoma = 3(13.6%)
Ovarian serous carcinoma = 4(10%)	Lung = 11 (13.2%)	Gastrointestinal tract= 2(9%)
Myeloid sarcoma = 3(7.5%)	Gastrointestinal tract= 7(8.4%)	Thyroid = 1(4.5%)
Ewing sarcoma = 2(5%)	Genitourinary tract = 5(6%)	Cervix = 1 (4.5%)
Leiomyosarcoma = 1(2.5%)	Gynaecological tract = 5(6%)	Sarcoma 3 (13.6%)
Anaplastic thyroid carcinoma = 1(2.5%)	Thyroid = 2(2.4%)	
Follicular thyroid carcinoma= 1(2.5%)	Skin/salivary gland/oral cavity=	
Clear cell renal cell carcinoma = 1(2.5%)	3(3.6%)	
Total Number of cases= 40	Total number of cases=83	Total number of cases=22



CONCLUSION

Metastasis to the breast, although rare, needs to be diagnosed in timely manner with the help of both pathologists and clinicians. Pathologists have a role to play by identifying the morphological patterns and immunohistochemistry, which do not match the primary breast tumor. On the other hand, clinicians are responsible to provide essential history and physical findings along with a biopsy to make sure that the diagnosis is made sooner to prevent any irrelevant treatment. It is the teamwork for the benefit of patients that can lead to appropriate and timely diagnosis and management.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest or any financial association with any organization.

ETHICS APPROVAL STATEMENT

We received an exemption letter from the IRB of Shaukat Khanam Memorial Cancer Hospital and Research center, dated 20-June 2020, No., EX-24-06-20-01.



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