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Case Report



# Lobular Carcinoma of the Breast Presenting as a Metastatic Melanoma to the Axilla: Report of a Case and Review of the Literature

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## Abstract

Metastatic melanoma may simulate a broad spectrum of primary malignant tumors. Significant similarity in cytomorphologic features can exist in both melanoma and lobular carcinoma of the breast. This can cause significant diagnostic difficulty, especially when there is inadequate patient history and/or limited biopsy material. The extraordinary phenotypic plasticity of metastatic melanoma adds to the diagnostic challenge of these tumors. Awareness of this pattern variance is essential to avoid diagnostic errors and inappropriate treatment. Here we present a case of metastatic lobular carcinoma, which was initially diagnosed as metastatic melanoma. Awareness of the similar cytomorphologic features of both melanoma and lobular carcinoma as well as the use of immunohistochemistry studies aided in providing the final diagnosis of this case and avoiding a diagnostic error.

**Keywords:** Immunocytochemistry, Invasive. Metastatic. Lobular. Carcinoma, Melanoma

## Abbreviations

FNA: Fine needle aspiration; ILC: Invasive Lobular Carcinoma; IDC: Invasive Ductal Carcinoma; BCS: Breast-Conserving Surgery; IHC: Immunohistochemistry; ICC: Immunocytochemistry; ER: Estrogen receptors

## Introduction

Excluding non-melanoma skin cancer, breast cancer is the most common cancer in women worldwide with over 2 million newly diagnosed cases per year. Breast cancer is the most common cause of cancer death worldwide in women and is the second most common cause of cancer deaths in women in the USA [1]. Invasive lobular carcinoma (ILC) represents 5-15% of all the breast cancer, making it the second most prevalent carcinoma of the breast. With approximately 25-38 thousand new cases annually, ILC is the 6th most prevalent form of cancer in women in the U.S. [1]. Trends over the past 20 years show an increased incidence of ILC in women over 50, which is thought to be due to postmenopausal estrogen hormonal therapy [2].

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Although metastatic melanoma is correctly identified largely by routine microscopic evaluation, in some cases its distinction from a primary breast tumor, especially invasive lobular carcinoma, may be difficult when the tumor presents as a metastasis to lymph node or distant metastasis. Metastatic malignant melanoma to the breast itself can be the cause of another challenging diagnosis [3]. The diagnostic challenge is even greater when a metastatic disease is detected in a patient with history of both malignant melanoma and invasive breast lobular carcinoma as the case in this report.

## Case Presentation

An 84-year-old woman presented with a right upper back, 1.8 cm irregular, and multihued, pigmented irregular skin lesion, which was excised and diagnosed as malignant melanoma extending to the lateral margin. Patient refused re-excision for a safe margin, but elected to receive post-operative radiation. The patient reported history of right breast infiltrating lobular carcinoma two years prior to current presentation, in addition to history of endometrial carcinoma five years prior to breast carcinoma. Breast carcinoma measured 1.7 cm, was ER positive and Her-2 negative with negative sampling of sentinel lymph node. It was treated with lumpectomy followed by external partial-breast irradiation and hormonal treatment. Endometrial carcinoma was localized and was surgically treated with total hysterectomy and bilateral salpingo oophorectomy. No additional post-operative treatment was provided.

Two weeks later, she returned to the hospital with a right axillary mass. Sonography demonstrated a 1.5-cm region of ill-defined mixed echogenicity corresponding with a firm palpable right axillary lymph node suspicious for metastasis. The patient underwent a fine-needle aspiration of the right axillary soft tissue nodule with the clinical differential diagnosis of metastatic melanoma, scar tissue, and metastatic carcinoma.

The cytology material was sufficient to produce a cellblock preparation. Cytology slides revealed a hypercellular specimen with numerous malignant single cells and rare crowded groups displaying anisonucleosis, eccentric nuclei, dense cytoplasm, and large conspicuous nucleoli, some binucleated (**Figure 1A**). The cellblock material showed an infiltrating solid tumor composed of single malignant cells with eccentric nuclei (**Figure 1B**). With the known recent history of malignant melanoma, these findings were highly suggestive of metastatic melanoma. The case was initially diagnosed as cytomorphologically consistent with malignant neoplasm, with features of malignant melanoma pending further characterization utilizing Immunocytochemistry studies on cellblock preparation. The tumor cells were negative for S100, HMB-45, Melan-A, and E-cadherin, with positive staining for cytokeratin AE1.3 (**Figure, 1C**), high-molecular-weight cytokeratin 903, and estrogen receptors (>90%) (**Figure 1D**). These findings confirmed the presence of invasive lobular carcinoma. Review and comparison with prior breast carcinoma showed similar cytomorphologic features and similar immunohistochemistry profile. Metastatic melanoma in the breast area is an uncommon finding but must be considered in cases with cytomorphologic features of melanoma presenting in breast cytology specimens. Despite the recent history of melanoma in our patient, it was important to consider the possibility of metastasis from a prior carcinoma (endometrial or lobular). Cytology material alone including cellblock preparation was sufficient to provide definitive diagnosis without the need of tissue biopsy. A full body scan showed no evidence of metastatic disease in any other sites. The lymph node was excised followed by radiation therapy to the right axillary region. Nine months later, the patient expired due to complicated heart failure unrelated to the prior carcinoma.

## Discussion

In comparison to patients with invasive breast ductal carcinoma, patients with breast invasive lobular carcinoma have been described to have significantly improved disease-free survival and overall survival in the initial years following the diagnosis of early-stage breast cancer. However, some studies have shown that this initial advantage is tempered by a higher risk for late recurrence for patients with ILC. Studies reviewing overall survival have not seen consistently significant differences between ILC and IDC [4]. Shakoor et al studied the unique presentations of invasive lobular breast cancer in three case series and concluded that a high level of suspicion is needed for metastatic breast cancer in patients with history of ILC, regardless of disease-free interval. Since it frequently metastasizes to unusual sites, presentation can be a wide spectrum of symptoms, and although the pattern of ILC metastasis may be debated, ILC has been shown to have the ability to be highly metastatic with frequent multiplicity and bilaterality [5]. Gonzalez et al, reviewed the pattern of ILC metastasis and its presentation at unusual sites such as the gastrointestinal tract, genitourinary system, peritoneum, retroperitoneum, bone, bone marrow, CNS, leptomeninges, and orbit. This knowledge may aid in accurate imaging interpretation and treatment planning in patients with metastatic ILC of the breast [6].

Melanoma often manifests with a diverse cytologic appearance that may include a dyshesive single cell pattern or a cohesive

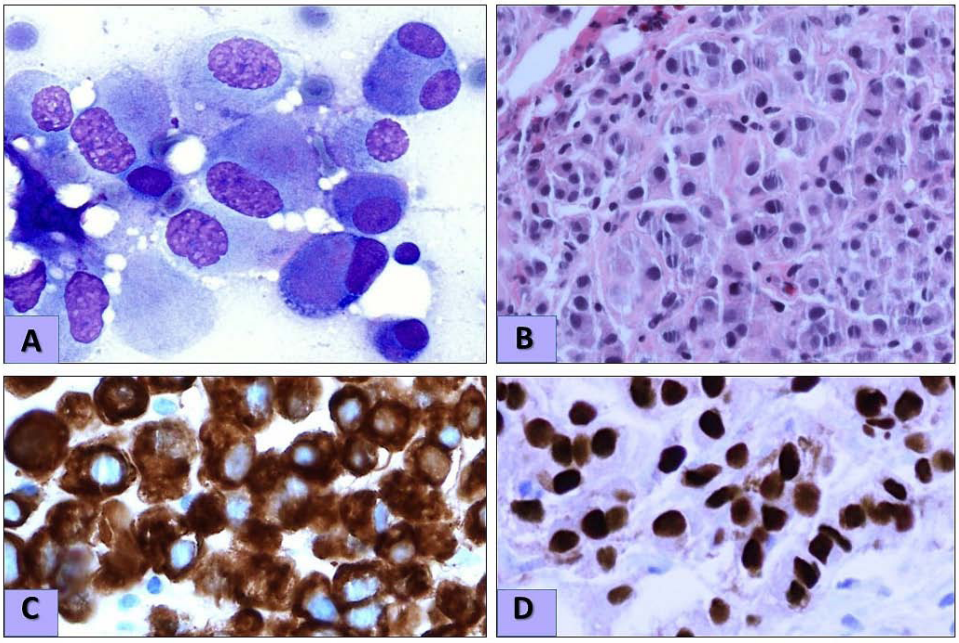


**Figure 1 A)** Cytology slides revealed a hypercellular specimen with numerous malignant single cells and rare crowded groups displaying anisonucleosis, eccentric nuclei, dense cytoplasm, and large conspicuous nucleoli (Diff Quick stain X100). **B)** The cellblock material showed an infiltrating solid tumor composed of single malignant cells with eccentric nuclei (H&E stain X60). **C)** Breast lobular carcinoma cells showing positive staining for cytokeratin AE1.3. **D)** Breast lobular carcinoma cells showing positive staining for Estrogen receptors (>90%).

cellular arrangement, which can mimic the cytomorphologic features of ILC. Cytologic evaluation in cases of ILC can be challenging, even with the known specific cytomorphologic guidelines, leading to a higher rate of reported false-negative results when compared to cases of invasive ductal carcinoma (IDC) [7]. As in our case with axillary metastasis, the axillary node status is the most important prognostic factor in patients with breast carcinoma [8]. Similarly, sentinel-node status, which is in the axillary region, is the most important independent predictor of survival, even among those patients with melanoma [9].

The immunohistochemistry profile of breast lobular carcinoma is well described. ILCs are estrogen receptor (ER) positive in approximately 93.1% of the cases [10], and while CCND1 amplification is frequently found in ILC, HER2 amplification is reported to be infrequent in ILC [11]. Cytokeratin positivity in malignant melanoma is extremely rare. A previous study found only a single case out of 117 FNA samples of metastatic melanoma that was positive for low molecular weight cytokeratin [12]. Through RNA expression, seven genes have been identified (VDAC, FBXL3, BAG4, NVL, ARGLU, ATOX1, KIF2C) that are prognostic in invasive lobular carcinoma (ILC) [13]. Certain alterations have been frequently observed in previous studies comparing IDC and ILC in highly recurrent regions such as 1q and 16p gains, 16q and 17p losses [14]. Recently, it has been proposed that FGFR1 could be the chromosome 8p12 driver amplicon, as was observed in 15% of ILC cases (14). More interestingly, ILC did not observe FGFR1 amplification in primary tumors, but three of 11 recurrent tumors harbored amplification [15]. When taking the context of tumor cells and the analytical sensitivity into consideration, BRAF mutations are found in 50–70% of metastatic melanoma patients [16] with V600E and V600K substitutions represent the 2 most common BRAF mutations in melanoma. This RAS-RAF-MEK-ERK pathway is constitutively activated in melanomas harboring mutations in oncogenes such as BRAF and NRAS, respectively mutated in about 50 % and 15 % of these tumors respectably [17]. Approximately half (52%) of the ILCs display either normal or long telomeres though a subset of ILCs demonstrated a unique bright telomere spot phenotype [18]. Similarly, in melanoma the h*TERT* (telomerase reverse transcriptase) is frequently overexpressed due to its promoter's activation, suggesting that telomerase could be necessary for melanoma development [19].

Sensitivity of MRI in the detection of invasive lobular carcinoma was recently shown to be 99%, which was higher than that of mammography and ultrasound. Mammography and ultrasound tended to underestimate ILC, and MRI estimates of final tumor size were concordant in the majority (58.6%) of cases, with a median discordance of 2 mm [20]. ILC is shown to be more prone to incomplete surgical excision and subsequent re-excision than other histological types of breast cancer. Reported re-excision rates in ILC after Breast-Conserving Surgery (BCS) can be as high as 60% [21]. The concern that tumor multicentricity could result in a negative margin but leave residual tumor in the breast has led some to advocate for wider margins in ILC, and even total mastectomy. Application of the margin consensus guidelines can result in significantly fewer re-excisions for patients with ILC [22].

Immunohistochemical staining for tumor diagnosis in breast carcinoma is, a vital tool in the diagnosis of ILC when multiple possible metastases are presented. Along these lines, Immunohistochemical studies of the basal/myoepithelial cell markers CK5, CK5/6 or CK14, and p63 have been reported to be useful for histological diagnoses in mammary tissues, including those retrieved by core needle biopsy [23]. Immunohistochemical assays have the advantage of being easier to perform, are applicable to all tumors irrespective of their size, and are less expensive. IHC is more sensitive, specific, and economical. One such example of its versatile use is an Immunocytochemistry antibody cocktail of P63/cytokeratin7/18/cytokeratin5/14 which showed good sensitivity and specificity for diagnosing breast cancers thus is a method useful for mammary cytology FNA [24].

Interestingly, Nicholas A et al reported an unusual case of two cancers in one: breast carcinoma with underlying Melanoma. They reported a 61-year-old woman who presented with a diagnosis of metastatic invasive lobular carcinoma of the right breast, and after treatment it had regressed and was stable except for a scalp nodule. When biopsied, the outer edges of the scalp lesion had findings consistent with breast carcinoma; however, the bulk of the tumor's pathology was consistent with melanoma. It appeared that most of the tumor was a highly vascularized melanoma with lobular breast carcinoma noted at its edges [25]. It is our hope that reporting this case will raise awareness of clinicians and pathologists to the cytomorphologic similarity between invasive lobular carcinoma and malignant melanoma. Immunocytochemistry is essential for confirmation and for definitive diagnosis even in presence of convincing cytomorphologic features. Cytology specimens alone such as Fine needle aspiration, especially when adequate to produce a cellblock is sufficient for all required testing including IHC and/or molecular testing to provide a definitive diagnosis without the need for surgical biopsy.

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