Cutaneous breast cancer of unknown primary

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INTRODUCTION

Metastatic breast carcinoma of unknown primary is a rare entity that can be mistaken for ectopic mammary neoplasm.[1] The axilla is the most common location for both diagnoses.[1,2] Although the pathogenesis of ectopic breast carcinomas is analogous to those arising from orthotopic tissue,[2] the mechanism of metastasis in the absence of an original tumor is still not fully understood. Metastasis is an intricate process resulting from interactions between tumor cells and their home and distant microenvironments.[3] This process is also influenced by epigenetic factors and orchestrated by local and systemic immune responses that either limit or enable the malignant growth of disseminated cells.[3] Herein, we present a case of axillary cutaneous invasive lobular carcinoma of breast origin with no detectable primary source, discuss plausible mechanisms for the pathogenesis of this lesion, and offer insights into treatment.

Abbreviation used:

EMT: epithelial to mesenchymal transition
HER2: human epidermal growth factor receptor 2

CASE REPORT

A 70-year-old woman presented with a firm, painless mass on the right axilla. Stable over the preceding year, the mass had begun increasing in size, causing friction with her undergarment. The patient had a personal history of melanoma in situ and a family history of maternal endometrial cancer, paternal glioblastoma, and cutaneous T-cell lymphoma in her daughter. Examination revealed a nontender 3.2-cm orange-pink firm plaque on the right medial axilla with a pitted surface and no secondary changes (Fig 1, *A*). The initial differential included xanthoma, spontaneous keloid, and adnexal gland neoplasms. The post-excision scar is shown in Fig 1, *B*, one year after diagnosis. A punch biopsy sample showed atypical intradermal epithelioid cells arranged singly and in cords (Fig 2, *A* and *B*). Immunohistochemistry was positive for estrogen receptor, cytokeratin 7 (Fig 2, *C* and *D*), BRST2, GATA3, and mammaglobin and negative for progesterone receptors, thyroid transcription factor 1, paired box gene 8, ERG, CK20, and E-cadherin. Overall findings were consistent with an intermediate-grade invasive carcinoma of breast origin and lobular type. Fluorescence in situ hybridization was negative for human epidermal growth factor receptor 2 (*HER2*)/*Neu* amplification. The patient was up to date with malignancy screening, and her last mammogram 1 year prior was unremarkable. Bilateral breast magnetic resonance imaging and repeated mammography showed no evidence of malignancy. Additionally, no lymph nodes or internal metastasis were appreciated on positron emission tomography scan. Chest computed tomography demonstrated no metastasis to the contralateral breast or axilla or internal mammary or axillary adenopathy. The patient underwent wide surgical excision of the mass (Fig 1, *B*) along

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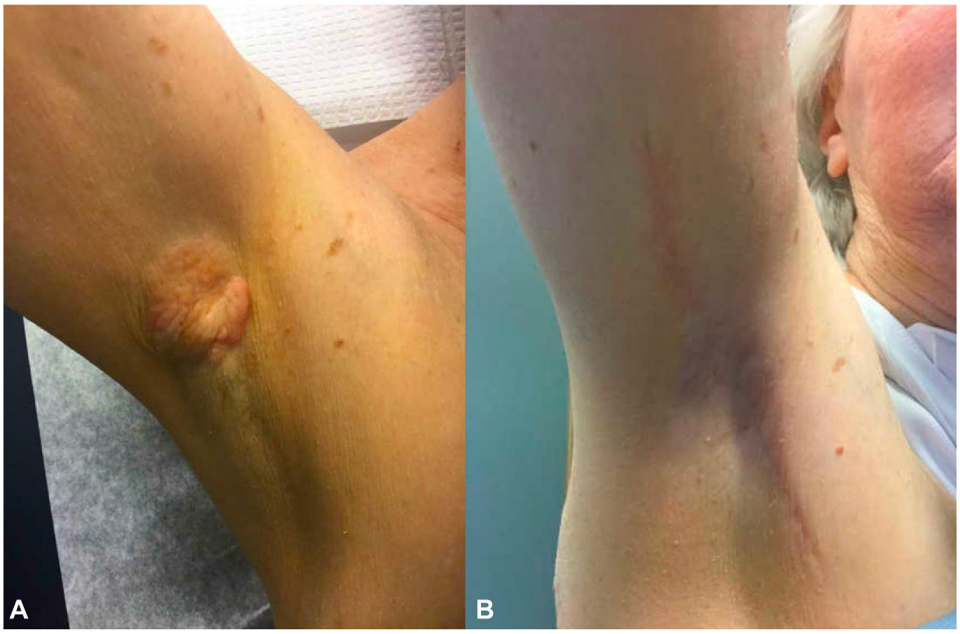

Fig 1. A, Initial clinical presentation of cutaneous breast cancer of unknown primary. The figure shows a firm orange-pink 3.2-cm plaque on the right axilla. **B,** Axillary site 1 year after excision.

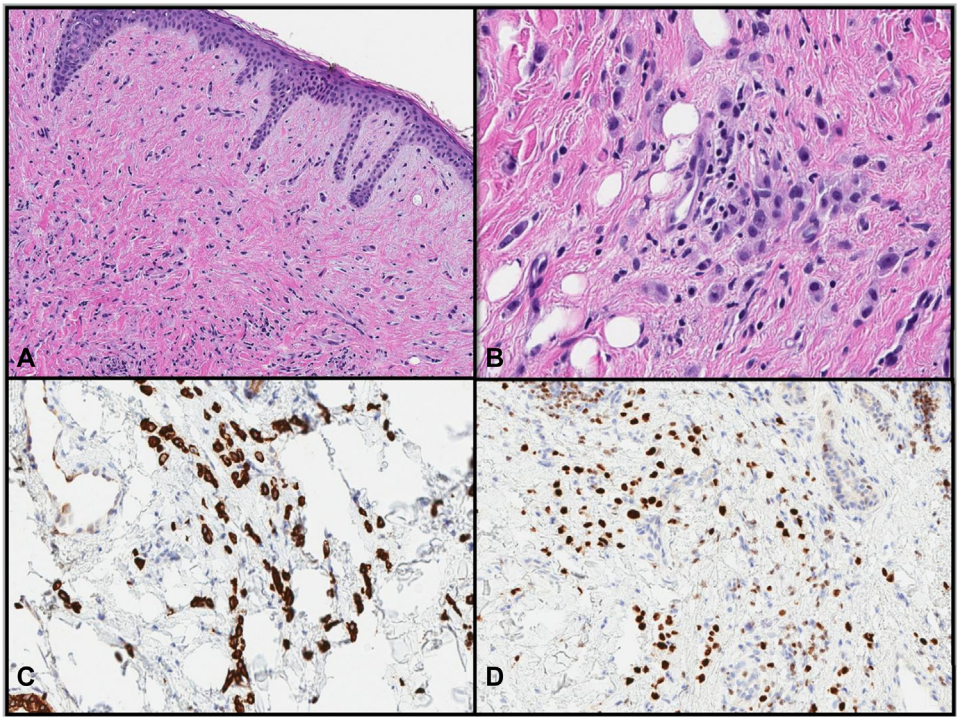

Fig 2. Invasive lobular breast carcinoma. **A,** A biopsy sample from the right axilla revealed a carcinoma directly invading into the dermis and epidermis without skin ulceration. **B,** Atypical epithelioid cells in between collagen bundles arranged singly and in cords. **C, D,** Immunohistochemistry stains for cytokeratin 7 and GATA-3 were positive. The tumor was also positive for estrogen receptor, BRST2, and mammaglobin, whereas it was negative for E-cadherin (not shown). The overall findings are compatible with a carcinoma of breast origin and lobular type. (**A** and **B,** Hematoxylin-eosin stain; **C,** cytokeratin 7 stain; **D,** GATA-3 stain; original magnifications: **A,** ×40; **B,** ×200; **C,** ×80; **D,** ×80.)

with endocrine therapy. Microscopic examination of the excised tissue showed no mammary glands or areolae to suggest ectopic breast tissue. Next-generation sequencing of the tumor showed missense alteration of the *PIK3CA*, *CDH1* p.Gly169AlafsTer46 frameshift-nonsense variant, and *BRCA2* p.S2186* pathogenic mutation. Hormonal treatment with letrozole followed by exemestane and anastrozole was discontinued after 15, 1, and 6 months, respectively, due to side effects, including arthralgia, weight gain, hair loss, and constipation. She has remained clinically and radiologically disease-free for 3 years.

DISCUSSION

Breast cancer is the most common cancer in females and the second most common cause of cancer-related death among American women.[4] It also constitutes a primary source of cutaneous metastases. However, very rarely, in the setting of metastatic disease, primary neoplasm is not detected despite exhaustive search—a presentation referred to as cancer of unknown primary site.[1] Cancer of unknown primary site represents approximately 2% to 5% of malignant neoplasms.[1]

Differential diagnosis of the skin tumor in our case included primary ectopic mammary carcinoma and cutaneous metastatic breast cancer of unknown primary, both being exceedingly rare diagnoses.[1-3] The location of the lesion supports the former diagnosis because ectopic breast cancer is most commonly reported in the axillae. However, typically ectopic mammary tissue undergoes changes in size, reflecting hormonal fluctuations in premenopausal, fertile females.[2] The de novo emergence of the lesion in this postmenopausal patient 1 year prior along with the absence of ectopic tissue in the excision specimen makes this diagnosis less likely.

Klein[5] described how breast cancer cells with certain molecular alterations can spread to distant organs prior to or without the development of a primary tumor. He postulated that the early dissemination of these cells occurs through a similar developmental process undertaken by the branching tree of breast milk ducts.[5] The 2 main pathways responsible for this process are the oncogene, *HER2*, and the tumor suppressor p38.[6] Turning off p38 and switching on *HER2* activates the epithelial to mesenchymal transition (EMT) signaling pathway. Down-regulation of E-cadherin expression secondary to *CDH1* mutations and signaling through progesterone receptors are critical for directing this pathway.[7] EMT is an evolutionarily developmental program implicated in cancer cell metastasis by enhancing cancer cell resistance to apoptotic stimuli, mobility, and invasion.[6] Despite the detection of *CDH1* mutations in our patient, the absence of *HER2* amplification and the lack of progesterone receptor protein expression suggest that the aforementioned model cannot fully explain a very complex biologic phenomenon.

Another explanation for the absence of a source for our patient's mass is spontaneous regression of the primary tumor. Spontaneous regression of cancers is a very rare biologic phenomenon in all cancer types with an incidence of <0.00001%.[8] This event is exceedingly uncommon in breast cancer in particular, with <100 reported cases.[8] Various theories have been proposed to explain this exceptional occurrence, including T-cell–mediated immunologic responses, cytokine-induced angiogenesis inhibition, tumor necrosis, and/or cellular differentiation, metabolic, and endocrine hypotheses.[8]

Elucidating the mechanism behind this and similar presentations is important in determining what, if any, adjuvant treatment is necessary. For example, if the source was thought to be genetically abnormal cells that spread early via the EMT pathway, chemotherapy might not be of benefit, especially in cases of invasive lobular carcinoma.[7] EMT involves the dedifferentiation of epithelial cells to fibroblastic migratory cells, which are generally resistant to chemotherapy.[7] Additionally, the current case showed *PIK3CA* mutations, which usually indicate a better prognosis but also a lower sensitivity to anthracycline-taxane–based chemotherapy.[9,10] As such, life-long hormonal treatment is the preferred alternative. However, our patient did not tolerate endocrine therapy and opted instead for close follow-up with mammography and a yearly check-up. We encourage further reporting of similar cases to enhance the understanding of the pathogenesis, provide insights into prognosis and guide next steps of management of these rare yet serious and often missed presentations.

Conflicts of interest

None disclosed.

REFERENCES

1. Lee MS, Sanoff HK. Cancer of unknown primary. *BMJ*. 2020;371:m4050. https://doi.org/10.1136/bmj.m4050
2. Salemis NS. Primary ectopic breast carcinoma in the axilla: a rare presentation and review of the literature. *Breast Dis*. 2021;40(2):109-114. https://doi.org/10.3233/BD-201027
3. Alečković M, McAllister SS, Polyak K. Metastasis as a systemic disease: molecular insights and clinical implications. *Biochim Biophys Acta Rev Cancer*. 2019;1872(1):89-102. https://doi.org/10.1016/j.bbcan.2019.06.002
4. Afifi AM, Saad AM, Al-Husseini MJ, Elmehrath AO, Northfelt DW, Sonbol MB. Causes of death after breast cancer

diagnosis: a US population-based analysis. *Cancer*. 2020; 126(7):1559-1567. https://doi.org/10.1002/cncr.32648

5. Klein CA. Parallel progression of primary tumours and metastases. *Nat Rev Cancer*. 2009;9(4):302-312. https://doi.org/10.1038/nrc2627
6. Mittal V. Epithelial mesenchymal transition in tumor metastasis. *Annu Rev Pathol*. 2018;13(1):395-412. https://doi.org/10.1146/annurev-pathol-020117-043854
7. Altundag K, Altundag O, Akyurek S, Karakaya E, Turen S. Inactivation of E-cadherin and less sensitivity of lobular breast carcinoma cells to chemotherapy. *Breast*. 2006;15(3):300. https://doi.org/10.1016/j.breast.2005.10.007
8. Takayama S, Satomi K, Yoshida M, et al. Spontaneous regression of occult breast cancer with axillary lymph node metastasis: a case report. *Int J Surg Case Rep*. 2019;63:75-79. https://doi.org/10.1016/j.ijscr.2019.09.017
9. Liu YR, Jiang YZ, Zuo WJ, Yu KD, Shao ZM. *PIK3CA* mutations define favorable prognostic biomarkers in operable breast cancer: a systematic review and meta-analysis. *Onco Targets Ther*. 2014;7:543-552. https://doi.org/10.2147/OTT.S60115
10. Yang L, Ye F, Bao L, et al. Somatic alterations of TP53, ERBB2, PIK3CA and CCND1 are associated with chemosensitivity for breast cancers. *Cancer Sci*. 2019;110(4):1389-1400. https://doi.org/10.1111/cas.13976