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Pleomorphic Adenoma in the Setting of Triple-Negative Breast Cancer: A Case Report

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ABSTRACT

We report a case of a patient-detected breast mass that revealed invasive carcinoma adjacent to a pleomorphic adenoma, which was treated with wide local excision. This case report highlights the importance of careful pathologic evaluation to guide appropriate local and systemic therapy and avoid the potentially harmful effects of overtreatment.

1 | Introduction

Pleomorphic adenoma is a benign mixed tumor consisting of an admixture of epithelial cells, myoepithelial cells, and stroma. These tumors are more commonly observed in the salivary glands, although rarely they can be found in the breast. Approximately 80 cases of pleomorphic adenoma of the breast have been described in the literature [1]. Previous reports have emphasized the risk of labeling these lesions invasive breast cancer, leading to overtreatment with breast and axillary surgery, radiation, and systemic therapy. The infrequency of pleomorphic adenoma of the breast does not allow for the development of treatment guidelines like those that exist for salivary gland tumors, and diagnostic challenges have led to variable treatment in previously reported cases. To highlight this dilemma, we report a unique case of pleomorphic adenoma adjacent to invasive carcinoma.

2 | Case History and Examination

A 96-year-old woman presented to her primary care physician with a self-detected, painless lump in her right breast. A physical exam of the right breast revealed a 4 cm mass in the upper outer quadrant. Her last screening mammogram was 4 years ago, read as BI-RADS 2. She had a core needle biopsy of the central posterior right breast 20 years ago that identified fibrocystic change with lobular involution and microcalcifications and a left mastectomy 60 years ago after a traumatic breast injury. The patient's past medical history was significant for atrial fibrillation, hypertension, and mild cognitive impairment. Her ASA physical status was Class III with good exercise tolerance, and her relative and healthcare proxy accompanied her at all medical appointments. Her past family history of breast cancer included one sister who developed breast cancer in her 70s.

3 | Differential Diagnosis, Investigations and Treatment

The patient's diagnostic mammogram revealed an irregular, isodense mass at the site of the palpable abnormality (Figure 1). Targeted breast ultrasound revealed a 3.6 cm irregular, mixed echogenicity mass at 10 o'clock, 7 cm from the nipple (Figure 2). Imaging was classified BI-RADS 4, and an ultrasound-guided core needle biopsy was recommended,

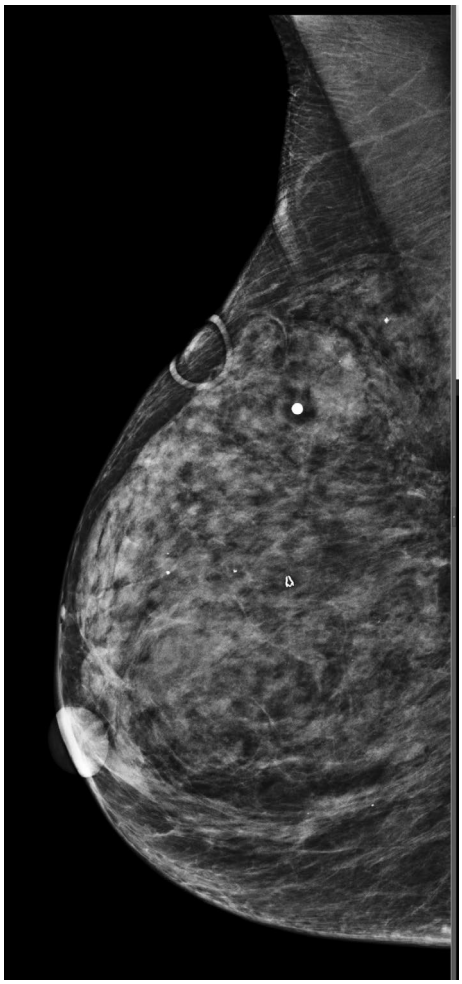

FIGURE 1 | Mammogram: Right MLO view shows an obscured 3 cm mass underlying the BB, noting a site of palpable concern in the right upper breast at posterior depth.

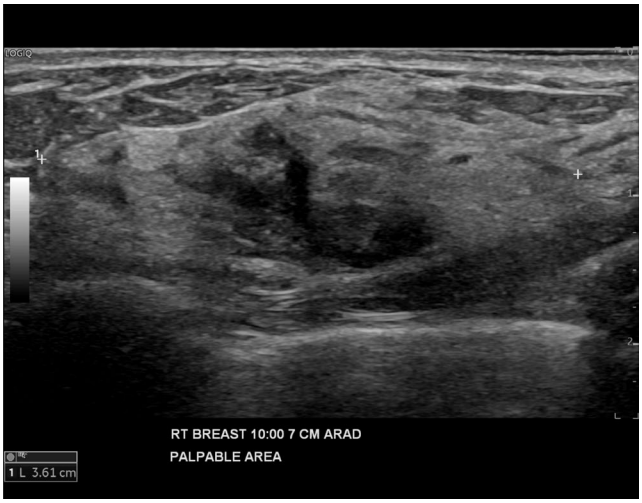

FIGURE 2 | Ultrasound: At the right 10:00, 7 cm from the nipple, a palpable site of concern, a mixed echogenicity mass measures up to 3.6 cm.

which demonstrated a mixed lesion composed of admixed spindled to ovoid epithelial cells with small round to oval nuclei embedded in a chondromixoid matrix. In addition, a 0.2 cm focus of infiltrating ductal cells with abundant eosinophilic cytoplasm and pleomorphic nuclei with prominent nucleoli was identified adjacent to the mixed tumor, consistent with invasive carcinoma. The differential diagnosis for the focus of invasion included malignant transformation of the mixed tumor or a separate breast primary, whereas the mixed lesion was favored to represent a pleomorphic adenoma of the breast. Breast biomarkers by immunohistochemistry demonstrated the invasive carcinoma was negative for estrogen receptor (ER, 0%), negative for progesterone receptor (PR, 0%), negative for HER2-Neu (Score 0), and expressed a low Ki-67 proliferative index (10%).

To better characterize the lesion, the patient underwent a breast MRI, which showed a 3.8 cm area of non-mass enhancement in the upper outer right breast and a 0.9 cm right lung nodule (Figure 3). Staging PET–CT revealed solid lung nodules in the left apex (1.2 cm), left lower lobe (0.9 cm), and right middle lobe (1.7 cm) with SUV max of 8.0, 5.8, and 5.2, which were indeterminate. It was unclear what proportion of the breast mass on imaging was malignant. Given the heterogeneous appearance of mixed tumors of the breast by imaging, the assessment of malignant transformation is particularly challenging if the invasive component is in the early stages, masquerading as a heterogeneous density within the lesion rather than the typical radiologic appearance of a stellate radiodensity of invasive carcinomas. The sequence of therapy would vary based on the pathologic diagnosis. Upfront wide local excision would be recommended for malignant transformation of the mixed tumor, whereas neoadjuvant therapy followed by surgery would typically be considered for a triple-negative, non-metaplastic invasive ductal carcinoma. Due to the patient's advanced age, however, upfront surgical excision was recommended to evaluate the entirety of the lesion prior to recommending additional therapy, with repeat chest CT in 3–4 months to evaluate the pulmonary lesions. Sentinel node biopsy was omitted because of the patient's age.

The patient underwent wire-localized wide local excision. H&E examination of the specimen demonstrated an invasive

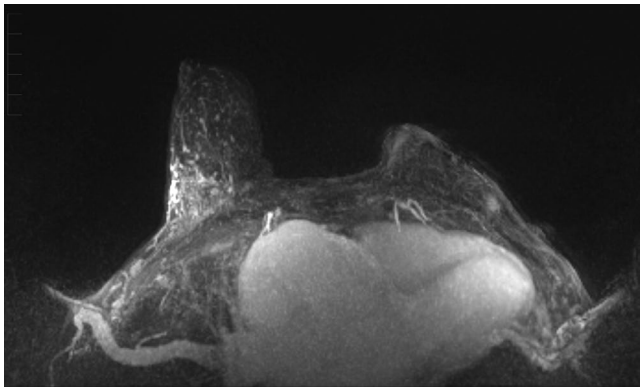

FIGURE 3 | MRI: Post-contrast subtraction MIP image shows regional non-mass enhancement in the right upper outer quadrant measuring up to 3.8 cm, correlating with the site of biopsy.

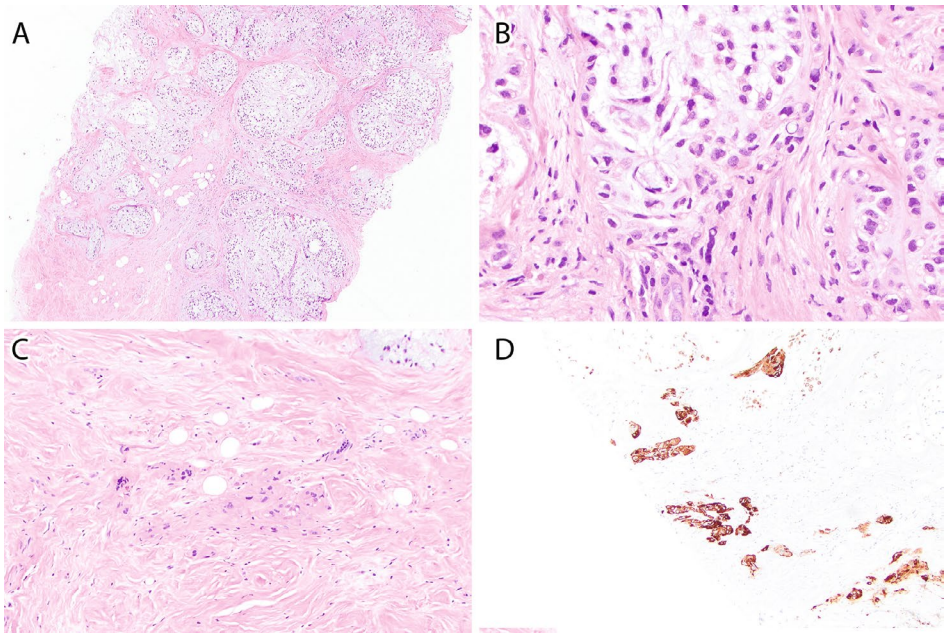

FIGURE 4 | (A) Representative section of the wire-localized 2.2 cm pleomorphic adenoma, demonstrating a characteristic chondromyxoid background (H&E), (B) composed of a mix of bland spindled and ovoid cells (H&E). (C) Invasive carcinoma adjacent to the pleomorphic adenoma, demonstrating small clusters and nests of infiltrating tumor cells, (D) best highlighted by cytokeratin AE1/3.

TABLE 1 | Timeline of care.

0 weeks	Initial presentation to primary care provider
3 weeks	Diagnostic mammogram and breast ultrasound
6 weeks	Ultrasound-guided core needle biopsy
8 weeks	Bilateral breast MRI
9 weeks	Patient seen in medical and surgical breast oncology clinics
10 weeks	Chest CT to evaluate lung nodule seen on MRI
3 months	Staging PET–CT
4 months	Wide local excision of right breast lesion
10 months (6 months post-op)	Mammogram and breast ultrasound with no evidence of disease recurrence
15 months (11 months post-op)	Chest CT with waxing and waning infectious nodules Breast ultrasound with postoperative seroma

carcinoma, SBR Grade 3 (glandular/tubular differentiation 3, nuclear pleomorphism 3, mitotic rate 2) with mixed ductal and lobular features, measuring 0.3 cm. The invasive carcinoma was associated with ductal carcinoma in situ (DCIS), nuclear Grade 3, and a 2.2 cm pleomorphic adenoma (Figure 4). Margins were negative for invasive carcinoma and DCIS. Given the presence of DCIS as a putative precursor, the invasive carcinoma was favored to arise from the DCIS, adjacent to but separate from the pleomorphic adenoma rather than representing malignant transformation of the pleomorphic adenoma (carcinoma ex-pleomorphic adenoma).

4 | Conclusion and Results

The patient tolerated the procedure well and had an unremarkable postoperative course. Her case was discussed at the multidisciplinary breast tumor board, where the consensus was that radiation and chemotherapy were not indicated. Her 6-month surveillance mammography and ultrasound showed no evidence of disease recurrence; repeat chest CT was suggestive of waxing and waning infectious nodules, and she continues to follow up with medical oncology at the time of this report, 1 year postsurgery. The patient's clinical course is summarized in Table 1.

5 | Discussion

Pleomorphic adenoma is a benign neoplasm consisting of epithelial cells, myoepithelial cells, and stroma—either myxoid, chondroid, osteoid, or a combination. Although it commonly arises in the salivary gland, it is an unusual finding in breast tissue where its rareness presents a diagnostic challenge on core needle biopsy. Though benign, pleomorphic adenoma of the breast carries a risk of malignant transformation to carcinoma ex-pleomorphic adenoma and recurrence if not completely excised [2–6]. This case highlights not only a rare case of pleomorphic adenoma of the breast but also the first to our knowledge that arose adjacent to an invasive breast primary.

Several key points influenced the patient's care. Initial suspicion for invasive cancer was supported by the presence of infiltrating atypical epithelial cells, devoid of lobular architecture, and the absence of myoepithelial cells seen on core needle biopsy. Core needle biopsies inherently carry a false positive rate, given the possibility of inadequate sampling regardless of imaging modality. These issues are usually mitigated by proper communication of the radiologic findings to the pathologist and the careful examination of the tissue by the pathologist in light of the imaging findings, highlighting the critical role of histopathologic examination and imaging correlation in determining sampling adequacy to minimize false negative results in the pre-analytical phase. Diagnosing a pleomorphic adenoma can also present difficulties in the analytical phase. Previous case reports have described the limitations of core needle biopsy in distinguishing pleomorphic adenoma from metaplastic carcinoma based on morphologic similarities like metaplastic stroma [1, 7, 8]. The histopathologic assessment plays the primary role in the distinction of these lesions. Pleomorphic adenomas are well-circumscribed lesions lacking cytologic atypia, whereas invasive carcinomas, whether arising from mixed tumors or DCIS, are characterized by cellular atypia, infiltrative or destructive patterns, increased mitotic activity, and necrosis. Immunohistochemical stains play a role in the distinction of these entities. Both pleomorphic adenomas of the breast and metaplastic carcinomas are usually triple-negative for ER, PR, and HER2-neu, and the use of myoepithelial cell markers (such as smooth muscle myosin, p63) could assist in differentiating these lesions, as metaplastic carcinomas would lack peripheral myoepithelial cells—a hallmark of infiltrative lesions of the breast in distinguishing it from in situ entities. An added challenge is that no characteristic imaging features distinguish pleomorphic adenoma from malignant tumors [9]. Similar to this case, other reports of pleomorphic adenoma in the literature have noted a BI-RADS 4 classification of the breast mass on imaging [9–11]. Therefore, the proper management of this case relied on the successful sampling of the focus of invasive carcinoma and the correct identification and workup by the pathologist. Core needle biopsy demonstrated a 0.2 cm focus of invasive carcinoma adjacent to a benign mixed tumor, which represented a focal element of the 3.6 cm mass seen on initial imaging constituted invasive carcinoma. This uncertainty impacted clinical staging and treatment discussions. Ultimately, the patient's age precluded any role for neoadjuvant or adjuvant systemic treatment for the invasive triple-negative breast cancer.

In the absence of invasive carcinoma, the recommended treatment would have been local excision with negative margins. One author suggests excising pleomorphic adenoma with margins of at least 3 mm, given reports of recurrence and malignant transformation [2, 6]. Indeed, cases of recurrent pleomorphic adenoma [2–4] and carcinoma ex-pleomorphic adenoma [5] have been described in the literature. Likewise, in the salivary counterpart, complete excision reduces the risks of recurrence and malignant transformation [12]. Another author suggests classifying pleomorphic adenoma of the breast and other entities as "lesions of uncertain malignant nature" to steer clinicians away from the most conservative management strategies typically associated with benign lesions [13]. Given that local excision is the preferred treatment of pleomorphic adenoma, it is critical to avoid misdiagnosis that could lead to overtreatment. Pleomorphic adenomas in the salivary gland can occasionally be misdiagnosed as malignancy, but the majority of cases are diagnostically straightforward given their commonality [14]. In the breast, however, the rarity of this tumor can lead to its misdiagnosis as metaplastic carcinoma [1, 7, 8] or other invasive carcinoma [11, 15–18]. A recent literature review by Ahmad et al. identified 18 out of 77 cases of pleomorphic adenoma of the breast that were treated with mastectomy, several of which were radical mastectomies [1] which included removal of the breast, nipple, areola, pectoral muscles, and axillary contents. Unnecessary treatment with this surgical approach would lead to significant chest wall deformity and risk of lymphedema. Though pleomorphic adenomas of the breast commonly have a triple negative immunohistochemical profile, rare ER-positive cases have appeared in the literature [19, 20], which in one case led to its misdiagnosis as invasive ductal carcinoma and inappropriate initiation of antiestrogen treatment [11].

In conclusion, we aim to raise awareness of a pleomorphic adenoma of the breast, which can occur alongside invasive breast cancer. Clinicians encountering a potential case of mixed tumor with adjacent invasive carcinoma should remain open to the possibility of salivary gland analogous tumors in the breast, whereas keeping in mind the morphologic and biomarker overlap with metaplastic carcinomas. Overtreatment is a concern because of the challenge of differentiating it from invasive breast carcinoma, but our case demonstrates that the two conditions can coexist. Seeking multiple opinions during the diagnostic process is advisable, and efforts should be made to obtain clear margins during excision.

Author Contributions

Michelle Guo: formal analysis, investigation, methodology, writing – original draft. **Jorge Novo:** conceptualization, data curation, formal analysis, methodology, validation, writing – review and editing. **David Schacht:** conceptualization, data curation, formal analysis, validation, writing – review and editing. **Swati Kulkarni:** conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing – original draft, writing – review and editing.

Consent

The authors have obtained written informed consent from the patient's healthcare power of attorney.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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