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(CASE REPORT)

Triple-negative breast ductal carcinoma with synchronous brain, lung, and bone metastases. A case report and literature review

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Abstract

Triple-negative breast cancer (TNBC) is an aggressive immunophenotypic category lacking estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, with a particular propensity for early visceral and central nervous system dissemination.

We report a 52-year-old woman with an untreated left breast mass, progressive headache and visual disturbance, back pain, and exertional dyspnea. Staging demonstrated a 4.8-cm left breast lesion with axillary adenopathy, three brain metastases, bilateral pulmonary nodules, and multifocal osseous metastases. Core biopsies of the breast and lung showed concordant grade 3 invasive breast carcinoma of no special type with extensive high-grade ductal carcinoma in situ. The tumor was ER-negative, PR-negative, and HER2-negative (IHC score 0, non-amplified), GATA3-positive, and TTF-1/Napsin A-negative. The tumor cells showed high proliferation (Ki-67, 78%); focal cytokeratin 5/6 and EGFR expression, together with TP53 and PIK3CA mutations, supported a biologically aggressive TNBC.

Symptomatic cerebral lesions were treated with stereotactic radiosurgery, painful vertebral disease with palliative radiation, and systemic chemoimmunotherapy plus bone-modifying therapy produced an initial response. However, new brain metastases, progressive skeletal disease with pathologic L2 fracture, and leptomeningeal dissemination developed rapidly. She died seven months after diagnosis.

This case highlights the need for urgent neurologic assessment, tissue-confirmed staging, assay-specific biomarker interpretation, and early multidisciplinary and supportive care in de novo metastatic TNBC with CNS involvement.

Keywords: Invasive breast carcinoma of no special type; Triple-negative breast cancer; Human epidermal growth factor receptor 2; Estrogen receptor; Progesterone receptor; Lung metastases; Brain metastases; TP53 and PIK3CA mutations

1. Introduction

Triple-negative breast cancer (TNBC) is an aggressive subtype of invasive breast carcinoma of no special type, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. [1] Representing approximately 10–20% of all breast cancers, TNBC is associated with high histologic grade, increased

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proliferative activity, early recurrence, and significantly poorer survival than other molecular breast cancer subtypes. [1,2]

Breast cancer demonstrates distinct metastatic patterns according to its molecular subtype, with basal-like and triple-negative tumors exhibiting a greater propensity for visceral dissemination, particularly to the lungs and brain; in contrast, hormone receptor-positive tumors more commonly metastasize to bone. [3] Brain metastases develop in approximately 25–46% of patients with metastatic TNBC and are associated with substantial neurologic morbidity, limited therapeutic options, and poor clinical outcomes despite advances in multidisciplinary treatment. [3]

Early recognition of metastatic disease, histopathologic confirmation of the primary tumor, and comprehensive staging are essential for accurate diagnosis and treatment planning. [3]

We report this case to highlight the aggressive clinical behavior of triple-negative invasive ductal carcinoma presenting with synchronous brain, lung, and bone metastases at initial diagnosis, emphasizing the importance of comprehensive diagnostic evaluation and multidisciplinary management.

2. Case Presentation

2.1. Clinical Presentation and Initial Management

A 52-year-old woman initially presented with progressive headaches and visual disturbances over six weeks, prompting neurological evaluation. Concurrently, she noticed a palpable left breast mass during the preceding three months, which she attributed to benign changes and delayed seeking attention. She also reported worsening lower back pain for two months, initially managed with over-the-counter analgesics, and progressive dyspnea on exertion over four weeks.

The constellation of neurological symptoms ultimately drove her to seek urgent medical care. Her primary physician initiated symptomatic management with corticosteroids for suspected cerebral pathology and urgently referred her to oncology for comprehensive evaluation, given the concerned breast finding and systemic symptoms.

2.2. Physical Examination, History, and Laboratory Findings

Physical examination revealed a 4.5 cm irregular, firm, fixed mass in the upper outer quadrant (UOQ) of the left breast with palpable axillary lymphadenopathy. Neurological examination demonstrated papilledema and subtle right-sided weakness. Initial laboratory studies showed elevated alkaline phosphatase (340 U/L), hypercalcemia (11.2 mg/dL), and mild anemia (hemoglobin 10.2 g/dL). Personal history included nulliparity and late menarche. Family history was significant for maternal breast cancer diagnosed at age 58 and paternal colon cancer. She reported that her last mammographic screening was 4 years ago. Performance status was ECOG 2. The clinical picture suggested widespread metastatic disease, requiring an urgent diagnostic workup and multidisciplinary coordination.

2.3. Radiographic Studies, Findings, and Differential Diagnosis

Bilateral mammography and breast ultrasound demonstrated a 4.8 cm spiculated mass in the UOQ of the left breast with suspicious microcalcifications extending to the nipple, accompanied by multiple enlarged axillary lymph nodes with cortical thickening and loss of fatty hilum. Contrast-enhanced brain MRI revealed three enhancing lesions: a 2.3-cm right frontal lobe mass with surrounding vasogenic edema, a 1.7-cm left parietal lesion, and a 1.2-cm right cerebellar hemisphere lesion, all of which demonstrated restricted diffusion and ring enhancement with central necrosis. Chest CT with contrast showed multiple bilateral pulmonary nodules ranging from 0.8 to 2.4 cm, predominantly in the lower lobes, along with mediastinal lymphadenopathy. Small bilateral pleural effusions were noted. Whole-body bone scan and correlative CT demonstrated multiple foci of increased radiotracer uptake in the thoracolumbar spine (T8, L2, L4), pelvis (bilateral iliac bones), and proximal femora, with corresponding lytic and sclerotic lesions on CT.

Differential diagnosis included: primary breast carcinoma with metastatic disease (most likely), primary lung malignancy with brain metastases, primary brain tumor with multifocal disease (less likely given imaging pattern), metastatic disease from occult primary, and lymphoproliferative disorder (least likely given imaging characteristics).

2.4. Multidisciplinary Tumor Board Discussion

The breast tumor board convened, comprising medical oncology, surgical oncology, radiation oncology, radiology, and pathology. Discussion centered on establishing tissue diagnosis while considering the patient's symptomatic burden

and performance status. The consensus prioritized obtaining adequate tissue for comprehensive pathological and molecular characterization.

The board recommended a core needle biopsy of the left breast mass as the primary sampling site, given its accessibility and the likelihood of yielding diagnostic tissue, and concurrent bronchoscopy biopsy of one of the central lung lesions. An additional biopsy of an axillary lymph node was suggested if breast sampling proved inadequate. Brain biopsy was deferred, given the surgical risks and the likelihood that cerebral lesions represent metastatic disease. Emergency neurosurgical consultation was arranged for symptom management.

2.5. Tissue Diagnosis and Pathological Evaluation

Ultrasound-guided core needle biopsy of the left breast mass yielded multiple tissue cores. Microscopic examination revealed infiltrating malignant cells arranged in solid sheets and irregular nests, composed of pleomorphic cells with a high nuclear-to-cytoplasmic ratio, prominent nucleoli, and numerous mitotic figures (32 per 10 high-power fields). Geographic necrosis was identified. The adjacent breast tissue demonstrated extensive high-grade ductal carcinoma in situ (DCIS) with comedo-type necrosis and cribriform architecture. (**Figure 1 A, B, C**) Initial differential diagnosis included poorly differentiated invasive ductal carcinoma and metaplastic carcinoma.

Immunohistochemical (IHC) profile was reported as follows: negative for estrogen receptor (ER, 0%) and progesterone receptor (PR, 0%). HER2 expression was absent by IHC (score 0) and confirmed as non-amplified by FISH (ratio <2.0). The Ki-67 proliferation index was high at 78%. Other markers showed focal cytokeratin 5/6 positivity and EGFR expression in 60% of tumor cells, while E-cadherin expression was retained. The tumor was GATA3-positive and negative for TTF-1 and Napsin A, supporting breast origin and arguing against primary lung origin. Next-generation sequencing identified TP53 and PIK3CA mutations. Germline BRCA1/2 testing was ordered, but the results were not reported.

The morphology and IHC studies of both breast and lung samples were identical (**Figure 2 A, B, C**), confirming metastatic disease to the lung. Final diagnosis was invasive breast ductal carcinoma of no special type (IBC-NST), triple-negative with pulmonary metastasis, Grade 3, with extensive high-grade DCIS, cT2N1M1 (stage IV at presentation).

2.6. Treatment Decision and Tumor Board Recommendations

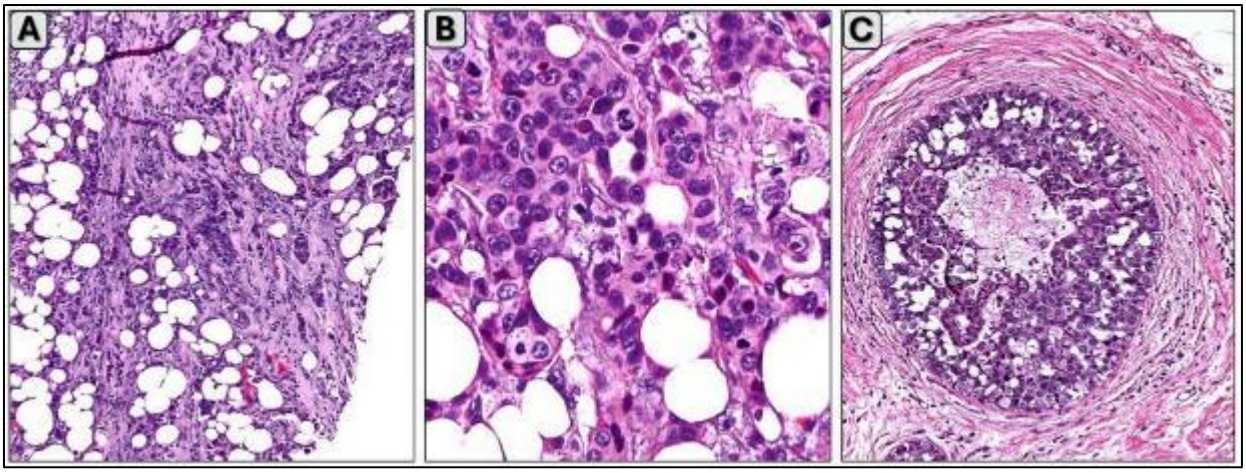
The tumor board reconvened to formulate a treatment strategy. Given symptomatic brain metastases, the patient underwent stereotactic radiosurgery to the three intracranial lesions; whole-brain radiotherapy (WBR) was reserved for diffuse intracranial recurrence or salvage. Palliative radiotherapy was delivered to the symptomatic T8 and L2 vertebral lesions. Following local CNS treatment, the multidisciplinary team selected carboplatin-paclitaxel plus pembrolizumab as individualized first-line systemic therapy. PD-L1 testing using the 22C3 pharmDx assay showed a CPS of 14, supporting pembrolizumab eligibility. Denosumab was initiated with a dental risk assessment, individualized calcium/vitamin D supplementation, and biochemical monitoring.

2.7. Follow-up and Clinical Outcome

Initial response assessment after three cycles demonstrated encouraging results: interval decrease in breast mass size (30% reduction), reduced pulmonary nodule burden, and stable brain lesions post-SRS. The patient reported symptomatic improvement with reduced headache severity and improved functional status (ECOG 1).

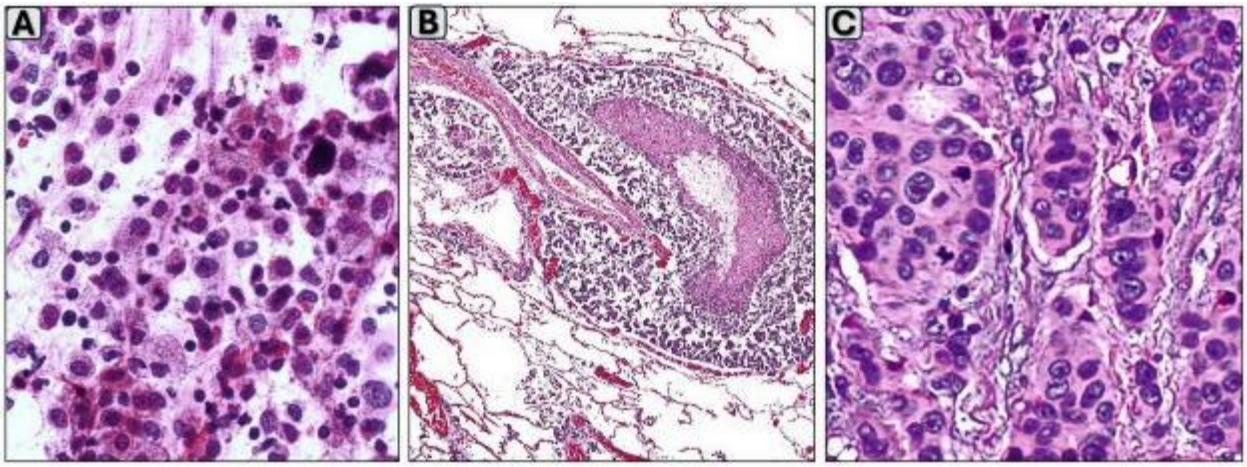
However, disease progression occurred rapidly thereafter. At four-month follow-up imaging, new brain metastases emerged despite previous SRS, and progressive lytic bone lesions developed with a pathological fracture of L2 requiring urgent surgical stabilization. Second-line therapy with capecitabine was initiated but poorly tolerated due to declining performance status.

By month six, the patient developed leptomeningeal disease confirmed by MRI and CSF cytology, presenting with intractable headaches, confusion, and cranial nerve palsies. She transitioned to hospice care, focusing on comfort measures. Despite initial therapeutic response, the aggressive biology of triple-negative disease with CNS involvement led to rapid deterioration. The patient expired seven months after initial diagnosis.



1A: Low-power view of core breast mass biopsy showing infiltrating sheets and masses within the breast parenchyma (H&E X20); 1B: High-power view showing nuclear details of high-grade breast ductal carcinoma (H&E X60); 1C: Intermediate-power view showing ductal carcinoma in situ component, high grade with central necrosis (H&E X40)

Figure 1 Microscopic features of the breast carcinoma primary



2A: Direct smear (touch preparation) prepared from the lung core biopsy at the time of sampling, showing dyscohesive pleomorphic malignant epithelial cells with high nuclear-to-cytoplasmic ratios and prominent Loose isolated malignant cells are identified with intact cytoplasm (High-Power H&E X60); 2B: Low-power view showing metastatic breast ductal carcinoma within the lung parenchyma (H&E X20); 2C: High-power view showing nuclear features of adenocarcinoma, like the breast ductal carcinoma (H&E X60)

Figure 2 Microscopic features of metastatic breast carcinoma to the lung

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification):

Triple-negative breast cancer became a clinically useful category after gene-expression studies identified biologically aggressive basal-like cancers in the early 2000s. It is defined by the absence of ER and PR expression and HER2-negative status on validated testing, and accounts for approximately 12%–17% of invasive breast cancers. [4] TNBC is an immunohistochemical surrogate phenotype rather than a single histologic entity. In World Health Organization terminology, most conventional "invasive ductal carcinomas" are invasive breast carcinoma of no special type (IBC-NST); "triple-negative" denotes receptor status, not morphology. [4,5]

Compared with hormone receptor-positive disease, TNBC more often affects younger and premenopausal women, is high grade and proliferative, and has a higher early risk of visceral recurrence, especially in the lung and brain. [4,6] Germline BRCA1 pathogenic variants are strongly associated with TNBC and are therapeutically relevant. A recent meta-analysis also associated family history, higher breast density, and longer oral-contraceptive exposure with TNBC risk, whereas breastfeeding, later menarche, and later age at first birth were protective; other associations were inconsistent. [7] The patient's maternal breast-cancer history therefore justified germline testing, but nulliparity and late menarche

should not be presented as established TNBC-specific causes. In metastatic TNBC, brain metastases occur in roughly 25%–46% of patients and often coexist with lung and bone disease. [3,7,8]

3.2. Pathogenesis, Pathophysiology

TNBC comprises molecularly heterogeneous tumors, although many high-grade IBC-NSTs exhibit a basal-like phenotype characterized by marked proliferation, genomic instability, and defective DNA damage repair. Recurrent alterations include TP53 mutation, BRCA1/2 dysfunction or homologous-recombination deficiency, RB1 loss, and PI3K-pathway abnormalities; the TP53 and PIK3CA mutations in this case were biologically compatible with, but not diagnostic of, a particular TNBC molecular subtype. [4] The high Ki-67 index, pleomorphism, necrosis, and rapid visceral spread reflect this aggressive biology.

Metastasis requires local invasion, intravasation, survival in the circulation, and colonization of organ-specific microenvironments. For cerebral dissemination, tumor cells must traverse a blood–tumor barrier with heterogeneous drug permeability and adapt to astrocytes, microglia, neuronal signaling, metabolic stress, and immune selection. [6] Branched clonal evolution can yield molecular divergence between primary and intracranial disease, explaining discordant response or receptor change at progression. [6] These mechanisms, coupled with limited CNS activity of many systemic agents and the absence of ER/HER2 therapeutic targets, help explain early intracranial relapse and subsequent leptomeningeal spread despite transient extracranial control. [3,6]

3.3. Comparative Analysis of Our Case with Existing Literature

This case was concordant with major TNBC brain-metastasis series in its high-grade ductal/NST morphology, symptomatic presentation, visceral disease, and unfavorable outcome. In a 433-patient metastatic TNBC cohort, Jin et al. found brain metastases in 29%; 12% presented with de novo stage IV disease, and 8.5% had three or more metastatic organ sites. [9] Thus, synchronous brain, lung, and bone involvement at presentation represents an unusually high burden even within metastatic TNBC. Among patients whose brain metastases were present at first metastatic presentation or recurrence, synchronous extracranial disease was common, with lungs and bone among the leading sites, closely mirroring this pattern. [9]

The neurologic presentation was likewise typical. In a 169-patient series, headaches occurred in 74% and weakness in 11.2% of patients with TNBC brain metastases; lung and bone metastases coexisted in 39.1% and 20.7%, respectively. [10] The patient's seven-month survival approximated the 7.3-month median survival after brain-metastasis diagnosis reported by Jin et al. Her subsequent leptomeningeal progression underscores a population underrepresented in systemic-treatment trials. [3,9] Stereotactic radiosurgery for three symptomatic lesions was consistent with guidance favoring prompt local therapy; whole-brain radiotherapy may be reserved for diffuse intracranial disease or later salvage. [8]

Abbreviations

- Invasive breast carcinoma of no special type (IBC-NST)
- Triple-negative breast cancer (TNBC)
- Human epidermal growth factor receptor 2 (HER2)
- Estrogen receptor (ER)
- Progesterone receptor (PR)
- Immunohistochemistry (IHC)

4. Conclusions and What Have We Learned from This Case?

This report adds a tissue-confirmed example of de novo TNBC presenting simultaneously with symptomatic brain, pulmonary, and skeletal metastases, followed by early leptomeningeal progression despite an initial radiologic and clinical response. Its value lies not in claiming that this metastatic pattern is unique, but in demonstrating how a seemingly delayed breast presentation can coexist with immediately life-threatening neurologic and skeletal disease.

Clinicians should treat persistent or progressive headache, visual symptoms, papilledema, focal deficit, seizure, or altered cognition in a patient with a suspicious breast mass as CNS red flags requiring urgent contrast-enhanced brain MRI and multidisciplinary review. Concurrent back pain, hypercalcemia, elevated alkaline phosphatase, or new dyspnea should trigger systematic extracranial staging and assessment for impending fracture, cord compression, and pulmonary compromise. Tissue confirmation from the breast and, when safely feasible, a metastatic site is essential to

establish the primary origin and reassess therapeutic biomarkers. In this case, the GATA3-positive/TTF-1- and Napsin A-negative phenotype, concordant lung morphology, and adjacent DCIS strongly supported breast origin.

The case also reinforces the need to interpret biomarker assays in a treatment-specific manner. SP142 immune-cell positivity and 22C3 combined positive score (CPS) are not interchangeable; eligibility for first-line pembrolizumab plus chemotherapy under the KEYNOTE-355 paradigm requires a documented 22C3 CPS of at least 10, which was 14 in our case. Germline BRCA1/2 testing is important for inherited-risk assessment and can expand treatment options. Prompt local therapy for symptomatic brain lesions, fracture-risk-directed bone management, serial CNS assessment after SRS, early palliative-care involvement, and transparent goals-of-care discussions are integral, not secondary to treatment. This case reinforces the point that an early extracranial response should never be mistaken for durable CNS control in metastatic TNBC.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

This work did not involve any studies on human or animal subjects performed by the authors. It was a retrospective review of archival pathology material collected during routine clinical care, and all data were fully de-identified before analysis.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

The patient expired, and all attempts to reach the family members were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

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