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When systemic therapy fails: Metaplastic breast carcinoma requiring urgent mastectomy

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Introduction

Metaplastic Breast Carcinoma (MpBC) is a rare histologic variant encompassing less than 1% of invasive breast cancers [1]. It consists of a heterogenous group of tumors displaying metaplasia of the glandular epithelium into squamous and mesenchymal cells. Among the most aggressive of the group is the squamous subtype, which often initially presents with a large, rapidly growing mass and exhibits early hematogenous spread despite limited lymphatic involvement [1].

MpBC can mimic inflammatory breast cancer, presenting with landmark symptoms including erythema, edema, peau d'Orange appearance, and ulceration of the overlying skin. Diagnosis requires a high index of suspicion and tissue confirmation. The biological behavior of MpBC differs markedly from conventional invasive ductal carcinoma, exhibiting poor responsiveness to standard anthracycline- and taxane-based chemotherapy [1]. Radiologically, MpBC presents as a circumscribed or partially spiculated mass, often with central necrosis. MRI commonly demonstrates heterogeneous enhancement, skin thickening, and non-mass enhancement, mimicking inflammatory breast carcinoma [2].

We present a case of a locally advanced metaplastic breast carcinoma in a patient who required urgent mastectomy after poor response to neoadjuvant chemo-immunotherapy.

Case report and discussion

This is a 56-year-old Asian female with no significant medical history presented to the emergency department with tachycardia, leukocytosis, and severe malnutrition (36.3 kg/ BMI 15.8). She reported noticing progressive enlargement of a right breast mass over 18 months and new-onset low-volume bleeding over the last two days. She had no prior screening

mammograms and denied any familial history of breast cancer. On examination, the right breast demonstrated a large fungating mass (~8 cm) with erythema, induration, and loss of the nipple-areolar complex. No contralateral breast mass or palpable lymphadenopathy were noted. Diagnostic mammography and ultrasound showed a 10 cm circumscribed mass in the central right breast and abnormal right axillary lymph nodes. The left breast demonstrated architectural distortion and dystrophic calcifications. A core needle biopsy of the right lesion revealed metaplastic carcinoma with squamous differentiation, grade 3. The axillary lymph node biopsies were negative for malignancy. Immunohistochemistry showed ER 25%, PR negative, HER2 1+, and Ki-67 90%. Additionally, the left breast biopsy resulted in DCIS ER 90%, PR 2% G2. A subsequent breast MRI demonstrated a 7.4×8.3×9.3 cm mass occupying most of the right breast, with an exophytic necrotic component, marked skin thickening, and edema tracking to the pectoralis fascia. PET-CT later confirmed one hypermetabolic right breast mass and bilateral axillary adenopathy without distant metastases. Germline testing revealed VUS in APC and NTHL1.

The tumor was staged cT4cN0M0 (AJCC 8th edition). After multidisciplinary discussion, the patient started neoadjuvant chemo-immunotherapy as per KEYNOTE-522 protocol (weekly carboplatin/paclitaxel + pembrolizumab, followed by doxorubicin/cyclophosphamide). Despite therapy (11 cycles of carboplatin/paclitaxel and 2 cycles of AC), the tumor progressed clinically. MRI showed interval enlargement to 11.1×14.7×13.4 cm with worsening skin involvement. The patient developed recurrent bleeding and ongoing transfusion dependency. Given her poor response to systemic treatment and the continuous bleeding, the decision was made to perform a bilateral mastectomy with both curative and palliative intent. Despite being debilitated from systemic treatment, the patient underwent bilateral total mastectomy, with right sentinel lymph node biopsy and wound-vacuum device placement (for a subsequent flap reconstruction) without complications. Gross examination of the right mastectomy specimen revealed a large, dark brown, ulcerating, fungating mass measuring 22.5×18.5 cm, occupying approximately 90% of the breast parenchyma. Representative sections demonstrated both solid and cystic components, hemorrhagic foci, and extensive necrosis. The left breast contained high-grade DCIS with uninvolved margins and 2/2 negative sentinel nodes.

She was planned to have staged reconstruction; however, post operative tachycardia and leukocytosis workup revealed an adrenal lesion extending to the right lobe of the liver concerning for metastasis. Given her poor prognosis and overall frailty, the decision was made to pursue palliative care and ultimately the patient was discharged home on hospice.

MpBC is an aggressive and rare subtype of breast cancer with overall poor response to cytotoxic chemotherapy [4]. Given its low prevalence, literature is sparse and current guidelines do not provide specific recommendations for management these rare breast cancer tumors. Outcome is generally poor, with 5-year overall survival rates ranging from 49% to 65%. The most common metastatic sites are lung, bone, and liver. Interestingly, nodal negativity does not necessarily confer improved survival, as hematogenous spread predominates [2]. In practice, MpBC is generally treated according to Triple-Negative Breast Cancer (TNBC) protocols as 70% of these tumors are TNBC [5]. Management generally follows the principles of aggressive locoregional therapy (surgery plus radiotherapy in high-risk cases, such as tumor size >5 cm or skin involvement). While systemic chemotherapy (e.g., anthracycline/taxane-based regimens) is commonly used in the neoadjuvant setting, its benefit remains ill-defined due to the tumor's chemoresistant biology and response rates to conventional chemotherapy remain low, at about 30% [6,4]. In recent years, National Cancer Database analyses have postulated neoadjuvant chemotherapy for MpBC is associated with lower 5-year overall survival rates [7,8], but the benefit of neoadjuvant chemo-immunotherapy and Antibody-Drug Conjugates (ADC) remains unexplored in the setting of TNBC and HER2-low subtypes of MpBC.

This case exemplifies the aggressive clinical trajectory of MpBC, which can mimic inflammatory breast cancer and progress despite complete surgical excision and negative nodal status. In our patient, receptor expression (ER^+/PR^-/HER2-low) is uncommon for this subtype but does not necessarily translate into hormonal responsiveness, as MpBC biology is dominated by basal-like gene signatures [9]. Review of imaging illustrated the rapid progression of the previously undetected metastatic disease. This pattern is consistent with prior reports describing early hematogenous spread in metaplastic carcinoma.

Although MBC is largely heterogeneous and difficult to predict, it has been found that tumor type and size, rather than nodal status, are the strongest prognostic determinants. Triple-negative MpBC tumors have been found to have a recurrence rate of at least 35% in 2 years, emphasizing the need for vigilant and aggressive follow-up [3,4]. MpBC tumors have reportedly responded better to a combination of platinum agents and immunotherapy in addition to standard chemotherapy regimens [4], but currently there is a gap in evidence for the management of locally advanced MpBC in which upfront surgery should be explored in further studies, given the low rates of response after first line systemic neoadjuvant options recommended in the guidelines. Metaplastic carcinoma of the breast is an uncommon but highly aggressive malignancy that may clinically and radiographically mimic inflammatory breast disease. Despite surgical and supportive interventions, the prognosis remains dismal due to chemoresistance and early hematogenous spread. This case underscores the need for high diagnostic suspicion, timely biopsy, and multidisciplinary coordination. Moreover, current guidelines lack specific recommendations to guide the treatment of patients with MpBC. Early recognition, prompt tissue diagnosis, molecular profiling, and early palliative integration are crucial for optimizing outcomes and quality of life.

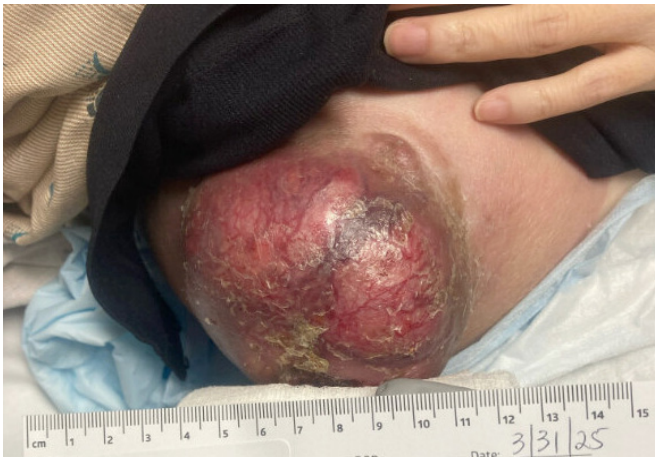

Figure 1: Initial presentation 3/31/25.

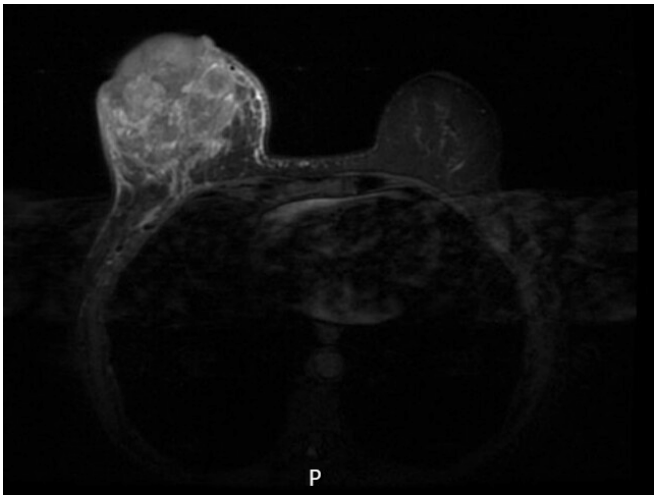

Figure 2: Staging Breast MRI (Axial T2 STIR sequence) 05/20/2025. 7.4×8.3×9.3 cm mass occupying most of the right breast, with an exophytic necrotic component, marked skin thickening, and edema tracking to the pectoralis fascia.

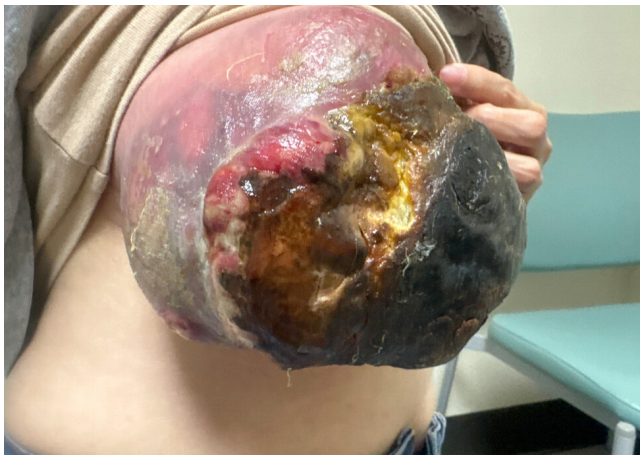

Figure 3: Post Neoadjuvant Systemic Therapy 8/27/2025

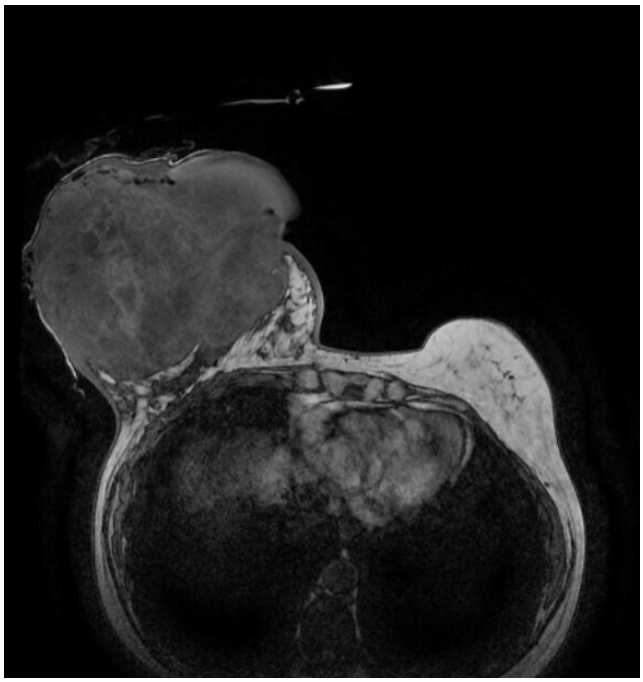

Figure 4: Preoperative Breast MRI (Axial T2 STIR sequence) after neoadjuvant chemo-immunotherapy 09/22/2025. Large heterogeneously enhancing mass now measuring 11.1×14.7×13.4 cm previously measuring 7.4×8.3×9.3 cm occupying most of the right breast.

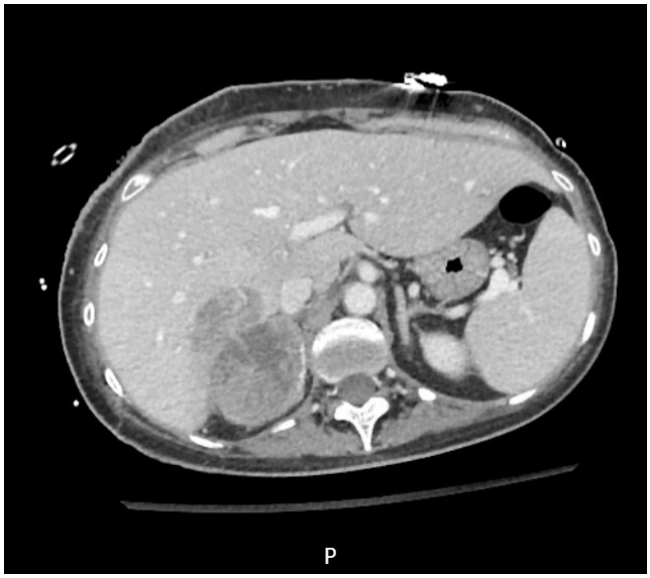

Figure 5: CT Abdomen and Pelvis with contrast 10/05/2025. 7.5 cm right adrenal metastasis with liver involvement and extension into right renal vein.

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