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Locally Advanced Chemoresistant Triple-Negative Metaplastic Breast Carcinoma: A Case Report

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Abstract:

- ***Background:***
Triple-negative metaplastic breast carcinoma (MBC) is a rare (<1% of breast cancers), biologically aggressive entity characterized by relative chemoresistance and poor prognosis. Its locally advanced presentation with skin ulceration poses major diagnostic and therapeutic challenges.

- ***Case Report:***
A 34-year-old patient (G1P1) presented with a grade III metaplastic infiltrating carcinoma of the left breast (ER 5%, PR 0%, HER2 score 0, Ki-67 90%), staged cT4bN1M0. Despite 8 cycles of neoadjuvant chemotherapy, the tumor progressed from 8×10 cm to 30×28 cm with extensive skin ulceration. In the absence of systemic alternatives, a left total mastectomy with axillary dissection (Patey procedure) was performed.

- ***Discussion:***
This case illustrates the intrinsic chemoresistance of MBC and highlights the limitations of conventional therapeutic strategies. New approaches (immunotherapy, targeted therapies, ADCs) offer promising perspectives.

- ***Conclusion:***
Salvage surgery remains an essential option in refractory cases. Prospective trials are needed to define optimal treatments for MBC.

Keywords: *Metaplastic Carcinoma; Triple-Negative; Locally Advanced; Patey Mastectomy; Neoadjuvant Chemotherapy; Ki-67; Skin Ulceration; Chemoresistance.*

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I. INTRODUCTION

Metaplastic breast carcinoma (MBC) is a rare malignant epithelial tumor of the breast, defined by the presence of differentiation toward non-glandular cell types: squamous cells, spindle cells, chondroid, osteoid, or myoepithelial components. This entity accounts for less than 1% of all breast cancers but concentrates some of the most unfavorable biological features among all breast tumors [1,2].

At the molecular level, more than 90% of MBCs display a triple-negative profile (estrogen receptor negative, progesterone receptor negative, HER2 non-amplified), classifying them among triple-negative breast cancers (TNBC). However, MBC constitutes a distinct subgroup within conventional TNBC: its transcriptomic profile resembles the claudin-low or mesenchymal-like subtype, with marked activation of epithelial–mesenchymal transition

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(EMT) pathways, high expression of tumor stem cell markers, and low expression of luminal genes [3,4].

These biological features confer on MBC a resistance to conventional chemotherapy protocols based on anthracyclines and taxanes—otherwise effective in the majority of TNBCs—and account for pathologic complete response (pCR) rates after neoadjuvant chemotherapy that are markedly lower than those observed in other triple-negative subtypes (10–20% vs 30–45%) [5,6].

Locally advanced presentation, with cutaneous invasion and ulceration, further worsens the prognosis and complicates therapeutic decision-making. In resource-limited countries, these advanced forms are frequent because of delayed diagnoses related to cultural, economic, and structural barriers to access to care [7].

We report the case of a young patient presenting with a locally advanced grade III triple-negative MBC, progressing under neoadjuvant chemotherapy, requiring total mastectomy with curative/palliative intent, and we discuss current and emerging therapeutic strategies in this rare entity.

II. CASE REPORT

➢ *Initial Presentation and History of the Disease*

The patient was a 34-year-old woman (born 01/04/1989), G1P1, with no notable personal or family history of breast cancer and no identified risk factors (no documented BRCA mutation on history-taking, no exposure to thoracic radiation). The WHO performance status was 0 and the ASA score was 1, reflecting good general condition on admission.

The patient was referred to the General Medical Surgery Department of the Sidi Mohamed Ben Abdellah National Institute of Oncology (INO — CHU Ibn Sina, Rabat) for management of an evolving left breast tumor. Initial examination revealed an upper-outer quadrant (UOQ) mass of the left breast measuring 8×10 cm, associated with an overlying inflammatory cutaneous plaque and clinically suspicious palpable ipsilateral axillary lymphadenopathy.

➢ *Paraclinical Workup and Histopathology*

Ultrasound-guided core needle biopsy established the histopathological diagnosis of metaplastic-type infiltrating carcinoma, SBR grade III. The complete immunohistochemical profile is summarized in the following table:

Table 1 Immunohistochemical Profile and Tumor Classification.

Marker	Result / Interpretation
Estrogen Receptors (ER)	5% — Weakly positive (non-functional)
Progesterone Receptors (PR)	0% — Negative
HER2 (IHC/ISH score)	Score 0 — Non-amplified
Ki-67 (proliferation index)	90% — Very high (paradoxical chemoresistance)
Vascular emboli (VE)	Absent
Histological type	Metaplastic — SBR grade III
Molecular status	Triple-Negative (TNBC, metaplastic subtype)
Clinical TNM stage	cT4b N1 M0 — Stage IIIB (AJCC 8th ed.)

The thoraco-abdomino-pelvic CT scan (TAP CT, 28/12/2023) showed a left breast tumor mass measuring 104×72×60 mm with suspicious ipsilateral axillary lymphadenopathy, with no distant secondary lesions. Breast ultrasound on 12/01/2024 confirmed an inflammatory mass of the upper-inner quadrant (UIQ) extending into the UOQ, BIRADS 6 ACR, with suspicious axillary lymphadenopathy. The contralateral breast was normal (BIRADS 1 ACR).

➢ *Neoadjuvant Treatment and Response Evaluation*

The patient received 8 cycles of neoadjuvant chemotherapy (anthracycline- and taxane-based regimen, standard TNBC protocol). Contrary to the expected effect, end-of-treatment clinical reassessment revealed clear tumor progression: the tumor now occupied the entire left breast (30×28 cm), with the appearance of extensive surface skin ulceration and persistence of axillary lymphadenopathy. Figures 1 and 2 illustrate the documented clinical appearance.

➢ *Figure 1 & Figure 2 — Clinical Appearance of the Left Breast*

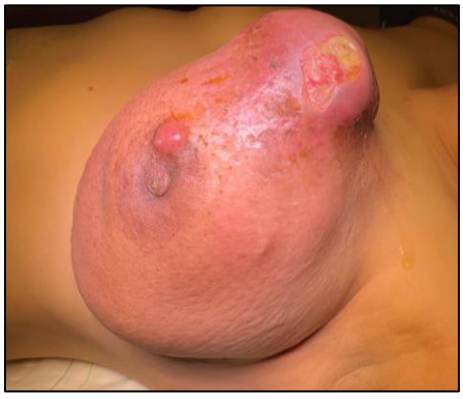

Fig 1 Lateral view. Enlarged, Erythematous Left Breast with Confluent Skin Ulceration at the Upper Pole. Generalized Peau D'orange Appearance.

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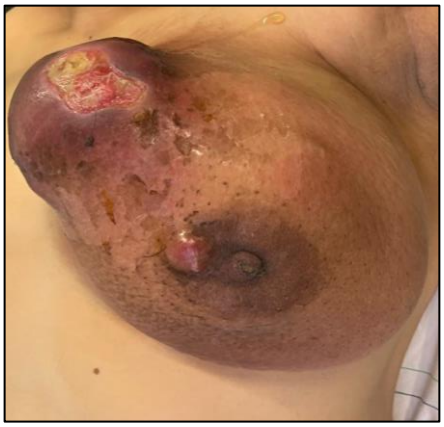

Fig 2 Anterior view. Tumor Progression with Violaceous Discoloration and Central Skin Necrosis Suggestive of Massive Dermal Involvement. Visible Serous Discharge. Palpable Left Axillary Lymphadenopathy.

Legend: 30×28 cm tumor with multiple skin ulcerations, dermal vascular congestion, and cutaneous breakthrough.

This progression constitutes a failure of neoadjuvant chemotherapy, characteristic of the metaplastic subtype. The Ki-67 of 90%, paradoxically, reflects here not chemosensitivity but primary resistance related to activation of cellular survival pathways (PI3K/AKT/mTOR, EMT, resistance to apoptosis).

➢ *Multidisciplinary Discussion and Therapeutic Decision*

The case was presented at a multidisciplinary team meeting (MDT):

- Oncology opinion: completion of chemotherapy cycles, no second-line protocol available in this context.
- Radiotherapy opinion: no indication for radiotherapy given the active progression and clinical context.
- Surgical opinion: surgical indication retained for left total mastectomy with axillary dissection (Patey procedure).

The patient was operated on. The postoperative course was uneventful. She was discharged on 14/10/2024 (length of stay: 6 days) with: dressing changes every two days, drain removal scheduled for day 12, and postoperative follow-up consultation at 3 weeks.

III. DISCUSSION

➢ *Epidemiology and Histological Classification of MBC*

MBC accounts for 0.2 to 1% of breast cancers [1,2]. It is defined by the WHO as a carcinoma showing differentiation into one or more non-glandular elements: squamous, spindle, chondroid, osseous, or myoepithelial [8]. This morphological heterogeneity reflects a unique tumor plasticity, resulting from dedifferentiation or transdifferentiation of mammary epithelial cells [9].

Several subtypes have been identified: squamous cell carcinoma, spindle cell carcinoma, low-grade adenosquamous carcinoma, fibromatosis-like carcinoma, and carcinoma with heterologous mesenchymal differentiation (osseous or cartilaginous). Our case corresponds to the mixed metaplastic type with a high-grade component [10].

➢ *Molecular Biology and Mechanisms of Chemoresistance*

The molecular profile of MBC is dominated by activation of key oncogenic signaling pathways. High-throughput sequencing studies have demonstrated frequent alterations of PIK3CA (30–50%), PTEN (30–40%), TP53 (50–70%), and Wnt/β-catenin pathway genes [11,12]. These alterations contribute to chemoresistance by maintaining cell-survival loops independent of the pro-apoptotic signals induced by chemotherapy.

EMT plays a central role in MBC biology. Activation of the transcription factors ZEB1, SNAIL, TWIST, and VIMENTIN, together with loss of E-cadherin, confers on tumor cells migratory and invasive properties as well as resistance to anoikis [13]. In addition, enrichment in tumor stem cells (CD44+/CD24-/ALDH1+ phenotype) accounts for resistance to conventional cytotoxic treatments and the capacity to generate recurrences [14].

The Ki-67 of 90% in our case deserves particular analysis. In conventional TNBCs, a high Ki-67 generally predicts a better response to chemotherapy (correlation with pCR). In MBC, this paradigm is inverted: intense proliferation is accompanied by resistance to antimitotic agents, probably related to abnormalities of cell-cycle checkpoints and to overexpression of P-glycoprotein (drug efflux) [15].

➢ *Locally Advanced Breast Cancer: Epidemiology and the Moroccan Context*

Locally advanced breast cancer (LABC) is defined as stage IIIA, IIIB, or IIIC according to the AJCC TNM classification. In Morocco, breast cancer is the leading cancer in women, with a steadily increasing incidence. Moroccan epidemiological studies show that 40 to 60% of patients are diagnosed at a locally advanced stage, compared with 10–15% in high-income countries [7].

Several factors account for this late diagnosis: delayed consultation (cultural barriers, fear of the diagnosis, lack of information), delays within the healthcare system, and inadequate organized screening programs. Awareness of breast self-examination and mammographic screening remains a major public health issue in the Maghreb [7].

➢ *Surgical Strategy: Patey Mastectomy in Locally Advanced Forms*

Modified radical mastectomy according to Patey (total mastectomy with axillary dissection and preservation of the pectoralis major) is the reference procedure for non-metastatic LABC after neoadjuvant chemotherapy [16]. In refractory forms—as in our case—salvage surgery aims at several objectives:

- Local control: reduction of the tumor mass and prevention of complications related to ulceration (hemorrhage, superinfection, refractory pain).

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- Improvement of quality of life: elimination of odor, suppression of discharge, and of the psychological distress associated with a visible, ulcerated tumor.
- Potential survival benefit: some studies suggest an overall survival advantage after salvage surgery even in the absence of complete response [17].

The associated axillary dissection is justified by the presence of suspicious lymphadenopathy confirmed on imaging. Controversy persists regarding the optimal extent of dissection (number of nodes harvested, Bergmann level), but the current recommendation is to retrieve at least 10 nodes for adequate staging [16].

➢ *Role of Adjuvant Radiotherapy*

According to ESMO and ASCO recommendations, chest-wall and nodal radiotherapy is indicated after mastectomy for T3–T4 tumors or with nodal involvement (N+) [18,19]. In our case, the radiotherapy team did not retain this indication, probably because of the context of active progression, the unfavorable short-term prognosis, and therapeutic logistics. This decision, although debatable with respect to standard recommendations, illustrates the reality of clinical trade-offs in a palliative setting.

➢ *New Therapeutic Perspectives*

Refractory triple-negative MBC represents a major unmet medical need. Several approaches are under evaluation:

- Immunotherapy (anti-PD-1/PD-L1): pembrolizumab (KEYNOTE-522) and atezolizumab (IMpassion130) have demonstrated a survival benefit in early-stage and metastatic TNBC [20,21]. Preliminary data suggest activity in MBC expressing PD-L1.
- Antibody–drug conjugates (ADCs): sacituzumab govitecan (anti-TROP2, ASCENT trial) has shown significant efficacy in refractory TNBC [22]. TROP2 is frequently expressed in MBC.
- PI3K/mTOR inhibitors: given the frequency of PIK3CA mutations and PTEN loss in MBC, alpelisib, everolimus, or copanlisib are rational therapeutic candidates [23].
- Anti-EGFR: EGFR is overexpressed in 50–80% of MBCs. Trials with cetuximab in combination with chemotherapy are ongoing [24].
- PARP inhibitors: although mainly indicated in the setting of germline BRCA mutation, some data suggest activity in tumors with homologous recombination deficiency (HRD) even without BRCA mutation [25].
- Anti-EMT therapies: experimental inhibitors targeting SNAIL, TWIST, or ZEB1 are under preclinical development [13].

Complete molecular profiling (next-generation sequencing, NGS) and BRCA1/2 testing would have been desirable in our case, given the patient's young age and the implications for subsequent management and family genetic counseling.

IV. CONCLUSION

We have reported an exemplary case of grade III triple-negative metaplastic breast carcinoma, stage cT4bN1M0, progressing refractorily under 8 cycles of neoadjuvant chemotherapy and resulting in a 30×28 cm tumor with extensive skin ulceration documented by clinical photographs. Left total mastectomy with axillary dissection (Patey procedure) constituted the only therapeutic option available in this oncological dead-end.

This case highlights several essential points: (1) the need for early diagnosis, particularly in young women; (2) the biological specificity of MBC and its intrinsic chemoresistance; (3) the importance of a complete molecular workup to guide referral to innovative therapies; (4) the central role of multidisciplinary discussion; (5) the irreplaceable place of salvage surgery in refractory locally advanced forms.

Prospective multicenter studies dedicated to triple-negative MBC are essential to identify new therapeutic targets and improve the prognosis of these patients.

➢ *Conflicts of Interest:*

The authors declare no conflicts of interest.

➢ *Funding:*

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