

Case report



## CHALLENGES IN THE MANAGEMENT OF METAPLASTIC SQUAMOUS CELL BREAST CARCINOMA

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### ABSTRACT

**Purpose:** To present a clinical case of metaplastic squamous cell sarcomatoid breast carcinoma – a rare entity within the spectrum of breast cancer, comprising up to 1% of all cases.

**Material/Methods:** We report the clinical course of a 68-year-old woman who sought medical attention regarding a locally advanced breast cancer characterized by exophytic growth.

**Results:** Despite initial systemic treatment, the tumor displayed rapid progression and extensive ulceration with spontaneous bleeding, prompting additional cycles of systemic and radiotherapy. Subsequently, the patient experienced life-threatening acute breast bleeding and hemorrhagic shock, leading to an admission to the Intensive care unit, followed by an emergent modified radical mastectomy. Histological examination of the specimen revealed a high-grade sarcomatoid variant of squamous cell metaplastic breast carcinoma (MBCa) without lymph node (LN) metastasis. Adjuvant radiation therapy was performed, yet a local recurrence was diagnosed, necessitating a second surgical intervention. Despite also receiving adjuvant systemic therapy, the patient presented with a second recurrence with distant metastases in the lungs. A transcatheter arterial embolization (TAE) of the tumor-supplying artery was performed, aiming to impede the tumor vasculature, thus reducing the risk of recurrent life-threatening hemorrhage. However, only a short-term effect was observed, and the patient experienced an unfavorable outcome.

**Conclusions:** This case underscores the challenges in managing advanced MBCa, its aggressive clinical course, and the struggles of achieving a favorable prognosis.

**Keywords:** metaplastic breast cancer, squamous cell, treatment, management, diagnosis,

### BACKGROUND:

Metaplastic breast carcinomas (MBCa) represent an exceedingly rare heterogeneous group of aggressive histopathologically diverse invasive breast cancers (IBC) that are reported to account for 0.2-1% of all breast cancer (BC) cases [1]. Their principal characteristic feature is the histological presence of at least two cellular types, usually comprising epithelial and mesenchymal components subjected to metaplastic differentiation, indicating cell conversion from glandular to non-glandular morphology [2, 3]. They are either monophasic, characterized by a single metaplastic component, or biphasic, involving two or more distinct components. According to the latest WHO Classification of Breast Tumors, MBCa is divided into six separate variants based on the histological pattern: (1) low-grade adenosquamous carcinoma, (2) fibromatosis-like metaplastic carcinoma, (3) spindle cell carcinoma, (4) squamous cell carcinoma, (5) metaplastic carcinoma with heterologous mesenchymal differentiation, and (6) mixed metaplastic carcinoma [1]. MBCa exhibits a high propensity to present in elderly patients at an advanced stage with accelerated progression and triple-negative immunophenotype, poor response to neoadjuvant systemic therapy (NAST), distant hematogenous dissemination without lymph node (LN) involvement, and skin or chest wall invasion. Accumulating research evidence indicates that MBCa is associated with a significantly higher risk of recurrence, shorter disease-free survival and overall survival in contrast to other subtypes of BC [2, 3, 4]. Despite its diverse histologic patterns and obscure clinical behavior, the management of MBCa is similar to that of triple-negative breast cancer of no special type (NST) [2]. Regarding its relative rarity in clinical practice, further intensive research on the convoluted pathogenesis of MBCa is mandatory to provide a solid foundation for improved treatment outcomes. Herein, we describe a rare case of highly aggressive MBCa with a more than one-year follow-up, treated with a multidisciplinary approach.

### CASE DESCRIPTION:

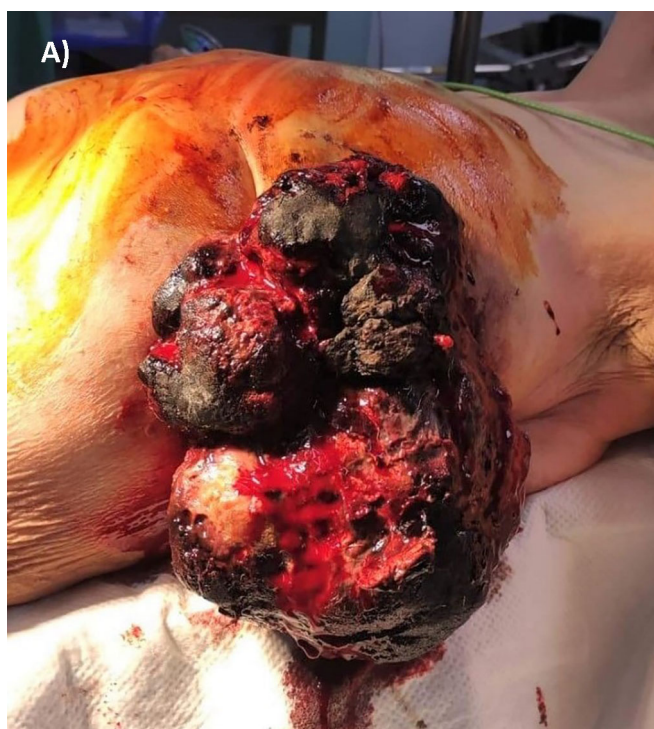
A 68-year-old woman sought medical attention at the Clinic of Surgery regarding a tumor on her left breast. Physical examination disclosed a 60/50 mm locally advanced exophytic ulcerative lesion with spontaneous bleeding in the lateral breast quadrants (Figure 1A). Detailed medical history was collected. Two months prior, she had undergone a core-needle biopsy for a palpable mass measuring approximately 20/20 mm in her left breast. The histology report revealed a high-grade pleiomorphic invasive breast carcinoma of NST with triple-negative phenotype and high Ki-67 proliferative index – 80%. A positive cytokeratin AE1/AE3 expression was noted; thereby, metastatic carcinoma was not excluded. The patient reported rapid growth of the formation with subsequent skin ulceration. A Fluorodeoxyglucose positron emission tomography/computed tomography scan uncovered a central tumor formation with increased metabolic activity (maximum standardized uptake value up to 21) measuring 90/60 mm with central necrosis. High metabolic activity was also observed in all three levels of axillary LNs and subpectoral LNs. The patient was staged as cT4cN3cM0. An oncologic committee assigned four cycles of NAST with CEF-90 (Cyclophosphamide, Epirubicin, 5-Fluorouracil) regimen. Throughout the first four cycles of NAST, regular follow-ups and dressing changes were performed due to spontaneous bleeding of the tumor. After completion of the initial treatment, the patient was assigned an additional four cycles of the same regimen with subsequent monotherapy with Docetaxel and radiotherapy (RT). However, during this period, the tumor exhibited rapid growth with extensive ulceration (Figure 1B). The patient was evaluated as unfit to undergo radiotherapy as she reported progressive deterioration of her general condition.

**Fig. 1.** A) Initial presentation. B) The exophytic tumor formation during follow-up in the period between the fourth and fifth course of NAST.



Between the fifth and sixth courses of NAST, she was admitted through the emergency department to the Clinic of Surgery with complaints of asthenia, adynamia and significant weight loss. Physical examination showed diffuse bleeding from the tumor. Laboratory findings revealed severe anemic syndrome (hemoglobin 77 g/L) and hemodynamic instability (blood pressure 70/40 mmHg) with severe tachycardia up to 120 beats per minute. Shortly after admission, she was transferred to the Intensive Care Unit for resuscitation due to hemorrhagic shock. Treatment included infusion and catecholamine therapy, as well as blood and plasma transfusions. After stabilization of the general condition, informed consent was obtained from the patient and her relatives, and an emergent operative intervention was initiated due to persistent bleeding from the tumor formation (Figure 2A).

**Fig. 2.** A) The patient before the emergency operation. B) 14th postoperative day (POD).

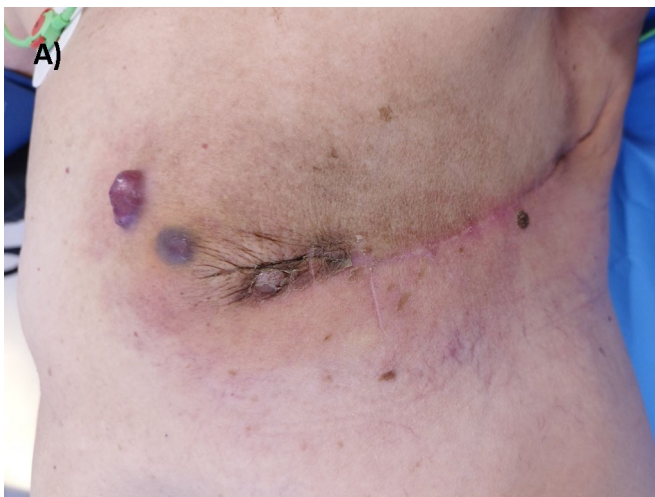




A modified radical mastectomy with axillary lymph node dissection on all levels was performed. The patient was discharged on the fifth POD without any complaints, reporting subjective improvement. The specimen from the operation was sent for histological examination, revealing a high-grade (Grade 3) sarcomatoid variant of squamous cell MBCa without metastatic LN. Tumor-free margins were confirmed. Immunohistochemical analysis revealed positive expression of cytokeratin AE1-AE3 and p63 markers. Negative expression of Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor-2 (HER2), and GATA3, CD20, CD30, S100, HMB45, and MelanA markers were observed.

The patient was assigned adjuvant intensity-modulated radiation therapy with simultaneous integrated boost and deep inspiration breath hold techniques. One month after the completion of RT, during a follow-up, we noticed two lesions in the vicinity of the operative cicatrix that were highly suspicious of recurrence (Figure 3A).

**Fig. 3. A) First recurrence. B) Second recurrence.**



The patient was admitted to the Clinic of Surgery, where a radical wide excision of the lesions was performed. The histological report confirmed that it was a local recurrence. Afterward, she was prescribed adjuvant systemic therapy with carboplatin and paclitaxel. Two months after the second operation, she presented at the Clinic of Surgery with a second recurrence (Figure 3B). Contrast enhanced computed tomography (CECT) was conducted, which uncovered disease progression with multiple soft tissue metastases on the left side of the thorax and distant metastases in the lungs (Figure 4).

**Fig. 4. CECT.**



We directed the patient for endovascular diagnosis, which revealed that the tumor formation was supplied by the left internal mammary artery (LIMA). The patient underwent coil embolization of the LIMA with polyvinyl alcohol foam (PVA) through the right femoral artery. She developed post-embolization syndrome (PES), which was managed successfully. The intervention demonstrated limited effectiveness, resulting in decreased yet persistent chronic bleeding, contributing to an ongoing deterior-

ration in the patient's overall health. She was deemed unfit to continue with the systemic therapy by the oncologic committee and was assigned palliative care. Unfortunately, the patient passed away after two months.

#### **DISCUSSION:**

In clinical practice, MBCa is a rarely encountered heterogeneous entity of BC, and there are no specific guidelines for its management. Characterized by rapid tumor growth, resistance to systemic therapy, increased proclivity for recurrence and poor prognosis, MBCa accounts for a significant increase in morbidity and mortality. Most cases present with higher nuclear grade and lack ER, PR and HER2 expression. Furthermore, MBCa shows increased predilection to hematogenous dissemination, particularly in the lungs, followed by bones and brain. At the same time, lymphogenous spread appears to be rare, regardless of tumor size and histologic grade [4, 5, 6]. Interestingly, MBCa typically exhibits benign imaging characteristics on both mammography (MG) and ultrasound [6]. Only 17% of patients with MBCa present with microcalcifications on MG, often linked to ductal carcinoma in situ and/or osseous differentiation [1, 2]. Additional characteristics encompass a round or oval shape with well-defined margins, in contrast to the irregular and spiculated features typically observed in IBC-NST [6]. Hu J. et al. [7] retrieved data from the Surveillance, Epidemiology, and End Results (SEER) database of 1665 patients with confirmed MBCa. A detailed analysis revealed age, tumor size, regional LN status and surgical treatment as prognostic factors. Furthermore, the molecular subtype and chemotherapy showed no impact on prognosis. Notably, RT was linked to a better prognosis in triple-negative MBCa. In recent years, research attention has expanded to explore and elucidate the intricate pathogenesis, molecular aberrations and clinical behavior of MBCa, aiming to develop effective therapeutic strategies. Currently, various theories attempt to elucidate the aggressive clinical course of MBCa. These include the collision hypothesis, suggesting that carcinomatous and sarcomatous components arise from distinct progenitor cells; the combination hypothesis, proposing a monoclonal origin; the conversion hypothesis, positing that carcinomatous components undergo metaplastic processes to form sarcomatous elements; and the myoepithelial origin hypothesis. The metaplastic theory is supported by the fact that both epithelial and mesenchymal components express cytokeratins (AE1/AE3) (positive in up to 85% of cases), S-100, and vimentin. In addition, most

tumors (77%) are positive for myoepithelial markers, such as p63, thus confirming the myoepithelial theory [1, 3]. Molecular analysis of MBCa has revealed that phosphatidylinositol 3 kinase signaling overexpression and epithelial-to-mesenchymal transition features may contribute to the chemoresistant and aggressive phenotype of MBCa [3].

In the case we described, the patient experienced no benefit from systemic treatment and RT. After applying all available multidisciplinary approaches, we hypothesized that impeding the blood supply of the tumor formation would lead to reduced bleeding from the tumor and improvement in the patient's performance status. Transcatheter arterial embolization (TAE) has been successfully employed in the management of patients with locally advanced or metastatic cancers (e.g. renal and liver) with acute hemorrhage. Acute life-threatening breast bleeding is rarely encountered, and the endovascular approach is reported to be a safe and effective procedure in such cases. Preoperative utilization of TAE can also serve as a preventive measure against excessive intraoperative bleeding in highly vascularized advanced tumors [8]. However, in our case, TAE yielded an unsatisfactory effect, probably attributed to the metastatic stage of the disease and the significantly compromised general condition of the patient.

#### **CONCLUSION:**

In conclusion, MBCa represents a distinctive and challenging entity within the spectrum of breast malignancies. Its rarity, diverse histologic subtypes, obscure clinical behavior and therapeutic resistance contribute to diagnostic and treatment complexities. Further research is mandatory to unravel the intricate nature of this enigmatic subtype of BC, ultimately paving the way for developing more effective therapeutic strategies.

#### **Abbreviations:**

- MBCa** – Metaplastic breast carcinoma
- LN** – Lymph node
- CECT** – Contrast enhanced computed tomography
- TAE** – Transcatheter arterial embolization
- IBC** – Invasive breast cancer
- NAST** – Neoadjuvant systemic therapy
- RT** – Radiotherapy
- NST** – Non-specific type
- ER** – Estrogen Receptor
- PR** – Progesterone Receptor
- HER2** – Human Epidermal Growth Factor Receptor-2

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