Metaplastic breast cancer with rapidly progressive recurrence in a young woman: case report and review of the literature

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Metaplastic breast carcinoma (MpBC) is a rare neoplasia. It accounts for less than 1% of all breast carcinomas (BC), and the incidence of this type of cancer has risen since 2000 (the World Health Organization (WHO) recognized MpBC as a distinct type of breast cancer). It is made up of heterogeneous subgroups of malignant tumors built of neoplastic epithelium differentiated into squamous cells and/or mesenchymal-looking elements [1–4]. The most common histopathological subtypes are squamous cell carcinoma and metaplastic carcinoma with mesenchymal differentiation [5–9]. Over 90% of MpBCs are ER, PR, and HER2 negative ("triple negative"), contrary to intraductal carcinomas, which are triple negative in 18% of cases [8, 10–14]. The mean age of MpBC patients is about 50 years of age [7, 15–17]. In most studied cases a diagnosis may not be achieved by use of core needle biopsies, and histological examination of the surgical specimen allows for the definitive diagnosis of MpBC [9, 18, 19]. There is no standard treatment regimen specific for MpBC, which is characterized by a poor prognosis. We present here a case of rapidly progressive recurrence of MpBC.

We present a case of a 22-year-old woman, with a negative family history of BC. She came to our clinic with right breast enlargement and had experienced pain in the preceding 3 months. Physical examination showed a tumor filling the right breast, with a maximum diameter of 20 cm. There was no skin or nipple retraction and no axillary lymphadenopathy. In ultrasound examination, the lesion appeared as a solid-liquid tumor with sharp borders, 20 cm in a diameter. The axillary lymph nodes were not affected. It was classified as BI-RADS category 4b. By means of a fine needle aspiration biopsy, 210 ml of serous-bloody fluid was obtained. A core needle biopsy was performed and histological examinations showed breast tissue with non-specific, chronic inflammation around the ducts and lobules with no evidence of a neoplasm.

The patient underwent a lumpectomy during which the nipple and part of the pectoralis major muscle were removed. A histological ex-

amination showed macroscopically a 20 × 18 cm encapsulated tumor infiltrating the muscle with central necrosis.

Microscopically, the tumor was well circumscribed and consisted of both spindle and poorly differentiated epithelial cells. The spindle cells formed long parallel fascicles (Figure 1) separated by collagen bands and deposits of amorphous extracellular material, which focally presented an osteoid-like appearance (Figure 2). The poorly differentiated epithelial cells created a solid texture (Figure 3) with extensive foci of necrosis and hemorrhages. Both spindle and epithelial cells are characterized by a high nuclear grade and high mitotic activity.

Immunohistochemical staining revealed that epithelial cells stained focally for cytokeratins CAM5.2 (Figure 4), whereas the spindle cell component reacted strongly to CD10, desmin (Figure 5), and P53 protein. Both constituents were characterized by an intensive, membranous reaction to EGFR protein (Figure 6) and were negative for
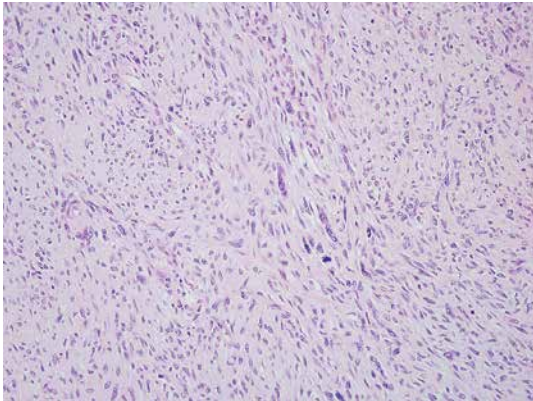

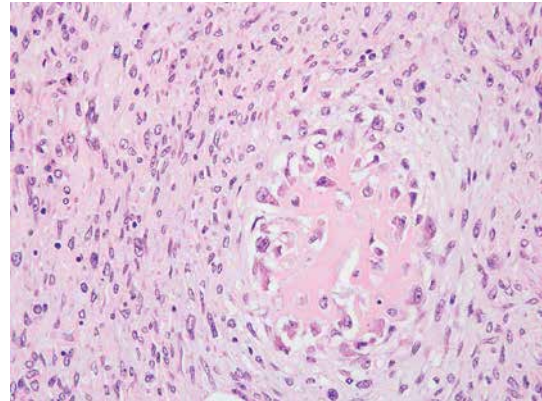**Figure 1.** Spindle cell component of the tumor; high nuclear grade, numerous mitoses

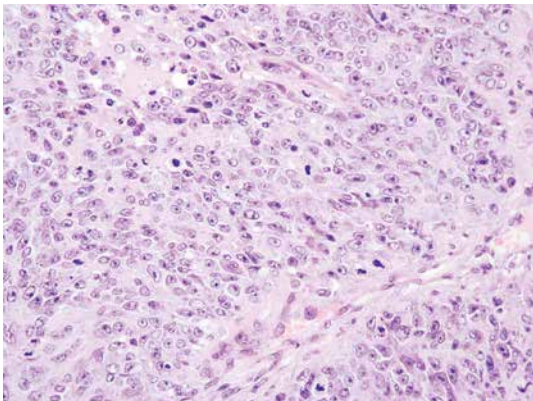**Figure 2.** Osteoid formation

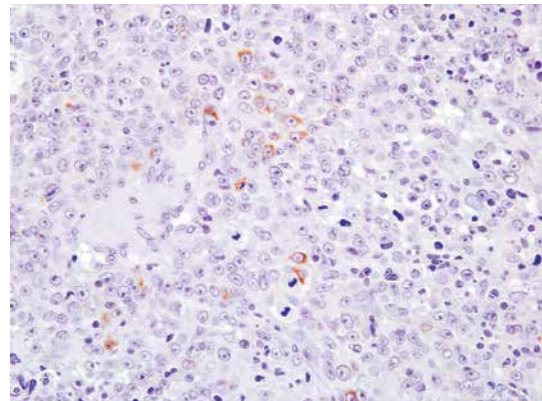**Figure 3.** Poorly differentiated epithelial component of the tumor

Figure 4. Anti-cytokeratin CAM5.2 positivity in the poorly differentiated epithelial tumor component
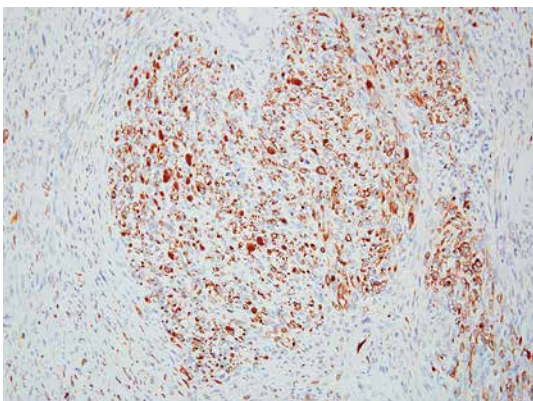

Figure 5. Positive reaction against desmin in the spindle cell component of the tumor
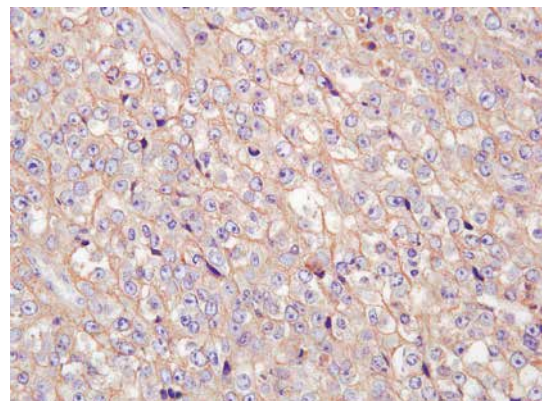

Figure 6. Diffuse membranous reaction to epidermal growth factor receptor (EGFR)

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steroid receptors (ER, PR) and HER2 protein. The Ki-67 index ranged from 89% (in the spindle cell component) to 91% (epithelial cells). According to the WHO 2012 Classification of Tumors of the Breast, the tumor was classified as breast carcinoma with leiomyosarcomatous and osseous metaplasia (metaplastic carcinoma) high grade (G3) [1]. Margins on all sides were tumor free. The postoperative staging was assessed as pT3 pN0 pM0 (stage IIB).

On 39 day following the operation (22 days after the last follow-up examination), the patient came for histopathology results, and a physical examination revealed two lesions above the surgical scar. An ultrasound examination showed the lesions to be 5.9 cm and 4.7 cm in diameter. The results of the fine needle aspiration biopsy and core biopsy confirmed the recurrence of the breast tumor. The lesions had almost doubled their diameter in 10 days. A computed tomography examination (CT) showed two tumors located in the right breast. Their maximum diameters were 7.7 cm and 6.7 cm. The CT scan did not show any other pathology.

The patient's tumor was excised 2 months after the primary operation followed by a Halsted reoperation of the right breast with stage I axillary lymph node dissection. A histological examination confirmed that the relapsed metaplastic breast carcinoma had been removed with a thin tumor margin diameter of 1 mm on the pectoral side. The lymph nodes appeared normal.

The patient was qualified for adjuvant chemotherapy comprising doxorubicin and cyclophosphamide. After the first chemotherapy cycle she received radiotherapy combined with hyperthermia. This decision was made on the grounds of dynamics of the chest wall recurrence in order to control the local process. Radiotherapy was carried out in the form of external radiation using mixed photon/electron beams generated in a linear ac-

celerator. It was planned using a computer-aided therapy planning system. The beam energy was individually adjusted in consideration of the patient's anatomical parameters. The planning target volume (PTV) included the chest wall and regional lymph nodes with 1 cm margin. The total dose given to the PTV was 50 Gy in 25 fractions. Local hyperthermia was applied using the BSD-500 system emitting electromagnetic radiation of 915 MHz and 35 W in order to obtain a therapeutic temperature in the range of 40–41°C. The patient was submitted to local hyperthermia 3 times a week (every second day) for 60 min immediately before each radiotherapy session. The area covered by hyperthermia involved the recurrence with an adequate margin. After the local treatment, the patient developed G3-skin reaction.

Following radiotherapy, chemotherapy was continued for a total of 4 cycles with good tolerance. The patient remains under clinical observation. Table I presents detailed clinical and pathological characteristics of the patient and therapeutic choices.

Recent studies show that MpBC has a worse prognosis and a higher risk of recurrence than similar stage invasive ductal carcinoma (IDC) of no special type [11, 20, 21]. Comparing patients with MpBC and triple negative IDC, MpBC has a lower survival rate, worse disease-free survival (DFS) (5-year DFS rate 39–56% vs. 60.3–77%) and a worse overall survival (OS) rate (5-year OS rate 44–54.5% vs. 73.3–78%) [2, 10, 13, 20, 22]. There are a few hypotheses that stress the pathogenesis of MpBC, but none of them is accepted in the literature as the main cause of MpBC, and the cellular origin of MpBC is not yet clear [3, 4].

Our patient developed early (during 2 months) and rapidly progressive recurrence of the disease, as was confirmed by the clinical observation and the results of molecular tests. Hyperthermia was administered in combination with radiotherapy be-

Table I. Patient characteristics

Clinical	22-year old women. T3N0M0, BI-RADS 4b, 20 cm solid-liquid tumor, sharp borders
Surgery	Lumpectomy (due to lack of preoperative histopatological conformation)
Pathological	Metaplastic carcinoma, G3 (leiomyosarcomatous and osseous metaplasia). ER, PR, HER2 negative. pT3pN0pM0
Clinical	Chest wall recurrence
Surgery	Halsted reoperation + stage I axillary lymph nodes dissection
Postoperative staging	pT4a pN0 pM0
Adjuvant chemotherapy	1 course (doxorubicin and cyclophosphamide)
Radiotherapy	Radiotherapy (50 Gy, 25 fractions) with hyperthermia (BSD-500 system, 915 MHz and 35 Watt) 3 times in a week
Adjuvant chemotherapy	3 courses (doxorubicin and cyclophosphamide)

cause of previous experience with this treatment in dealing with inoperable or non-radically operable chest wall recurrence of breast cancer [23].

This variant of BC is very rare, which is why only small groups of patients are presented in the literature. The rarity of the disease makes it impossible to conduct studies focused on this patient population. When comparing MpBC with breast adenocarcinomas, the tumor size is usually larger and the axillary lymph node metastases are less common in MpBC patients (22% in MpBC vs. 34% in IDC) [13, 16, 22]. Hormone and HER2 receptor positivity rates are also lower in MpBC [2, 13, 15, 24]. According to the literature, the cancer cells are positive for p63 in more than 90% of MpBCs, so this marker may be useful in differential diagnosis with other spindle and mesenchymal tumors [12, 25]. A Ki-67 index higher than 30% is observed in 50% of MpBC cases compared with 81% observed in patients with invasive ductal carcinomas [2, 20, 22]. EGFR overexpression is involved in 80% of MpBC cases, and p53 overexpression can be observed in 32–71% of cases of MpBC [26–29].

In reviewed studies lung and bone metastases were found to be more frequent than lymphatic spread [6, 17]. This behavior of MpBC resembles that of sarcomas. Luini *et al.* reported 3 locally recurrent and 8 lung and bone metastatic patients in their 37 MpBC series [2]. The main distant metastatic sites are the lungs, bone and the brain [2, 7, 8, 15]. The literature shows this histologic subtype of BC to be chemoresistant. In a high portion of cases chemotherapy is used as adjuvant systemic treatment [15, 21, 24]. However, new chemotherapeutic drugs should be considered when treating metaplastic subtypes to overcome resistance to cytotoxic agents. In addition to MpBC chemoresistance, most of them are hormone receptor negative and hormone therapy is unnecessary [18, 21, 24, 29].

In conclusion, because of the rarity of the disease and the variety of histological subtypes that exist, the opportunities for conducting studies on this patient population are limited. Therefore the role of radiotherapy and chemotherapy is not yet clearly established, and surgical treatment is often the only choice available. Hormone therapy is unnecessary. Early diagnosis and surgical treatment are crucial to achieve an optimal outcome in patients with MpBC.

Conflict of interest

The authors declare no conflict of interest.

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