Primary angiosarcoma of the breast: A clinical case and review of the literature

Lena Marinova† Bistra G. Yordanova2 Doroteya V. Malinova3

Abstract: We present here a rare case of primary mammary angiosarcoma in a 48-year-old female patient. After 3 years without treatment, the woman presented to the hospital with locally advanced tumor in right mammary gland, involving the overlying skin and bleeding. Radical mastectomy was performed with axillary lymph-node dissection. The CT scan revealed solitary liver metastasis. After an overview of different cases of primary angiosarcoma of the breast published in the literature, we discuss the importance of histological criteria and immunohistochemical methods, as well as the optimal multimodal treatment in these patients. Poorly differentiated primary mammary angiosarcoma (grade 3) is an invasive neoplasm with high risk of local recurrence and distant metastases. The multimodal treatment involves radical mastectomy with or without axillary lymph-node dissection. Adjuvant radiotherapy and adjuvant chemotherapy help the local tumor control, reduce recurrences and increase overall survival.

Keywords: primary mammary angiosarcoma, radical mastectomy, radiotherapy, chemotherapy, multimodal treatment

1 Introduction

Angiosarcoma (AS) is a rare aggressive tumor which arises from endothelial cells lining vascular structures[1,2]. Breast is one of the most common primary sites of angiosarcoma[3]. Mammary AS accounts for 1% of all soft tissue tumors[4,5] and 0.04% of all primary breast tumors[4,6–11]. According to the etiology, angiosarcoma of the breast can be primary and secondary[12]. Secondary tumors are associated with chronic lymphedema in the upper limb after axillary lymph-node dissection and radiotherapy in patients with mammary carcinoma. The condition is known as Stewart-Treves syndrome[4,8,13,14]. Secondary angiosarcoma is also considered a complication from radiotherapy and breast-conserving surgery (BCS) in patients with breast carcinoma[15]. Primary mammary AS is usually found in young patients (20-50 years) with no history of breast carcinoma[16–19]. Secondary AS is found in older patients (67-71 years), usually 5 to 10 years after radiotherapy for breast carcinoma[4,20–22].

2 Clinical case

We report a case of primary angiosarcoma of the breast in a 48-year-old woman. Three years prior to admission to the hospital the woman noticed a lump in the right mammary gland, which slowly had enlarged. In the last three months the lesion had enlarged more rapidly and reached the skin with ulcer formation. The woman was admitted to the University Hospital in Ruse with severe bleeding from the ulcerated area. On examination, the right mammary gland was three times larger than the left one, with bluish colour and palpable firm tumor mass. In the outer upper quadrant of the affected breast the skin was ulcerated and bleeding. On palpation, right axillary lymph nodes were enlarged but painless. Right radical mastectomy was performed with axillary lymph-node dissection. Chest and abdominal CT scan revealed bilateral pneumofibrotic changes in dorsobasal areas of the lungs, no pathological mediastinal and axillary lymphadenopathy, no pleural effusions. In 8th segment of the liver, oval shaped metastasis was found.

Gross examination of the resected breast showed no evidence of mammary gland parenchyma. Subcutaneously, a cavity, 13 cm in diameter was found. It was filled with dark red blood and blood clots. The nipple was not affected. Histology revealed a tumor composed of anastomosing densely packed vascular spaces of variable sizes,
lined with atypical endothelial cells with severe nuclear polymorphism and hyperchromasia, prominent nucleoli and atypical mitotic figures. Intraluminal papillary projections composed of endothelial cells were found, as well as solid areas of spindle shaped cells between the described vascular spaces (Figure 1). Histological examination of the resected axillary lymph nodes showed sinus histiocytosis. The final diagnosis was angiosarcoma of the right mammary gland, grade 3 (G3). Immunohistochemical study revealed a neoplasm positive for CD34 antibody, confirming the vascular nature of the tumor (Figure 2). The epithelial marker, Cytokeratin 1/3, was negative (Figure 3). Estrogen (ER) was negative (Figure 4) and Progesteron (PR) was negative (Figure 5).

After the surgery, the woman was assessed for chemotherapy, which was not carried out, due to a deterioration in her condition. Within six months the dis-
ease quickly progressed. The patient developed a local relapse in the right chest, metastases in the hilar lymph nodes in the right lung with compression of the right pulmonary artery, pulmonary metastases, hepatic metastases, bone and brain metastases. The patient succumbed to her disease eight months after the surgery.

3 Discussion

The first case of primary angiosarcoma of the breast is published in 1907 by Borrman and the first case of seconday mammary angiosarcoma is described by Body et al. in 1987[7,20,21]. Primary AS of the breast is aggressive tumor with high risk of local recurrence and distant metastases[8,22,23]. The lack of prospective randomized studies on the role of the systematic therapeutic approach in the literature is due to the rarity of this tumor. The major problems concerning AS are: (1) difficult histological diagnosis and broad differential diagnosis, requiring immunohistochemical analysis; (2) choosing the most reliable multimodal treatment for these patients.

Clinically, patients with primary mammary AS present with rapidly growing painless palpable tumor mass[24,25]. In 2% of the cases patients present with increased breast volume and bluish red coloration of the overlying skin[13,25]. Usually, the axillary lymph nodes are not enlarged. In the majority of cases published in the literature, the size of the tumor is more than 4 cm. in diameter[26].

Preoperative diagnosis with fine needle biopsy (FNB) is difficult. Chen et al. reported false negative diagnosis after FNB in 37% of the cases[3]. Differential diagnosis includes hemangioma, benign vascular proliferation[27], hamartoma[28], stromal hyperplasia, phylloides tumor, stromal sarcoma, metaplastic carcinoma, other sarcomas, like fibrosarcoma and liposarcoma[26,29]. Large-core biopsy might facilitate the accurate diagnosis, but such a biopsy is difficult to perform due to the vascular nature of the neoplasm. Final diagnosis usually is made after surgical resection and histological examination of the specimen. Three main histopathological patterns of mammary AS have been described according to the grade of differentiation:

Grade I (G1) is characterized by anastomosing vascular channels, lined by a single layer of endothelial cells; these channels dissect through the stroma causing distortion but little destruction of the preexisting lobules and ducts.

Grade II (G2) is similar to grade II tumors but with increased mitoses, endothelial tufting and foci of papillary formations and/or solid growth pattern.

Grade III (G3) is characterized by marked pleomorphism, mitoses, necrosis and solid growth, may show epithelioid and spindled cytology (Figure 1)[31,32].

Different areas from one and the same tumor can be with different tumor grades. The degree of differentiation can’t be defined properly on core-biopsy[1].

Immunohistochemical analysis can prove the endothelial differentiation of the tumor cells. CD31 is one of the most sensitive and specific markers for endothelial cells. Tumor cells are also positive for Factor VIII, Fli1 and CD34[13,31,33–35]. In some cases papillary proliferations are found in the vascular spaces and these areas can resemble ductal carcinoma in situ. Estrogen receptors are reported to be negative in most cases[26,36]. In the case reported here, estrogen and progesterone receptors were both negative (Figure 4 and Figure 5).

Soft tissue sarcomas depending on histology and G are aggressive neoplasms with varying degrees of local invasiven and risk of hematogenous dissemination. In the presented clinical case, there is an aggressive G3 sarcoma with high metastatic potential.

There is no optimal treatment for breast angiosarcoma due to the rarity of this tumor[15]. Similar to other soft tissue sarcomas, prognostic factors include tumor size, degree of differentiation, margin status at the time of surgery[15,37,38]. Disease recurrence rate increases in the case of residual tumor and grade 3 AS[21,37,39,40]. Three studies reported longer disease free survival (DFS) in grade I and grade II tumors, compared to grade III neoplasms[2,37,41]. It has been reported that the five year survival rate in well differentiated AS is 76%, and in poorly differentiated angiosarcomas, it is 15%[13].

3.1 Surgical treatment

Mammary AS is treated surgically, but also with chemotherapy and radiotherapy. The treatment lacks uniformity and criteria for surgery and adjuvant therapy are still discussed in the literature[42]. Breast-conserving therapy is recommended for small, grade I tumors, if there is a chance of achieving negative surgical margins[32]. Some authors recommend aggressive surgical treatment with removal of muscle tissue[21,22]. Radical mastectomy alone or with axillary lymph-node dissection is the preferred surgical treatment[14]. However, nodal metastases are rare in AS and the necessity for nodal dissection is obscure[15]. A study from 2017 reported worse overall survival (OS) in patients with primary AS who received mastectomy, when compared with patients who received breast-conserving surgery[43].

3.2 Adjuvant chemotherapy and radiotherapy

Chemotherapy and radiotherapy have been used in the adjuvant setting of mammary AS, but these therapies need
further examination and clear criteria\textsuperscript{[12,29,38,44]}. Literature lacks prospective randomized trials on the effect of adjuvant chemotherapy and radiotherapy and they are used only for tumors with high risk of recurrence\textsuperscript{[13]}. Radiotherapy is based on tumor characteristics and the type of surgical treatment\textsuperscript{[22]}. Radiotherapy is beneficial for patients with histologically positive surgical margins after mastectomy\textsuperscript{[45]}. In two studies, a benefit to the 5 and 10 year recurrence free survival (RFS), disease free survival (DFS) and overall survival (OS) was observed following radiation treatment\textsuperscript{[46,47]}. Some authors report that Anthracycline-based therapy can improve DFS and OS\textsuperscript{[48]}. A meta-analysis of patients treated with Doxorubicin and an anthracycline-based regimen showed prolonged DFS and OS\textsuperscript{[49,50]}. In two studies, adjuvant chemotherapy had no effect on DFS or OS\textsuperscript{[2,51]}. In the majority of the reported cases patients are treated with Cyclophosphamide, Anthracycline or alkylating agents in combination with pyrimidine analog\textsuperscript{[24]}. Paclitaxel is proven to be active and is commonly used in advanced angiosarcomas from different primary tumor sites\textsuperscript{[51–53]}. T Sher et al. report that anthracycline-ifosfamide and gemcitabine-taxane chemotherapy regimens appear to be highly active in 48% of the cases\textsuperscript{[36]}.

3.3 Neoadjuvant chemotherapy and radiotherapy

Primary mammary AS can spread through blood to lungs, liver, skin and contralateral mammary gland\textsuperscript{[13]}. Retrospective analysis of 41 patients with metastatic angiosarcomas from different primary tumor sites showed an improved OS from 10.4 to 23.7 months with taxane based regimens compared to non-taxane based adjuvant chemotherapy\textsuperscript{[54]}. Paclitaxel therapy shows promise in the treatment of angiosarcoma\textsuperscript{[55]}. Immunotherapy with IL-2 (interleukin-2) is also part of the treatment\textsuperscript{[43]}. Different drugs that suppress endothelial proliferation can be used\textsuperscript{[13]}. There are few papers that have examined the use of angiogenesis inhibitors like bevacizumab\textsuperscript{[55,56]} and rapamycin\textsuperscript{[18]}.

4 Conclusion

The reported primary AS of the breast is a rare aggressive tumor with bad prognosis. The final diagnosis is based on specific histological criteria and immunohistochemical analysis. Prospective randomized trials are requested to reach a consensus on the optimal multimodal treatment. The gold-standard treatment in patients affected by primary angiosarcoma of the breast is surgery. Adjuvant chemotherapy and radiotherapy are recommended in G3 tumors with high risk of recurrence and distant metastases. The presented primary AS of the breast is a rare aggressive G3 sarcoma with high metastatic potential.

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