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Case report

SECONDARY ANGIOSARCOMA AS A COMPLICATION OF RADIOTHERAPY OF THE BREAST CARCINOMA: 3 CASES REPORT AND LITERATURE REVIEW

SEKUNDARNI ANGIOSARKOM KAO KOMPLIKACIJA RADIOTERAPIJE KARCINOMA DOJKE: PRIKAZ 3 SLUČAJA I PREGLED LITERATURE

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Ključne reči
angiosarkom, karcinom dojke, radioterapija

Abstract

Introduction: Angiosarcomas are aggressive malignant neoplasm of vascular endothelial origin most frequently compelling the skin. Secondary angiosarcoma of the breast or a cheast wall, is a late and rare sequela of radiotherapy for breast carcinoma after radical of breast conserving surgery. **Case presentation**: We report 3 cases of patients who initially underwent conserving surgical treatment of primary breast cancer, followed by adjuvant chemo- and radiotherapy. Seven years in first, and five years in other two cases, after initial treatment, all patient presented with painless, colored skin lesions, in area of surgical scar. Biopsy of these lesions revealed diagnosis of angiosarcoma. Shortly afterward, despite radical excision followed by adjuvant chemotherapy, two reported patients developed local recidivies and distant metastases. **Conclusion**: Due to unspecific behavior of secondary angiosarcoma of the breast, and a great potential for local recurrence, the extra caution should be paid in order to prevent the substantial time delay between final diagnosis and treatment of the secondary angiosarcoma of the breast.

INTRODUCTION

Angiosarcoma (AS) is an uncommon malignant neoplasm characterized by extensively infiltrating anaplastic cells derived from endothelial cells and lining irregular vascular spaces(1). World Health Organisation (WHO), in fourth edition of classification of breast tumors, defines breast AS as malignant proliferation showing endothelial differentiation(2). Based on the WHO classification, it is derived in two distinct groups: primary, arising de novo and within breast parenchyma and secondary, which develops in chest wall, skin or breast parenchyma, associated with radiation or chronic lymphedema after breast surgery. Recently, a possible association of AS with silicone breast implants has also been described(3). Because of the very low incidence of this disease, there are only a few studies regarding its optimal therapeutic management.

CASE REPORTS

Case 1.

A 69-year old patient came to our center surgical department in 2013. for a performing of conserving surgical treatment of breast tumor. The patient underwent segmentectomy with sentinel node biopsy. After histopathological examination of the resected specimen the final diagnosis was grade 2, hormone receptore positive and HER-2 negative invasive ductal carcinoma. Biopsy of sentinel node was performed and its histopathological examination confirmed one lymph nodes metastasis. There was no family history of breast malignancy, radiation or trauma. Surgical treatment was followed by conformal radiotherapy which included doses TD=50Gy/25 fraction followed by "boost" TD=14Gy/7 fraction and adjuvant hormonal treatment and regular follow up. The patient came back 7 years after initial

treatment with hematoma of the right inner quadrant of her left breast, palpatory non-resistant. Excision was performed and the biopsy showed infiltrative tumor composed of anastomosing and brunching, partly dilatated vascular channels lined by atypical endothelial cells, with small nuclei, prominent nucleoli, and a few atypical mitotic figures. Immunohistochemically, tumor cells expressed CD34 and F VIII. (figure 1A). The diagnosis was grade 2 AS of the breast. Tumor distribution was multifocal (diameter was 11 and 5 mm) with 1.5 mm wide margins. Tumor was growing infiltratively. 2.5 mounths after the previous surgical treatment, patient came back reporting yellow coloring of the chest wall. The patient underwent a left-sided simple mastectomy. Patohistologically, two focuses of recurrent AS were found, 17 and 30 mm in diameter. The tumour infiltrated the skin and the chest-wall muscle (figure 1B). The postoperative period occurred without incident and the patient was discharged 14 days after the procedure. The patiente is asymptomatic until the time of this report.

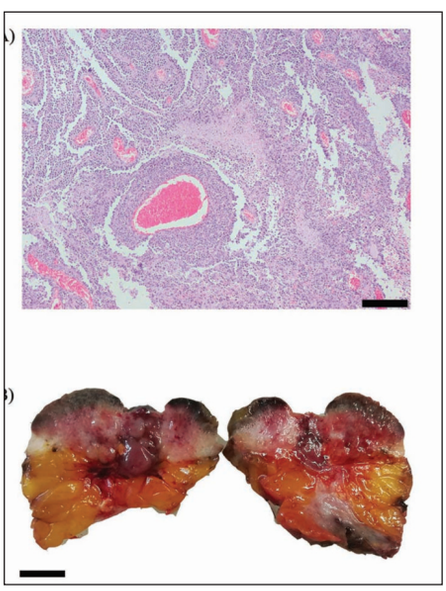

Figure 1. *A) Tumor consisted of anastomosing and brunching, partly dilatated vascular channels lined by atypic cells, with small nuclei and prominent nucleoli; H&E; x20 (scale bar 200 µm); B) Grossly, breast AS is presented as telangiectasia-like formations, multiple and distinct, appearing as nodules or plaques. (scale bar 1 cm).*

Case 2.

61 year old women came to our center in 2015. year after she detected a painful node of the left breast. Examination revealed palpable lesion in upper left quadrant of the left breast, 4 x 4 x 3 cm in diameter, bipolar, firm and relatively well defined, without infiltrating skin above. After core-needle biopsy and confirmation of the breast invasive cancer diagnosis, the patient was presented to the surgical department and underwent superolateral quadarantectomy of the left breast and dissection of ipsilateral axilla. The histopathologic analysis confirmed diagnosis of the infiltrative poorly differentiated ductal carcinoma of the breast, diameter 6. Histopatological examination confirmed metastases in 6 of 22 axillar lymph nodes. Adjuvant chemotherapy and conformal radiotherapy treatment (TD=50Gy/25 fraction) followed by five years of hormonal treatment have been administrated without incident. Five years after the initial treatment, follow up ultrasound revealed subcutaneous lymphangiosis associated withan area of posterior acoustic shadowing showing minimal internal vascularity on color Dopler assessment. Clinically, this area presented as a painless, macules or papules associated with discoloration of the skin. Core biopsy of these lesions confirmed high grade AS of the breast. The immunohistochemistry was performed and tumor cells were positive for CD31, CD34, and FVIII. Surgical treatment was recommended. The left mastectomy was performed and the postoperative period occurred without incident. (figure 2). Histopathological examination of the resected breast revealed multiple tumor focuses of high grade breast AS (dimater up to 2.5 cm) at the level of the deep dermis and subcutaneous tissue. Two mounths later, a small, purple, oval skin lesion of 1.2 cm in diameter was noted in the projection of the surgical scar. CT imaging of the thorax was performed, revealing pre- and para-sternal subcutaneous lesions with infiltration of chest wall and nodular lesions with hemorrhagic component and perifocal edema in both lung, suggestive of lung metastasis. Excision of the skin lesions was perfomed and local reccurence of high grade AS was confirmed. Due to visualized nodular lesions in both lung, Video Assisted Thoracoscopy (VATS) was performed with biopsy of these lesions. The presence of high grade AS was pathohistologically verified.. The disease progressed rapidly, culminating in the patient's death 3 months after the onset of metastatic disease.

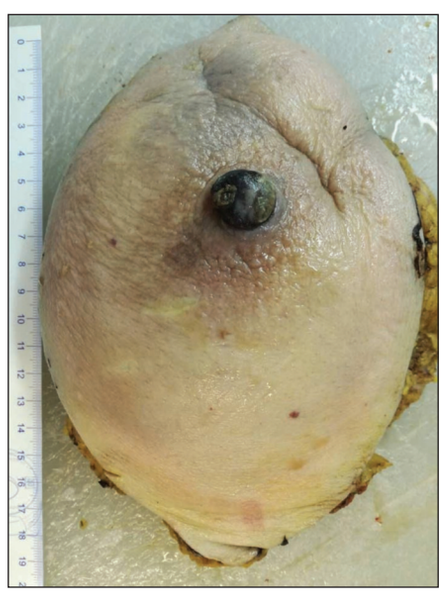

Figure 2. *The patient developed multiple red papules on the inferior portion of her left breast, five years after initial irradiation treatment following breast conserving surgery.*

Case 3.

A 76-year-old female was diagnosed with hormone receptor positive and Her-2 negative invasive lobular carcinoma. The patient came to our centre and conserving surgery followed by conformal radiotherapy treatment, which included doses TD=50Gy/25 fraction, was performed, followed by "boost" TD=14Gy/7 fractions and adjuvant

endocrine therapy with an aromatase inhibitor. Five years after the initial diagnosis, the patient reported paraareolar, painless, colored papules with initial biopsy showing postiaridational dermatitis. Five years later after the diagnosis of postradiational dermatitis, the patient developed multiple red papules on the inferior portion of her left breast. To our surprise, the surgical pathology result of excised lesions showed multifocal high grade AS located mainly in the dermis, with focal infiltration into the subdermal adipose tissue. Immunohistochemically, tumour cells were CD34, Vimentin, and FVIII positive, whereas CKae1ae3 was negative. Due to concern for possible recurrence, left mastectomy was performed and the histology report confirmed multifocal high grade cutaneous AS. Two months after mastectomy, patient presented with a well circumscribed discolorations in lateral area of the surgical scar, 4-5 mm in diameter, without any palpable mass. Local excision followed by pathological examination confirmed local recccurence of high grade AS. Shortly afterward, patient developed the same lesions on a skin of abdominal wall and in a region of left shoulder blade. Due to rapid dissemination, neoplastic lesions were technically inoperabile. The palliative radiotherapy was indicated, but due to general condition of the patient it was not performed.

DISCUSSION

Angiosarcoma (AS) is a rare disease with aggressive clinical course. AS may occur in any part of the body, most commonly in the skin of the head, neck, and scalp; however. AS of the breast is rare [4].

It has been shown that there are some risk factors associated with developing of AS. They can, directly or indirectly, lead to genetic mutations and change the genetic clustering. AS shows high levels of expression of genes known as markers of endothelial function, and form a tight genomic group distinct from all other sarcomas [5]. Recent studies have shown that radiation-induced AS have distinct genetic profile compared to primary AS. A high level of amplification of MYC on 8q24.21 is found in most radiation-induced AS while it is extremely rare in de novo AS[6].

Primary breast AS is a very rare disease with incidence about 0,05% of all breast malignances. It is, usually, seen in younger women, between 20 and 40 years, without previous family history or potential risk factors[7]. Although estrogen and progesterone receptors were reported to be negative in most cases, up to 12% of primary AS are diagnosed during pregnancy or lactation or any kind of hormonal involvement[8].

The first documented case of the breast AS was presented by Borrman in 1907 [4].

AS following the treatment of breast cancer was first described in 1948. It was a case of the secondary AS developed as a complication of the edematous forearm after radical mastectomy and axillary lymph node dissection (also called Stewart–Treves syndrome). This type of breast AS is most common in older women in sixth and seventh decade [9].

In the last 20 years, breast conservation therapy (a combination of surgery, radiotherapy, and endocrine or chemotherapy) has become the standard of care for eearly-stage breast cance patientsr. This has also led to increasing of radiotherapy-associated soft-tissue sarcomas, with AS being the most common malignancy[10]. NCI SEER database of estimated that secondary AS of the breast occurred in 0.9 out of 1,000 cases. They estimated that adjuvant radiotherapy increases the risk of AS of the breast by 9-fold[11]. The average latency of secondary, radiation associated AS is around 6 years, as soon as 1-2 years and as late as 41 years after radiation, which differs from latency of radiation induced sarcomas in general, which is usually 10-12 years [12]. The radiation dose of 50 Gy plus a booster dose of 16 Gy received by the patient, correlates with the increased incidence of AS induced by irradiation[13]. Cao et al. have reported a case of primary AS in the breast of a woman after trauma [14]. All of our reported patients had a history of previous breast irradiation.

Primary AS is generally presented as painless, rapidly growing (to 4 cm), palpable mass. Only 2% of patient experience pain and breast enlargement [8]. Usually, there is no nipple retraction or any discharge or axillary nodes enlargement.

The clinical presentation of radiation associated breast AS is different. It is generally reported asinitialy small, rapidly progressing, different in color, telangiectasia-like formations, multiple and distinct, appearing as nodules or plaques[15].

The diagnostic features of breast AS are variable and sometimes can be misleading. ASs can be present as ill-defined or poorly marginated masses, without posterior shadowing hypoechoic or mixed echogenicity on ultrasonography, which is rarely seen in breast malignances. On color Doppler ultrasound, tumour can be present as hypervascular lesions [16]. Low grade AS may be detedted as undefined mass that show hypointensity on T1-weighted images and hyperintensity on T2 weighted images, whereas high grade AS shows hyperintenstiy on both images, with heterogenous intensity due to hemorrhage or venous lakes inside the tumor [7]. MRI and PAT imageing with 18F-fluorodeoxyglucose may be used for staging and planning father surgery treatment.

Three main histopathologic types of breast AS were described: **I** - well differentiated-open anastomosing vascular channels lined by a single layer endothelial cells (flat cells with hyperchromatic nuclei containing small nucleoli that proliferate within dermis, subcutaneous tissue or breast tissue. They dissect through the stroma causing distortion of lobules and ducts. **II** - moderately differentiated- additional cellular foci of solid spindle cell proliferation. Slightly increased mitotic activity is observed. **III -** poorly differentiated-endothelial tufting and papillary formations are prominent. Mitoses may be brisk, especially in more cellular areas. Areas of hemorrhage, known as ‘blood lakes’ and necrosis are also seen. Immunohistochemically studies play a great role in differentiating breast AS. In well differentiated AS, neoplastic cells have strong positive staining patterns for CD34, CD31, vimentin, and factor VIII-related antigens. However, in high grade AS, neoplastic cells may react weakly and focally with CD31 and CD34, but a diffuse staining pattern with factor VIII-related antigen strongly suggests endothelial origins[17]. All lesions should be thor-

oughly studied because the prognosis is significantly related to the type of angiosaroma. Rosen et al. estimated probabilities of disease-free survival 5 years after initial treatment: Type I: 76%; Type II: 70%; and Type III: 15%. The median length of disease-free survival was also related to tumor type (Type I: greater than 15 years; Type II: greater than 12 years; and Type III: 15 months)[18]. The commonest sites of spread, apart from loco regional recurrences, are lung, bone, and liver. Most metastases arise from hematogenous dissemination, and nodal metastases are relatively uncommon[19].

There is no consensus about standard treatment of breast AS because of its rarity. However, radical mastectomy with negative margins is recommended for localized disease. There are some benefits of chemotherapy, especially in case of disseminated or recurrent disease [6]. An antiangiogenic treatment with vascular endothelial growth factor (VEGF), is a highly promising therapeutic approach [20].

Sažetak

Uvod*:* Angiosarkomi su agresivne neoplazme porekla krvnih sudova koje najčešće zahvataju kožu. Sekundarni angiosarkom je retka i kasna komplikacija zračne terapije nakon poštedne operacije karcinoma dojke. **Prikaz slučajeva**: Prikazali smo tri slučaja pacijentkinja koje su inicijalno podvrgnute poštednoj operaciji primarnog karcinoma dojke, praćenim adjuvantnom hemio - i zračnom terapijom. Sedam godina u prvom, I pet godina u druga dva slučaja, nakon inicijalnog tretmana, sve pacijentkinje se javljaju se sa nalazom palpabilnih, bezbolnih, tamnije prebojenih promena kože dojke, u regiji prethodno operisanog karcinoma. Biopsijom uočenih promena postavlja se dijagnoza angiosarkoma. Uprkos radikalnoj eksciziji praćenoj adjuvantnom hemioterapijom, kod dva prikazana slučja razvili su se lokalni recidivi i udaljene metastaze. **Zaključak**:. Usled nespecifične prezentacije sekundarnog angiosarkoma dojke, i velike verovatnoće nastanka lokalnog recidiva, potreban je dodatan oprez kako bi se sprečilo odlaganje postavljanja defintivne dijagnoze a sasim tim i terapijskog tretmana

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