ISSN: 2577 - 8005

Research Article

Medical & Clinical Research

Apocrine Breast Carcinoma - Pathohistological And Immunohistochemical Analysis, Prognosis and Complex Treatment

Lena Marinova[*1], Snezhinka Vicheva[2] and Dorothea Malinova[3]

[1]*Department of Radiotherapy, Oncology center, Russe, Bulgaria*

[2]*Department of Clinical Pathology, Oncology center, Varna, Bulgaria*

[3]*Department of General and Clinical Pathology, Medical University, Varna, Bulgaria*

[*]Corresponding author
Marinova Lena, Department of Radiotherapy, Oncology center, Russe, Bulgaria.

Submitted: 19 Jan 2021; **Accepted**: 25 Jan 2021; **Published**: 05 Feb 2021

Citation: *Lena Marinova, Snezhinka Vicheva and Dorothea Malinova (2021). Apocrine Breast Carcinoma-Pathohistological And Immunohistochemical Analysis, Prognosis and Complex Treatment. Journal of Medical & Clinical Research 6(2):391-394.*

Abstract

Apocrine breast cancer (ABC) is a rarely diagnosed pathomorphological subtype of invasive ductal carcinoma of the breast. We present a clinical case of apocrine breast cancer in a 36-year-old woman. A left-sided breast-preserving surgery (quadrantectomy am blok with underlying muscle fascia) and axillary lymph dissection at all three levels were performed. The complex treatment is continued with adjuvant chemotherapy, followed by radiotherapy of the left mammary gland. The pathomorphological and immunohistochemical characteristics of apocrine breast cancer, the prognosis and the necessary complex treatment are discussed. Immunohistochemical (IHC) analysis of apocrine carcinoma cells reported a characteristic steroid receptor profile with negative IHC expression for estrogen and progesterone receptors and positive for androgen receptors. ABC is prognostically similar to invasive ductal carcinoma / NOS. Apocrine breast cancer needs to be classified as a separate nosological unit, due to growing evidence of a different hormonal profile with different clinical behavior following androgen deprivation therapy.

Keywords: Apocrine Breast Cancer, Breast Cancer, Pathomorphology, Immunohistochemistry, Prognosis, Complex Treatment

Introduction

Apocrine breast carcinoma (ABC) is a rare subtype of invasive ductal carcinoma, accounting for about 1%-4% of all breast cancers (BC) [1-4]. The pathomorphology of apocrine carcinoma cells is represented by a characteristic granular, eosinophilic cytoplasm, sharply demarcated cell boundaries, round nuclei, and distinct nucleoli [5]. It is most often diagnosed in women aged 60-70 years [6]. The manifestation of this tumor varies from benign cyst to invasive cancer with metastases [7]. The development and progression of BC is strictly related to steroid hormone levels. IHC analysis of estrogen receptor (ER) and progesterone receptor (PR) expression in BC is important for determining tumor biology, prognosis, and complex treatment, including hormone therapy [8, 9].

Clinical Case: We present a rare clinical case of apocrine breast cancer in a 36-year-old woman, who noticed a painless lump in the left mammary gland.

Preoperative Local Status: In the lower outer quadrant of the left mammary gland, a tumor formation with a diameter of 2.5 cm, mobile, painless is palpated. Left axilla is without pathological changes. Ultrasound revealed a hypoechoic lesion with dimensions 24x15 mm in diameter in the lower lateral quadrant of the left breast. Mammography also revealed a round homogeneous formation measuring 24x12 mm in the lower lateral quadrant of the left breast. Left axilla - without pathological changes.

A left-sided breast-preserving operation (quadrantectomy an blok with underlying muscle fascia) and axillary lymph dissection at all three levels were performed. Intraoperatively, a formation measuring 2x2 cm was found, which was sent to Gefrir.

Histological Result

Macroscopic Characteristics: Material with dimensions 6x5x3 cm with a node with a diameter of 18 mm with a yellowish granular cut surface.

Microscopic description: Part of the mammary gland with nests and stems from tumor cells with abundant eosinophilic cytoplasm, PAS (+) granules in the cytoplasm and PAS (+) material between cells after diastasis digestion, with large polymorphic nuclei with nucleoli and mitoses, areas of necrosis with tumor emboli in the lymph vessels. Outside the described tumor cells, there are nests of ductal in situ carcinoma (Figure 1 & Figure 2).

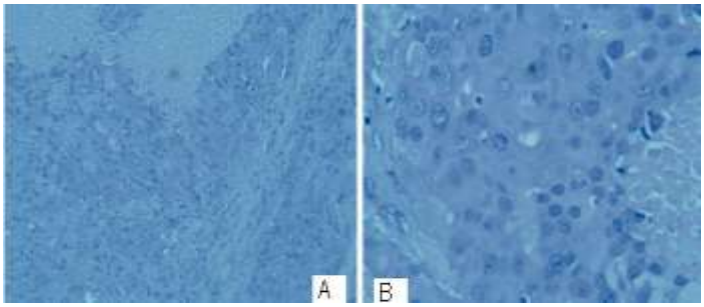

Figure 1: Photomicrography of apocrine breast cancer A/ Tumor cells of adenosis with apocrine metaplasia / H&E: 10x; B/ Large tumor cells with abundant granular eosinophilic cytoplasm and large round nuclei / H&E: 40x

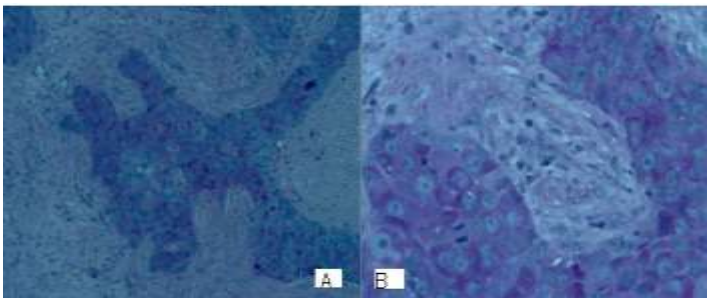

Figure 2: Photomicrography of apocrine breast cancer A/ Positive PAS reaction of tumor cells of adenosis with apocrine metaplasia: 10x B/ Positive PAS reaction of large tumor cells with abundant granular eosinophilic cytoplasm and large round nuclei: 40x

Second material - A strip of skin in a section of mastopathic areas with dimensions 3x4x2 cm. - Fibrocystosis with intraductal cell proliferation (in situ ductal carcinoma) in one of the tubules (Figure 3). In the material with appearance of adipose tissue 12 lymph nodes were found, all of which with reactive changes.

Immunohistochemistry: Tumor cells with positive expression of cytokeratin / CK34BE12 (Figure 4); CK 5/6 - negative, HER2 - strongly positive (3+) (Figure 5); tumor cells with negative expression of Bcl 2 and positive in the ducts of the normal mammary gland (Figure 6); Estrogen receptor (ER) - negative; Progesterone receptor (PR)-negative; Androgen receptor (AR) - positive; CISH (+) positive.

Diagnosis - Apocrine carcinoma of the left breast/ III degree of malignancy - pT1c No Mx G3

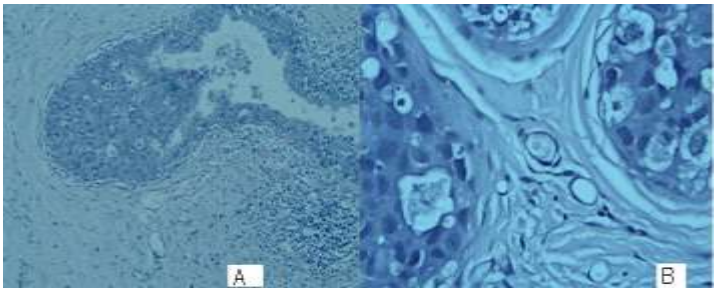

Figure 3: Photomicrography with intraductal cell proliferation. A/ Fibrocystosis with in situ ductal carcinoma H&E:10x; B/ Intraductal cell proliferation in one of the tubules H&E: 40x

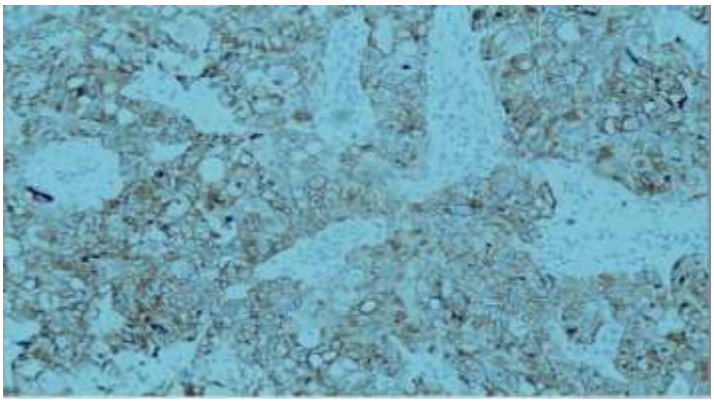

Figure 4: Photomicrography of apocrine breast cancer - Tumor cells with positive IHC expression of cytokeratin / CK34BE12: 40x

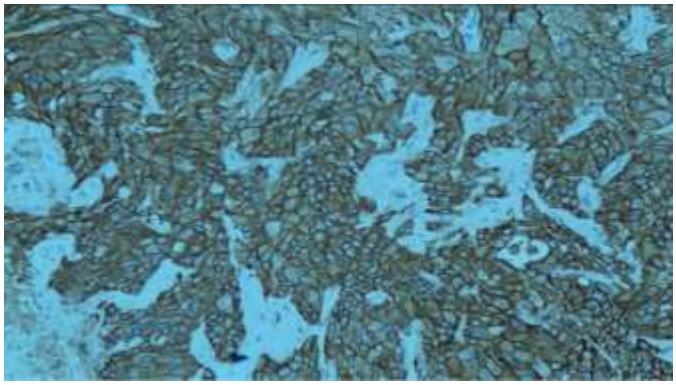

Figure 5: Photomicrography of apocrine breast cancer - Tumor cells with strongly positive HER2 expression (3+): 40x

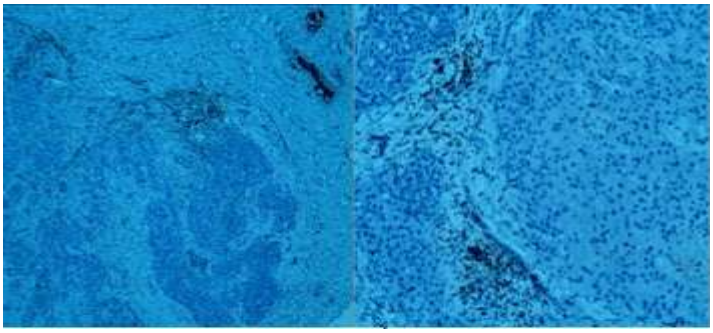

Figure 6: Photomicrography of IHC -tumor cells with negative Bcl 2 expression and positive in the ducts of the normal mammary gland : 10x and 40x

After surgery, 8 courses of adjuvant systemic chemotherapy (Ch) /4 courses of the EU regimen (Epirubicin and Endoxan) and 4 courses of monotherapy with Paclitaxel were prescribed. After Ch, radiotherapy of the left mammary gland with IMRT - VMAT technique with a daily dose (DD) 2 Gy to total dose (TD) 50 Gy in 25 fractions was performed (Figure 7). The complex treatment continued with targeted therapy with Herceptin. 5 years after the complex treatment the patient is in good general condition, without

recurrence of the disease and without distant metastases.

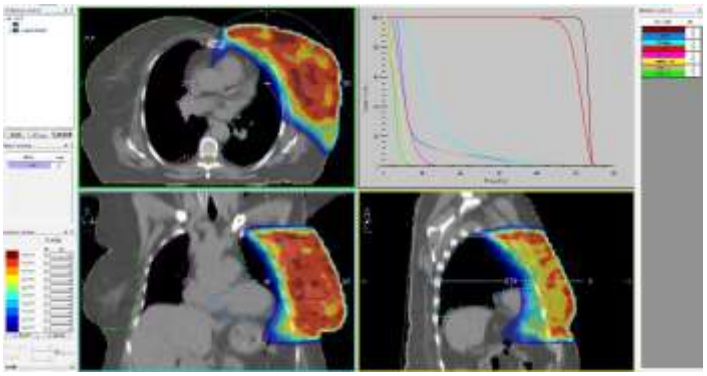

Figure 7: Radiotherapy of the left mammary gland with IMRT - VMAT technique with DD 2 Gy to TD 50 Gy in 25 fractions

Discussion

Physical examination in ABC varies from asymptomatic to the presence of unilateral formation with unclear boundaries, with or without retraction of the nipple and skin [10]. Clinically, insignificant differentiation between ABC and invasive ductal carcinoma is possible [7]. The microscopic cellular growth characteristic of ABC resembles invasive ductal carcinoma (IDC-NOS) with the only difference in cytology [3]. Apocrine metaplasia is characterized by granular, pale eosinophilic cytoplasm and a tendency to apically budding cytoplasm, which is usually considered as an indicator of low potential of a given lesion undergoing malignant transformation. The malignant transformation of the apocrine epithelium was first described by Krompecher in 1916 [11, 12]. Cells are characterized by a typical apocrine characteristic with abundant eosinophilic granular cytoplasm and distinct nucleoli Apocrine adenosis is defined as the presence of apocrine cytology in a recognizable terminal duct lobular unit (TDLU) associated with sclerosing adenosis. Atypical apocrine adenosis may progress to apocrine DCIS and apocrine carcinoma [13, 14]. Different data on the incidence of ABC determine the definition of standard pathohistological criteria. Japaze et al./2005 propose the following criteria: 1/ apocrine characteristics of 75% of cells; 2/ large cells with granular eosinophilic cytoplasm; 3/ nucleus/ cytoplasm ratio 1:2 or more; 4/ large, round nucleus - vesicular or pleomorphic; 5/ sharply demarcated cell boundaries [2]. Roychowdhury M./2021 summarizes the requirement for apocrine carcinoma cells, namely > 90% of tumor cells must contain cytologic or immunohistochemical features of apocrine cells [4]. Microscopically two types of apocrine tumor cells are observed: 1/ type A - abundant granular and intensely eosinophilic cytoplasm, granules are PAS+ diastase resistant, nuclei vary from globoid with prominent nucleoli to hyperchromatic; 2/ type B - abundant cytoplasm with fine empty vacuoles, creating a foamy appearance resembling histiocytes, nuclei are similar to type A cells [4].

The presented clinical case with apocrine cancer contains type A tumor cells and meets all of the five above described requirements (Figure 1-3). Optional criteria include distinct nuclei in more than 50% of the field and apical cytoplasmic prominence in the lumen spaces [2]. The mitotic index varies from 1 to 3. Most of the ABCs are G2 or G3 according to the Scarff-Bloom-Richardson modification [15]. The molecular classification of BC in routine practice is based on the IHC expression of the hormone ER and PR receptors, as well as the human epidermal growth factor receptor 2 (HER2), a member of the epidermal growth factor receptor family). Apocrine breast carcinoma is characterized by the following IHC expression: positive for Keratin, 33% positive for HER2 and 54% positive for Androgen receptor [4] (Figure 4 & Figure 5). Apocrine tumor cells are characterized by negative IHC expression for Bcl 2, shown in Figure 6. However, the androgen receptor (AR), another member of the steroid receptor family, expressed in > 70% of BC, plays an important role in the pathogenesis of carcinoma [16]. ABC is usually positive for human epidermal growth factor receptor 2 (HER2), negative for the two hormone receptors - estrogen and progesterone and with increased expression of Gross cystic disease protein fluid-15 (GCDPF-15), which is normally positive in all apocrine, lacrimal, ceruminous and Moll glands [17]. IHC analysis for GCDFP-15 protein is used to detect breast ABC, although reduced levels have been reported in advanced metastatic lymph node disease [18-20]. In an attempt to better determine ABC, the authors recommend further testing for androgen receptors (AR) by routine IHC analysis, due to a positive test in 55-100% (6). AR expression is highly positive in apocrine (100%), tubular (100%), lobular (83.3%) and papillary (81.8%) carcinomas and largely negative in metaplasia (0%), medullary (25%) and mucinous (41.7%) carcinomas [21]. As an ER-positive BC may benefit from estrogen deprivation treatment, some studies demonstrates that an AR-expressing ABC may respond to androgen deprivation [22]. Taking into account the androgen-receptor sensitivity of ABC may facilitate receptor-targeted therapy [23]. Although ABCs are rare, it is important to distinguish them from other subtypes of invasive ductal carcinoma, as they do not respond to typical hormonal treatment. Given the positive ARs, apocrine mammary carcinoma has a very good androgen response (fluoxymesterone) as part of hormone therapy [16].

Among ER-negative tumors, several teams have identified molecular apocrine breast cancer (MABC subtype) characterized by AR expression, paradoxical expression of genes known as ER-targets or expression in ER-positive tumors, and HER2 overexpression in about 50 % of clinical cases [24, 25]. The expression of this MABC subgroup points to a new molecular classification of BC, including the subgroups luminal, molecular apocrine (MA) and basal cell breast carcinoma (BCBC) [26]. The prognosis of ABC is similar to invasive ductal carcinoma (IDC)-NOS and depends on the clinical stage and the degree of cell differentiation (G) [27]. In retrospective studies with a small number of patients, MA phenotypic tumors have been reported to be more aggressive in the presence of prognostically unfavorable factors such as G3, lymphatic invasion, pN+. These tumors have a poor therapeutic outcome, despite systemic Ch [28]. Iwase et al./2010 believe that ABC should be considered as a different cancer from the more common basal-like breast cancer [29]. ABC had unique clinicopathological characteristics and it tended to be a more aggressive type than IDC. Deeper insights into ABC are in need to contribute to individualized and tailored therapy, which thereby may improve clinical management and outcomes [30]. 5 years after the complex treatment the patient is in good general condition, without recurrence of the disease and without distant metastases.

Conclusion

Mammary apocrine carcinoma is a rare, other subtype of invasive breast cancer with different morphological, immunohistochemical and molecular genetic characteristics. In most cases of ABC, the apocrine epithelium shows a characteristic steroid receptor profile with negative estrogen and progesterone receptors and positive androgen receptors. ABC is prognostically similar to invasive ductal carcinoma / NOS. Apocrine breast cancer needs to be classified as a separate nosological unit, due to growing evidence of a different hormonal profile with different clinical behavior after androgen deprivation therapy.

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