ORIGINAL RESEARCH

DOI: 10.37047/jos.2020-78231

Rare Breast Cancer Types: A Study About Characteristics, Outcomes, and Peculiarities

Nadiye AKDENİZ[a], Muhammet Ali KAPLAN[b], Mehmet KÜÇÜKÖNER[b], Zuhat URAKÇI[b], Oğur KARHAN[b], Yasin SEZGİN[b], Senar EBİNÇ[b], Erkan BİLEN[b], Mustafa NACİR[c], Hüseyin BÜYÜKBAYRAM[c], Abdurrahman IŞIKDOĞAN[b]

[a]Department of Medical Oncology, Adiyaman Training and Research Hospital, Adiyaman, Turkey
[b]Department of Medical Oncology, Dicle University Medical Faculty, Diyarbakır, Turkey
[c]Department of Pathology, Dicle University Medical Faculty, Diyarbakır, Turkey

ABSTRACT Objective: We aimed to explore different features of rarely seen breast cancer (BC) subtypes, including their stage, molecular subtypes, treatment choices, and prognosis. **Material and Methods:** We retrospectively screened patients who were diagnosed with BC in our hospital between July 2010 and June 2018. A total of 97 patients who had micropapillary, cribriform, mucinous, papillary, tubular, apocrine, metaplastic, medullary, and myoepithelial subtypes of BC were finally included in the current study.**Results:** Ninety-four (96.9%) patients were females. Patients with cribriform and mucinous subtypes were in the younger median age of 41 and 45 years, respectively, whereas papillary cases were reported in the oldest median age (64.5 years). Lymph node and TNM stages showed a statistical difference between the subtypes (p=0.029 and p=0.008, respectively). Most of the cribriform (60%), metaplastic (66.7%), and papillary (70%) cases were diagnosed without lymph node involvement. Apocrine (79%) and micropapillary (75%) tumors mostly presented with nodal involvement. While medullary (75%), tubular (66.7%), and cribriform (66.7%) carcinomas were more likely to be diagnosed at stage II, micropapillary (70.8%), and apocrine (62.5%) carcinomas were mostly diagnosed at stage III. Mucinous, tubular, and cribriform tumors were noticed in the luminal group. Medullary, metaplastic, apocrine, and papillary tumors included triple-negative subgroups. HER2-enriched tumors included apocrine (62.5%), medullary (50%), and micropapillary (25%) subtypes. Disease-free survival and overall survival of the patients showed marginal statistical significance according to tumor subtypes (p=0.086, p=0.085, respectively). **Conclusion:** In this study, we investigated important features, clinical behavior, management, and outcomes of several rare BC subtypes. We opine that the current study may prove instrumental and informative for both daily clinical practice and future studies.

Keywords: Breast cancer; rare subtypes; prognosis, apocrine; cribriform; micropapillary carcinoma

==Breast cancer (BC) is the most common type of cancer found among women worldwide and has heterogeneity as one of the most important features.[1] BC heterogeneity can be seen in both classic histopathological characterization and molecular classification. BC consists of various conditions characterized by different pathological and biological features, clinical presentation and behavior, treatment responses, and outcomes. According to the World Health Organization (WHO) classification, BC can be classified in up to 21 different histological types based on varying patterns of morphologic features, growth, and architecture. Invasive ductal carcinomas (IDC) are the most common types of BC and are responsible for approximately 60% to 75% of all breast cancers, whereas 25% of breast cancers are special subtypes.[2]

Although clinical, pathological, and epidemiological differences between ductal and lobular carcinomas have been examined in several studies, rarer histologic types of BC like mucinous, tubular, medullary, and papillary carcinomas are poorly known.[3] Our understanding of these subtypes is primarily based on several case reports, small clinical series, and numerous population-based studies.[4] The

Correspondence: Nadiye AKDENİZ
Department of Medical Oncology, Adiyaman Training and Research Hospital, Adiyaman, TURKEY
E-mail: nadiyeakdeniz21@gmail.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 23 Jul 2020 ***Received in revised form:*** 13 Nov 2020 ***Accepted:*** 20 Nov 2020 ***Available online:*** 11 Dec 2020

objective of this study was to reveal different features, subtypes, stage, size, lymph node status, molecular subtype, and treatment choice of rarely seen types of BC. Evaluations of these differences may provide valuable insight into nature, clinical features, and treatment interventions in these rare tumors.

MATERIAL AND METHODS

PATIENTS AND METHODS

We retrospectively screened patients who were diagnosed with BC at Dicle University Department of Oncology, between July 2010 to June 2018. The clinicopathological data were collected from the hospital database. A total of 1,500 patients were screened; 1,156 patients had IDC, 177 had invasive lobular carcinoma, 80 had ductal carcinoma in situ, and 97 patients had rare histologic subtypes of BC. These 97 patients with micropapillary, cribriform, mucinous, papillary, tubular, apocrine, metaplastic, medullary, and myoepithelial subtypes of BC were included in the study. Patients with IDC, invasive lobular carcinoma, malign phyllodes, ductal carcinoma *in situ,* and stage IV were excluded. Histological types were classified according to the WHO classification criteria. Age at diagnosis, tumor location, tumor sizes, axillary lymph node status, histological type, hormone receptor status, molecular types, tumor node metastasis (TNM) stages, cancer grades, and treatment modality were evaluated. The study was approved by the local Ethics Committee and was conducted in accordance with the Helsinki Declaration and Ethical principles, 1996 (permission: 300/2018).

IMMUNOHISTOCHEMICAL CRITERIA

In this study, estrogen receptor (ER) and progesterone receptor (PR) were accepted as positive if nuclear staining was observed in at least 1% of tumor cells and if there was a high presence of Ki-67 expression in more than 20% of tumor cells.[5] Human epidermal growth factor receptor 2 (HER2) staining was classified as negative if the score was 0 and 1+, whereas score 3+ was accepted as positive. Fluorescence *in situ* hybridization was used to confirm the presence of HER2 when the scores were more than 2.[6] Molecular subtypes of BC were described based on the expression of ER/PR, HER2, and Ki-67: luminal A if ER/PR(+), low Ki-67 and HER2(-); luminal B if ER/PR(+) and either Ki-67 value was high or HER2 was overexpressed; triple-negative or basal-like if ER/PR(–) and HER2(–); HER2 positive if ER/PR(–) and HER2(+).

TREATMENT

Modified radical mastectomy (MRM) or breast-conserving surgery (BCS) and, if required, axillary sentinel lymph node biopsy or complete lymph node dissection were performed. Systemic adjuvant therapy was recommended according to the guidelines. Chemotherapeutic interventions included anthracycline-containing or non-anthracycline-containing regimens. Also, endocrine therapy, including tamoxifen or an aromatase inhibitor, or an aromatase inhibitor after tamoxifen was used.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 19.0 software. Chi-square ($\chi 2$) test was employed to assess the association between clinicopathological characteristics and histological subtype. Disease-free survival (DFS) was defined from the date of diagnosis until any event related to BC or death from any cause. Overall survival (OS) was defined from the date of diagnosis to the date of the last follow-up visit or death from any cause. Kaplan–Meier curves were used to estimate survival, and the log-rank test was employed to compare differences between various BC subtypes. P-value of less than 0.05 was considered statistically significant.

RESULTS

Among 97 patients studied, 94 (96.9%) patients were female, and 3 (3.1%) were male. Male patients had micropapillary, mucinous, and papillary histological subtypes. The characteristics of patients, according to histological subtype, are shown in Table 1. The median age of the patient varied according to the histological type of the BC. The median age of cribriform and mucinous cases was 41 and 45 years, respectively, while cases with papillary subtype had the highest median age (64.5 years). No differences between tumor (T) stages in different subtypes were observed (p=0.625). Despite this insignificance, 44.4% of metaplastic and 38.5% of mucinous carci-

TABLE 1: Characteristics of patients according to histological subtype.

	Micropapillary N=24 (%)	Cribriform N=15 (%)	Mucinous N=13 (%)	Papillary N = 10 (%)	Tubular N = 9 (%)
Age median (min-max)	51.5 (25-84)	41 (23-73)	45 (34-88)	64.5 (41-79)	51 (33-69)
Tumor location±	13 (54.2)	6 (40)	4 (30.8)	4 (40)	4 (44.4)
Right					
Menopause status*					
Postmenopause	11 (45.8)	3 (20)	6 (46.2)	5 (50)	4 (44.4)
Median tumor size (cm)					
(min-max)	4.5 (1.2-15)	2.5 (1-7)	5 (1.5-8)	2.5 (1-13)	3.8 (1.3-8)
Tumor stage					
T1	4 (16.7)	4 (26.7)	1 (7.7)	4 (40)	2 (22.2)
T2	12 (50.0)	10 (66.7)	7 (53.8)	3 (30)	4 (44.4)
T3	5 (20.8)	1 (6.7)	4 (30.8)	2 (20)	3 (33.3)
T4	3 (12.5)	0 (0)	1 (7.7)	1 (10)	0 (0
Nodal stage					
N0/NX	5 (20.8)	9 (60)	6 (46.2)	7 (70)	3 (33.3)
1-3 positive	4 (16.7)	5 (33.3)	1 (7.7)	1 (10)	4 (44.4)
≥4 positive	15 (62.5)	1 (6.7)	6 (46.2)	2 (20)	2 (22.2)
AJCC stage					
1	2 (8.3)	4 (26.7)	1 (7.7)	4 (40)	0 (0)
2	5 (20.8)	10 (66.7)	6 (46.2)	3 (30)	6 (66.7)
3	17 (70.8)	1 (6.7)	6 (46.2)	3 (30)	3 (33.3)
ER status					
Positive	16 (66.7)	15 (100)	12 (92.3)	8 (80)	9 (100)
PgR status					
Positive	16 (66.7)	13 (86.7)	12 (92.3)	7 (70)	9 (100)
HER2 status					
Positive	11 (45.8)	2 (13.3)	1 (7.7)	2 (20)	1 (11.1)
Ki- 67 ≥%20					
Yes	15 (62.5)	4 (26.7)	3 (23.1)	5 (50)	0 (0)
Molecular type					
Luminal A	9 (37.5)	11 (73.3)	9 (69.2)	6 (60)	8 (88.9)
Luminal B	9 (37.5)	4 (26.7)	4 (30.8)	2 (20)	1 (11.1)
HER2/ER	6 (25)	0 (0)	0 (0)	1 (10)	0 (0)
Basal Like/Triple negative	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)
Type of Surgery					
BCS	3 (12.5)	7 (46.7)	1 (7.7)	5 (50)	4 (44.4)
Mastectomy	21 (87.5)	8 (53.3)	12 (92.3)	5 (50)	5 (55.6)
Radiotherapy					
Yes	22 (91.7)	12 (80)	9 (69.2)	8 (80)	8 (88.9)

continued →

TABLE 1: Characteristics of patients according to histological subtype *(continued)*.

	Apocrine N = 8 (%)	Metaplastic N = 9 (%)	Medullary N = 8 (%)	Myoepithelial N = 1 (%)	Total N = 97 (%)
Age median (min-max)	47 (36-86)	57 (31-72)	54.5 (31-83)	45	49 (23-89)
Tumor location±					
Right	4 (50)	4 (44.4)	2 (25)	1 (100)	42 (43.3)
Menopause status*					
Postmenopause	3 (37.5)	4 (44.4)	4 (50)	1 (100)	41 (43.6)
Median tumor size (cm) (min-max)	2.7 (1-7)	3.5 (1-9)	2.45 (1.7-8)	5	3.5 (1-15)
Tumor stage					
T1	2 (25)	2 (22.2)	1 (12.5)	0 (0)	20 (20.6)
T2	5 (62.5)	3 (33.3)	6 (75)	0 (0)	50 (51.5)
T3	1 (12.5)	4 (44.4)	1 (12.5)	1 (100)	22 (22.7)
T4	0 (0)	0 (0)	0 (0)	0 (0)	5 (5.2)
Nodal stage					
N0/NX	2 (2)	6 (66.7)	3 (37.5)	1 (100)	42 (43.3)
1-3 positive	1 (12.5)	1 (11.1)	5 (62.5)	0 (0)	22 (22.7)
≥4 positive	5 (62.5)	2 (22.2	0 (0)	0 (0)	33 (34)
AJCC stage					
1	0 (0)	2 (22.2)	1 (12.5)	0 (0)	14 (14.4)
2	3 (37.5)	5 (55.6)	6 (75)	1 (100)	45 (46.4)
3	5 (62.5)	2 (22.2)	1 (12.5)	0 (0)	38 (39.2)
ER status					
Positive	2 (25)	0 (0)	1 (12.5)	0 (0)	63 (64.9)
PgR status					
Positive	1 (12.5)	0 (0)	0 (0)	0 (0)	58 (59.8)
HER2 status					
Positive	6 (75)	3 (33.3)	4 (50)	0 (0)	30 (30.9)
Ki- 67 ≥%20					
Yes	6 (75)	8 (88.9)	7 (87.5)	1 (100)	49 (50.5)
Molecular type					
Luminal A	1 (12.5)	0 (0)	1 (12.5)	0 (0)	45 (46.4)
Luminal B	1 (12.5)	0 (0)	0 (0)	0 (0)	21 (21.6)
HER2/ER	5 (62.5)	3 (33.3)	4 (50)	0 (0)	19 (19.6)
Basal Like/Triple negative	1 (12.5)	6 (66.7)	3 (37.5)	1 (100)	12 (12.4)
Type of Surgery					
BCS	4 (50)	2 (22.2)	4 (50)	1 (100)	31 (32)
Mastectomy	4 (50)	7 (77.8)	4 (50)	0 (0)	66 (68)
Radiotherapy					
Yes	6 (75)	5 (55.6)	7 (87.5)	1 (100)	78 (80.4)

ER: Estrogen receptor, PR: Progesterone receptor, BCS: Breast conserving surgery.

±One of micropapillary tumor was bilaterally.

*The number of female patients was 94.

nomas were larger than 5.0 cm in size at the time of diagnosis, while 40% of papillary carcinomas were smaller than 2.0 cm. Lymph node positivity differed between various subtypes (p=0.029). Most of the cribriform, metaplastic, and papillary cases (60%, 66.7%, and 70%, respectively) were diagnosed without lymph node involvement. On the other hand, apocrine (79%) and micropapillary (75%) tumors mostly presented with nodal involvement. The clinical stages were also significantly different among the subtypes (p=0.008). While medullary (75%), tubular (66.7%), and cribriform (66.7%) subtypes were more

often diagnosed at stage II, micropapillary (70.8%), and apocrine (62.5%) subtypes were mostly diagnosed at stage III.

The subtypes showed different molecular features. All of the mucinous, tubular, and cribriform tumors were found in the luminal group, whereas 75% of micropapillary and 80% of papillary tumors were in the luminal group. Medullary, metaplastic, apocrine, papillary, and myoepithelial tumors consisted of basal-like or triple-negative subgroups. HER2-enriched tumors included 62.5% of apocrine, 50% of medullary, and 25% of micropapillary subtypes.

TREATMENT

Treatments received by the patients are shown in Tables 1 and 2. A total of 66 (68%) patients underwent MRM, and 78 (80.4%) patients received radiotherapy. Seventy-nine (81.4%) patients received adjuvant therapy, five (5.2%) of the patients received adjuvant endocrine therapy alone, and 67 (69.1%) patients received anthracycline-containing chemotherapy. There were no significant differences recorded between the subtypes according to adjuvant treatment choices (p = 0.638). Endocrine treatment options are shown in Table 2.

PATIENTS SURVIVAL

During the follow-up period, disease recurrence was observed in 20 (20.6%) patients, and 16 (16.5%) deaths had occurred. Locoregional relapses were observed in 5 (5.1%) patients, and distant metastases were observed in 15 (15.5%) patients. DFS and OS of the patients showed marginal statistical significance (p=0.086, p=0.085, respectively) according to the tumor subtypes. Also, the DFS and OS of the patients were evaluated individually according to the stage for histological subtypes (Figure 1 and Figure 2).

DISCUSSION

The less frequent histological types of BC are different from ductal carcinoma in terms of age at diagnosis, stage, and grade distribution. Also, incidence and survival rates are different in uncommon breast tumors.[7] Treatment of uncommon breast tumors has rarely been studied because of associated challenges in obtaining sufficient numbers of patients in each subtype.

Previous studies have documented the age distribution of different histological types of BC. For instance, Li et al. showed that papillary carcinoma cases were in the oldest age (65.8 years); this finding is consistent with the results in our study (64.5 years). Medullary carcinoma cases had the youngest age (52.8 years) among all subtypes in the study by Li et al., but 54.5 years in the current study, whereas cribriform and mucinous subtypes had the youngest median age (41 and 45 years, respectively).[3] This difference may be attributed to genetic factors/predispositions and the relatively low number of patients in the current study.

Invasive micropapillary carcinomas well-known for its lymphotropic nature. It tends to present at a locally advanced stage. Lymph node metastases (44-

TABLE 2: Adjuvant treatment according to histological subtype.

	Endocrine Therapy N (%)			Adjuvant Chemotherapy N (%)		
	None	Tamoxifen	Aromatase inhibitor	None	Anthracycline-containing Chemotherapy N (%)	Non-Anthracycline-containing Chemotherapy N (%)
Micropapillary	7 (29.2)	10 (41.6)	7 (29.2)	5 (20.8)	17 (70.8)	2 (8.3)
Cribriform	0	12 (80)	3(20)	2 (13.3)	12 (80)	1 (6.7)
Mucinous	1 (7.7)	7 (53.8)	5 (38.5)	3 (23.1)	9 (69.2)	1 (7.7)
Papillary	2 (20)	4 (40)	4 (40)	7 (70)	3 (30)	0
Tubular	0	5 (55.6)	4 (44.4)	2 (22.2)	7 (77.8)	0
Apocrine	6 (75)	0	2 (25)	1 (12.5)	6 (75)	1 (12.5)
Metaplastic	9 (100)	0	0	2 (22.2)	6 (66.7)	1 (11.1)
Medullary	7 (87.5)	0	1 (12.5)	1 (12.5)	6 (75)	1 (12.5)
Myoepithelial	1 (100)	0	0	0	1 (100)	0

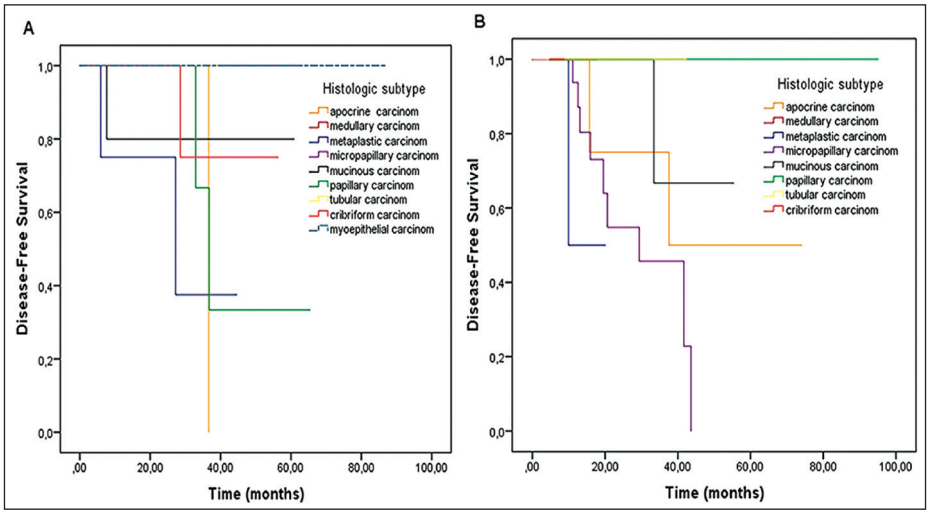

FIGURE 1: Disease-free survival according to histological subtypes for stage 2 (A) and 3 (B).

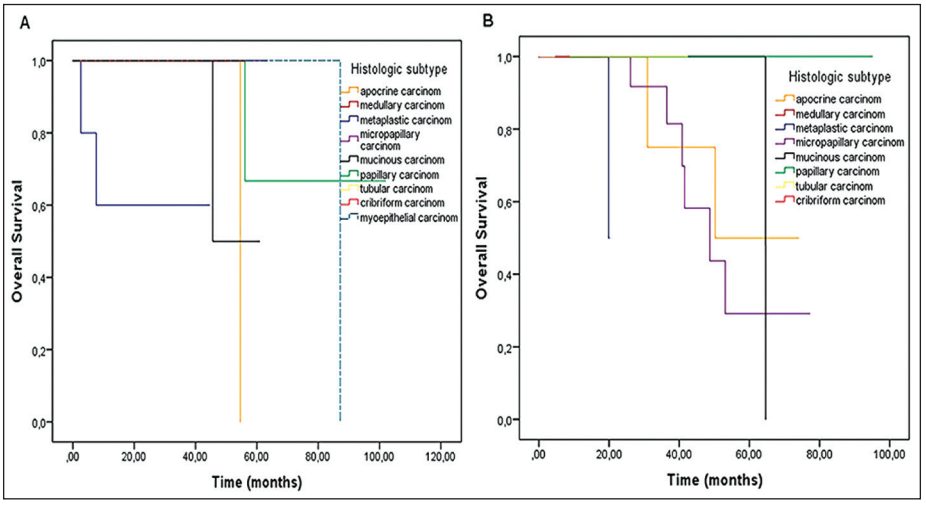

FIGURE 2: Overall survival according to histological subtypes for stage 2 (A) and 3 (B).

100%) and lymphatic invasion (35-75%) were frequently described in some studies.[8] We noticed a high (79.2%) lymph node positivity. A previous study reported hormone receptor (HR) positivity in approximately 66% of the patients and the HER2-positivity in about 50% of the patients.[9] These findings were corroborated in our findings wherein 75% of the cases were in the luminal group, but 25% of the cases had HER2 positivity. Despite the association with an unfavorable outcome, the standard treatment for invasive micropapillary carcinoma is the same as for IDC. In the current study, 70.8% of patients received anthracycline-containing chemotherapy and endocrine therapy. Nine recurrences were observed, and six deaths were reported.

Cribriform carcinomas were reported in about 0.1% to 0.6% of all breast cancers.[7] We observed cribriform carcinoma in 1% of all patients. Cribriform carcinoma shows axillary lymph node metastases in approximately 10% of the cases, higher ER and PR positivity, lower proliferation indices, and improved survival rates.[10] In our study, 60% of patients with this subtype were diagnosed with lymph node-negative disease, and all patients were in the luminal group. Colleoni et al., in their study, documented that favorable histotypes of luminal tumors like cribriform

subtype might be treated with endocrine therapy or followed without treatment. However, chemotherapy and radiotherapy may still be considered for high-risk patients.[11] All patients with cribriform subtype received endocrine therapy in the current study. During the follow-up period, recurrence was reported in only one case, and no recurrence was seen in other cases on the routine follow-up.

Mucinous carcinoma, another rare subtype of BC, accounts for up to 1-6% of all BC.[12] We found 0.9% of all patients in our study affected with mucinous carcinoma. The tumor size may vary from non-palpable to 20 cm. They are in the luminal subtype and are usually detected at an early stage with low histologic grade.[12] In our study, tumor sizes were greater than 5.0 cm in 38.5% of cases. More than 50% of patients reported tumor stage I and II. As documented in the literature also, we found all our cases in the luminal group. Adjuvant treatment of this subtype included chemotherapy, radiotherapy, and/or hormonal replacement therapy depending on the histopathology and lymph node involvement. Since most cases show positive hormonal status, hormonal status should be reevaluated in the case of negative receptor expression.[13] If hormone receptor negativity is confirmed, patients should be treated like those with usual breast cancer histology. In our study, the majority of the patients received chemotherapy and endocrine therapy due to larger tumor sizes and lymph node involvement.

Papillary carcinoma was diagnosed at older ages, with a median age of 65-70 years, and 3.5% of cases were males.[3,14] Of the ten studied cases, only one was male; the median age of our patients was 64.5 years. This finding confirmed previous ones. These tumors have low proliferative activity; most are ER and PR positive and have a low frequency of lymph node involvement.[3,15] In our study, similar results were obtained, 70% of patients had negative axillary lymph nodes and 80% of patients revealed HR positivity. Adjuvant endocrine therapy is the main treatment option in ER-positive tumors, while chemotherapy is seldom indicated.[16] Most of the patients received endocrine therapy, and only three patients received chemotherapy.

Tubular carcinoma is mostly reported in older patients, but some reviews have reported a median age between 51 years and 62 years.[17,18] In our cases, the median age was also 51 years. The classical radiological finding reveals a spicular mass that mimics IDC or radial scars.[19] These tumors are almost HR-positive, well-differentiated, and have low Ki-67 values. HER2 gene is generally neither overexpressed nor amplified.[20] Lymph node positivity was reported in 4-17% of cases. For these reasons, most of the patients present in the early stages and are usually detected by screening mammography. In our study, 66.7% of patients were diagnosed at stage II; all of the patients were found HR-positive and had low Ki-67 values. According to the most recent NCCN guidelines, the typical treatment for these tumors includes lumpectomy, sentinel lymph node biopsy, and adjuvant whole or partial breast irradiation. In patients with positive HR and no nodal involvement, adjuvant endocrine therapy may be avoided in case of tumor size up to 1 cm, should be considered for tumor size between 1 to 3 cm, and is recommended for 3 cm or larger tumors. For node-positive or ER/PR(-) cases, adjuvant chemotherapy is recommended based on the recurrence score, such as Oncotype Dx.[13] All of our patients received endocrine therapy, and most of them received chemotherapy due to lymph node metastasis.

Apocrine carcinoma, reported in, accounts for 1-4% of all breast cancer cases and 0.5% of our patients had this subtype. It can be found in all ages but is more common in the postmenopausal period. It is a high risk-grade tumor and presents with a higher stage. Much more lymphovascular invasion occurs in this subtype than in IDC. Pure apocrine carcinomas are usually ER(-), and PR(-), androgen receptor (AR) positive, and HER2 overexpression is seen in up to 54% of the patients.[21] Similar to earlier studies, in our study, 75% of our patients had nodal involvement, and 62.5% of them were at stage III disease while HER2 was overexpressed in 62.5% of the cases. Also, most of the patients were ER or PR negative and had high Ki-67 values.

Metaplastic carcinomas are a heterogeneous group of tumors that shows squamous and mesenchymal differentiation.[2] Metaplastic BC comprises approximately 0.2-0.62% of all breast cancers, and 0.6% of our patients had this subtype. The reported

median age was 47–61 years, while in our cases, it was 57 years. These tumors are generally in the basal-like or triple-negative group and are poorly differentiated with high Ki-67 value and p53 positivity.[22-24] Most of these tumors are node-negative but have a high metastatic spread potential. At the time of diagnosis, they tend to present with larger tumors when compared to IDC.[22] In our study, 66.7% of the cases were in the basal-like group. Our metaplastic carcinoma cases were diagnosed mostly with lymph node-negative disease, and 44.4% of patients had tumors larger than 5 cm. The prognosis and treatment response rates are poorer than triple-negative IDC, so once diagnosed, these patients need aggressive treatment regimens, including mastectomy and/or chemotherapy.[25,26] In our study, the majority of patients were treated with chemotherapy, and unlike other subtypes, three of nine patients had died.

Medullary carcinoma is most likely to present at a younger age and makes up for less than 2% of BC cases. In our study, it accounted for 0.5% of all patients. Though about one-fourth of cases are diagnosed before 35 years of age, only 13% of them show Brest Cancer Susceptibility Gene 1(BRCA1) germline mutations.[2,27] Most of the medullary cancer cases are triple-negative and may be clinically and radiologically confused with benign cases like fibroadenoma. Despite unfavorable histologic features like aneuploidy, high proliferative index, and triple negativity, the prognosis of patients is generally good.[28,29] In a study, nearly half of medullary type BC patients, were in the basal-like subgroup and lymph node metastases were found in less than 30%.[30] Consistent with finding in previous studies, 37.5% of cases in the current study were in the basal-like subgroup, but lymph node metastasis rate was higher with 62.5% of cases. Most of the cases were in stage II, and all patients remained under follow-up.

LIMITATIONS OF THE STUDY

There are some limitations to this study. It was conducted with a retrospective effect. There were a limited number of patients. Pathological evaluations were not performed by a single pathologist, so individual biases or lack of understanding of rare cases might have affected their observations. Also, inadequate data about familial history, risk factors, BRCA1 and BRCA2 mutations, and tumor grades are other limitations. Despite these drawbacks, we elaborated on relatively comprehensive clinicopathologic and immunohistochemical features of rare breast tumors, in addition to evaluating treatment regimens and survival.

CONCLUSION

Though various abovementioned histologic subtypes of BC are seen infrequently, they are still increasingly reported in clinical practice. In this study, we examined important features, clinical behavior, management, and outcomes of rare BC subtypes. It is highlighted that this study would be very useful and informative for both daily clinical practice and future studies. It will also guide future large scale prospective meta-analyses and contribute to derive better timely therapeutic interventions to reduce mortality and morbidity worldwide, especially in women.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Nadiye Akdeniz, Muhammet Ali Kaplan, Mehmet Küçüköner;* ***Design:*** *Nadiye Akdeniz, Muhammet Ali Kaplan Mehmet Küçüköner;* ***Control/Supervision:*** *Nadiye Akdeniz, Muhammet Ali Kaplan, Zuhat Urakçı;* ***Data Collection and/or Processing:*** *Nadiye Akdeniz, Mustafa Nacir, Oğur Karhan;* ***Analysis and/or Interpretation:*** *Nadiye Akdeniz, Muhammet Ali Kaplan, Senar Ebinç;* ***Literature Review:*** *Oğur Karhan,Yasin Sezgin, Senar Ebinç, Erkan Bilen;* ***Writing the Article:*** *Nadiye Akdeniz, Zuhat Urakçı, Oğur Karhan;* ***Critical Review:*** *Hüseyin Büyükbayram, Abdurrahman Işıkdoğan, Mehmet Küçüköner;* ***References and Fundings:*** *Zuhat Urakçı, Mustafa Nacir;* ***Materials:*** *Nadiye Akdeniz, Mustafa Nacir.*

KAYNAKLAR

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30. [Crossref] [PubMed]
2. Tavassoli FA, Devilee P. Pathology and Genetics of Tumors of the Breast and Female Genital Organs. World Health Organization Classification of Tumors. 1st ed. Lyon: International Agency for Research on Cancer (IARC); 2003.
3. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. Br J Cancer. 2005;93(9):1046-1052. [Crossref] [PubMed] [PMC]
4. Cadoo KA, McArdle O, O'Shea AM, Power CP, Hennessy BT. Management of unusual histological types of breast cancer. Oncologist. 2012;17(9):1135-1145. [Crossref] [PubMed] [PMC]
5. Coates AS, Winer EP, Goldhirsch A, et al; Panel Members. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015;26(8):1533-1546. [Crossref] [PubMed] [PMC]
6. Wolff AC, Hammond ME, Hicks DG, et al; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med. 2014;138(2): 241-256. [Crossref] [PubMed] [PMC]
7. Louwman MW, Vriezen M, van Beek MW, et al. Uncommon breast tumors in perspective: incidence, treatment and survival in the Netherlands. Int J Cancer. 2007;121(1):127-135. [Crossref] [PubMed]
8. Gokce H, Durak MG, Akin MM, et al. Invasive micropapillary carcinoma of the breast: a clinicopathologic study of 103 cases of an unusual and highly aggressive variant of breast carcinoma. Breast J. 2013;19(4):374-381. [Crossref] [PubMed]
9. Chen L, Fan Y, Lang RG, et al. Breast carcinoma with micropapillary features: clinicopathologic study and long-term follow-up of 100 cases. Int J Surg Pathol. 2008;16(2):155-163. [Crossref] [PubMed]
10. Liu XY, Jiang YZ, Liu YR, Zuo WJ, Shao ZM. Clinicopathological characteristics and survival outcomes of invasive cribriform carcinoma of breast: a SEER population-based study. Medicine (Baltimore). 2015;94(31): e1309. [Crossref] [PubMed] [PMC]
11. Colleoni M, Russo L, Dellapasqua S. Adjuvant therapies for special types of breast cancer. Breast. 2011;20 Suppl 3:S153-S157. [Crossref] [PubMed]
12. Komenaka IK, El-Tamer MB, Troxel A, et al. Pure mucinous carcinoma of the breast. Am J Surg. 2004;187(4):528-532. [Crossref] [PubMed]
13. NCCN Clinical Practice Guidelines in Oncology. NCCN Guidelines, Breast Cancer v6.2020. (Accessed December 05, 2020) [Link]
14. Grabowski J, Salzstein SL, Sadler GR, Blair S. Intracystic papillary carcinoma: a review of 917 cases. Cancer. 2008;113(5):916-920. [Crossref] [PubMed] [PMC]
15. Rakha EA, Gandhi N, Climent F, et al. Encapsulated papillary carcinoma of the breast: an invasive tumor with excellent prognosis. Am J Surg Pathol. 2011;35(8):1093-1103. [Crossref] [PubMed]
16. Lefkowitz M, Lefkowitz W, Wargotz ES. Intraductal (intracystic) papillary carcinoma of the breast and its variants: a clinicopathological study of 77 cases. Hum Pathol. 1994;25(8):802-809. [Crossref] [PubMed]
17. Rakha EA, Lee AH, Evans AJ, et al. Tubular carcinoma of the breast: further evidence to support its excellent prognosis. J Clin Oncol. 2010;28(1):99-104. [Crossref] [PubMed]
18. Javid SH, Smith BL, Mayer E, et al. Tubular carcinoma of the breast: results of a large contemporary series. Am J Surg. 2009;197(5):674-677. [Crossref] [PubMed]
19. Günhan-Bilgen I, Oktay A. Tubular carcinoma of the breast: mammographic, sonographic, clinical and pathologic findings. Eur J Radiol. 2007;61(1):158-162. [Crossref] [PubMed]
20. Oakley GJ 3rd, Tubbs RR, Crowe J, et al. HER-2 amplification in tubular carcinoma of the breast. Am J Clin Pathol. 2006;126(1):55-58. [Crossref] [PubMed]
21. Vranic S, Tawfik O, Palazzo J, et al. EGFR and HER-2/neu expression in invasive apocrine carcinoma of the breast. Mod Pathol. 2010;23(5):644-653. [Crossref] [PubMed]
22. Pezzi CM, Patel-Parekh L, Cole K, Franko J, Klimberg VS, Bland K. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. Ann Surg Oncol. 2007;14(1):166-173. [Crossref] [PubMed]
23. Al Sayed AD, El Weshi AN, Tulbah AM, Rahal MM, Ezzat AA. Metaplastic carcinoma of the breast clinical presentation, treatment results and prognostic factors. Acta Oncol. 2006;45(2): 188-195. [Crossref] [PubMed]
24. Rakha EA, Coimbra ND, Hodi Z, Juneinah E, Ellis IO, Lee AH. Immunoprofile of metaplastic carcinomas of the breast. Histopathology. 2017;70(6):975-985. [Crossref] [PubMed]
25. Jung SY, Kim HY, Nam BH, et al. Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer. Breast Cancer Res Treat. 2010;120(3):627-637. [Crossref] [PubMed]
26. Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN. Metaplastic breast cancer: prognosis and response to systemic therapy. Ann Oncol. 1999;10(4):413-419. [Crossref] [PubMed]
27. Lakhani SR, Gusterson BA, Jacquemier J, et al. The pathology of familial breast cancer: histological features of cancers in families not attributable to mutations in BRCA1 or BRCA2. Clin Cancer Res. 2000;6(3):782-789. [PubMed]
28. Vincent-Salomon A, Gruel N, Lucchesi C, et al. Identification of typical medullary breast carcinoma as a genomic sub-group of basal-like carcinomas, a heterogeneous new molecular entity. Breast Cancer Res. 2007;9(2):R24. [Crossref] [PubMed] [PMC]
29. Work ME, Andrulis IL, John EM, et al. Risk factors for uncommon histologic subtypes of breast cancer using centralized pathology review in the Breast Cancer Family Registry. Breast Cancer Res Treat. 2012;134(3):1209-1220. [Crossref] [PubMed] [PMC]
30. Chu Z, Lin H, Liang X, et al. Clinicopathologic characteristics of typical medullary breast carcinoma: a retrospective study of 117 cases. PLoS One. 2014;9(11):e111493. [Crossref] [PubMed] [PMC]