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Review

Apocrine carcinoma of the breast: A comprehensive review

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Summary. Apocrine carcinoma of the breast is a rare, special type of breast carcinoma showing distinct morphologic, immunohistochemical and molecular genetic features. Apocrine epithelium has a characteristic steroid receptor profile that is estrogen receptor and progesterone receptor negative and androgen receptor positive. This combination of morphologic and immunohistochemical characteristics is essential for the proper recognition of the apocrine carcinomas. Strictly defined, apocrine carcinomas express either Her-2/neu or EGFR, which along with androgen receptor positivity make patients with the apocrine carcinoma eligible for targeted therapies.

Key words: Breast cancer, Special types, Apocrine carcinoma, Androgen receptor

Introduction

Invasive carcinoma of the breast is the most common malignancy affecting women worldwide (Lakhani et al., 2012). It is a heterogeneous disease in morphologic, molecular and clinical terms (Weigelt and Reis-Filho, 2009; Weigelt et al., 2010a). It encompasses at least 20 different morphologic variants among which invasive ductal carcinoma of no-special-type (NST) is the most common type constituting up to 75% of all breast carcinomas (Lakhani et al., 2012). The remaining 25% are so-called special histologic types including invasive apocrine carcinoma of the breast (Weigelt and Reis-Filho, 2009; Weigelt et al., 2010a).

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Definition

Mammary apocrine cells have abundant eosinophilic and granular cytoplasm ("type A" cells), centrally to eccentrically located nuclei with prominent nucleoli and distinctive cell borders (Eusebi et al., 1986; Tavassoli, 1999; Jones et al., 2001; Page, 2005) (Figs. 1A, 2A). Another, less common type of apocrine cells, called "type B" cells (Lakhani et al., 2012), has more foamy and vacuolated cytoplasm (Fig. 1B). Apocrine differentiation (metaplasia) is commonly seen in breast tissue, particularly in the context of fibrocystic disease of the breast, although it may be associated with other benign and malignant conditions (Durham and Fechner, 2000; O'Malley and Bane, 2004, 2008; Masood and Rosa, 2009). The benign breast lesions with apocrine morphology include papillary apocrine changes, apocrine cysts, apocrine adenosis (sclerosing adenosis with apocrine metaplasia), and apocrine adenoma (Durham and Fechner, 2000). Malignant apocrine lesions of the breast include apocrine ductal carcinoma in situ (DCIS) and invasive apocrine carcinoma (Gerhard et al., 2012).

The presence of malignant apocrine cells in more than 90% of the tumor population defines invasive apocrine carcinoma (O'Malley et al., 2011). The lack of uniform acceptance/application of diagnostic criteria has resulted in various and frequently confusing definitions and thresholds for definitions of apocrine carcinoma in the available literature (Bundred et al., 1990; Matsuo et al., 1998; Japaze et al., 2005; Rosen and Hoda, 2006; Tanaka et al., 2008; Iwase et al., 2010; Lewis et al., 2011; Lakhani et al., 2012; Cha et al., 2012; Dag et al., 2012; Tsutsumi, 2012; Choi et al., 2012). Moreover, the most recent WHO classification of breast tumors offers an imprecise definition of apocrine carcinoma of the breast (Lakhani et al., 2012).

We prefer to base the diagnosis of apocrine carcinoma on the typical cell morphology present in >90% of the tumor population (the same criteria used for all other special histologic subtypes) and on the distinctive immunohistochemical profile: Estrogen receptor- (ER) negative, Progesterone receptor (PR) negative and Androgen receptor (AR) positive tumors (Fig. 2B-C), because this profile matches closely the normal (and mammary metaplastic) apocrine epithelium.

Epidemiology

Invasive apocrine carcinoma of the breast is rare, constituting between 0.3 and 4% of all invasive cancer in women. This reported tenfold variation is probably due to the lack of consistent and accepted criteria (Mossler et al., 1980; Eusebi et al., 1986; Pagani et al., 1994; Takeuchi et al., 2004; Japaze et al., 2005; Celis et al., 2006; Rosen and Hoda 2006; Wells and El-Ayat, 2007; Kreike et al., 2007; Weigelt et al., 2008; Kaya et al., 2008; Tanaka et al., 2008; Bhargava et al., 2009; Neimer et al., 2010; Iwase et al., 2010; Lewis et al., 2011; Tan et al., 2011; Choi et al., 2012; Monhollen et al., 2012, Lin Fde et al., 2012; Choi et al., 2012; Lakhani et al., 2012; Dellapasqua et al., 2013).

Rare cases of in situ and invasive apocrine carcinomas among men have also been described (Shah et al., 1980; Bryant, 1981; Arnould et al., 2006; Dag et al., 2012).

Histologic and ultrastructural characteristics

Apocrine carcinomas typically exhibit growth patterns similar to invasive ductal carcinomas, NST, including a rare encysted (encapsulated) apocrine papillary carcinoma of the breast that usually presents grossly as a cyst and is microscopically well demarcated (Seal et al., 2009; Laforga et al., 2011).

Apocrine carcinomas are graded according to Elston-Ellis modification of the Bloom and Richardson grading system (Elston and Ellis, 1991). The majority of apocrine carcinomas are grade 2 and 3 (Eusebi et al., 1986; Tanaka et al., 2008; Vranic et al., 2010; Bhargava et al., 2010; Tsutsumi, 2012; Cha et al., 2012; Alvarenga et al., 2012). Mitotic activity in apocrine carcinomas is usually moderate to high, particularly in triple negative apocrine carcinomas (Choi et al., 2012; Tsutsumi, 2012; Alvarenga et al., 2012).

Like the more common invasive ductal carcinoma NST, invasive apocrine carcinoma may be associated with an in situ apocrine component (apocrine DCIS). The relationship of apocrine carcinoma of the breast with other benign apocrine lesions is not well established although some of them (e.g. apocrine metaplasia/hyperplasia, apocrine adenosis) may harbor clonal origins and premalignant potential (Selim et al., 2000; Schmitt and Reis-Filho, 2002).

Ultrastructurally, apocrine cells have a rich cytoplasm with well-defined outlines. Their cytoplasm contains electron-dense membrane granules, empty vesicles, prominent Golgi apparatus and large mitochondria with incomplete cristae (Mossler et al., 1980; Roddy and Silverberg, 1980; Eusebi et al., 1986; Alexiev et al., 1994). Like normal apocrine glands, the cytoplasm of the apocrine tumor cells may also accumulate lipids but the extent of accumulation (measured by the specific lipid marker adipophilin) is never as prominent as in lipid-rich breast carcinomas (Moritani et al., 2011). The nuclei tend to be round with condensed chromatin and large nucleoli (Eusebi et al., 1986). Grekou et al. also described the presence of intranuclear helioid inclusions in the apocrine tumor

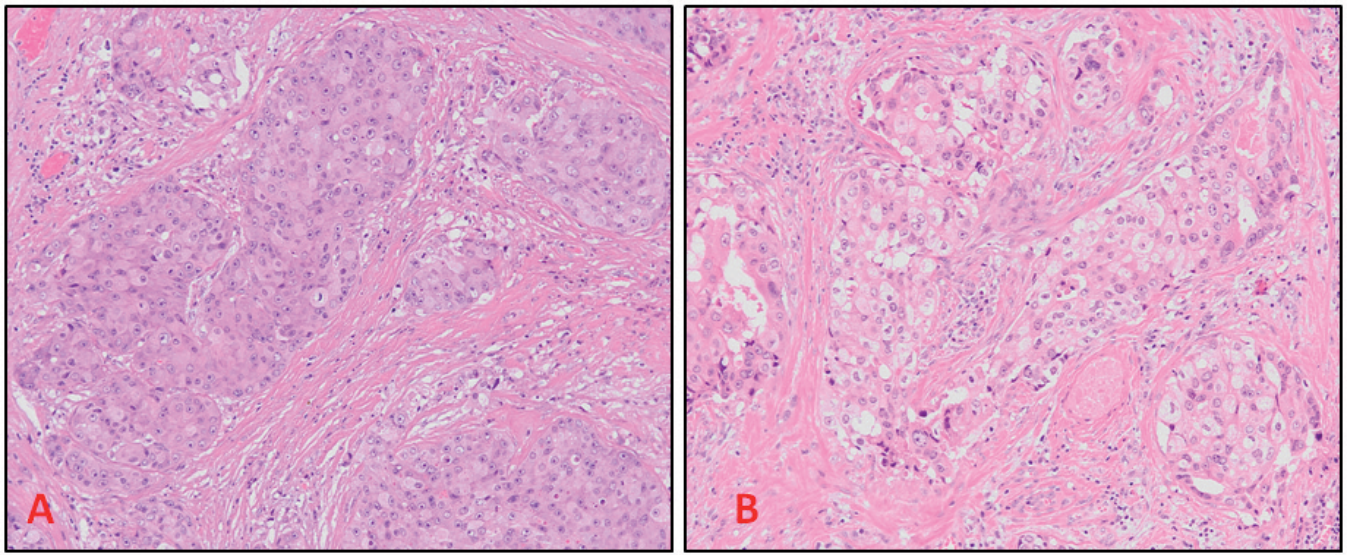

Fig. 1. Two different apocrine carcinoma cases. **A.** A case composed predominantly of the *Type A cells* with abundant eosinophilic cytoplasm and large nuclei with prominent nucleoli. **B.** A case composed of the *Type B cells* with foamy cytoplasm. H-E, x 10

cells. These inclusions represent single membrane-bounded bodies that have also been described in other benign breast lesions (e.g. benign hyperplasia) and extramammary malignancies (e.g. acinic cell carcinoma of the salivary gland) (Grekou et al., 1999).

Apocrine differentiation can be seen in other breast carcinoma subtypes including papillary, micropapillary, tubular, medullary, and lobular carcinoma (Eusebi et al., 1984, 1992; Page, 2005; Wells and El-Ayat, 2007; Lakhani et al., 2012). Of particular interest is pleomorphic lobular carcinoma, a rare but more aggressive variant of lobular carcinoma that may exhibit morphologic similarities with apocrine carcinoma and frequently clusters with it creating "molecular apocrine tumors" (Eusebi et al., 1992; Weigelt et al., 2008). Pleomorphic lobular carcinomas also show GCDFP-15 positivity, but typically have discohesive pleomorphic tumor cells that lose E-cadherin expression as other lobular carcinoma variants (Eusebi et al., 1992; Palacios et al., 2003; Reis-Filho et al., 2005; Simpson et al., 2008; Weigelt et al., 2008, 2010b; Monhollen et al., 2012). Pleomorphic lobular carcinomas tend to be ER and PR positive (~80%) but may also be positive for AR and Her-2/neu protein (Middleton et al., 2000; Reis-Filho et al., 2005; Simpson et al., 2008; Chen et al., 2009). They may also show foci of classical lobular carcinoma and are frequently associated with LCIS (or pleomorphic LCIS) (Eusebi et al., 1992; Middleton et al., 2000; Reis-Filho et al., 2005). In contrast, in typical apocrine carcinomas, cells do not tend to show discohesiveness and retain E-cadherin expression (Weigelt et al., 2008; Paredes et al., 2008; Choi et al., 2012). A histiocytoid variant of lobular carcinomas is another differential diagnosis because a subset of apocrine carcinomas may have the tumor cells with foamy vacuolated cytoplasm ("type B" cells) (Damiani et al., 1998; Lakhani et al., 2012). Histiocytoid lobular cells however tend to show a bland cytomorphology, loss of E-cadherin expression,

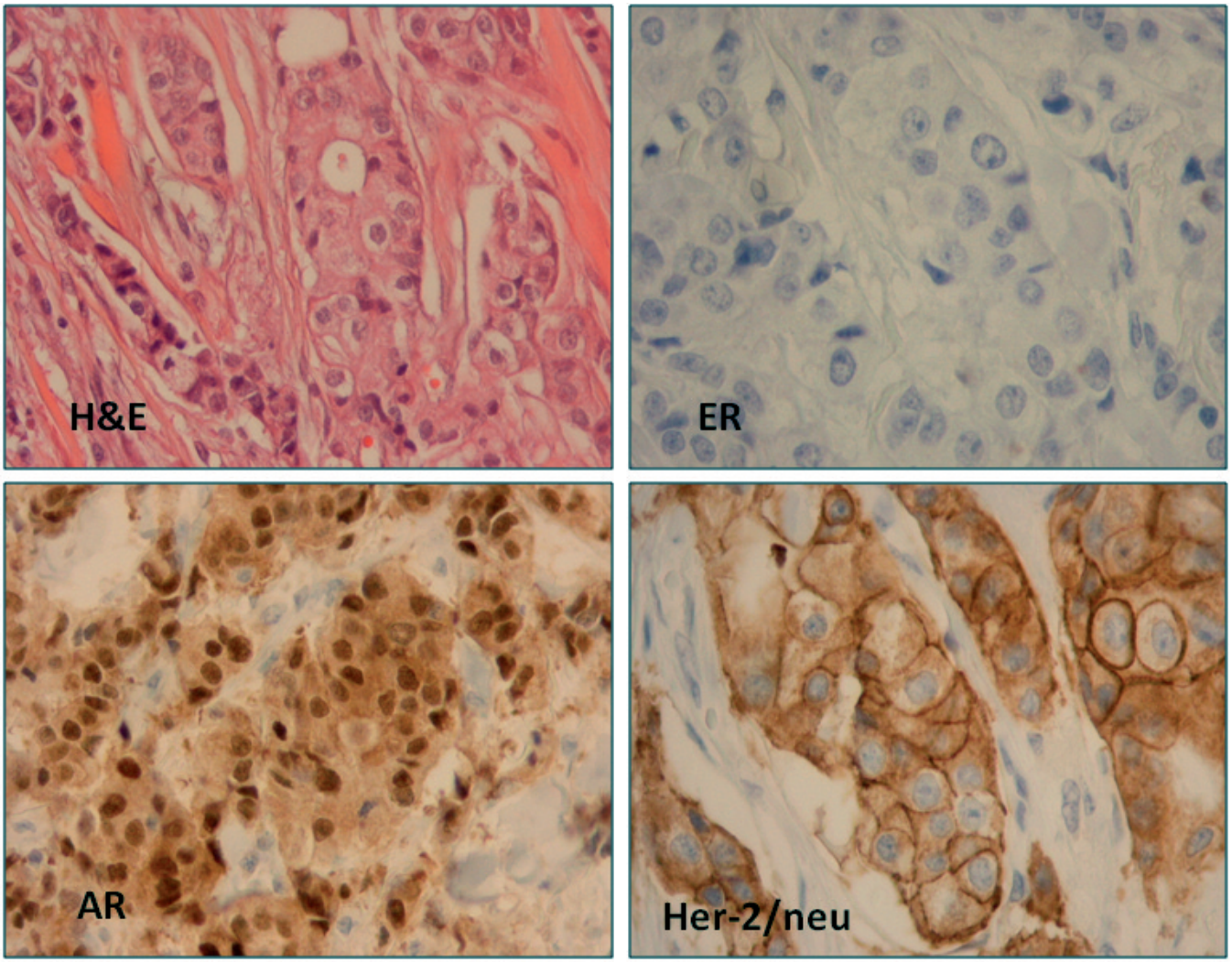

Fig. 2. A. A case of invasive apocrine carcinoma with characteristic morphology. **B-C.** Steroid receptor profile: Estrogen receptor (ER)-negative **(B)**; Androgen receptor (AR)-positive **(C)**. **D.** The tumor cells also exhibited Her-2/neu protein overexpression (score 3+).

and exhibit strikingly different ultrastructural features (Gupta et al., 2002; Tan et al., 2011). Histiocytoid carcinomas are also associated with lobular carcinoma in situ (LCIS) (Gupta et al., 2002). In rare cases, foamy apocrine cells may be mistaken for inflammatory reaction with abundant histiocytic proliferation. In such cases antibodies to cytokeratins (e.g. AE1/AE3, CAM5.2) may be helpful (Lakhani et al., 2012).

Steroid receptor profile of apocrine carcinomas

Apocrine epithelium of the breast shows a characteristic steroid receptor profile: ER negative, PR negative, and AR positive (Tavassoli et al., 1996; Gatalica, 1997; Selim and Wells, 1999; Zagorianakou et al., 2006; Gatalica and Tawfik, 2006). AR activation and signaling is a hallmark of apocrine differentiation in breast pathology, although AR expression (along with other steroid receptors) has been described in other breast lesions, particularly in breast carcinomas (Isola, 1993; Tavassoli et al., 1996; Gatalica, 1997; Moinfar et al., 2003; Rakha et al., 2007; Micello et al., 2010; Castellano et al., 2010; Collins et al., 2011; Hu et al., 2011).

Due to the lack of consistent application of the morphologic criteria, there is a substantial variation in the reported literature on the status of steroid receptors (ER/PR/AR) in invasive apocrine carcinoma (Kaya et al., 2008). Other reasons for discrepancy may include different cutoff values for positivity and the methods used for detection of ER and PR as the historic studies were mainly based on the radioimmunoassay for steroid receptor detection (Eusebi et al., 1986; Bundred et al., 1990).

Of note, other isoforms of full length *ER-alpha66* have been described in apocrine carcinomas. We showed the presence of ER-alpha36, a 36 kDa alternatively spliced variant of full *ER-alpha66* gene transcript, in the vast majority of invasive apocrine carcinomas of the breast (Vranic et al., 2011a). ER-alpha36 is predominantly expressed on the cell membrane and in the cytoplasm of tumor cells and mediates non-genomic (rapid) estrogen signaling through the mitogen-activated protein kinase (MAPK/ERK) signaling pathway and EGFR (Wang et al., 2006; Zhang et al., 2011). An earlier study of Bratthauer et al. reported that ER mRNA was detectable in apocrine carcinoma despite a complete absence of ER protein using the commercially available immunohistochemical assay against ER-alpha 66 (Bratthauer et al., 2002). The authors studied the ER mRNA using primers that covered the first and second exon of the *ER-alpha66* messenger RNA and found them to be intact. It is therefore possible that detectable ER mRNA in apocrine carcinomas might well be one of the alternatively spliced isoforms of ER-alpha including ER-alpha36 (Vranic et al., 2011a).

Estrogen receptor-beta (ER-beta) which shares a high degree of amino acid homology with ER-alpha66 has been found overexpressed in ER-alpha66 negative breast carcinomas including invasive apocrine carcinoma of the breast (Sakamoto and Honma, 2009; Yan et al., 2011). Honma et al. showed the presence of ER-beta and ER-beta1 isoforms in apocrine carcinoma with beta1 isoform exhibiting a favorable prognostic value in invasive apocrine carcinoma (Honma et al., 2007, 2008). The precise role of ER-beta in apocrine carcinoma remains to be determined.

Markers of apocrine differentiation

Androgen receptor (AR) is a member of the steroid receptor family. It is a single polypeptide with various domains that mediate different functions (Gucalp and Traina, 2010). Its activity has been implicated in breast cancer development and progression. AR exerts anti-estrogenic, growth-suppressive effects in normal breast tissue and ER-positive breast carcinomas (Hickey et al., 2012). However, in ER-negative breast carcinomas, including invasive apocrine carcinoma, it has the opposite effect, promoting cell growth and tumor development (Hickey et al., 2012). FoxA1 transcription factor appears to be a key mediator of AR signaling in breast cancer, including apocrine carcinoma of the breast (Robinson et al., 2011; Dumay et al., 2013). Naderi et al. also found a significant functional cross-talk between AR and HER-2 that involves FoxA1 activity as well as extracellular signal-regulated kinase (ERK) signaling pathway (Naderi and Hughes-Davies, 2008; Naderi and Liu, 2010; Naderi et al., 2011; Naderi and Meyer, 2012). Moreover, Naderi and Meyer showed that prolactin-induced protein (PIP) (or GCDFP-15) is the most actively regulated gene by the AR/ERK feedback loop in apocrine tumor cells (Naderi and Meyer, 2012).

The expression of AR has been observed in up to 80% of breast carcinomas including ER-/PR- breast carcinomas. The percentage of AR expression in some subtypes is higher than ER and PR (up to 90% in low grade invasive ductal carcinomas) (Isola, 1993; Moinfar et al., 2003; Agoff et al., 2003; Miccelo et al., 2010). Owing to its consistent overexpression in apocrine epithelium, AR has been designated as an apocrine differentiation marker (Miller et al., 1985; Gatalica, 1997; Sapp et al., 2003; Vranic et al., 2010). AR has been associated with HER-2/neu signaling in breast cancer (Moinfar et al., 2003; Micello et al., 2010; Collins et al., 2011) including special types like Paget's disease of the breast and apocrine carcinoma (Diaz de Leon et al., 2000; Varga et al., 2004; Liegl et al., 2005; Naderi and Hughes-Davies, 2008; Vranic et al., 2010; Micello et al., 2010; Bhargava et al., 2010; Neimeier et al., 2010; Naderi et al., 2011).

AR gene mutations have not been described in breast carcinoma tissue samples but a mutation of the *AR* gene has recently been described in an apocrine cell line, MDA-MB-453 (Moore et al., 2012). AR gene microsatellite polymorphisms and active gene losses, which have been described, may contribute to AR protein status in female breast carcinomas with potential implications on tumor initiation and progression (Shan et al., 2000; Kasami et al., 2000). Thus, AR immunohistochemical detection may correlate with CAG repeats on AR gene with a higher number of repeats being linked to

a higher AR expression (Narita et al., 2010). In male breast cancer, AR gene alterations were proposed to initiate the tumor development, but mutations appear to be exceedingly rare (Wooster et al., 1992; Lobaccaro et al., 1993; Syrjäkoski et al., 2003).

Gross cystic disease fluid protein 15 (GCDFP-15), identified by Haagensen et al. in 1977, is a 15-kDa protein mapped to chromosome 7. GCDFP-15 acts as an aspartyl protease with fibronectin as its substrate. Its expression has been associated with apocrine differentiation, including apocrine carcinoma (Eusebi et al., 1986; Mazoujian et al., 1989; Haagensen et al., 1990; Pagani et al., 1994; Alexiev et al., 1994; Rakha et al., 2006; Banneau et al., 2010; Naderi and Meyer, 2012), although its positivity has been confirmed in other breast carcinoma subtypes (Pagani et al., 1994; Sapino et al., 2001; Lewis et al., 2011). However, GCDFP-15 protein expression appears to be decreased in advanced apocrine carcinomas, leading some authors to question GCDFP-15 as a definite marker of apocrine carcinoma (Honma et al., 2005). Similarly, an autopsy based study by Cimino-Mathews et al. demonstrated a gradual loss of AR expression during breast cancer progression from initial diagnosis to end-stage metastases (Cimino-Mathews et al., 2012).

Celis and colleagues did extensive proteomic studies on apocrine carcinomas defining a specific *apocrine protein signature* which was analogous to that of apocrine sweat glands (Celis et al., 2009) (Table 1). The signature includes markers which are consistently expressed (AR, CD24, 15-PDGH [prostaglandin dehydrogenase], ACMS1 [acyl-CoA synthetase medium-chain family member 1]), and markers that are not expressed (ER-alpha, PR, Bcl-2, GATA-3) (Celis et al., 2008, 2009). Several additional proteins (markers) have been shown to be characteristically upregulated in apocrine carcinomas, including psoriasin, S100A9, p53, hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase), and cyclooxygenase-2 (COX-2) (Celis et al., 2006).

5alpha-reductase is an enzyme that converts testosterone to the potent androgen dihydrotestosterone (DHT). Its expression has been observed in approximately 60% of apocrine carcinomas and correlated with adverse parameters, including angiolympathic invasion, higher histologic grade, and poor clinical outcome (Kasashima et al., 2012).

Other markers that have been proposed to be specific for apocrine differentiation include *gama-glutaminyl transferase 1* (GGT-1) (Banneau et al., 2010; Choi et al., 2012; Kim et al., 2012; Cha et al., 2012) and *tumor-associated glycoprotein-72*, a high molecular weight glycoprotein that appears to be a more sensitive marker of apocrine differentiation than GCDFP-15 (Honma et al., 2006).

Table 1. A summary of the most relevant morphologic, immunohistochemical, cytogenetic, molecular and clinical characteristics of apocrine carcinoma of the breast.

Characteristic	Apocrine carcinoma
Morphology	The presence of the cells with abundant eosinophilic and granular cytoplasm, centrally to eccentrically located nuclei with prominent nucleoli and distinctive cell borders
Steroid receptor profile	ER-α-, PR-, AR+
Specific apocrine markers	GCDFP-15+, AR+, GGT-1+, 5α-reductase+
"Apocrine protein signature"	a) Positive markers: AR, CD24, 15-PDGH, ACMS1 b) Negative markers: ER, PR, Bcl-2, GATA-3
Growth Factor receptors	EGFR+/-, HER-2/neu +/-, IGF-1R -
Basal/Myoepithelial Markers	Variable positivity for basal cytokeratins (CK5, CK5/6, CK14, CK17), P-cadherin, and p63 Negative for CD10, c-Kit (CD117), CD109 and vimentin
Cytogenetic characteristics	a) Gains of 1q, 2q, 1p, 7, and 17 b) Losses of 1p, 22q, 17q, 12q, and 16q
Molecular characteristics	"Molecular apocrine group" - increased AR and HER-2/neu signaling Loss of PTEN gene Loss of TP53 gene
Clinical characteristics	Similar to invasive ductal carcinoma (NST); outcome studies contradictory (see Table 2)

The erbB/HER (human epidermal growth factor receptor) family in apocrine carcinomas

The erbB (HER, human epidermal growth factor receptor) family is composed of four homologous transmembrane receptors that mediate growth factor cellular signaling. The family includes EGFR (HER-1, ErbB1), ErbB2 (HER-2/neu), ErbB3 (HER-3), and ErbB4 (HER-4) (Foley et al., 2010).

Epidermal Growth Factor Receptor (EGFR/HER-1)

EGFR status has been extensively studied in breast cancer (Foley et al., 2010). EGFR protein has been variably overexpressed in breast carcinoma with the highest rate in triple-negative breast carcinomas (Masuda et al., 2012). *EGFR* gene (on chromosome 7p11.2) alterations (amplification and gene mutations) appear to be rare, particularly gene mutations (Bhargava et al., 2005). In contrast to benign apocrine lesions (e.g. apocrine metaplasia), EGFR protein expression has been commonly observed in apocrine carcinomas (up to 60%) while *EGFR* gene alterations (gene amplification and mutations) appear to be rare (Feuerhake et al., 2001; Vranic et al., 2010; Bhargava et al., 2010; Banneau et al., 2010; Alvarenga et al., 2012; Cha et al., 2012; Tsutsumi, 2012; Wen et al., 2012). Similar to invasive ductal carcinomas (NST), a substantial proportion of apocrine carcinomas also exhibits amplification of the centromeric region of chromosome 7 (detected by the chromosome enumeration probe 7, CEP7 polysomy

defined as three or more CEP7 copies in FISH studies) (Vranic et al., 2010, Grob et al., 2012). Koletsa et al. also reported a common *CEP7* polysomy in HER-2-positive breast carcinomas but without association with EGFR protein status (Koletsa et al., 2010). They found no *EGFR* gene amplification but confirmed the activation of EGFR protein through its phosphorylation (Koletsa et al., 2010). *CEP7* polysomy has also been described in breast carcinomas with EGFR protein overexpression, including triple-negative basal-like breast carcinomas as well as in some special types (e.g. metaplastic carcinoma of the breast) (Gwin et al., 2011; Shao et al., 2011; Martin et al., 2012).

Human Epidermal Growth Factor Receptor 2 (erbB2/HER-2/neu) status

Her-2/neu protein is overexpressed in approximately 15% of all breast carcinomas (Baehner et al., 2010). The primary mechanism of Her-2/neu activation is *HER-2/neu gene* (located on 17q12) amplification. In apocrine carcinoma, the rate of Her-2/neu overexpression (*HER-2/neu* gene amplification) is approximately 50% (between 44% and 54%) (Moinfar et al., 2003; Varga et al., 2004; Vranic et al., 2010) (Figs. 2D, 3B) although some studies, on the basis of a limited number of cases, reported a significantly lower rate of Her-2/neu positivity (~17%) (Weigelt et al., 2008; Banneau et al., 2010). Other studies also showed strong association between HER-2/neu activation and apocrine differentiation (androgen receptor expression) in breast cancer (Farmer et al., 2005; Naderi and Hughes-Davies, 2008; Bhargava et al., 2009; Rydén et al., 2010; Naderi and Liu, 2010; Bhargava et al., 2010; Niemeier et al., 2010; Park et al., 2011; Dumay et al., 2013). CEP17 polysomy (three or more CEP17 copies in FISH assays) appears to be a common event in apocrine carcinomas, either as the sole finding or in combination with *HER-2/neu* gene amplification (Schmitt et al., 1998; Vranic et al., 2010). Several investigators considered CEP17 polysomy as a potential cause for the equivocal *HER-2/neu* results by FISH or immunohistochemistry (Yeh et al., 2009; Ross, 2010; Vranic et al., 2011b). Of note, Her-2/neu protein expression may also be seen in some benign apocrine lesions such as apocrine adenosis, but without underlying *HER-2/neu* gene alterations (Selim et al., 2000).

Other immunohistochemical markers in apocrine carcinomas

Cytokeratin profile and basal/myoepithelial markers

Apocrine carcinomas retain reactivity for epithelial markers using immunohistochemical assays, including wide-spectrum cytokeratins [CK] (e.g. AE1-AE3), luminal cytokeratins including CK7, CK8, CK18, and CK19, and EMA (Weigelt et al., 2008; Alvarenga et al., 2011). In contrast to most other breast carcinoma subtypes, CK20 positivity has also been reported in breast carcinomas with apocrine differentiation (Shao et al., 2012). The expression of basal cytokeratins (e.g. CK5, CK5/6, CK14) is somewhat controversial (Hasegawa et al., 2008; Weigelt et al., 2008; Bhargava et al., 2010; Vranic et al., 2011d; Shao et al., 2012; Alvarenga et al., 2012; Cha et al., 2012; Tsutsumi, 2012; Wen et al., 2012). The expression of other basal/myoepithelial markers [e.g. p63, P-cadherin, Insulin-like growth factor-II mRNA-binding protein 3 (IMP3)] may be only sporadically seen (Hasegawa et al., 2008; Vranic et al., 2011d; Alvarenga et al., 2012) whereas S-100 protein, CD10 (Neprilysin), c-Kit (CD117), CD109, and Vimentin tend to be negative in the majority of apocrine carcinomas (Weigelt et al., 2008; Hasegawa et al., 2008) (Table 1). The immunohistochemical profile along with microarray profiling studies indicates that a majority of

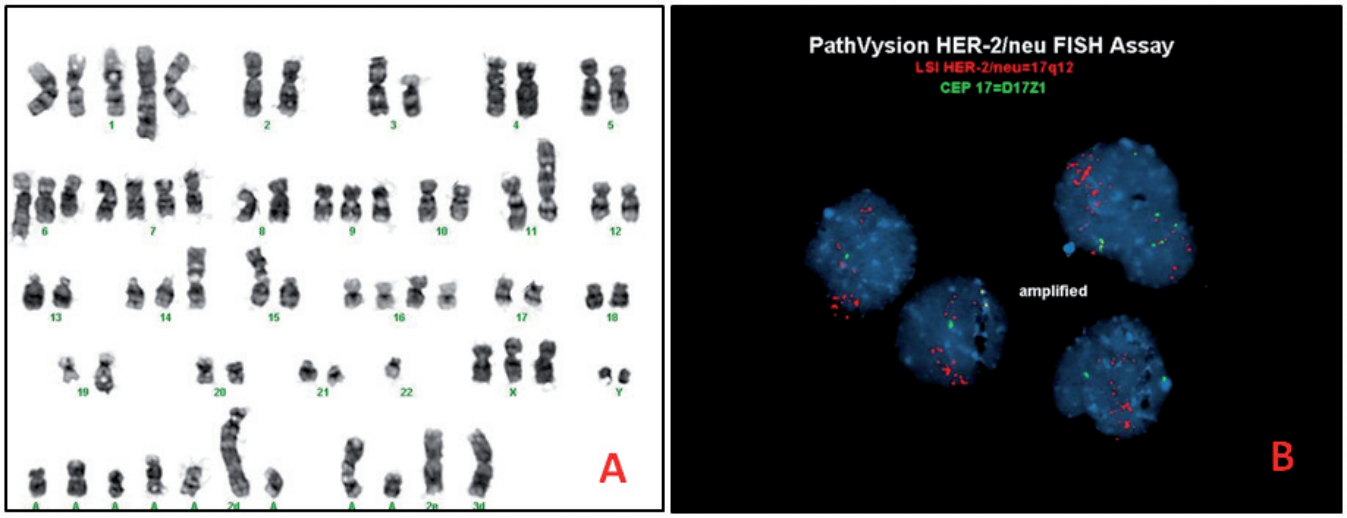

Fig. 3. A. Conventional cytogenetics performed on a case of invasive apocrine carcinoma revealed extensive structural and numeric alterations. **B.** An interphase Fluorescent in Situ Hybridization (FISH) assay performed on the same case confirmed the presence of the *HER-2/neu* gene amplification.

apocrine carcinomas, including the triple-negative ones, do not exhibit basal-like phenotype (Farmer et al., 2005; Weigelt et al., 2008; Sanga et al., 2009; Ni et al., 2011; Vranic et al., 2011d; Dumay et al., 2013).

Insulin-like growth factor receptor 1 (IGF-1R) status

IGF-1R is a transmembrane receptor with tyrosine kinase activity whose activation has been associated with trastuzumab resistance (Lu et al., 2001). IGF-1R appears to be significantly downregulated in apocrine breast lesions including apocrine carcinoma of the breast as in other ER-negative breast carcinomas (Bhargava et al., 2011).

Neuroendocrine markers

Apocrine carcinomas are typically negative for neuroendocrine markers (e.g. synaptophysin, chromogranin-A, CD56) (Weigelt et al., 2008). On the contrary, neuroendocrine carcinomas may express apocrine markers (GCDFP-15) in up to 50% of cases (Sapino et al, 2001).

Stem cell markers

CD44+/CD24-/low immunophenotype along with aldehyde dehydrogenase 1 (ALDH-1) positivity have been associated with stem-cell characteristics of breast cancer tumor cells (Currie et al., 2013). These markers have been described in invasive ductal carcinomas (NST) (Currie et al., 2013) as well is in some special types, including medullary and metaplastic breast carcinomas (de Beça et al., 2013). In contrast, apocrine carcinomas do not appear to be enriched with this immunophenotype (de Beça et al., 2013).

Cell cycle markers

While some of the key cell cycle regulatory proteins (p16, p21, p27, Rb, Cyclin D1, Cyclin A) have been well studied in benign apocrine lesions (apocrine metaplasia, apocrine adenosis) (Moriya et al., 2000; Elayat et al., 2009a,b, 2011) their role in invasive apocrine carcinoma remains largely unknown. A study of Moriya et al. found no significant difference in p21 and p27 expression between benign and malignant apocrine lesions (Moriya et al., 2000). Another flow cytometry study performed on a series of apocrine carcinomas showed an aneuploid DNA pattern, a high S-phase fraction and a moderate MIB-1 index (19%) in apocrine carcinomas (Gatalica and Tawfik, 2006). A study on MDA-MB-453 cell line showed a loss of the *P16-INK4a* gene (at 9p.21) followed by the loss of the p16 protein (Vranic et al., 2011c). However, apocrine carcinoma tissue samples retain p16(INK4a) protein expression (Vranic et al., 2011c).

C-Myc status

C-MYC gene located at 8q.24 plays an important role in various cell functions, including cell proliferation, differentiation, senescence, and apoptosis (Schmitt and Reis-Filho, 2002). It has been shown to be altered in breast carcinomas, particularly in high grade carcinomas (Selim et al., 2002; Schmitt and Reis-Filho, 2002). Interestingly, c-myc oncoprotein appears to be overexpressed in benign apocrine lesions (apocrine metaplasia and apocrine adenosis) without underlying C-MYC gene alterations (Selim et al., 2002). The status of C-MYC oncogene in apocrine carcinoma remains unknown.

Neoangiogenesis in apocrine carcinomas

Numerous studies confirmed the importance of development of new blood vessels (neoangiogenesis) as an essential step in tumor progression and metastasis. Neoangiogenesis in apocrine carcinomas is largely unknown, with only one study that included a small subset of apocrine carcinomas, although the authors, primarily focusing on invasive ductal carcinomas (NST), did not specify the profile of apocrine carcinomas (Charpin et al., 2004).

Autophagy-related proteins status

Autophagy is a component of lysosomal degradation and plays an important role in cellular adaptation to stress of both normal and malignant cells (Choi et al., 2013). It is involved in cell survival and cell death during cancer progression and cancer treatment (Rosenfeldt and Ryan, 2011). A study of Kim et al. indicated that triple-negative apocrine carcinomas (AR+ and/or GGT-1+) overexpressed autophagy-related proteins, including p62 and beclin-1 (Kim et al., 2012).

TGF-beta family members' status

Inhibin and activin are two closely related proteins with opposite effects involved in regulation of follicle-stimulating hormone secretion by the pituitary gland (Shim et al., 2006). They have been shown to be expressed in various tissues, including breast tissue (Shim et al., 2006). A study of Shim et al. indicated that inhibin/activin subunits tend to be more expressed in apocrine lesions, including apocrine carcinoma of the breast, than in non-apocrine lesions. The precise role of inhibin/activin complex in apocrine carcinoma remains to be elucidated.

Aquaporin3 (AQP3) status

AQP3 protein is widely distributed in human tissues and is involved in fluid homeostasis (Niu et al., 2012). AQP3 is also involved in cytotoxic activity of some chemotherapeutic drugs [capecitabine catabolite 5'-deoxy-5-fluorouridine (5'-DFUR) and gemcitabine] in the breast cancer cell line MCF-7 (Trigueros-Motos et al., 2012). It has been shown to be overexpressed in various human malignancies, including apocrine

carcinoma of the breast (Niu et al., 2012).

Cytogenetic characteristics of apocrine carcinoma

Very few studies specifically addressed cytogenetic features of apocrine carcinoma. Most of these studies included a limited number of cases with contradictory results. In contrast to some other special types (e.g. adenoid cystic carcinoma, secretory carcinoma), characteristic translocations specific for apocrine carcinoma have not yet been described (Weigelt et al., 2010a).

A study of Jones et al. showed that apocrine DCIS and invasive apocrine carcinoma frequently show gains of 1q, 2q, 1p, and losses of 1p, 22q, 17q, 12q, and 16q as their most common chromosomal changes (Jones et al., 2001). Our study based on three apocrine carcinomas studied by conventional cytogenetics and single nucleotide polymorphism (SNP) array assay revealed complex cytogenetic alterations in apocrine carcinomas with consistent gains of chromosomes 7 and 17 (Vranic et al., 2010) (Fig. 3A). Conventional cytogenetic analysis of MDA-MB-453 cell line revealed a hypertriploid clone characterized by extensive numerical and structural abnormalities that include gains of chromosomes 7, 11, 17, 19 and 21 and losses of chromosomes X, 3, 4, 9, 13, 14, 16 and 18 (Vranic et al., 2011c). Of particular interest is CEP17 polysomy without *HER-2/neu* gene amplification (defined as a ratio of *HER2* to *CEP17* > 2.2), which is a common event in apocrine carcinoma and may be associated with Her-2/neu protein overexpression (scores 2+ and 3+) when the absolute *HER2* gene copy number exceeded 6 per nucleus (Vranic et al., 2010).

Another study found a loss of heterozygosity at chromosomes 1p35-36 (NB), 3p25 (VHL), 16p13 (TSC2/PKD1), and 17p13 (TP53) in microdissected apocrine carcinomas of the breast (Lininger et al., 1999). Notably, several studies found the *TP53* gene mutation (followed by p53 protein overexpression) commonly present in apocrine carcinoma and associated with Her-2/neu overexpression (Karameris et al., 1995; Moriya et al., 2000; Gatalica and Tawfik, 2006; Tsutsumi, 2012; Dumay et al., 2013) although Tsutsumi (2012) reported a higher p53 protein expression in triple-negative than HER-2/neu positive apocrine carcinomas. A recent study of Dumay et al. confirmed a high frequency of the *TP53* gene mutations in "molecular apocrine tumors" (defined by ER-AR/+/FOX1A+ profile by microarray), particularly non-truncating mutations (Dumay et al., 2013). p53 protein expression has also been observed in apocrine DCIS (Leal et al., 2001) in contrast to benign apocrine lesions (Moriya et al., 2000).

Molecular features of apocrine carcinoma

Seminal gene expression profiling studies, based mainly on the analysis of invasive ductal carcinomas (NST), revealed the existence of five molecular subtypes of breast carcinoma, including luminal subtype (further subclassified into A and B), basal-like, normal-like, and HER-2 subtype (Perou et al., 2000; Sørlie et al., 2001, 2003). Additional gene expression microarray studies of breast cancers also discovered a characteristic gene expression profile found in apocrine carcinomas ["molecular apocrine group"] (Farmer et al., 2005; Doane et al., 2006; Kreike et al., 2007; Sanga et al., 2009; Guedj et al., 2012; Dumay et al., 2013). These studies showed that apocrine tumors are different from common luminal and basal-like breast carcinoma subtypes, and are characterized by increased AR signaling along with increased *HER-2/neu* gene signaling (Farmer et al., 2005; Sanga et al., 2009; Ni et al., 2011; Dumay et al., 2013). Ni et al. discovered, studying the MDA-MB-453 cell line, that AR mediates ligand-dependent activation of Wnt and HER2 signaling pathways through transcriptional activation of WNT7B and HER3 (Ni et al., 2011). A study of Kreike et al. based on triple-negative apocrine carcinomas identified two apocrine clusters: a) Apocrine-basal gene cluster (EGFR, CLDN1, VLDLR) and b) Apocrine-luminal gene cluster (AR, FASN, MSX2) that was identical to the "molecular apocrine group" described by Farmer et al. Other authors (Weigelt et al. 2008) in their comprehensive study on special histologic subtypes of breast carcinoma showed that apocrine carcinomas (ER-/AR+, GCDFP-15+) showed a heterogeneous gene expression profile pertaining to multiple molecular subtypes, although apocrine carcinomas clustered together with pleomorphic lobular carcinomas forming "molecular apocrine" signature (Weigelt et al., 2008). The study was limited by a small (n=6) number of apocrine carcinomas (Weigelt et al., 2008). Robbinson et al. study on apocrine cell line model (MDA-MB-453) showed that AR binds and regulates ER cis-regulatory elements in molecular apocrine tumors leading to the transcriptional program reminiscent of ER-mediated transcription in luminal type carcinomas (Robbinson et al., 2011). The reasons for discrepancies that lead some investigators to question the existence of apocrine carcinoma as a distinct entity may be related to the specific biology of interaction between steroid receptors ER and AR (Iggo, 2011). Iggo (2011) summarizing the key findings of Ni et al. and Robinson et al. gives an elegant explanation why apocrine carcinomas may exhibit luminal phenotype: "AR substitutes for ER at the enhancers of ER target genes to sustain the broad luminal profile. At the same time, AR binds to the enhancers of a smattering of its own target genes to give the expression profile its apocrine flavor."

Importantly, a study of Banneau et al. showed that patients with a germline mutation of the PTEN [Phosphatase and tensin homolog] gene (Cowden syndrome, OMIM #158350) are prone to develop breast carcinomas with apocrine differentiation that also show *HER-2/neu* gene activation (Banneau et al., 2010). Furthermore, a gene expression profiling study of breast carcinomas developed in patients with Cowden syndrome revealed a significant overlap with a "molecular apocrine carcinoma" profile described

previously (Farmer et al., 2005; Banneau et al., 2010). The authors concluded that the activation of the *ERBB2-PI3K-AKT* signaling axis caused by loss of *PTEN* gene may promote development of breast carcinomas with apocrine differentiation (Banneau et al., 2010). In addition, a study of Wang et al. on patients with Cowden syndrome indicated that *PTEN* gene germline mutations affect the 3' end of the AR-binding motif resulting in abrogation of androgen-mediated transcriptional activation of PTEN with possibly organ-specific and sex-specific tumor predisposition in these patients (Wang et al., 2011a). Similarly, a mutation of the *PTEN* gene has been described in the apocrine cell line MDA-MB-453 (Singh et al., 2011). Also, a study of Maruyama et al. reported *PIK3CA* gene mutations in two cases of invasive apocrine carcinomas (Maruyama et al., 2007). Taken together, these studies indicate the importance of deregulation of the PI3K/PTEN/Akt signaling pathway in the pathogenesis of mammary apocrine carcinoma.

Although a substantial proportion of apocrine carcinomas are of triple-negative phenotype and the loss of PTEN function may be predictive of familial breast cancer (Phuah et al., 2012), no study has identified an association between familial breast cancer (BRCA1 and BRCA2 carriers) and (strictly defined) apocrine carcinoma. An important negative regulator of *BRCA1* gene expression, the inhibitor of DNA binding (ID)-4 (Id4 protein), appears also to show a negative effect in triple-negative apocrine carcinomas in contrast to the most non-apocrine triple-negative breast carcinomas (Roldán et al., 2006; Wen et al., 2012). Another negative regulator of DNA, named Id1 protein, also appears to be lower in apocrine carcinomas than in invasive ductal carcinomas (NST) (Jang et al., 2006).

Clinical characteristics of apocrine carcinoma

Clinical and radiological presentations of apocrine carcinoma do not differ from those seen in invasive ductal carcinomas (NST) (d'Amore et al., 1988; Gilles et al., 1994; O'Malley et al., 2011; Lakhani et al., 2012). Some studies however indicated a higher rate of apocrine carcinoma (and AR expression) in the elderly (Matsuo et al., 1998, 2002; Honma et al., 2003; Agoff et al., 2003).

Clinically, apocrine carcinomas usually present with palpable tumor mass, rarely with nipple bloody discharge or as a cyst (Gilles et al., 1994; Mardi et al., 2004; Lakhani et al., 2012). Apocrine carcinomas tend to be unilateral but are frequently multifocal/ multicentric (Takeuchi et al., 2004; Unal et al., 2007) although exceptional cases of bilateral apocrine carcinomas have been described (Schmitt et al., 1998; Wells and El-Ayat, 2007). Metastatic pattern appears to be similar to that seen in invasive ductal carcinoma (NST) although unusual cases with endometrial polyp metastasis have been described (Lambot et al., 2001).

A gene expression profiling study of Weigelt et al. indicates that "molecular apocrine" carcinomas exhibit prognostically poor gene signature with a high-risk recurrence score and a poor 70-gene prognosis signature (Weigelt et al., 2008). Apocrine carcinomas also tend to exhibit a high expression of chemokine receptor CXCR4 that plays an important role in tumor migration, invasiveness and metastasis (Salvucci et al., 2006).

Prognosis of patients with apocrine carcinoma remains largely unknown as the conducted studies recruited a small number of patients (Table 2) and have not used well-defined criteria for apocrine carcinoma.

Table 2. Overview of the most relevant clinical studies on apocrine carcinoma

Author (year)	Number of patients	Criteria for inclusion	Prognosis in comparison with IDC, NST
Frable and Kay (1968)	18	In situ and invasive carcinomas	Similar prognosis
D'Amore et al. (1988)	34	Invasive carcinoma	Similar prognosis
Aoyagi et al. (1990)	10	Invasive carcinomas	Better prognosis
Abati et al. (1990)	72	Both in situ and invasive carcinoma	Similar prognosis
Gilles et al. (1994)	17	Invasive carcinomas	Not given
Matsuo et al. (1998)*	12	In situ and invasive carcinomas*	Invasive carcinoma do worse
Takeuchi et al. (2004)	33	Invasive carcinomas	Similar prognosis
Japaze et al. (2005)	37	PAC	Better prognosis
Tanaka et al. (2008)	57	Invasive carcinomas	Similar prognosis
Iwase et al. (2010)	78	TN-apocrine carcinomas	Better prognosis than non-apocrine
Park et al. (2011)	49	MAC	Worse prognosis
Cha et al. (2012)	26	MAC	Similar prognosis
Nagao et al. (2012)	5	Invasive carcinomas	Good prognosis
Choi et al. (2012)	12	TN-apocrine carcinomas	Better that non-apocrine TNBC
Montagna et al. (2013)	29	TN apocrine carcinomas	Similar prognosis
Dellapasqua et al. (2013)*	72	Invasive carcinomas	Poor in PAC compared with ALC
Dreyer et al. (2013)	14	TN-apocrine carcinomas	Similar

IDC, NST: Invasive Ductal Carcinoma, no-special-type; PAC: Pure apocrine carcinomas; ALC: Apocrine-like carcinomas; MAC - Molecular apocrine carcinomas; TN - Triple-negative carcinomas; TNBC - Triple-negative breast carcinomas. * These studies focused only on apocrine carcinomas (in situ and invasive).

Consequently, the available prognostic data are contradictory (Table 2).

Some studies also indicated a poor response to chemotherapy in patients with apocrine carcinomas (Nagao et al., 2012), although HER-2/neu enriched breast carcinomas tend to have the highest rate of complete response to neoadjuvant chemotherapy (Matsubara et al., 2013). Recently, Iizuka et al. described a case of triple-negative apocrine carcinoma with a complete pathologic response to neoadjuvant chemotherapy (Iizuka et al., 2012).

Targeted therapy options for apocrine carcinoma: The role of personalized medicine

As a substantial proportion of apocrine carcinomas is HER-2/neu positive, these patients may benefit from anti-HER-2/neu therapy and anthracycline-based chemotherapy (Gennari et al, 2008; Fountzilas et al., 2012). *EGFR* and *HER-2/neu* play important roles in the pathogenesis of apocrine carcinoma and these findings may have significant therapeutic implications, as both tyrosine kinase receptors can be targeted by the appropriate drugs. EGFR status in breast cancer, as a predictor of the response to the EGFR-based targeted therapy is still not well established; however it is important to point out that apocrine carcinomas do not tend to harbor *KRAS* or *BRAF* gene mutations (Vranic et al., 2011c). In regards to HER-2/neu status, the single targeted therapy may not be effective and the treatment strategies are now shifting toward a dual anti-HER2 therapeutic approach (Konecny, 2012). Given that the deregulation of the PI3K/PTEN/Akt signaling pathway appears to play an important role in the development of trastuzumab and lapatinib resistance (Wang et al., 2011b; Chandarlapaty et al., 2012) and its importance in apocrine carcinomas (Maruyama et al., 2007; Banneau et al., 2010; Wang et al., 2011a), novel therapeutic strategies that bypass the potential resistance should be considered. Thus, a study of Naderi et al. showed that the trastuzumab resistance in apocrine carcinomas can be successfully overcome by the combined actions of AR and MEK inhibitors [MEK is a part of ERK signaling pathway] given that AR regulates ERK (MEK) phosphorylation via HER-2/neu in apocrine cell lines (Naderi and Liu, 2010; Naderi et al., 2011). On the other hand, a potential loss of PTEN function in apocrine tumor cells may increase their sensitivity to mTOR inhibitors (Steelman et al., 2008). A feedback loop has been demonstrated between AR and ERK where HER-2/neu is activated by AR, while CREB1 (a downstream target of ERK) regulates transcription of AR (Chia et al., 2011).

In addition, a consistent AR expression in apocrine carcinomas could also have a potential therapeutic impact. Experimental data from the cell lines indicate that triple-negative breast carcinomas with increased AR signaling (= "molecular apocrine tumors") may be sensitive to AR antagonists (e.g. bicalutamide) (Lehmann et al., 2011). There are also several ongoing and completed clinical trials with antiandrogen drugs aimed at treating metastatic and ER-negative breast cancers (available at: www.clinicaltrials.gov, visited: January 5, 2013), (McGhan et al., 2012). These trials should result in definitive guidance in regards to the effects of these drugs in treatment of AR-positive breast cancer (McGhan et al., 2012).

Conclusions

Apocrine carcinoma of the breast is a rare, special type of breast carcinoma showing distinct morphologic, immunophenotypic and molecular features. Apocrine carcinomas are characterized by the apocrine epithelium steroid receptor profile that is ER and PR negative and AR positive. The combination of morphologic and immunohistochemical criteria (steroid receptors) are essential for the proper identification of apocrine carcinomas. When these criteria are strictly applied, apocrine carcinomas express either Her-2/neu or EGFR, which along with AR positivity, make the apocrine carcinoma patients eligible for the targeted therapy. Clinical outcome of the patients with apocrine carcinoma is unclear and further clinical studies, based on more strict selection criteria, are warranted.

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