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Acinic Cell Carcinoma of the Breast (ACC): Morphological and Molecular Features of Rare Breast Cancer

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Abstract

Acinic Cell Carcinoma of the breast (ACC) is a very rare subtype of breast cancer, being of bland cellular morphology, but having a triple-negative phenotype. Usually, it was thought to be indolent, but a few cases have been reported highly aggressive. The molecular studies showed similar features in diagnosing to the Triple-Negative Breast Cancer (TNBC), which usually had the aggressive clinical course. This mini review comprehensively summarizes the recent literature on the molecular features of this rare breast cancer. We try to explain why some ACC have not the indolent course as we thought previously.

Keywords: Acinic Cell Carcinoma (ACC); Molecular features; Cytoplasm; Triple-Negative Breast Cancer (TNBC)

Introduction

Acinic Cell Carcinoma of the breast (ACC) is an exceedingly rare histological type of breast cancer, first described by Roncaroli [1]. To date, no more than 100 cases have been published in the literature [1,2]. Morphologically, ACC of the breast shares similarities with its salivary gland counterparts and have triple-negative phenotype [3]. In early case series, pure ACCs of the breast are thought to be low-grade carcinomas [4]. However, there have been cases reported with poor prognosis recently [5]. With the development of the molecular techniques, more and more studies show the similar feature between ACC and the TNBC [6,7] which may be the foundation of the ACC development and progressive. Here, we review its morphological and molecular pathological changes, with a particular focus on molecular changes, in order to help us better and more comprehensively understand the disease.

Literature Review

Histological features and its prognosis

Morphologically, ACC of the breast shares similarities with its salivary gland counterparts and have triple-negative phenotype [3]. ACC consists of serous differentiation cells containing zymogenic granules in the cytoplasm. These granules stain positive for Periodic Acid-Schiff (PAS) with diastase (PAS-D). ACC exhibits various growth patterns, with cells arranged in solid and/or micro-glandular growth patterns. The cells demonstrate diffuse serous differentiation with abundant eosinophilic to amphophilic cytoplasm and coarse or fine granules resembling Paneth cells. Additionally, the nuclei are always centrally located with prominent nucleoli [3]. Clear cells with a hypernephroid appearance or non-specific glandular cells may also be present in certain areas [3,6,8]. Atypia is usually seen in solid areas, and mitotic figures may be observed but are typically not marked.

Despite their triple-negative phenotype [3] pure ACCs of the breast are low-grade carcinomas that usually exhibit an indolent clinical behavior as reported in early case series [1,4]. The Ki-67 range is 5%-71% (most studies: 5%-30%) [3], which is consistent with the few mitoses observed on H&E slides and the intermediate clinical course of ACC [3]. Axillary lymph node metastasis appears to be a rare event in ACCs, although local recurrence has been reported [2]. However, there have been cases reported with poor prognosis [5]. Based on the available data, prognosis seems to be largely driven by the presence of poorly differentiated components in these tumors, which are associated with or progress to high-grade Triple-Negative Breast Cancer (TNBC) [6,9]. The tumor cells in the solid and nested infiltrative areas display the high-grade features of triple-negative breast carcinomas, whereas the well-differentiated acinar-like components show a lower mitotic rate and nuclear pleomorphism score [9]. In fact, one-third of reported cases of breast Acinic Cell Carcinoma (ACC) have been associated with the presence of a ductal carcinoma (referred to as mixed type), which is frequently poorly differentiated [9]. It seems that the prognosis is largely determined by the presence of the poorly differentiated component, although the exact prognosis is difficult to determine due to the rarity of this subtype.

Genomic features compared with its counterparts in the salivary

Different with breast ACCs, molecular features typical of salivary gland ACC, such as the recurrent genomic rearrangement (q13;q31), are generally absent in its mammary counterparts [7,10]. Piscuoglio, et al. conducted a comparative molecular study between breast carcinoma and salivary ACC, finding TP53 (80%) and PIK3CA (10%) mutations only in mammary ACC, while no somatic mutations were observed in these two genes in the twenty salivary ACC cases [7]. And consistent with the previous results, unlike most salivary ACC,

breast ACC always lacks NR4A3 rearrangement or overexpression [11]. The above research results have led to the authors to conclude that from a molecular pathology perspective, breast ACCs have more similarities with triple negative breast cancer than salivary ACCs.

Genomic features compared with microglandular adenosis

Genomic features of ACCs of the breast have been revealed that they are genetically heterogeneous and exhibited genomic characteristics that overlap not only with microglandular adenosis (MGA) in terms of histological characteristics and genomic features but also with TNBC [6,10,12]. A comparative study by Geyer et al. explored the molecular genomic features of ACC and microglandular adenosis of the breast, revealing similar genomic alterations in both lesions, including TP53, BRCA1, PIK3CA, and INPP4B [10]. However, the association between ACC and microglandular adenosis, which was thought as a precursor lesion of ACC, remains controversial [10,13,14]. Rosen questioned the existence of ACC as a distinct entity and instead favors the term "invasive carcinoma with acinic cell differentiation arising in microglandular adenosis" [13]. Conversely, Geyer et al. have presented molecular evidence supporting the notion that microglandular adenosis and ACC represent the low-grade spectrum of TNBC lesions with an indolent clinical course and share some molecular features, such as TP53 mutations and common copy number alterations (including gains of 1q, 2q, 7p, and 8q and losses of 3p, 5q, 6q, 14q, 17p and 17q) [10,14]. It is worth noting that both ACC and microglandular adenosis exhibit a similar immunophenotype, including S-100 expression [15]. In practice, distinguishing between ACC with a predominant microglandular growth pattern and microglandular adenosis can pose a big challenge [16].

Genomic features compared with TNBC

Due to its rarity, limited information is available on the molecular genomic features of ACC. But there are some key insights to consider. Primarily, no pathognomonic genomic alterations have been described in breast ACC. Molecular studies have shown that mammary ACC shares a similar molecular profile with TNBC [7,10]. The most consistent molecular event in ACC appears to be TP53 mutations, while other genetic alterations, such as PIK3CA mutations, have also been observed in a subset of cases [6,7,10]. Additionally, some breast ACC cases exhibit alterations in the BRCA1 gene, including mutations and gene deletions [6,10,17,18]. In a study by Beca, et al. whole-exome and RNA sequencing of three ACC cases revealed mutations in genes related to homologous recombination and DNA repair in two cases, and a pathogenic MLH1 germline mutation in the third case [18]. Guerini-Rocco, et al. studied eight cases (two pure ACC and six mixed) using massively parallel sequencing and identified identical genomic alterations in both pure ACC and mixed cases which including TP53, PIK3CA, MTOR, CTNNB1, BRCA1, ERBB4, ERBB3, INPP4B and FGFR2 [6]. These lesions exhibited a repertoire of somatic mutations comparable to TNBC, along with complex gene copy changes such as gains and losses of specific chromosomal regions [10]. Recently, a case of breast ACC with clear cytoplasm and high-grade morphology was reported, and molecular analysis revealed point mutations, small fragment insertions or deletions affecting genes including TP53, PRKAA1, FAS, ARID2, MET, FLT3, TP63 and PIK3CG. TP53 mutation frequency was found to be 19.9% and a pathogenic heterozygous germline variant of BRCA1 was detected [8].

Discussion

Overall, BRCA1 and TP53 gene mutations are frequently observed in ACC. The pathological features of breast cancers in BRCA1 mutation carriers usually associated with high-grade invasive ductal carcinoma, not otherwise specified, or medullary-type cancers, which do not align with the typically low-grade characteristics of ACC. This suggests that breast ACC may exhibit a diverse range of characteristics. Among the 26 reported cases of ACC with molecular testing, BRCA1 mutations (germline or somatic) were identified in 6 cases, including three cases with germline mutations. In two cases, metachronous carcinomas occurred in the breast and the histological type of the primary breast tumor on one side was invasive ductal carcinoma, not otherwise specified. It is worth noting that BRCA1 mutation carriers frequently exhibit TP53 gene mutations [19]. As mentioned earlier, TP53 was the most commonly mutated gene in ACC, present in 21 out of 26 cases (81%) [20]. In a study by Piscuoglio, TP53 mutations were detected in 8 out of 10 (80%) breast ACC cases. In The Cancer Genome Atlas breast carcinoma study, TP53 mutations were found in 37% of all breast carcinomas tested, making it the most common mutation in breast cancer [21]. Supporting these findings, Guerini-Rocco performed massively parallel sequencing analysis on the same cohort of breast ACCs as Piscuoglio and demonstrated a pattern of complex copy number aberrations that resembled those observed in TNBC. Beca, et al. further supported the association between breast ACC and Homologous Recombination Deficiency (HRD) through BRCA1 inactivation.

Conclusion

In conclusion, breast ACCs, despite being thought to be low grade and exhibiting indolent clinical behavior, demonstrate similar genetic alterations commonly associated with high-grade TNBC. These alterations include complex patterns of gene copy number alterations and recurrent TP53, BRCA1 mutations. This genetic evidence may explain why ACCs sometimes showed an aggressive form of high-grade TNBC. Loss-of-function alterations affecting BRCA1, along with TP53 somatic mutations, appear to be common in breast ACCs, even in cases lacking a high-grade TNBC component. However, this combination may not be sufficient to lead TNBC to high-grade TNBC. Further studies on the molecular aspects of these rare tumors with their relationship with histological characteristics are still warranted.

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