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High grade acinic cell carcinoma of the breast with clear cytoplasm mimics clear cell carcinoma in a BRCA1 mutation carrier: a case report and review of the literature on the molecular analysis

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Summary. Acinic cell carcinoma of the breast is an extremely rare tumor. To the best of our knowledge, only one case is reported to have bilateral tumors and had both BRCA1 and TP53 mutation. Herein, we report another case of acinic cell carcinoma of the breast in a 29-years-old female carrying germline BRCA1 and TP53 mutation, and the tumor showed a complex combination of histological features which had not only the reported common features such as diffuse infiltrative small acinar or glandular structures mixed with solid nests, but also the uncommon widespread clear cells, high grade tumor cells. The immunohistochemical profile of the tumor cells was strongly positive for lysozyme and triple negative for ER, PR, HER2. Although she had bilateral high grade breast cancers, this patient refused postoperative adjuvant therapy this time and has been doing well in the past 12 months. As a rare form of triple-negative breast cancer with a relatively not so bad prognosis, more reports are needed to understand its biological characteristics.

Key words: Acinic cell carcinoma of breast, Clear cell carcinoma, BRCA1 mutation

Introduction

Acinic cell carcinoma (ACC) is a rare subtype of malignant epithelial neoplasms of breast characterized by obvious serous acinar cell differentiation with zymogen-type cytoplasmic granules and immunohistochemical expression of amylase, lysozyme and alpha-1 anti-chymotrypsin, similar to those seen in salivary glands (Kravtsov and Jorns, 2020). The first case in breast was reported by Roncaroli et al. (1996) and is now classified as an exceptionally rare and salivary gland-type breast carcinoma entity (WHO Classification of Tumours Editorial Board, 2019).

Although ACC of the breast is similar to its salivary gland counterpart in the morphological, immunohistochemical and ultrastructural aspects (Damiani et al., 2000; Limite et al., 2014), some morphological features that have been reported frequently in ACC of parotid gland are not usually seen in the breast counterpart, including pushing borders, prominent intratumoral lymphoid infiltrate and variegated architectural growth patterns with solid and cystic areas. In fact, the secretory granules in breast and salivary gland ACCs are distinct: in the former, pink, eosinophilic granules are common, in the latter, the granules are predominantly basophilic. The molecular analysis of breast acinic cell carcinoma showed a DNA copy-number and mutation landscape similar to that of triple-negative breast carcinomas (TNBC) of conventional histology, but others had similar characteristics to micro glandular adenosis (Guerini-Rocco et al., 2015; Piscuoglio et al., 2015; Geyer et al., 2017). On the other hand, the mutation profiles of breast acinic cell carcinomas differed greatly from those of acinic cell carcinomas of the salivary gland-like tumors of the breast (Piscuoglio et al., 2015).

Herein, we present a case of acinic cell carcinoma of the breast in a 29-year-old female patient with BRCA1 and TP53 mutation and a family history of breast cancer, clear cell morphology with high-grade cells and microglandular adenosis area. We also reviewed the reports concerning this rare entity which had the molecular test results.

Materials and methods

One case of breast ACC was identified from the

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Immunohistochemistry was undertaken as part of the diagnostic workup in the case, and the antibodies and dilutions used are summarized in Table 1. The case underwent molecular analysis using her tumor tissues and peripheral blood samples tested for exons captured sequencing (all exons captured for 170 genes and partial exons captured for 851 genes which related to tumor genesis and development. More details are in S1) based on second-generation sequencing technology. Somatic mutations, copy number alterations, mutational signatures and fusion genes were determined using state-of-the-art bioinformatics methods. Also we reviewed the reports concerning this rare entity which had the molecular test results in the English language literature to date.

Results

A 26-year old woman presented with a left breast mass. The core biopsy of the tumor in the left breast was invasive breast carcinoma of no special type, grade 2 and immunohistochemistry showed faint staining positive for estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2) protein were negative, Ki-67 index 67%; epidermal growth factor receptor (EGFR) and GATA binding protein 3 (GATA3), TP53 were all strongly positive (Fig. 1A-F). The core biopsy of left axillary lymph node showed cancer metastasis. The patient had neoadjuvant chemotherapy and subsequent total mastectomy. The final pathological report was ypT0N0. Her mother died of breast cancer at the age of about 40, and the mother's younger sister and her grand-mother were still alive and well.

The patient had been accepting regular physical examination on the diseased side, then three and half years after surgery, the patient presented with a contralateral breast mass, which was a palpable, hard, immobile, irregular mass in the lower outer quadrant of the right breast, approximately 4.0 cm in diameter. No skin retraction or nipple discharge was noticed. Ultrasonography showed a heterogeneous hypoechoic/anechoiccystic and solid nodule with an ill-defined border. Enhanced magnetic resonance imaging (MRI) revealed an irregular lesion of high intensity. Both the ultrasound and MRI classified it as BIRAD-S IV-b. Core needle biopsy of the lesion revealed the tumor cells to be solid, glandular, clear cytoplasm. The tumor cells of the ductal carcinoma in situ (DCIS) also had clear cytoplasm. Invasive carcinoma with clear cytoplasm was diagnosed. Further thorough examinations, including computed tomography of the thorax and abdomenand bone scintigraphy, showed no signs of metastatic lesions. Laboratory examination, including cancer antigen 72-4 (CA72-4), CA242, CA15-3, Carcinoembryonic Antigen (CEA), CA125, CA19-9, Alpha fetoprotein (AFP) and Prolactin were all within normal ranges.

Her mass in the right breast was diagnosed as cT2N0M0, stage IIA. She underwent modified radical mastectomy. The intraoperative sentinel lymph nodes were negative. Two sentinel lymph nodes in the ipsilateral axilla were examined; with a maximum diameter of 1.5cm and 0.3 cm. Frozen sections and serial sections of paraffin embedded blocks were applied. Macroscopically, a friable white-yellow-colored cystic and solid lesion measuring 4.2×3.0×2.0cm was found, ill-defined and obvious dilated ducts were seen, which was finally diagnosed as $pT2N0_{sn}$ Mx. Histologically, patterns of the arrangement of tumor cells included the presence of solid, cribriform, micropapillary, papillary, and microglandular. Most of the cells (80%) had clear cytoplasm, well to moderately differentiated cells with round or oval nuclei, and hyaline balls in the center (Fig. 2A). It was also noticed that some cells with lightly eosinophilic bubbly cytoplasm contained large, coarse, and bright red zymogene granules in the cytoplasm (Fig. 2B). DCIS with or without necrosis were around or in the invasive area. Most of the tumor cells were grade 2, however, there were small areas corresponding to the

Table 1. Immunohistochemical antibodies used.

Antibody	Clone	Vendor	Working dilution
ER	SP1 (Rabbit)	Ventana	RTU
PR	1E2 (Rabbit)	Ventana	RTU
HER2	4B5(Rabbit)	Ventana	RTU
Ki-67	UMAB107 (Mouse)	Sino Biological	RTU
EGFR	UMAB95 (Mouse)	Sino Biological	RTU
TP53	DO-7 (Mouse)	Sino Biological	RTU
Amylase	OTI6D4 (Mouse)	Origene	1:50
Lysozyme	polyclonal (Rabbit)	Sino Biological	RTU
α1-ACT	polyclonal (Rabbit)	Sino Biological	RTU
EMA	UMAB57 (Mouse)	Sino Biological	RTU
S100	15E2E2+4C4.9 (Mouse)	Sino Biological	RTU
SOX10	EP268 (Rabbit)	Sino Biological	RTU
CD117	YR145 (Mouse)	Sino Biological	RTU
CK8/18	B22.1&B23.1 (Mouse)	Sino Biological	RTU
E-cadherin	UMAB184 (Mouse)	Sino Biological	RTU
SMA	UMAB237 (Mouse)	Sino Biological	RTU
p63	4A4+UMAB4 (Mouse)	Sino Biological	RTU
CK5/6	OTI1C7 (Mouse)	Sino Biological	RTU
AR	EP120 (Rabbit)	Sino Biological	RTU
GCDFP-15	EP95 (Rabbit)	Sino Biological	RTU
GATA-3	EP368 (Rabbit)	Sino Biological	RTU
Mammaglobin	304-1A5 (Mouse)	Sino Biological	RTU
PAX8	OTI6H8 (Mouse)	Sino Biological	RTU
PLAP	EP194(Rabbit)	Sino Biological	RTU
SALL4	6E3 (Mouse)	Sino Biological	RTU
HNF1β	polyclonal (Rabbit)	Sino Biological	RTU
CK20	EP23 (Rabbit)	Sino Biological	RTU
Synaptophysin	UMAB112 (Mouse)	Sino Biological	RTU
Chromogranin	LK2H10 (Mouse)	Sino Biological	RTU

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; α1-ACT,α-1-antichymotrypsin;EMA, epithelial membrane antigen; SOX10, SRY-Box transcription factor 10; SMA, smooth muscle actin; AR, androgenreceptor; GCDFP-15, gross cystic disease fluid protein 15; GATA3, GATA binding protein 3; PAX8, paired box gene 8; PLAP, Placental-like alkaline phosphatase; SALL4, Spalt-like transcription factor 4; HNF1β, hepatocyte nuclear factor 1β; RTU, ready to use.

dedifferentiation region (solid areas, grade 3, mitotic activity 20 mitosis /10HPF) (Fig. 2C). A small area of microglandular adenosis was also noted at the periphery of the tumor (Fig. 2D).

With immunohistochemistry most of the tumor cells stained strongly for amylase, lysozyme, α-1-antichymotrypsin (α1-ACT) (Fig. 2E), epithelial membrane antigen (EMA), S-100 (Fig. 2F) and EGFR protein, SRY-Box transcription factor 10 (SOX10), CD117, cytokeratin (CK) 8/18 and membrane E-cadherin. Smooth muscle actin (SMA), P63, CK5/6, ER, HER2, and androgen receptor (AR) were all negative, but PR stained faintly positive in 15% cells. The Ki-67 index in the hot spots was 40%. GCDFP-15 was partially positive, but GATA-3 negative. TP53 had null expression. Mammaglobin, paired box gene 8 (PAX8), Placental-like alkaline phosphatase (PLAP), Spalt-like transcription factor 4 (SALL4), hepatocyte nuclear factor 1β (HNF1β), CK20, Chromogranin A (CgA) and synaptophysin (Syn) were negative. Considering all the morphology and immunohistochemistry results, we diagnosed the tumor as breast ACC. The histological features of the heterochrony nodules in bilateral breast are compared in Table 2.

Molecular analysis of exons captured sequencing based on the second-generation sequencing technology revealed that point mutations, small fragment insertions, or deletions affected genes including TP53, PRKAA1, FAS, ARID2, MET, FLT3, TP63 and PIK3CG. TP53 mutation frequency was 19.9% and *BRCA1* pathogenic heterozygosity germline variant was found. Copy number analysis revealed the focal amplification of *MYC* and *RECQL4*. No fusion gene was identified in this patient including *ETV6-NTRK3*.

The patient refused any adjuvant treatment after 2nd surgery. She is disease-free up to 12 months after her last operation.

Discussion

Despite a relatively small number of reported breast ACC, the genomic features of them had been studied thoroughly. It was found that breast ACC not only overlap with MGA in both the histologic characteristics and genomic features, but also overlap with TNBC (Guerini-Rocco et al., 2015; Tsang and Tse, 2016; Geyer et al., 2017). ACC mainly occurred in salivary glands, but also could be occasionally observed in other organs. Breast ACC was first described in 1996 by Roncaroli et al. (1996). Morphologically, breast ACC resembled the

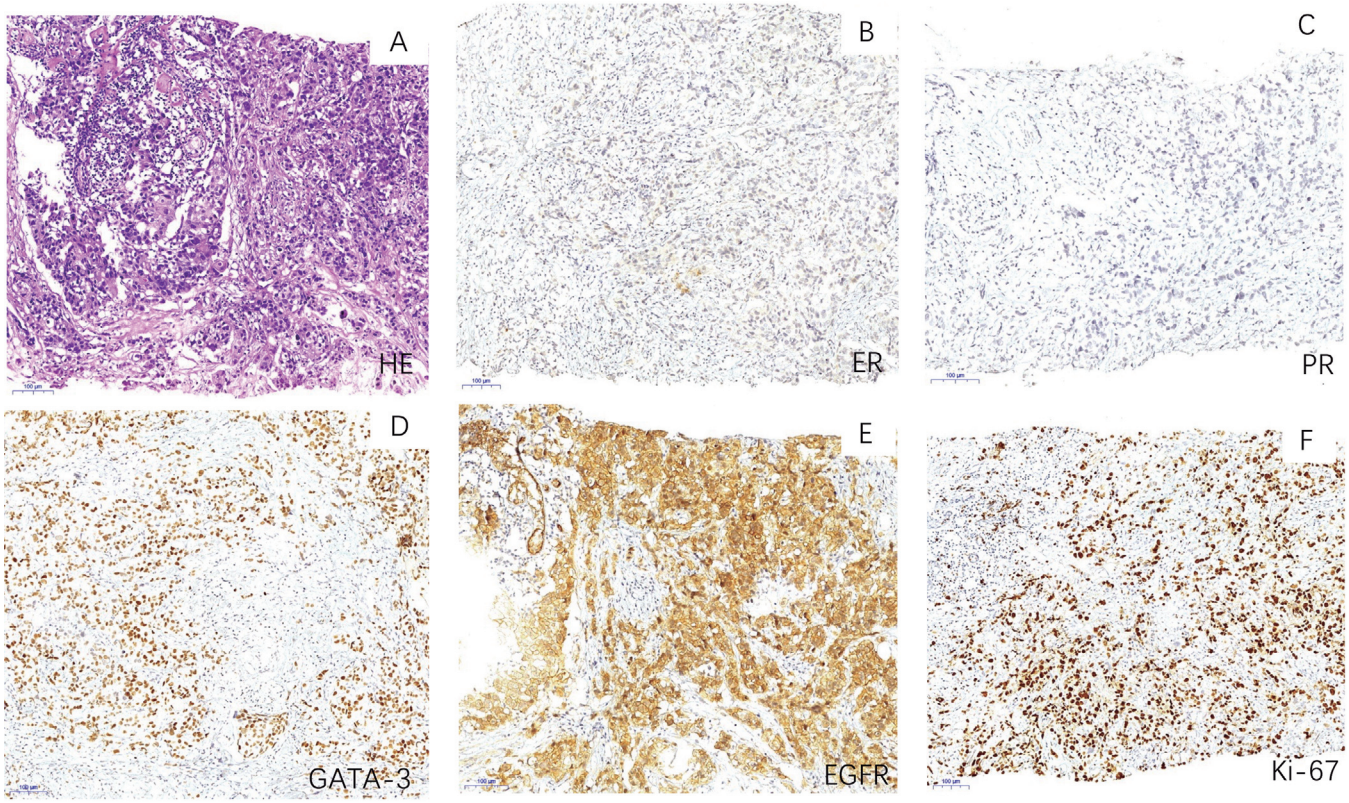

Fig. 1. A. Patterns of the tumor cells in the left breast mass were arranged in solid and diagnosed as invasive breast carcinoma of no special type, grade2. **B-F.** Immunohistochemistry showed faint positive staining for estrogen receptors (ER), negative staining for progesterone receptors (PR) and positive for GATA-3 and EGFR, Ki-67 index was high (67%). x 20.

counterparts in salivary glands which have two distinct patterns of growth: the first is the tumor cells being poorly circumscribed, infiltrating in solid or nest pattern, often with focal necrosis; the second is the polygonal or round, containing coarse brightly eosinophilic granules in the amphophilic cytoplasm tumor cells forming acinar, tubular, microglandular or microcystic structures (Chang et al., 2011; Beca et al., 2019). At present, it is generally accepted that microglandular adenosis and acinic cell carcinoma are part of the same spectrum of lesions and represent low-grade forms of triple-negative disease with no or minimal metastatic potential (Geyer et al., 2017). But occasionally, it was seen that a small subset could progress to high-grade triple-negative breast cancer. Areas composed of clear cells with hypernephroid appearance were also reported, which means breast ACC could have a wide morphologic spectrum of appearances (Conlon et al., 2016). Uniquely in our present case was the vast area of the striking clear tumor cells arranging in solid, cystic, tubular, papillary structures which led us to think it was a clear cell carcinoma of the ovary counterpart at first glance. Also,

Table 2. Comparing the heterochrony nodules histological features in bilateral breast.

Side	Histological Subtype	Gross morphology (pattern)	Arrangement of the tumor cells	Peripheral of the tumor	ER	PR	HER-2	Ki-67	TP53	GATA-3	Axillary lymph node (ipsilateral)
Left	invasive carcinoma of no special type, Grade 2	6cm (solid)	glands and acini	unknown	faint staining	negative	0	67%	strong positive	positive	+
Right	breast ACC, Grade 2&3	4cm (solid and cystic)	solid, cribriform, micropapillary, papillary, and microglandular with clear cytoplasm	DCIS with clear cytoplasm, including a small area of microglandular adenosis	negative	15% weakly positive	0	40%	null expression	negative	-

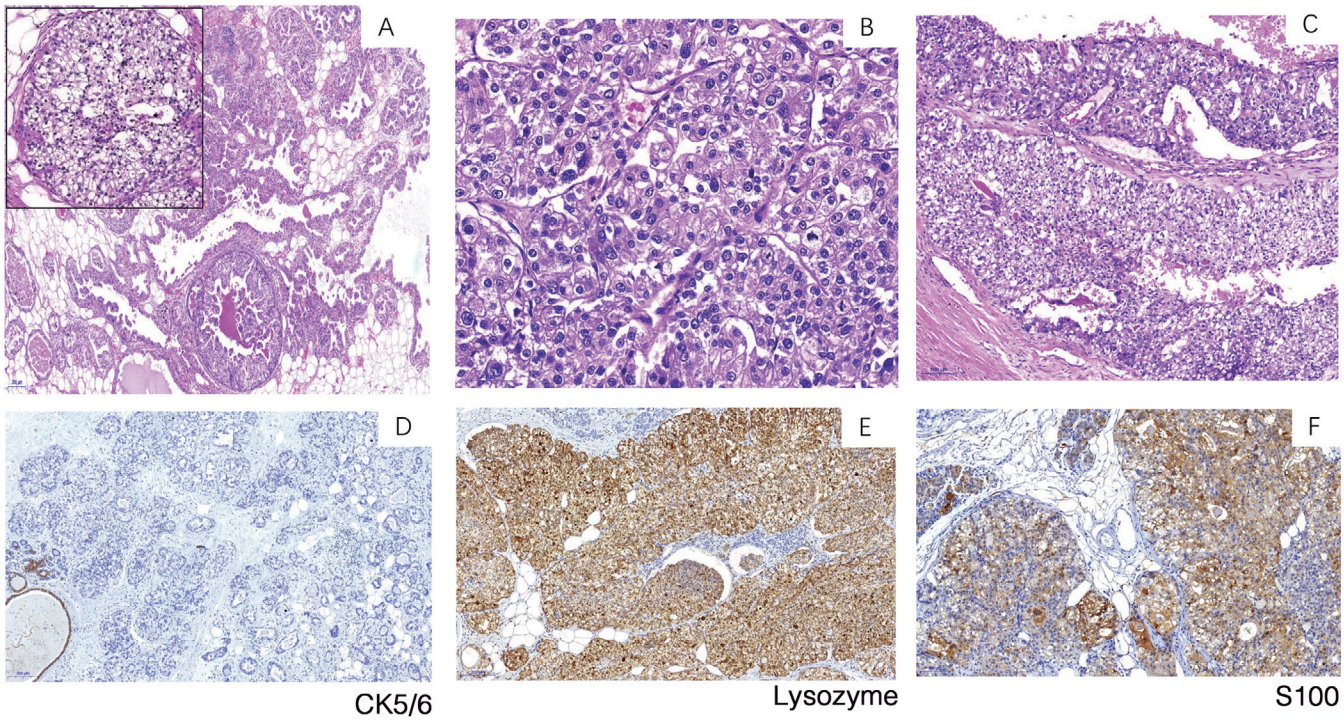

Fig. 2. A. Patterns of the tumor cells in the right breast mass were arranged in solid, cribriform, micropapillary, papillary, and microglandular. Most of the cells (80%) had clear cytoplasm, well to moderately differentiated cells with round or oval nuclei, and hyaline balls in the center; the Insertion Fig. show clear cytoplasm of the tumor cells. **B.** Some cells with lightly eosinophilic zymogen granules in the cytoplasm. **C.** The high-grade dedifferentiation region with brisk mitotic activity (showing transition of conventional ACC and high-grade dedifferentiation area). **D.** Microglandular adenosis was also noted at the periphery of the tumor (CK5/6 staining). **E.** Tumor cells stained strongly positove for lysozyme. **F.** Tumor cells stained strongly positive for S-100 staining. A, D, x 10; insertion in A, B, x 40; C, E, F, x 20.

there was a small area of typical micro-glandular adenosis at the periphery of the tumor in our case, but it was also found that small part of the tumor had high grade morphology with brisk mitosis and obvious atypical tumor cells. In fact, the morphological diversity of ACC suggests that a considerable number of ACC might have been overlooked (Choh et al., 2012). It was advocated that microglandular adenosis-like areas at the periphery of a breast acinic cell carcinoma should be considered part of the carcinomatous process (Conlon et al., 2016).

Immunohistochemically, most of the breast ACC cells displayed the characteristic triple-negative phenotype, expression of S100-protein, epithelial membrane antigen (EMA) and serous differentiation markers, including amylase, lysozyme and alpha 1-antichymotrypsin (Limite et al., 2014). TP53 revealed null expression in the cases harboring a p53 missense mutation, GATA3 was almost negative (Matoso et al., 2009). These features could be seen in our present case similar to the former reported paper, with the exception that PR was faintly expressed in 15% tumor cells in our case, though ER was negtive.

Approximately 10% of breast cancers have hereditary predisposition, among them nearly 20-30% are linked to germline mutations in BRCA1 and/or BRCA2 genes. The mutation carriers face a lifetime risk to develop breast or ovary cancer ranging from 57% to 65%, as well as prediction of contralateral breast cancer (Chen and Parmigiani, 2007; Mavaddat et al., 2013). BRCA1 mutation carriers frequently have mutations of the TP53 gene (Roncaroli et al., 1996; Chen and Parmigiani, 2007). In BRCA1 mutation carriers, the pathological features of breast cancers are usually high grade invasive ductal cancer, not otherwise specified or with high proliferative index medullary type. They are also commonly triple negative (ER, PR, HER2 being negative). These features could all be seen in our present case which had P53 mutation, BRCA1 germline mutation and part high-grade differentiation. But these morphological features did not match the usually low grade ACC which means breast ACC perhaps has a diverse range of characteristics.

Breast ACC that occurred in a BRCA1 mutation carrier was first described by Ripamonti et al in 2013 year (Ripamonti et al., 2013). At present, among the 21 reported ACC with molecular tests (including our case) (Table 3), we found BRCA1 mutation (germline or somatic) occurred in 6/21 patients, and with three germline mutations (including Ripamonti's case and our present case), two cases were metachronous carcinomas in breast, in which the histological type of primary breast tumor on one side was invasive ductal carcinoma, with no special type. So it seemed that the germline mutation of BCRA1 had a potential role in causing bilateral malignant breast tumors, including ACCs. This observation was consistent with what Shen et al. (2014) observed in the salivary gland cancers in BRCA1 mutation-positive family members, they found out incidence rate of head and neck cancers was much higher in persons with the germline mutation of BCRA1 than the background incidence rate (0.052% vs. 0.003% per year).

TP53 was the most commonly mutated gene in

Table 3. Mutations detected by sequencing in reported ACC cases.

Number of cases	Bilateral	Grade	Family history	Methods of gene tests	BRCA1	TP53	other mutations	Ref.
1	YES	NA	YES*	LOH and sequencing	constitutional mutation; somatic loss of the wild-type allele	c.654_655insGTG mutation	Not available	Ripamonti et al., 2013
2 pure and 6 mixed	NA	G1-2	NA	sequencing	1 somatic mutation; 1 germline mutation	7/8Mutations (one pure and six mixed cases)	PIK3CA, MTOR, CTNNB1, ERBB4, ERBB3, INPP4B and FGFR2	Guerini-Rocco et al., 2015
2 pure and 6 mixed	NA	G1-2	NA	sequencing	1 somatic mutation (E1419* coupled with loss of heterozygosity)	7/8Mutations	somatic mutations, ERBB4 (2/8; G6V and c.2203-1G-T) FGFR2 (S252W), ERBB3 (R667S), INPP4B (N223Y) and PIK3CA (E542Q) genes; an amplicon spanning MYC, SLA and COL14A1(1/8)	Geyer et al., 2017
3 (1 reported in 2015)	NA	NA	NA	sequencing	1 somatic homozygous deletion	2/3hotspot mutations	DNA repair-related genes (2/3), MLH1 pathogenic germline variant (1/3), focal amplification of 12q14.3–12q21.1 (encompassing MDM2, HMGA2, FRS2 and PTPRB)	Beca et al., 2019
1	NO	G3	NA	sequencing	NO germline/somatic mutation	mutation (c.747G>T)	RET (c.2899G>A)	Weaver et al., 2021
Our case	YES	G3	Yes**	sequencing	heterozygosis germline mutation (p.R1751*)	mutation (c.323_329dupGTTCCG)	PRKAA1, FAS, ARID2, MET, FLT3, TP63, PIK3CG;focal amplification of MYC and RECQL4	Our case

*Mother (ovarian cancer), maternal aunt (breast cancer and ovarian cancer); **Mother (breast cancer). NA, Not Available; LOH, loss of heterozygosity; H&E, hematoxylin and eosin stain.

ACCs, being present in 19/21 cases (Ripamonti et al., 2013; Guerini-Rocco et al., 2015; Geyer et al., 2017; Beca et al., 2019; Sarsiat et al., 2022). Conditional mouse models of BRCA1 and TP53 have been shown to result in the development of rather heterogeneous tumors with the majority of lesions being of histologically high grade TNBCs (Liu et al., 2007; Molyneux et al., 2010; Ripamonti et al., 2013). Beca et al. (2019) also thought the loss of function of BRCA1 and TP53 may not be sufficient to lead TNBC to high-grade TNBC since in their studies all the ACC were low grade and had indolent behavior. They speculated the MLH1 germline mutations may have relationship with breast ACCs (Beca et al., 2019), but our study and other studies did not find any MLH1 gene mutation. Some other reports showed that CTNNB1 N387K and K335T mutation may trigger the potential progression mechanism (Guerini-Rocco et al., 2015). Though our case did not display CTNNB1 mutation, we found some other mutations which include PRKAA1, FAS, ARID2, MET, FLT3, TP63, PIK3CG besides TP53 and BRCA1, which may exert a role in tumor dedifferentiation. More studies on the molecular aspect of these rare tumors are still warranted.

The differential diagnosis includes glycogen-rich clear cell carcinoma (GRCCC), lipid-rich carcinoma, secretory carcinoma, clear cell myoepithelial carcinoma or carcinoma in situ. In this case, there were eosinophilic granules in the cytoplasm of tumor cells, which were positive of lysozyme and alpha1-antichymotrypsin by immunohistochemical staining and were not completely transparent, so GRCCC was excluded. Also, as we did not find the solid tumor nest surrounded by glassy basement membrane like material and immunohistochemical staining results did not show positive of myoepithelial markers, so clear cell myoepithelial carcinoma were not be considered. Furthermore, Molecular analysis results did not find the ETV6-NTRK3 translocation in tumor, secretary carcinoma was excluded too.

Most acinar cell carcinoma had a favorable outcome based on early case series (Choh et al., 2012; Shingu et al., 2013; Limite et al., 2014), but there were cases with poor prognosis (Chang et al., 2011; Sarsiat et al., 2022) and usually related to the presence of a poorly differentiated invasive component. In fact, one-third of reported cases of breast acinic cell carcinoma have been associated with the presence of a ductal carcinoma (not the acinar cell carcinoma component), and which is frequently poorly differentiated (Conlon et al., 2016) as showing in our case. But the exact prognosis was hard to know because of the rarity of this subtype. The patient in our case rejected the adjuvant therapies including the chemotherapy and had an uneventful process during the past 12 months.

Our study had several limitations. First, we did not compare the microgladular adenosis with the clear tumor cell area and the high-grade area; we could not know the relation or disparities among these cells. Second, we did not have a comparative sequencing of her previous tumor, and could not know the difference between the two tumors in her bilateral breast. However, it was the second germline BRCA1 mutation patient with ACC of the breast in our case and it was the first one which had obvious clear cell differentiation and high-grade tumor cell area, neither was usual feature observed in the other reported ACC cases. We are sure our case would consummate useful information about this rare entity in its histology, molecular changes and prognosis.

In general, our case showed some similar genomic profiles (like the BRCA1 and TP53 mutations) as reported ACCs in breas in the literature, but also our case had some unique features including very young age, bilateral tumors, relatively favorable prognosis despite the high grade tumor morphology and rejecting the adjuvant treatment. Further studies are warranted to elucidate the true face of ACCs in breast.

Ethical approval. This study was approved by Beijing Hospital of Traditional Chinese Medicine, Capital Medical University. A written consent was obtained from the patient.

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