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CASE REPORT

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A new subtype of papillary ductal carcinoma in situ with tall cell and reversed polarity morphology: a rare case report

Ruiqi Zhong[1†], Ziyi Chang[2†], Xiuhong Wang[2*] and Dingrong Zhong[2*]

Abstract

Background According to previous studies, tall cell carcinoma with reversed polarity can be easily distinguished from ductal carcinoma in situ based on the absence of myoepithelium and a typical histologic feature. However, to the best of our knowledge, no cases of papillary ductal carcinoma exhibiting tall cell and reversed polarity features with intact myoepithelium have been reported, and thus its diagnosis and prognosis remain unclear.

Case presentation A 54-year-old female with a palpable lump in her right breast for 3 years. There were no other symptoms found. A preoperative ultrasound examination showed an oval, well-circumscribed, anechoic cystic appearance with hypoechoic adnexal nodules, classified as 3-4a in the Breast Imaging Reporting Data System. Surgical excision revealed an in-situ breast carcinoma exhibiting a solid papillary pattern and tall cell with reversed polarity of nuclei. After thorough postoperative pathology, immunohistochemistry, and next-generation sequencing, we hypothesized that it might be a new ductal carcinoma in situ subtype with tall cells and reversed polarity of the mammary gland.

Conclusions We herein present a rare case of papillary ductal carcinoma in situ with tall cell and reversed polarity morphology breast cancer, which can closely mimic tall cell carcinoma with reversed polarity and ductal carcinoma in situ. Thorough evaluations of histologic features, immunohistochemistry results, and genetic alterations are significant in identifying this rare entity. In addition, this type of breast cancer is low-malignant and has a favorable prognosis without any adjuvant therapy after complete resection.

Keywords Tall cell carcinoma with reversed polarity, Papillary ductal carcinoma in situ, Breast cancer, Triple-negative phenotype, Case report

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Background

Tall cell carcinoma with reversed polarity (TCCRP) is a rare subtype of breast cancer with a low degree of malignancy. In 2016, Chiang et al. found that TCCRP is morphologically characterized by solid, circumscribed nodules of columnar epithelial cells, papillary architecture, and polarity-reversed nuclei. Immunohistochemically, TCCRP lacks myoepithelium and highly expresses CK5/6. In terms of genetic landscape, *IDH2 R172* and *PIK3CA p. H1047R* are the hotspot mutations [1]. On the basis of the features mentioned above, this rare tumor was included in "Rare and Salivary Gland Type Tumors" in the 5th edition WHO classification of breast tumors [2]. To date, there are only about 80 TCCRP cases reported in the literature. Almost all of them were invasive carcinomas (lack of myoepithelial expression). Histological examination, immunohistochemical and molecular studies help to distinguish TCCRP from other types of breast neoplasm. Papillary ductal carcinoma in situ is a subtype of ductal carcinoma in situ (DCIS) characterized by the neoplastic proliferation of epithelial cells with a papillary structure and confined to the mammary ductal-lobular system, having intact myoepithelial. It has been previously noted that TCCRP can be distinguished from DCIS based on the characteristic tall columnar cells with nuclei at the apical poles of the cells and the absence of myoepithelium [3]. Here, we report a rare and unusual case of papillary ductal carcinoma in situ whose tumor had a morphology partially consistent with TCCRP, a frameshift mutation of *PIK3R1*, but had an intact myoepithelium. We identified this tumor as a novel subtype of DCIS.

Case presentation

A 54-year-old female came to our hospital in August 2021 with a palpable mass in her right breast for 3 years. The patient underwent a total hysterectomy and adnexal resection for high-grade serous carcinoma of the left ovary in 2018, after which she underwent paclitaxel 270 mg IV+cisplatin 90 mg intraperitoneal chemotherapy ×6 times. And there was no other medical history of breast disease. On clinical examination, a hard regular lump with clear margin in the upper outer quadrant of the right breast, mearsuring 3–4 cm in size was palpated. The ultrasonographic screening revealed an ovoid, well-circumscribed, anechoic cystic appearance with hypoechoic adnexal nodules (Fig. 1A), classified as 3-4a in the Breast Imaging Reporting Data System (BI-RADS), indicating there is a 2–10% chance of malignant for the lesion. However, in recent years, the size of the lump has progressively increased, expandind from 0.9*0.5 cm in June 2018 to 3.8*2.5 cm in August 2021. The patient soon underwent radical mastectomy and sentinel lymph node biopsy for right breast cancer. The resection margins were clear and the sentinel lymph node was negative for metastasis. The intraoperative frozen section showed a piece of breast tissue measuring 4.3*1.2 cm with a visible cystic cavity and a solid nodal inside. The surface area of the cyst wall measured 4.5*2 cm, with a thickness ranging from 0.1 to 0.3 cm. Additionally, the inner wall of the cyst was rough with papillary projections (Fig. 1B).

Histologic examination revealed the neoplasm characterized by papillary architecture consisting a proliferation of epithelial cells surrounding fibrovascular cores in both cystic and solid areas (Fig. 2A-D). Further examination showed that neoplastic epithelial cells were tall columnar in shape with abundant eosinophilic cytoplasm, and the nuclei displayed a distinct "reversed polarity" appearance. However, the identification of columnar cells and nuclei was partially hindered by the presence of intact myoepithelium along the periphery of the fibrovascular axis. Serial 4 μm-thick sections were stained with hematoxylin-eosin staining (H&E) and P63 immunostaining to reevaluate histological features. Combining the two staining methods, we found that P63-negative tumor cells were tall columnar with nuclei oriented away from

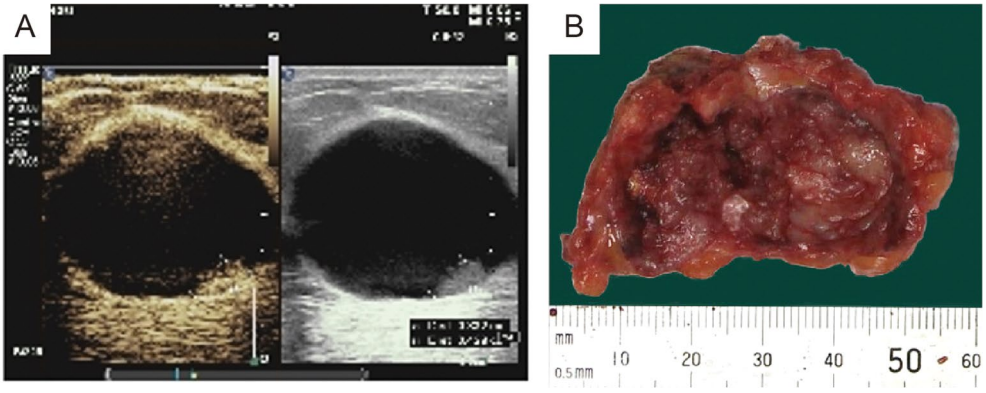

Fig. 1 Ultrasonographic screenings and macroscopic examination (**A**) Mammary ultrasonographic screenings revealed a non-echoic oval cystic lesion with a hypoechoic attached wall nodule. (**B**) Macroscopic examination of the mass shows a cystic-solid nodule with well-demarcated margins

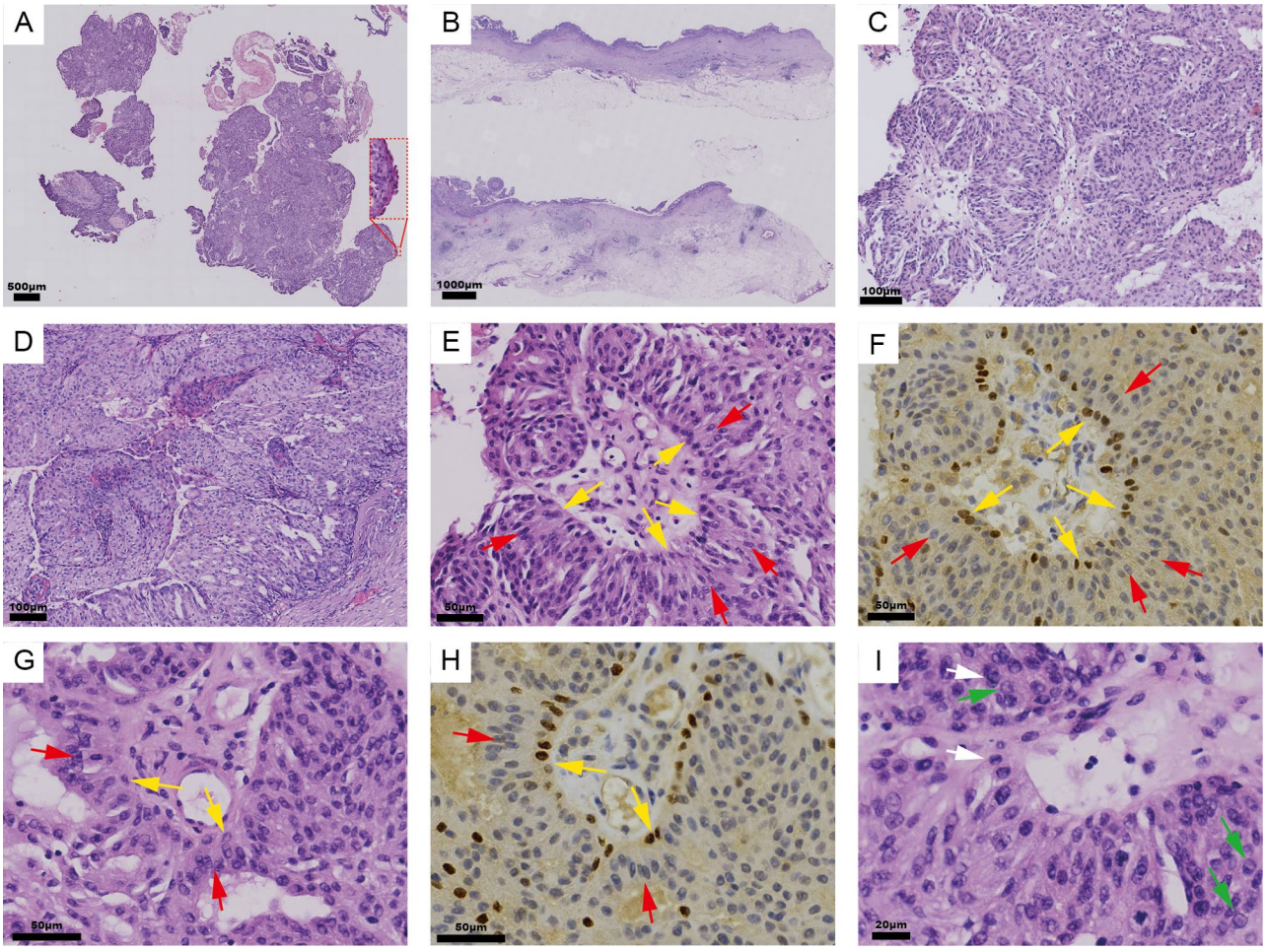

Fig. 2 Histological examination (**A**,**B**) At low magnification, the solid and the cystic portions of the tumor exhibited a pattern of confined growth (the red dashed box is a magnification of the margin). (**C**,**D**) At high magnification, the solid and the cystic portions of the tumor cells showed a distinct papillary growth pattern with partially fused papillae. (**E**-**H**) E and F were serial sections. **G** and **H** were serial sections. E and G were stained for H&E, while F and H were stained for P63 (positive for myoepithelial nuclei). There was an intact myoepithelium along the periphery of the fibrovascular axis (yellow arrows). In the outer rim of the myoepithelium, we found that P63-negative tumor cells had a columnar morphology, with nuclei oriented away from the basement membrane (red arrows). (**I**) Nuclei were round or ovoid with mild-moderate heterogeneity. Some nuclei showed distinct nuclear grooves (white arrows) and some nuclei exhibited pseudo-inclusion bodies (green arrows)

the basement membrane (Fig. 2E-H). Additionally, the tumor cells exhibit occasional nuclear grooves and intranuclear inclusions (Fig. 2I).

The patient underwent a total hysterectomy and adnexal resection for high-grade serous carcinoma of the left ovary in 2018, postoperative pathology immunohistochemistry (IHC) showed positive for pair box gene 8 (PAX8), negative for CK5/6, 50% positive for cellular proliferation index (Ki67), negative for estrogen receptor (ER), 30% weak positive for progesterone receptor (PR). To diagnose the origin of the breast cancer and further determine its characteristics, we performed IHC for the breast cancer subsequently. The results showed negative expression of PAX8, Thyriod transcription factor-1 (TTF-1), and positive for GATA binding protein 3 (GATA3) (Fig. 3A-C). In addition, P63 and Calponin were positive showing visible myoepithelial cells in and around the tumor-cell nest, and in both solid and the cystic portions (Fig. 3D-G). Besides, ER, PR, and Human epidermal growth factor receptor (HER2) were negative, indicating a triple-negative phenotype. CK5/6, CK7, E-cadherin, Epidermal growth factor receptor (EGFR), and calretinin were diffusely and strongly positive; Ki67 was 15%+ (Fig. 3H-L); Chromogranin A (CgA) and Synapsin (Syn) were negatively staining.

We also conducted molecular genetic studies to further reveal the characteristics of the disease. Next-generation sequencing further revealed a frameshift mutation of *PIK3R1 p.(L570_T576del)* and an amplification in *HIF1A* (Fig. 4).

This case is a rare entity with an indolent tumor and a favorable prognosis with no indication of benefit from systemic adjuvant chemotherapy. The patient didn't

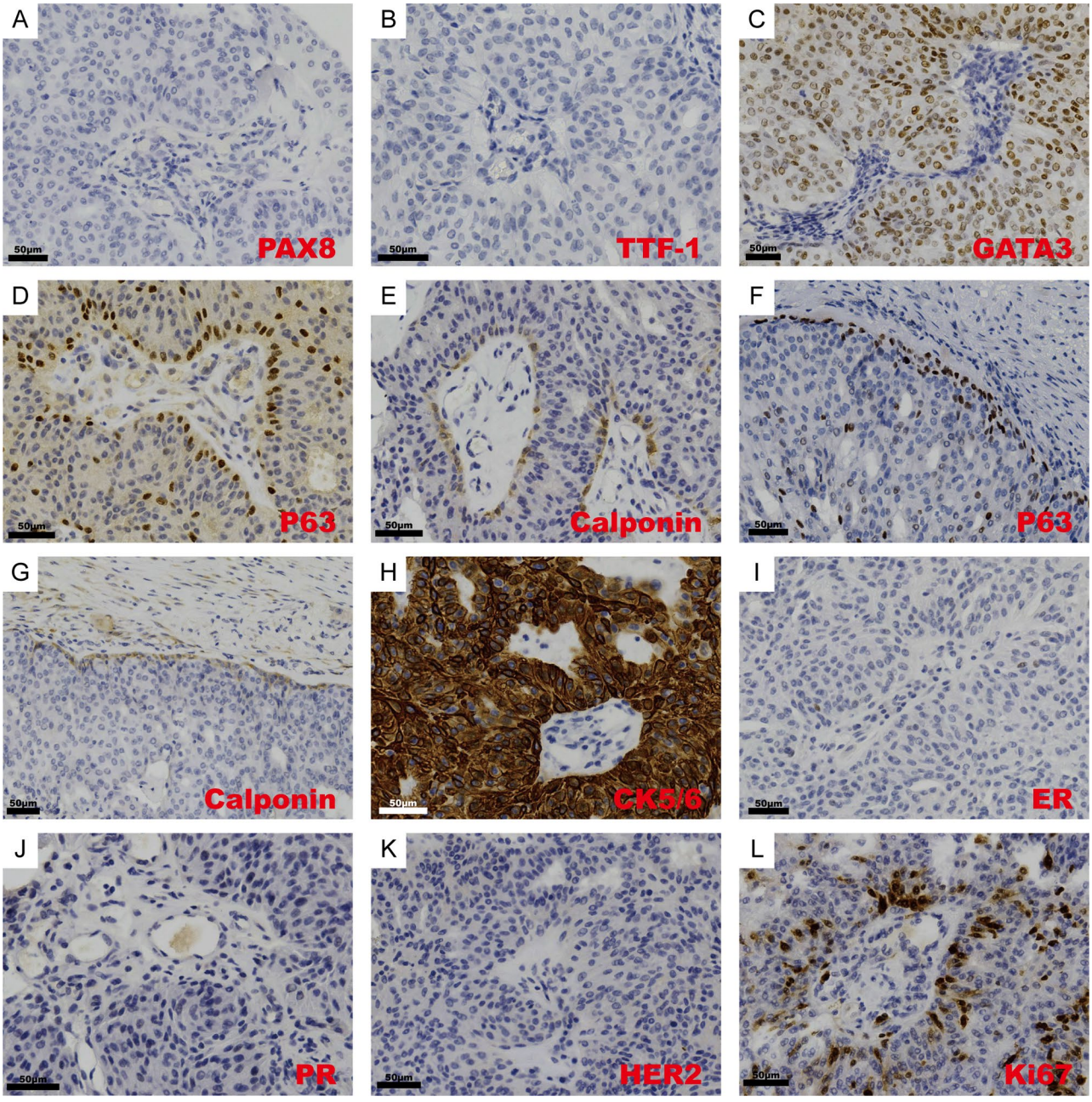

Fig. 3 The results of the immunohistochemistry test (**A**-**C**) Tumor were negative for PAX8, TTF-1 but positive for GATA 3. (**D**-**G**) P63 and Calponin were positively expressed in and around the tumoral nests, indicating the presence of myoepithelial cells. D and E presented tumor cells in the solid area of the lesion. F and G were the cyst of the lesion (**H**) The tumor was diffusely and strongly positive for CK5/6. (**I**-**K**) Tumoral cells were negative for ER, PR, and HER-2, presenting a triple-negative phenotype. (**L**) Tumoral cells were 15% positive for Ki67

receive any postoperative treatment and was followed up for 29 months with no tumor recurrence.

Discussion and conclusions

TCCRP was first reported in 2003 by Eusebi et al. who described a new entity of primary breast carcinoma resembling the morphology of the tall cell variant of papillary thyroid carcinoma [4]. Consequently, it was initially named "Breast tumor resembling the tall cell variant of papillary thyroid carcinoma". This rare tumor was included in "rare and salivary gland type tumors" in the 5th edition WHO classification of breast tumors, named as "Tall Cell Carcinoma with Reversed Polarity" officially [2], and is characterized by tall columnar epithelial cells, papillary architecture, and polarity-reversed nuclei. In terms of immunohistochemistry, TCCRP is mainly characterized by a lack of myoepithelium and high expression of CK5/6. Almost all of TCCRP cases, which have been

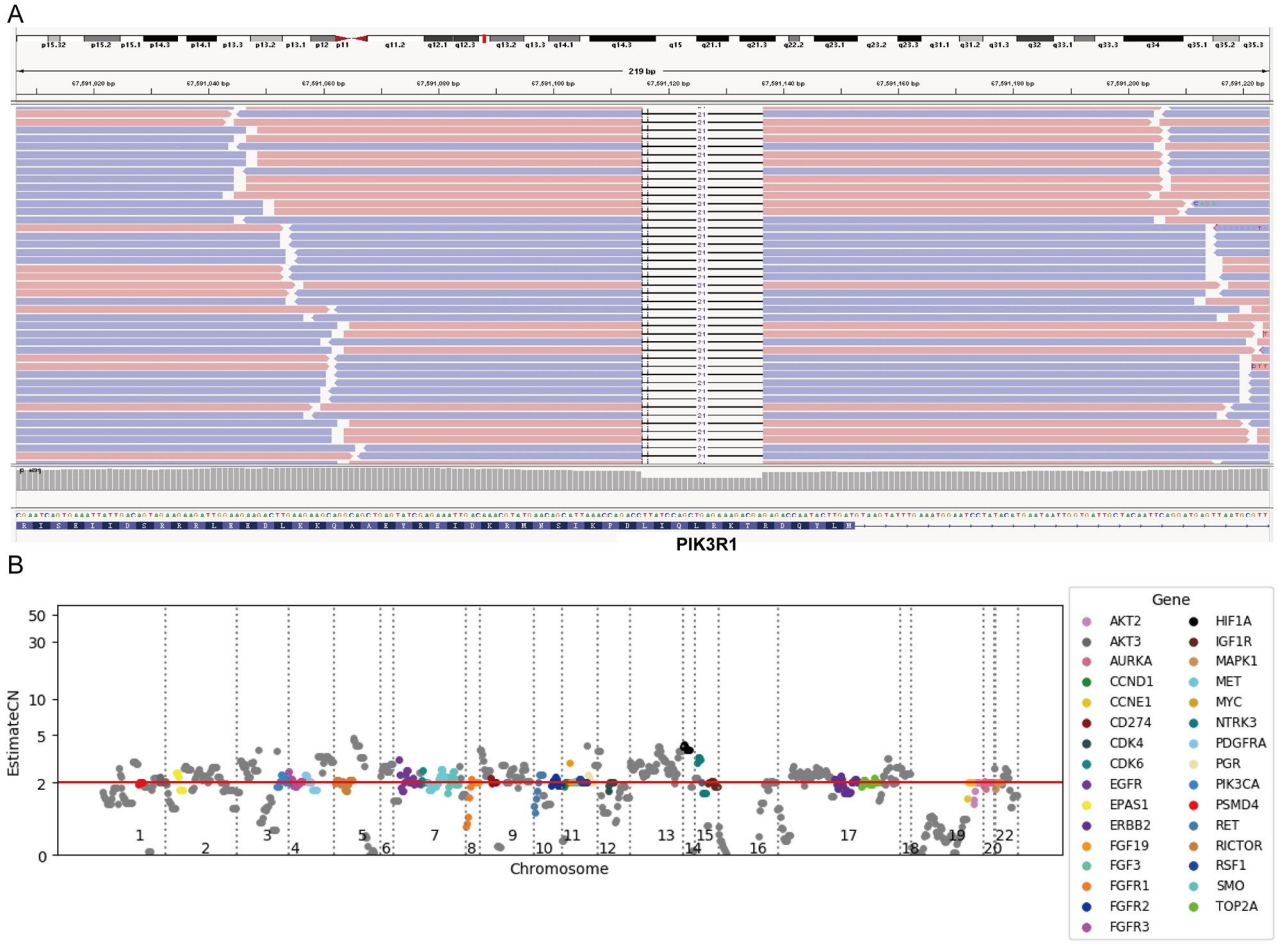

Fig. 4 The results of the gene sequencing (**A**) Next-generation sequencing showed that this patient had a 21-nucleotide deletion in the coding region of *PIK3R1* on chromosome 5, resulting in the loss of 7 amino acids (from 570th to 576th). (**B**) The patient also had a slight amplification in *HIF1A*

reported, were invasive carcinomas, with only 2 cases suggestive of microinvasion and 3 suspicious for in situ. However, none of the previously reported in situ and microinvasive carcinomas had well-established immunohistochemical evidence. Eusebi et al., claimed the diagnosis of carcinoma in situ in one patient and microinvasive carcinoma in two patients on the basis of the presence of basement membrane material staining positively for Laminin and Collagen IV around the nests of tumor clusters or HE morphology rather than the presence of myoepithelium, which was not persuasive enough [4]. Tosi et al., demonstrated TCCRP in situ by a scattered pattern with P63-positive cells around the periphery of tumor nests, and it has been shown that some specific malignant epithelial cells can also be P63-positive, therefore, the diagnosis was remained controversial [5]. As a consequence, TCCRP is identified as an invasive cancer [4, 6–18]. In terms of genetic alterations, the majority of TCCRPs have mutations in *IDH2* (hot spot mutations in residue 172) and *PIK3CA* (hot spot mutations in p. H1047R), and some studies have claimed that mutations in these two loci may be the driver mutations of TCCRPs, resulting in their polarity-reversed phenotype. *TET2* truncating mutation was also detected in one case, while *PIK3R1* missense mutation, which is a known hot spot mutation in PI3K signaling pathway among Chinese breast cancer patients [19], was reported in three cases [1, 20]. According to previous reports, TCCRP has an indolent biological behavior with a low potential to metastasis or local recurrence, therefore, TCCRP shows favorable clinical outcomes in most cases.

In our case, the patient's tumor had a great degree of similarity to TCCRP. The histological examination found abundant fibrovascular cores and highly columnar adenoepithelial cells with "reversed polarity" nuclei within the cystic and solid areas of the lesion, displaying a typical growth pattern of TCCRP. Although this patient had a history of ovarian high-grade serous carcinoma, the IHC tests showed PAX8(-), TTF-1 (-), and GATA3 (+), which both excluding the possibility of metastatic carcinoma of the ovary and thyroid, suggesting that the tumor was of breast origin. In addition, the tumor presented a

triple-negative phenotype, with CK5/6 and calretinin strongly positive; and Ki67 was 15%+ showing a poor ability in proliferation. These results were consistent with the characteristics of TCCRP. In addition, we performed a 116-gene-panel next-generation sequencing analysis, covering all the hot spot mutation sites (as shown in the method section below). The result showed an absence of *IDH2* and *PIK3CA* mutations, instead, she got a slight amplification in *HIF1A*, which is related with metabolic reprogramming, and a frameshift mutation of *PIK3R1 p.(L570_T576del)* [19, 21, 22]. *PIK3CA* and *PIK3R1* are mutually exclusive mutations, and both encoding active subunits of PI3K, their mutations can result in a constitutively active state of PI3K/AKT pathway respectively, which is associated with the proliferation of the tumor cells. This case further validates that this pathway may be associated with the specific phenotype of TCCRP. Meanwhile, to our knowledge, *PIK3R1 p. (L570_T576del)* mutation has never been reported before, further functional exploration is required to explore whether this segment of *PIK3R1* gene is associated with tall and polarity-reversed phenotype.

However, our case also presented several unique features, completely different from TCCRP but consistent with DCIS. First of all, the postoperative specimen of this patient was a complex cystic and solid mass with a well-defined cystic wall and internal structures, however, no previous reports have ever mentioned a cystic structure in TCCRP. Secondly, on histological examination, most TCCRP neoplastic lesion were composed with various patterns of nests, for example, solid, papillary or cribriform, nevertheless, our case exhibited a typical papillary structure with a well-defined fibrovascular axis. Besides, IHC studies is the key for differential diagnosis, our case showed continuous positive in P63 and Calponin indicating visible integrated myoepithelial cells in and around the tumor-cell nest which suggested to be carcinoma in situ whose characteristic agrees with DCIS.

Combining all the results of the mammary ultrasonographic screenings, histological examination, IHC tests, and molecular genetic studies for a comprehensive analysis. This patient has a combination of TCCRP and DCIS features, especially the reliable results of IHC showed that this patient has carcinoma in situ, which is not consistent with typical TCCRP. Therefore, we believe that this patient may be a new pathological subtype.

In conclusion, TCCRP is an infrequent clinical entity of invasive breast cancer recently included in the WHO classification, with a triple-negative expression, low Ki67 index, and showed pretty excellent prognosis in most cases. In this case, although the morphology characteristics, partial of the IHC findings, and the genetic mutation of the tumor are quite similar with TCCRP to some degree, it presents positive expression of P63 and Calponin indicating a proliferation pattern that is confined to the mammary ductal-lobular system. Therefore, we suggest that this case may be a new subtype of DCIS with tall cell and reversed polarity morphology, representing a dangerous diagnostic pitfall that can also lead to unnecessary clinical investigations, for example, generally DCIS requires radiotherapy after breast-conserving surgery, whereas DCIS with all cell and reversed polarity morphology does not. Given the fact that this rare type of DCIS has intact myoepithelium and typical phenotype, more attention should be paid to evaluating histologic features and genetic alterations when distinguishing it from TCCRP and other types of DCIS.

Method

Histologic staining and antibodies

All the hematoxylin-eosin staining (H&E) and Immunochemistry staining (IHC) were asseseed at the laboratory of Pathology department of China-Japan Friendship Hospital by certificated technicians and pathologists with the following antibodies overnight: anti-PAX-8 (ZSGB-BIO, ZM-0468), TTF-1(ZSGB-BIO, ZM-0270), GATA3 (ZSGB-BIO, ZA-0661), P63(ZSGB-BIO, ZM-0406), Calponin(ZSGB-BIO, ZM-0176), CK5/6(ZSGB-BIO, ZM-0313), ER(Roche, Ventana SP1), PR(Roche, Ventana 1E2), HER-2 (Roche, Ventana 4B5) and stained with goat anti-rat IgG Ab (MXB, KIT-5030) at room temperature for 50 min and counterstained with hematoxylin.

Next generation sequencing

We performed second-generation gene sequencing on this patient using a panel containing 116 genes. All the genes that were shown here: ABCB1, ARID1A, BRCA2, CDKN2B, EPAS1, FBXW7, FLT3, JAK1, MAPK1, MYC, NTRK3, PMS2, RASAL1, SMAD4, TSC2, AKT1, ATM, CCND1, CREBBP, EPCAM, FGF19, GNAS, JAK2, MET, NE1, PALB2, POLD1, RB1, SMARCA4, TSHR, AKT2, ATR, CCNE1, CTNNB1, ERBB2, FGF3, GSTP1, JAK3, MLH1, NF2, PAX8, POLE, RET, SMO, UGT1A1, AKT3, AURKA, CD274, CYP2D6, ERBB3, FGFR1, HIF1A, KDM5C, MRE11, NOTCH1, PDCD1, PSMD4, RICTOR, STK11, VHL, ALK, BAP1, CDK12, DDR2, ERBB4, FGFR2, HRAS, KDR, MSH2, NRAS, PDGFRA, PTCH1, RIT1, TERT, APC, BCL2L11, CDK4, DPYD, ESR1, FGFR3, IDH1, KIT, MSH6, NRG1, PGR, PTEN, ROS1, TOP2A, AR BRAF, CDK6, EGFR, ETS2, FGFR4, IDH2, KRAS, MTHFR, NTRK1, PIK3CA, RAF1, RSF1, TP53, ARAF, BRCA1, CDKN2A, EIF1AX, FANCA, FLCN, IGF1R, MAP2K1, MTOR, NTRK2, PIK3R1, RASA1, SF3B1, TSC1.

Abbreviations

DCIS	Ductal Carcinoma in Situ
TCCRP	Tall Cell Carcinoma with Reversed Polarity
IHC	Immunohistochemistry

H&E	Hematoxylin-Eosin Staining
PAX8	Pair Box Gene 8
Ki67	Cellular Proliferation Index
ER	Estrogen Receptor
PR	Progesterone Receptor
TTF-1	Thyriod transcription factor-1
GATA3	GATA binding protein 3
HER2	Human Epidermal Growth Factor Receptor
EGFR	Epidermal Growth Factor Receptor
CgA	Chromogranin A
Syn	Synapsin
PI3K	Phosphatidylinositol-3-Kinase

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Author contributions
DZ and XW studied the concept and design. RZ and ZC collected the data and drafted the manuscript. DZ and XW critically revised the manuscript. All authors approved the final version of the manuscript.

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Data availability
The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive [23] in National Genomics Data Center [24], China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA005620) that are publicly accessible at https://ngdc.cncb.ac.cn/gsa-human.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki. All procedures in this study were approved by the Ethics Committee of China-Japan Friendship Hospital (#2021-135-K93-2).

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any associated images. A copy of the consent form is available for review by the Editor of this journal.

Competing interests
The authors declare no competing interests.

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