Case Report

Tall cell carcinoma with reversed polarity: case report with gene sequencing and literature review

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Abstract: Tall cell carcinoma with reversed polarity (TCCRP) is an extremely rare type of invasive breast cancer with only 17 literatures and 75 cases reported. Knowledge on TCCRP is still scanty. The present study reported 2 cases of TCCRP, analyzed their clinicopathological characteristics, and used whole exome sequencing to perform genetic testing. Both two cases were proved to have typical clinicopathological manifestations (solid and papillary architectures lined by tall columnar cells with nuclei displaying "reverse polarization") and hotspot mutations (*IDH2* and *PIK3CA* mutations) of TCCRP. Furthermore, positive expression of TTF-1 was found in a small number of tumor cells nuclei and normal ductal epithelial cells, while the negative rate of TTF-1 in previous case reports was 100%. Attention should be paid in core needle biopsy to avoid misdiagnosis. In addition, this article also reviewed all previous cases and demonstrated that the positive expression of calretinin might have an indicative significance for TCCRP, which could be used as one of the auxiliary diagnosis tools. The diagnosis of TCCRP requires comprehensive analysis of clinical pathology and genetic testing results. There is no clear treatment standard for TCCRP currently, further research should be reported to characterize and deeply investigate the diagnosis and treatment criteria of TCCRP.

Keywords: Tall cell carcinoma with reversed polarity (TCCRP); breast cancer; genetic testing; *IDH2* mutation; case report

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Introduction

Tall cell carcinoma with reversed polarity (TCCRP) is a rare subtype of breast cancer. It was first reported by Eusebi *et al.* in 2003 under the name of "breast tumor resembling the tall cell variant of papillary thyroid carcinoma (BTRPTC)" (1). Since subsequent studies found that it lacked the unique histologic and genetic properties of PTC, Masood *et al.* proposed that the terminology should be changed to "tall cell variant of papillary breast carcinoma (TCVPBC)" (2). In 2016, Chiang *et al.* pointed out that the tumor showed solid and papillary structures lined by columnar epithelial cells with "reverse polarity" significantly, and suggested it be renamed "solid papillary carcinoma with reverse polarization (SPCRP)" (3). In 2019, the World Health Organization (WHO) officially classified the tumor as "rare and salivary gland tumors". TCCRP usually presents with well-circumscribed nodule, and is composed of solid and papillary architectures lined by tall columnar cells with nuclear grooves and nuclear pseudo-inclusions morphologically. The most characteristic feature of TCCRP, as it is called, is the apical location of the nuclei, displaying "reverse polarization". Furthermore,

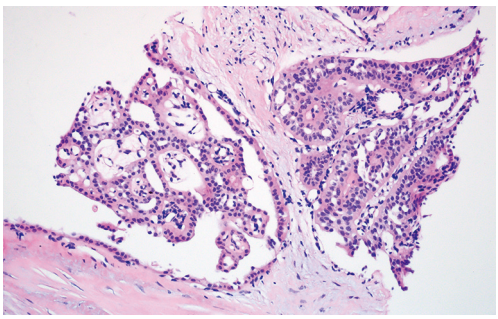

Figure 1 Histopathological features of core needle biopsy of Case 1 (H&E staining; ×20). The tumor cells grow in a papillary pattern, a small part of the tumor cell nucleus is far away from the base and close to the lumen edge, and most of the tumor cells are distributed in a non-polar direction.

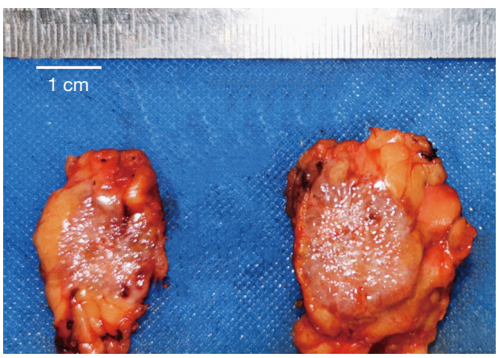

Figure 2 Macroscopic appearance of breast mass of Case 1.

the tumor often shows a triple-negative profile, with *IDH2* and *PIK3CA* simultaneous gene mutations. Since TCCRP is generally believed as a low-invasive tumor with indolent behavior, the patients mainly undergo breast conserving surgery at present. However, there are still a few cases reported with local recurrence and distal metastasis. And no clear description was found about TCCRP in National Comprehensive Cancer Network (NCCN) clinical practice guidelines in breast cancer. Up to now, only 17 literatures and 75 cases of TCCRP have been reported, and further research should be conducted to determine the diagnosis and treatment criteria for this tumor (1-17).

Here, we report 2 cases of TCCRP, investigate their clinicopathological features, and analyze in terms of genetic mutations by using whole exome sequencing (WES) to confirm the specific mutations previously described as well as search for other meaningful genetic alterations. In addition, we reviewed all previous case reports of TCCRP in comparison with our cases. Typical clinicopathological features consistent with TCCRP and hotspot mutations (*IDH2* and *PIK3CA*) were found in our cases.

We present the following cases in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/gs-21-591).

Case presentation

Case 1

The patient was a 72-year-old woman with a palpable mass located in the upper outside quadrant of the right breast. The mammary ultrasonography revealed a well-circumscribed hypoechoic area of 2.3×1.7×1.7 cm^3 in size at 9 o'clock, with an irregular shape, blood flow signals at the periphery, and a score of 5 under the Breast Imaging Reporting and Database System (BI-RADS). No significant abnormality was found in thyroid ultrasonography. The core biopsy specimen showed that most of the neoplastic cells were arranged in a papillary architecture, with the mesenchyme of tumor tissues accompanied by hyaline degeneration. The tumor cells were filled with eosinophilic cytoplasm, characterized by oval nuclei, clear chromatin, and occasional nuclear pseudo-inclusions (*Figure 1*). These results indicated a high possible diagnosis of TCCRP. The right breast mass was resected and sent for intraoperative freezing pathology later. Grossly, the cut surface showed a light red area of 2.2×2.2×1.8 cm^3, with the macroscopic appearance of breast mass showed in *Figure 2*. A well-circumscribed and multinodular tissue was shown at low power. Under high magnification, it grew in a multi-nodular shape (*Figure 3A*). Because it was challenging to determine the existence of myoepithelial cells, we diagnosed it as papillary tumor, leaving the specific nature to be confirmed by postoperative paraffin pathology. Postoperative paraffin pathology confirmed the diagnosis of TCCRP and showed most of the tumor cells grew in nodular and infiltrating pattern with papillary architecture centered by fibrovascular cores. Some cystic spaces were filled with eosinophilic colloid-like material, accompanied by cystic dilatation. The neoplastic cells were columnar in shape, with eosinophilic cytoplasm, and showed grooves and eosinophilic pseudo-inclusions occasionally. Some nuclei are distributed near the lumen and the lumen edge of the cyst (*Figure 3B-3D*).

The immunohistochemistry (IHC) showed negative expression of SMMHC and P63, indicating the absence of myoepithelial cells around and within the tumor nests.

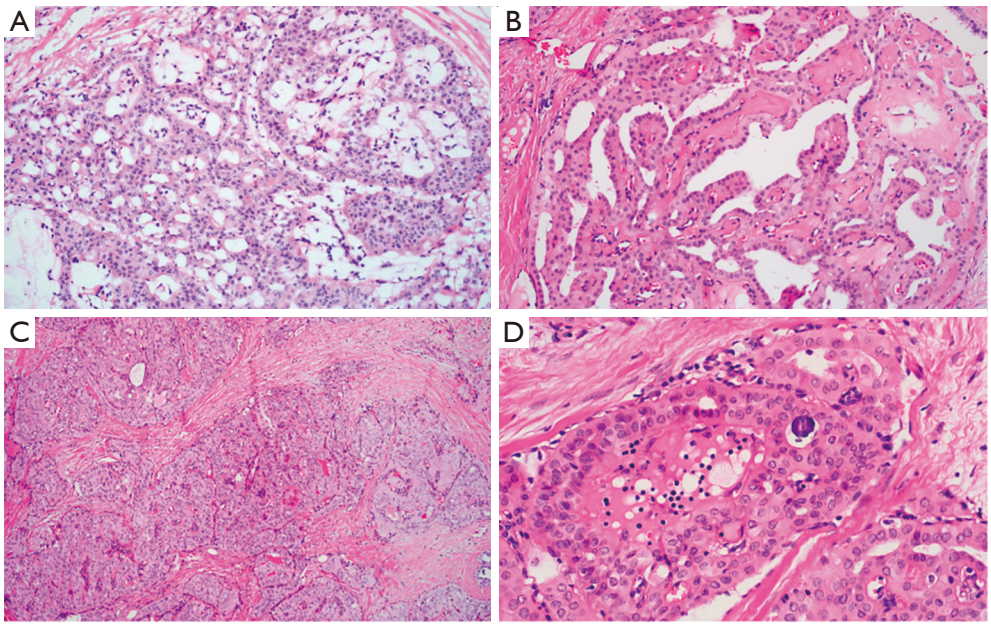

Figure 3 Histopathological features of intraoperative frozen section and postoperative paraffin pathology of Case 1. (H&E staining; A, ×20) Intraoperative frozen section of Case 1 showed irregular small cavities surrounded by tumor cells in the tumor nodules, and the fibrovascular interstitial edema was so significant that the nipple structure was not obvious. The distribution of tumor cells is disordered, and the boundaries between cells are unclear. (H&E staining; B, ×10) The tumor of Case 1 was multi-nodular with interstitial fibrosis in low power fields. (H&E staining; C, ×20) The tumor cells of Case 1 form the papillary structure, similar to classic papillary thyroid carcinoma. The tumor cell nucleus is close to the lumen edge showing reversed polarity with fibrovascular interstitial hyalinosis. (H&E staining; D, ×40) In high power fields, tumor cells are rich in oncocytic cytoplasm with low grade nuclei, fine chromatin, and small nucleoli. Psammoma bodies are occasionally formed in the gland cavity.

Expression of ER was focal positive, with a rate of <1%. PR was negative and HER-2 expressed weak complete membrane staining observed in <10% of tumor cells. The Ki-67 proliferative index was around 5%. The cytoplasm of tumor cells showed diffuse reactivity for CK5 and calretinin and the nucleus of tumor cells diffusely expressed SOX-10, the cytoplasm of some tumor cells and the secretion in the dilated tube lumen were positive for GCDFP-15. The nucleus of a few tumor cells was positive for TTF-1. GATA-3 was focal positive and TG was negative. Laminin showed negative staining around the tumor nest. EMA showed positive staining in a few cytoplasm of tumor cells and the lumen edge (*Figure 4A-4D*). Subsequently, the patient underwent right mastectomy plus sentinel lymph node biopsy, and postoperative paraffin pathology showed no metastasis in axillary lymph nodes. Molecular genetic analysis was conducted using WES, and the results showed concurrent *IDH2 p.R172S* and *PIK3CA p.H1047R* hotspot mutations (Table S1). Chromosomal aberrations were not analyzed. The patient was alive and well for 6 months at the last follow-up.

Case 2

Our team has previously reported a 70-year-old woman with a palpable mass, measuring 2.0 cm in diameter, located in the upper outside quadrant of the left breast (18). The mammography revealed a nodule-like density increase area and no significant abnormality was found in thyroid ultrasonography. Wide local excision was conducted and sent for postoperative paraffin pathology. A gray-white, gray-yellow nodular mass of 1.6 cm in diameter with unclear boundary was found on the cut surface. Histologically, most of the tumor cells nuclei presented away from the stromal surface, giving the expression of reversed polarity. The cytoplasm of the neoplastic cells was eosinophilic, with ovoid nuclei, fine chromatin, small nucleoli and occasional grooves and pseudo-inclusions. The mesenchyme of tumor was fibrous tissue with hyaline degeneration (*Figure 5*).

The results of IHC showed that SMMHC and p63 were

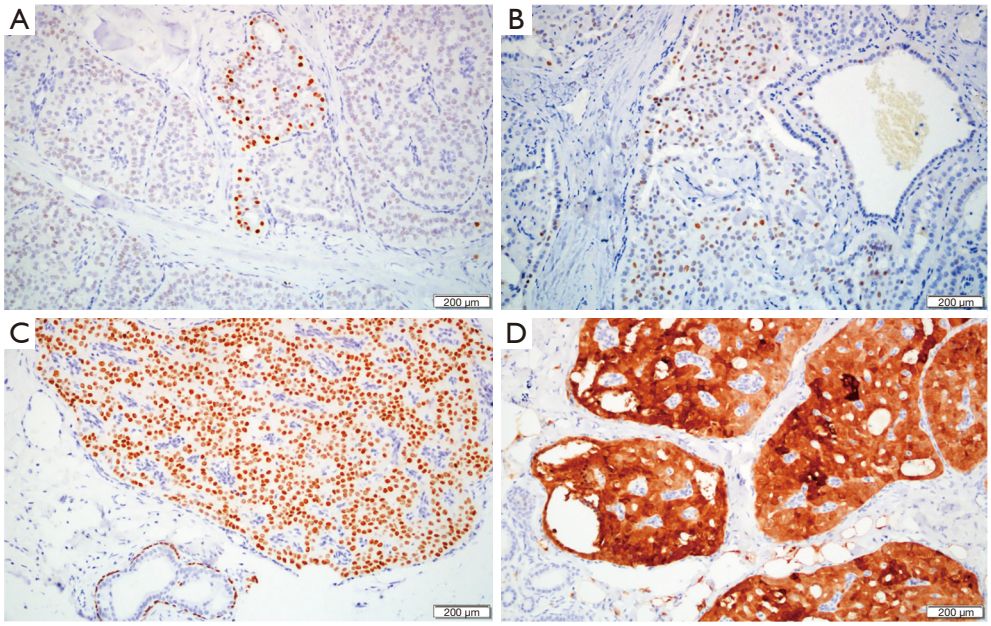

Figure 4 The immunohistochemistry results of Case 1. (A, ×60, scale bar=200 μm) The tumor cells of Case 1 are focally positive for GATA-3. (B, ×200) Tumor cells of Case 1 diffusely express SOX-10 and myoepithelial cells of normal ducts adjacent to the tumor express SOX-10. (C, ×20) A small number of tumor cells of Case 1 are TTF-1 positive. (D, ×20) Tumor cells of Case 1 diffusely express calretinin in the cytoplasm.

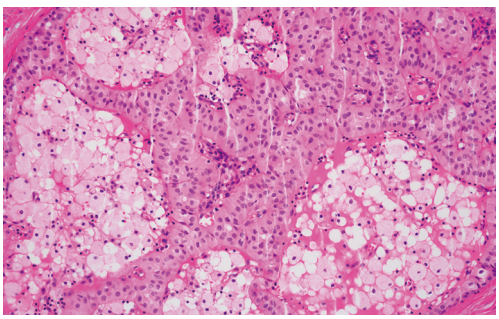

Figure 5 Histopathological features of postoperative paraffin pathology of Case 2 (H&E staining; ×40). Most tumor cells form solid papillary structures. And the tumor of case 2 shows cystic expansion of the fibrovascular axis of the papillae, in which pink secretions and foam tissue cells accumulate.

negative staining, indicating the absence of myoepithelial cells. Focally positive expression of ER was found, with a rate of <1%. PR and HER-2 were negative staining. The Ki-67 proliferative index was low (2%). Tumor cells express diffuse positive in CK5 and Calretinin in the cytoplasm. Almost all tumor cells are positive for S0X-10 in the nucleus and GCDFP-15 was focally positive. Tumor cells nuclei were negative for TTF-1, but some normal duct epithelial cells around the tumor were positive for TTF-1. The tumor cells were focal positive for GATA-3 and negative for TG. Laminin around the tumor cell cluster was negative. EMA was negative staining (*Figure 6A-6D*). Molecular genetic analysis was conducted using WES, and the results showed concurrent *IDH2 p.R172W* and *PIK3CA p.H1047R* hotspot mutations (Table S1). Chromosomal aberrations were not analyzed. All of the results confirmed the diagnosis of TCCRP. The patient was alive and well for 33 months at the last follow-up.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The 2 cases we reported had typical pathological morphology

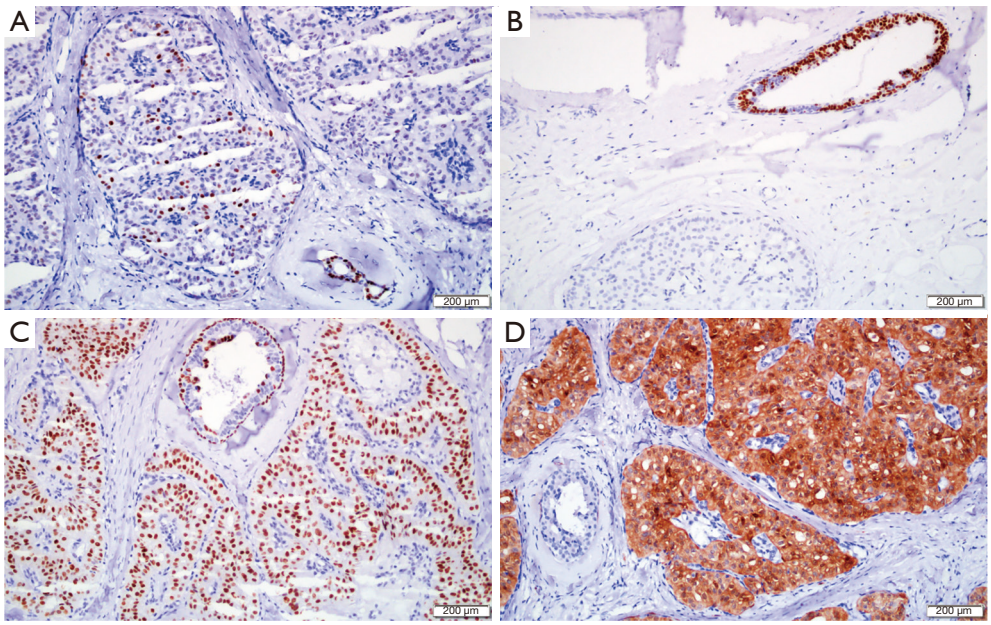

Figure 6 The immunohistochemistry results of Case 2. (A, ×60, scale bar=200 μm) The tumor cells of Case 2 are focally positive for GATA-3, which is expressed in normal ductal epithelium. (B, ×200) Tumor cells of Case 2 diffusely express SOX-10. And SOX-10 is also expressed in both myoepithelial cells and ductal epithelial cells with differentiation of basal cells of normal ducts adjacent to the tumor. (C, ×20) The tumor cells of Case 2 are negative for TTF-1, and the normal ductal epithelial cells adjacent to the tumor express TTF-1. (D, ×20) Tumor cells of Case 2 diffusely express calretinin.

of TCCRP, that is, solid and papillary structures, tall columnar tumor cells with nuclear groove and nuclear inclusion formation, similar to the high cell subtype of thyroid papillary carcinoma. Histologically, case 1 showed few cyst-like expansions in the ducts which was also seen in some spaces between fibrous vessel cores in case 2. Colella *et al.* reported a case of diffuse cystic dilatation of the duct, which appeared macroscopically as a special brownish translucent multinodular tissue (7). Case 2 was consistent with the typical TCCRP, demonstrated a well-circumscribed gray-white mass. Case 1 showed light red in color due to the blood on the surface. In addition, case 1 underwent core needle biopsy and intraoperative freezing pathology, but none of them could diagnose exactly. Since the core biopsy specimen showed most of the tumor cells neither had polar distribution or tall columnar character, it was easy to be misdiagnosed as papilloma (6,8,14). It may be related to tissue compression during the puncture process. The intraoperative freezing pathology may diagnose it as papillary lesions of the breast due to the extremely disordered distribution of tumor cells nuclei and the inability to determine the presence of myoepithelial cells, and TCCRP diagnosis might be delayed. These results indicated that the precise diagnosis of TCCRP required the combination of specific immunophenotype to avoid misdiagnosis.

IHC confirmed the diagnosis of TCCRP. The 2 cases in our group were all triple-negative phenotypes, CK5/6 was diffusely positive, and myoepithelial markers were negative, which were consistent with the phenotype of TCCRP in the literature previously reported (Table S2). GATA-3 were focally expressed in both cases of our group. Of the patients we evaluated from the previous cases, 42.9% were diffuse positive and 42.9% were focal expression. Studies have shown that as a marker for primary breast cancer, the sensitivity of GATA-3 is up to 94%, especially for ER-positive breast cancer. However, the sensitivity can reach only 43–66% to diagnose metastatic triple-negative breast cancer (TNBC). SOX-10 was diffusely expressed in our cases. The previous 75 cases of TCCRP were not tested for SOX-10. SOX-10 is mainly expressed in TNBC and metaplastic breast cancer, regulating the process of mesenchymal transition of breast epithelial cells. In addition, its expression in TNBC is significantly higher than other breast cancer subtypes, with a sensitivity of 69%.

It is suggested that the simultaneous staining of GATA-3 and SOX-10 can improve the sensitivity of TCCRP to justify the origin of breast and distinguish from other carcinomas including metastatic thyroid carcinoma, etc. In our cases, positive expression of TTF-1 was found in few tumor cells and a small number of ductal epithelial cells at the periphery, while the negative rate of previous cases was 100%. TTF-1 is often expressed in thyroid cancer and lung adenocarcinoma, and is used to determine the primary site of metastatic cancer. However, it can also have varying degrees of positive expression in 2.5% of breast cancers, such as invasive ductal carcinoma, lobular carcinoma and other subtypes. The expression of TTF-1 in normal breast tissue needs to be further explored. TCCRP needs to be differentiated from metastatic PTC. The possibility of breast origin should not be denied because of focal TTF-1 expression, especially in core needle biopsy, and the results of breast-derived markers and TG staining should be comprehensively evaluated. It is worth noting that calretinin was positively expressed in previous case reports. Calretinin is mainly used for the diagnosis of mesothelioma, accounting for only 15% of breast cancers. Studies have shown that calretinin is often expressed in high-grade, basal-like phenotypes of breast cancer, with a positive rate of 67%. Our cases were also positive for calretinin. Calretinin is expected to become one of the auxiliary indicators of TCCRP diagnosis.

Our cases had hotspot mutations of *IDH2* and *PIK3CA*. In the previous literature, 88% of patients had *IDH2* mutations, 65% had *PIK3CA* mutations, and simultaneous mutations accounted for 60% (Table S2). IDH mutations are common in many tumors, such as acute myeloid leukemia, oligodendroglioma and chondrosarcoma, etc., resulting in abnormal epigenetic regulation, cell differentiation, and thus tumorigenesis. In 2016, Chiang *et al.* detected the *IDH2* and *PIK3CA* mutations for the first time and proposed that they might be the driving factors of TCCRP and contacted them with the "reverse polarization" of tumor cells (3). In addition, *IDH2 R172W* mutation was detected in case 2, which was not belong to the common *IDH2* single-nucleotide variants of TCCRP, namely *R172S*, *R172G*, *R172T*. Zhong *et al.* reported 1 case of *IDH2 R172W* mutation in the previous cases (13). Bhargava *et al.* and Alsadoun *et al.* indicated that some TCCRP cases did not have *IDH2* mutations, but had mutations in genes such as *PRUNE2*, *ATM*, and *KIT* (8,10). Whether other mutations besides the hotspot mutations have indicative significance for TCCRP still needs more follow-up case reports to explore. Currently, *IDH2* mutation is specific for the diagnosis of TCCRP, and the combination with clinicopathological features can clarify the diagnosis of TCCRP, which is conducive to the clinical treatment and prognosis evaluation. Additionally, Pareja *et al.* and Alsadoun *et al.* used monoclonal antibodies of *IDH2* to perform IHC and compared that with the sequencing results. The results showed that IHC has good sensitivity and specificity for the detection of *IDH2* mutation in TCCRP. It can be used as a diagnostic tool of TCCRP, particularly in biopsy and after resection (10,16). Relatively, *PIK3CA* mutation does not appear specific in TCCRP which indeed can also be found in various types of breast cancer including papilloma.

TCCRP should be distinguished from PTC and breast papillary lesions, including papilloma and papillary carcinoma. TCCRP is similar to PTC in histology, but lacks TG positive expression and *RET* gene rearrangement or *BRAF* gene mutation, excluding its thyroid origin (19). TCCRP is easy to be confused with breast papillary lesions as it shares papillary architecture with lack of myoepithelial cells. Nevertheless, TCCRP can be differentiated from these entities by the characteristic morphology of cells with reverse polarity and immuno-positivity for calretinin. The myoepithelial surrounding the infiltrating epitheliosis of the breast (IE) is intact, discontinuous or completely absent, and has similarity with TCCRP in terms of immunophenotype. Eberle *et al.* used massively parallel sequencing to detect related genes of IE, and the results showed that more than half of the cases had *PIK3CA* hotspot mutations (20). Therefore, the characteristic "reverse polarity" distribution of TCCRP, the positive expression of calretinin and the *IDH2* mutation are still the main points of differentiation from IE.

Given the rarity and limited reports of TCCRP, there is no clear guidance regarding its treatment at present. TCCRP is generally considered to be a low-invasive tumor with indolent behavior. Patients mainly receive breast conserving surgery, including local extensive resection and segmental resection. No clear indications exist for lymph node dissection, radiotherapy and chemotherapy. Bhargava *et al.* treated a patient with contralateral invasive ductal carcinoma after neoadjuvant chemotherapy, but no significant change was found in TCCRP lesions (8). The average follow-up time of previous cases was 29 months (3–132 months). During the follow-up period, most patients were alive and well, with only 1 case of local recurrence and 1 case of bone metastasis. Cameselle-Teijeiro *et al.* reported the only case of bone metastasis, but due to poor

quality of the picture, it was difficult to recognize its typical morphology to eliminate the diagnosis of ER-positive breast cancer (4).

In summary, TCCRP is an extremely rare invasive breast cancer with a solid papillary structure lined by tall columnar cells and "reverse polarity" nucleus distribution. However, the diagnosis of TCCRP by core needle biopsy can be challenging due to the atypical histochemical characteristics. Despite *IDH2* and *PIK3CA* hotspot mutations, other gene mutations including *PRUNE2* and *ATM*, etc. could also be found in TCCRP. Reviewing previous cases, we found that calretinin was positively expressed, which was expected to become one of the auxiliary diagnostic indicators in the future. Additionally, given the two cases we reported expressed TTF-1 focally in a few tumor cells and normal ductal epithelium cells, awareness should be taken during biopsy to avoid misdiagnosis. The diagnosis of TCCRP requires comprehensive analysis of pathological features, special immuno-phenotypes and gene mutations. Further research should be reported to characterize and deeply investigate the diagnosis and treatment criteria of TCCRP.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/gs-21-591

Peer Review File: Available at https://dx.doi.org/10.21037/gs-21-591

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/gs-21-591). Xi-ru Li serves as an Editor-in-Chief of *Gland Surgery* from May 2017 to April 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Supplementary

Table S1 Gene mutations of Case1 and Case2 using whole exome sequencing

Case1	Mutation site	Allele frequency	Mutation type	Case2	Mutation site	Allele frequency	Mutation type
Type II (indicate potential clinical significance)							
IDH2 p.R172S	c.516G>T	19.44%	missense mutation	IDH2 p.R172W	c.516G>T	18.87%	missense mutation
PIK3CA p.H1047R	c.3140A>G	25.36%	missense mutation	PIK3CA p.H1047R	c.3140A>G	16.67%	missense mutation
SOX 9 p.Q401*	c.1201C>T	2.11%	nonsense mutation	KMT2D p.Q2816*	c.8446C>T	1.38%	nonsense mutation
				TP53 p.P151S	c.451C>T	0.60%	missense mutation
				FGFR3 p.G380R	c.1138G>A	0.51%	missense mutation
				SPEN p.R844*	c.2530C>T	2.44%	nonsense mutation
				ELAC2 p.Q611*	c.1831C>T	1.46%	nonsense mutation
				FGFR2 p.M538I	c.1614G>A	1.07%	missense mutation
				ADGRA2 p.W281*	c.843G>A	1.06%	nonsense mutation
				SMARCA4	c.4170+1G>A	1.04%	shear mutation
				ERBB2 p.R487W	c.1459C>T	0.81%	missense mutation
Type III (unknown clinical significance)							
KDM5C p.E439D	c.1317G>T	15.13%	missense mutation	PIK3CG p.D946N	c.2836G>A	3.59%	missense mutation
BRAF	c.627T>C	15%	synonymous mutation	NCOA2 p.G1306R	c.3916G>A	3.18%	missense mutation
ERCC3 p.K528R	c.1583A>G	4.92%	missense mutation				

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Table S2 Clinical history, immunohistochemistry, gene mutation and follow-up information of the patients

Case#	Author[ref.]	Clinical History			Immunohistochemistry								Gene Mutation		Follow-up
		Sex/age	Size	Treatment	TTF-1	Calretinin	GATA-3	SOX-10	CK5/6	ER	PR	Her-2	IDH2	PIK3CA	
1-5	Eusebi *et al.* (1)	F/58	1.2	W	-	ND	ND	ND	ND	-	-	ND	ND	ND	A&W 26
		F/70	1.3	M	-	ND	ND	ND	ND	-	-	ND	ND	ND	A&W 54
		F/57	1.6	W	-	ND	ND	ND	ND	-	-	ND	ND	ND	A&W 28
		F/74	2	W	-	ND	ND	ND	ND	-	-	ND	ND	ND	A&W 108
		F/56	0.8	UK	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	UK
6	Cameselle-Teijeiro *et al.* (4)	F/64	4.1	M+AL+ C/XRT/HT	-	ND	ND	ND	ND	+	+	-	ND	ND	Alive with bone metastasis
7-10	Tosi *et al.* (5)	F/80	2.5	Q	ND	ND	ND	ND	ND	-	-	ND	ND	ND	A&W 3
		F/45	5	Q	ND	ND	ND	ND	ND	+	+	ND	ND	ND	A&W 5
		F/61	2	Q	ND	ND	ND	ND	ND	+	-	ND	ND	ND	A&W 8
		F/47	2.3	Q	ND	ND	ND	ND	ND	+	+	ND	ND	ND	A&W 10
11	Chang *et al.* (6)	F/66	1.1	S+SLN	-	ND	ND	ND	ND	+	-	-	ND	ND	A&W 12
12	Masood *et al.* (2)	F/57	3.7	M	-	ND	ND	ND	ND	+	+	-	ND	ND	UK
13	Colella *et al.* (7)	F/79	3	M+AL	-	ND	ND	ND	ND	-	-	-	ND	ND	A&W 18
14-26	Chiang *et al.* (3)	F/68	0.9	UK	-	ND	ND	ND	+	-	-	ND	-	+	UK
		F/52	0.8	UK/XRT	-	ND	ND	ND	+	-	-	-	+	+	A&W 77
		F/63	1.2	UK	ND	ND	ND	ND	+	+	+	ND	+	+	UK
		F/79	UK	UK	-	ND	ND	ND	+	-	-	ND	+	+	UK
		F/64	1.8	UK	-	ND	ND	ND	+	-	-	-	+	+	A&W 31
		F/51	0.8	UK	-	ND	ND	ND	+	+	+	-	-	+	A&W 30
		F/64	1.4	UK/XRT	-	ND	ND	ND	+	+	-	-	+	-	A&W 29
		F/58	0.6	UK	-	ND	ND	ND	+	-	-	-	+	+	UK
		F/66	0.9	UK/C	-	ND	ND	ND	+	-	-	-	+	+	A&W 20
		F/65	1.5	UK/XRT/C	-	ND	ND	ND	+	+	-	-	+	+	A&W 37
		F/70	1.3	UK	-	ND	ND	ND	+	+	-	-	-	+	A&W 12
		F/65	1.2	UK	-	ND	ND	ND	+	-	-	-	+	-	UK
		F/65	0.9	UK	-	ND	ND	ND	+	-	-	-	+	+	UK
27-39	Foschini *et al.* (9)	F/58	1.2	W+SLN	-	ND	+/-	ND	+	-	-	-	+	-	Recurrence 60
		F/80	2.5	W	-	ND	+/-	ND	+	-	-	-	ND	ND	A&W 120
		F/61	2	W+SLN	-	ND	-	ND	-	+	-	-	ND	ND	A&W 132
		F/62	1	W	-	ND	ND	ND	ND	-	-	-	ND	ND	A&W 96
		F/51	2	W	-	ND	ND	ND	-	-	-	-	ND	ND	UK
		F/58	0.8	W+SLN	-	ND	ND	ND	ND	+	+	-	ND	ND	A&W 24
		F/61	0.6	W	-	ND	ND	ND	+	-	-	-	ND	ND	A&W 124
		F/50	0.8	W/XRT/C	-	ND	+/-	ND	-	-	-	-	ND	ND	A&W 84
		F/59	2.5	W	-	ND	-	ND	+	-	-	-	+	+	A&W 76
		F/48	2.2	W	-	ND	ND	ND	+	-	-	-	ND	ND	A&W 24
		F/85	1.5	W	-	ND	ND	ND	+	-	-	-	+	+	UK
		F/64	2	W+ AL	-	ND	+/-	ND	ND	-	-	-	ND	ND	A&W 36
		F/77	1.2	W	-	ND	+/-	ND	+	+	+	-	+	+	A&W 24
40-42	Bhargava *et al.* (8)	F/65	0.9	UK	ND	ND	ND	ND	+	-	-	ND	+	-	A&W 19
		F/77	1.7	UK	-	ND	ND	ND	+	+	+	ND	-	-	UK
		F/48	1.2	UK+NAC	ND	ND	ND	ND	+	+	ND	ND	+	+	A&W 19
43	Gai *et al.* (11)	F/55	UK	M+SLN	-	ND	+	ND	+	-	-	-	ND	ND	UK
44-46	Lozada *et al.* (12)	F/60	1.1	UK+SLN	ND	ND	ND	ND	+	-	-	-	+	+	UK
		F/60	2.1	UK	ND	ND	ND	ND	+	-	-	-	+	+	UK
		F/67	0.6	UK	ND	ND	ND	ND	+	-	-	-	+	-	UK
47-54	Zhong *et al.* (13)	F/63	0.6	UK	ND	ND	ND	ND	ND	-	-	-	+	+	UK
		F/63	1	UK	-	ND	ND	ND	ND	-	-	-	+	-	UK
		F/79	1.6	UK	-	ND	ND	ND	+	ND	ND	ND	+	+	UK
		F/69	1.2	UK	ND	ND	ND	ND	ND	+	-	+	+	+	UK
		F/69	1.8	UK	-	ND	+	ND	ND	-	-	-	+	+	UK
		F/71	1.7	UK	-	ND	+	ND	ND	-	-	-	+	+	UK
		F/74	0.8	UK	ND	ND	ND	ND	ND	-	-	ND	ND	ND	UK
		F/76	0.7	UK	ND	ND	ND	ND	ND	+	+	ND	+	+	UK
55-63	Alsadoun *et al.* (10)	F/63	1.6	S	ND	+	ND	ND	-	+	+	-	-	ND	UK
		F/70	1.1	S	ND	+	ND	ND	-	-	-	-	+	ND	UK
		F/72	1.0	S	ND	+	ND	ND	-	+	-	-	+	ND	UK
		F/64	1.5	S	ND	+	ND	ND	-	-	-	-	+	ND	UK
		F/71	0.9	S	ND	+	ND	ND	-	-	-	-	+	ND	UK
		F/52	4.0	S	ND	+	ND	ND	-	+	+	-	+	ND	UK
		F/69	1.0	S+SLN	ND	+	ND	ND	+	-	-	-	+	ND	A&W 53
		F/57	1.2	S	ND	+	ND	ND	-	+	-	-	+	ND	UK
		F/75	3.0	S	ND	+	ND	ND	-	+	+	-	-	ND	UK
64	Haefliger *et al.* (14)	F/60	0.8	UK+SLN	-	ND	ND	ND	+	-	-	-	+	+	A&W 8
65	Jassim *et al.* (15)	F/40	5.5	M+AL	-	+	+	ND	+	+	+	-	+	ND	A&W 6
66-74	Pareja *et al.* (16)	F/67	1	UK	ND	+	ND	ND	+	-	ND	ND	+	-	UK
		F/59	1.5	Partial M/XRT	ND	+	ND	ND	ND	+	ND	ND	+	-	UK
		F/64	1.2	Partial M/XRT	ND	+	ND	ND	+	+	ND	ND	+	-	UK
		F/70	1.3	UK	ND	ND	ND	ND	+	-	ND	ND	+	+	UK
		F/67	1.7	UK	ND	+	ND	ND	+	-	ND	ND	+	+	UK
		F/60	2.6	UK	ND	+	ND	ND	+	+	ND	ND	+	+	UK
		F/47	1.3	UK	ND	+	ND	ND	+	-	ND	ND	+	-	UK
		F/80	0.6	UK	ND	+	ND	ND	+	+	ND	ND	+	-	UK
		F/46	0.6	UK	ND	+	ND	ND	+	-	ND	ND	+	-	UK
75	Zhang *et al.* (17)	F/45	1.0	W+SLN +C/XRT	-	ND	+	ND	+	-	-	-	+	+	A&W 12
Present 76-77	Wei *et al.*	F/72	2.2	M+SLN	+/-	+	+/-	+	+	-	-	-	+	+	A&W 6
		F/70	1.6	M	-	+	+	+	+	-	-	-	+	+	A&W 33
Sum		F/40-80 (64)	0.6-5.5 (1.4)	W 17/43(39.5%); S 10/43(23.3%); Q 4/43(9.3%); M 6/43(14%)	- 43/44; +/- 1/44	+ 19/19	+/- 6/14; + 6/14; - 2/14	+ 2/2	+ 42/53	TNBC 33/50(66%)			IDH2 46/52(88.5%); PIK3CA 30/42(71.4%); Both 26/42(61.9%)		3-132 (29) Local recurrence1, Bone metastasis 1

F, female; UK, unknown; AL, axillary lymph node dissection; W, wide excision; Q, quadrantectomy; S, segmental resection; M, mastectomy; SLN, sentinel lymph node excision; C, chemotherapy; XRT, irradiation; HT, hormonal treatment; ER, estrogen receptor; PR, progesterone receptor; AR, androgen receptor; HER-2, human epidermal growth factor receptor 2; CK, cytokeratin; TTF-1, thyroid transcription factor-1; +\–, focal positive; +, positive; –, negative; ND, not done; A&W, alive and well.

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