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Tall Cell Carcinoma with Reversed Polarity in the Breast: A Case Report with Review of Literature

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Abstract

Tall cell carcinoma with reversed polarity (TCCRP) is a relatively new entity that is recognized as a subtype of epithelial tumors of the breast in the latest World Health Organization classification of breast tumors (fifth edition). This tumor bears close morphological resemblance to the tall cell subtype of papillary carcinoma of the thyroid. TCCRP is recognized by its distinct morphologic and immunohistochemical patterns, occasionally aided by molecular analysis for the presence of associated characteristic *IDH2* mutations.

A 42-year-old woman with a left breast lump was evaluated at another institute and diagnosed with invasive mammary carcinoma (no special type), and subsequently underwent a modified radical mastectomy. Our institute received the case for review. On histopathological examination, the sections revealed a fairly circumscribed lesion composed of nests of tall cells with apically located nuclei. After correlation with immunohistochemistry markers, a diagnosis of TCCRP was established. The patient was further managed with adjuvant chemotherapy and was declared disease-free on 1-year follow-up.

We report this lesion as it is a novel breast tumor, and a thorough understanding of its morphological appearance is essential to establish the diagnosis. A lack of awareness may result in misdiagnosis, with the lesion possibly being categorized as a nonspecific malignancy or misinterpreted as another papillary breast lesion. Given its favorable prognosis, accurate diagnosis of this tumor is imperative. When evaluating papillary breast lesions, TCCRP should be a key differential consideration.

Keywords
- tall cell carcinoma
- *IDH2* mutation
- TCCRP
- reversed polarity
- case report

Introduction

Tall cell carcinoma with reversed polarity (TCCRP) is a rare malignancy introduced as a new subtype under epithelial tumors of the breast as per the fifth edition of World Health Organization (WHO) classification of breast tumors, 2019.[1] TCCRP has been categorized under "rare and salivary gland–type tumors" due to its hallmark histological characteristics and molecular alterations. Crucially, this distinction helps differentiate it from other papillary breast lesions.[1] TCCRP was formerly described by a variety of other terminologies, which are now discouraged, including solid papillary carcinoma with reversed polarity, breast tumor resembling tall cell variant of papillary thyroid cancer, and solid papillary breast carcinoma resembling tall cell variant of papillary thyroid cancer.[1–3]

These tumors show morphological similarity to the tall cell subtype of papillary thyroid carcinomas (PTCs) but are

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negative for thyroid transcription factor-1 (TTF-1) and thyroglobulin. Additionally, *RET/BRAF* mutations, which are typically associated with PTC, are absent in these tumors.[2,4,5]

Identifying and categorizing this tumor as a separate entity is important due to its indolent nature. TCCRP has characteristic histologic, immunohistochemical, and molecular features that help distinguish it from other papillary lesions of the breast, as well as PTC. We document this case for its rarity, unique histopathological and immunohistochemical features, and the fact that it has a better clinical course, and may be misdiagnosed as its more aggressive counterpart.

Case Report

A 42-year-old woman presented with a complaint of a lump in the left breast for over 3 months at an outside institution. Following initial evaluation, a wide local excision was performed, which was histologically reported as invasive ductal carcinoma (no specific type). A modified radical mastectomy was then scheduled and completed in 1 month. The slides and tissue blocks were sent to our institute for a second opinion and further evaluation.

Microscopy

Histopathological examination revealed a fairly circumscribed breast tumor composed of tall cells arranged predominantly in solid nests (►**Fig. 1A**). These nests were surrounded by dense fibrous stroma, with some of the nests containing central, thin fibrovascular cores (►**Fig. 1B**), and collections of foamy histiocytes (►**Fig. 1C**). Cystic areas filled with acellular, homogenous, eosinophilic material were also noted within the tumor (►**Fig. 1D**). The individual cells were columnar with abundant eosinophilic cytoplasm, arranged in a palisading manner perpendicular to the basement membrane. The tumor cells had round-to-ovoid bland nuclei, which demonstrated reversal of polarity, being localized at the apex. Mitosis was relatively rare.

Immunohistochemistry

By immunohistochemistry (IHC), the tumor cells were positive for androgen receptor (AR) and epidermal growth factor receptor (EGFR), focally positive for estrogen receptor (ER) and progesterone receptor (PR). The cells were negative for human epidermal growth factor receptor 2 (HER2/neu) (►**Fig. 2**). E-cadherin positivity was noted, which was localized along the lateral membranes (►**Fig. 3**). The expression of p63 protein was negative in the tumor cells. Ki-67 labeling index was 10% in the hot-spot areas, suggesting reduced proliferative activity.

With the above characteristic morphologic features and IHC staining pattern, a diagnosis of TCCRP was rendered in accordance with the essential criteria as per WHO.

The patient received four cycles of adjuvant chemotherapy and has remained disease-free during the last 1 year of follow-up.

Discussion

As described initially in a series of five cases by Eusebi et al in 2003 as a breast lesion with morphologic features strongly resembling PTC, our understanding of this infrequent subtype of mammary carcinoma has grown over the years. Eusebi et al utilized IHC to rule out thyroid metastasis and prove the origin

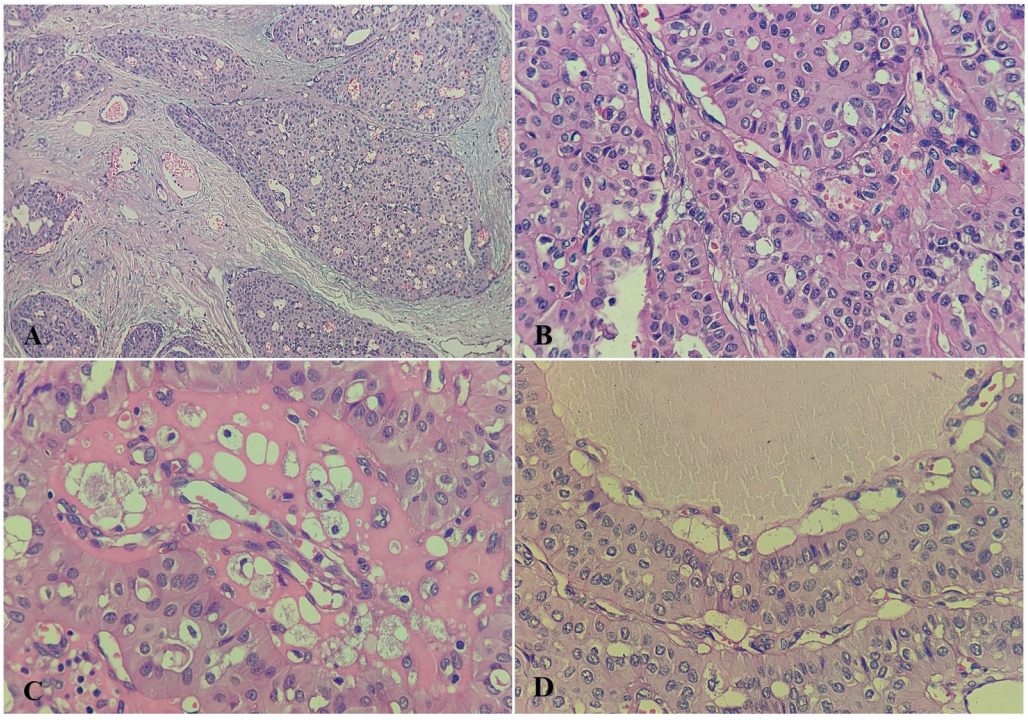

Fig. 1 (**A**) Nests of tumor cells (H&E, ×100). (**B**) Tumor nests with central fibrovascular cores (H&E, ×400). (**C**) Cyst macrophages within eosinophilic material (H&E, ×400). (**D**) Cystic space containing acellular eosinophilic material, lined by columnar cells with reversed nuclear polarity (H&E, ×400). H&E, hematoxylin and eosin.

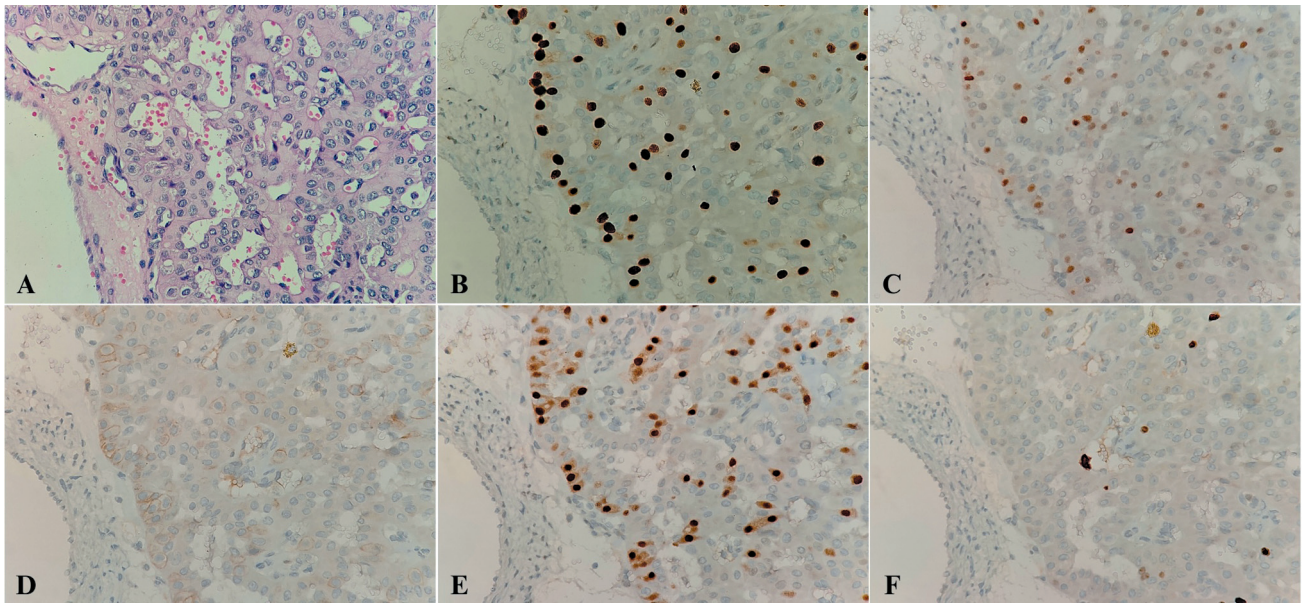

Fig. 2 (**A**) Tumor (H&E, ×400). (**B**) Focal positivity for ER (IHC, ×400). (**C**) Weak positivity for PR (IHC, ×400). (**D**) HER2/neu negative (IHC, ×400). (**E**) Positive AR expression (IHC, ×400). (**F**) Ki-67 labeling index 10% (IHC, ×400). AR, androgen receptor; ER, estrogen receptor; H&E, hematoxylin and eosin; IHC, immunohistochemistry; PR, progesterone receptor.

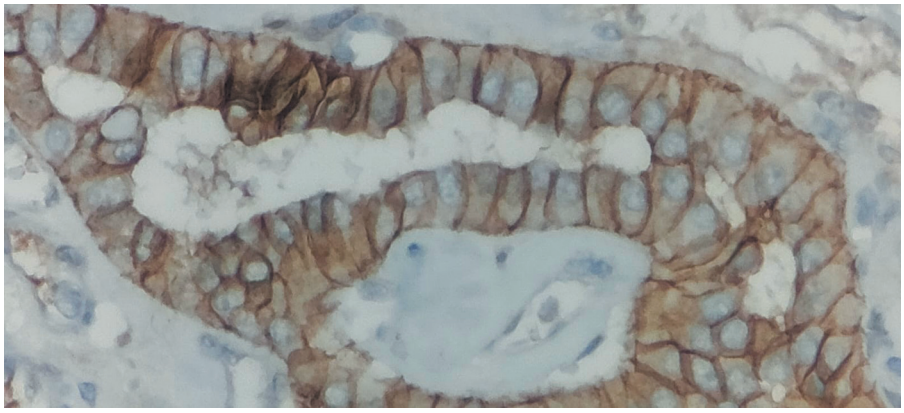

Fig. 3 Characteristic lateral membrane E-cadherin staining (IHC, ×400). IHC, immunohistochemistry.

of the lesion from the breast (the lesional cells were consistently negative for TTF-1 and thyroglobulin).[2]

TCCRP has been reported only in women to date, and is known to occur at a median age of 64 years with an age range between 39 and 89 years.[1,6] In the case described earlier, the tumor measured 2.2 cm in the biggest dimension, which falls within the reported size range of 0.6 to 5 cm.[1,7] TCCRP has an excellent prognosis and very low metastatic potential, with very few cases in the literature showing nodal metastasis.[1,7–9]

TCCRP shows considerable variation in its morphology. The tumor is composed of infiltrative neoplastic cells often arranged in solid nests, follicular, and papillary patterns, interspersed with occasional thin fibrovascular cores. Varying proportions of a cribriform pattern may be identified in the tumor. In their case series, Chiang et al highlighted that TCCRP characteristically demonstrated double layering of the columnar cells with apically located nuclei and correlated the absence of apical and basal membrane E-cadherin expression as confirmatory of the reverse polarization.[10,11]

Aggregates of foamy macrophages may be seen within the tumor nests. A few tumors also show cystic areas filled with colloid-like material. The individual cells are cuboidal to columnar with eosinophilic cytoplasm and a round to oval nucleus situated at the apex. The abundance of mitochondria contributes to cytoplasmic eosinophilia.[11] Other features include the presence of nuclear grooving or pseudo-nuclear inclusions. The tumor nests are often surrounded by a dense fibrous stroma.[1,2,12] The case we have described displayed many of these features. In addition, some cases of TCCRP may be atypical with polygonal tumor cells, with only a few of them showing reversed polarity.[13]

Based on histomorphology, the differential diagnosis includes metastatic deposits from PTC or papillary lesions native to the breast, such as papillary carcinoma. The thyroid rarely metastasizes to the breast and around 5% of such metastatic lesions may be deposits from PTC.[5] In such instances, a detailed history, diagnostic imaging, and an appropriate IHC panel are effective in delineating the

origin of the lesion. In our patient, a thorough physical examination was done at the time of presentation, and due to the lack of findings suggestive of a thyroid lesion, the need to do thyroid imaging and thyroid profile testing was ruled out.

TCCRP has its own specific immunohistochemical expression pattern. The tumor cells are triple negative or may show focal weak positivity for ER and PR, but consistently lack overexpression of HER2/neu. Low-molecular-weight cytokeratin CK7 and high-molecular-weight cytokeratin CK5/6 show positive expression, a pattern resembling intraductal papilloma with usual ductal hyperplasia, which is also a differential diagnosis. However, intraductal papillomas are surrounded by myoepithelial cells, which are highlighted by p63 or calponin, whereas TCCRP shows loss of the myoepithelial layer around the tumor nests.

Calretinin expression is frequently observed.[11,14] AR may or may not be expressed. In doubtful cases, origin from the breast is verified by the expression of mammaglobin, GCDFP-15, or GATA3. TCCRP is invariably negative for markers that denote thyroid origin, including TTF-1 and thyroglobulin. Ki-67 labeling index is often low (<10%).[7,12,14,15]

Chiang et al described a series of 13 cases in which 10 cases (77%) harbored a hotspot somatic mutation at R172 (Arg residue 172) of the *IDH2* gene. This mutation allows gain of function with subsequent blockade of cellular differentiation via hypermethylation of epigenetic sequences. Additionally, Chiang et al documented the presence of concurrent mutations in PI3K pathway-related genes such as *PIK3CA*.[1,3,10,16] Breast carcinomas rarely have characteristic genotype–phenotype mutations. Some breast malignancies associated with specific mutations include mucoepidermoid carcinoma (*CRTC3–MAML2*), adenoid cystic carcinoma (*MYB–NFIB*), lobular carcinoma (*CDH1*), etc. TCCRP falls into this category with an associated *IDH* mutation.[17,18] *IDH* mutations are often detected in glioma, chondrosarcoma, cholangiocarcinoma, and acute myeloid leukemia. TCCRP is the only invasive mammary carcinoma with an associated *IDH2* mutation.[1,6,17] Identification of *IDH2* mutations in this tumor opens the door to the possibility of targeted therapy.[10] TCCRP may also show the presence of *TET2* mutations.[3,16] Additional mutations associated with TCCRP in published literature include *PRUNE2* mutations with *ATM*, *KIT*, and *MET* alterations.[7,14,19]

This is the first case of TCCRP reported at our institute. Though the diagnosis was rendered mainly based on histomorphology, the use of IHC as a supplementary tool lent strength to it. A molecular test may prove useful due to the characteristic mutations associated with TCCRP; however, this is not mandatory for diagnosis as per the essential and desirable diagnostic criteria outlined by WHO.[1] It is essential to precisely identify and document newer morphological subtypes, as these are gray areas and will contribute critical information to the existing data on their behavior and response to therapy over time. Our case report is limited by the lack of molecular profiling data as well as the paucity of references available, given that TCCRP is a newly classified entity.

Conclusion

TCCRP is a lesion that requires a high index of suspicion for diagnosis. We document this case of breast tumor with specific histopathological features to contribute to the growing body of literature on TCCRP. Understanding their morphology, which strikingly resembles the tall cell subtype of PTC, is key to a precise assessment. IHC workup and molecular analysis may be employed as ancillary studies to assist in doubtful situations to distinguish it from its morphological mimickers. The favorable prognosis associated with this malignancy underscores the importance of its accurate identification.

Authors' Contributions

M.S.K. was involved in data collection, manuscript preparation, and literature search. S.B. contributed to manuscript preparation and manuscript editing. S.S. gave the concept design and was involved in manuscript editing and final manuscript review. M.M. contributed to manuscript review and clinical treatment. All authors have read and approved the final manuscript and believe that the manuscript represents honest work.

Patient's Consent

Written informed consent was obtained from the patient for the publication of this case report, including clinical details, pathological findings, and associated images. The patient understands that their identity will be protected, and the information will be used for educational and scientific purposes.

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None.

Conflict of Interest

None declared.

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