Encapsulated Papillary Carcinoma of the Breast: Two Cases with Literature Review and Molecular Insights

KOMEIL MIRZAEI BABOLI, MD; SARA SALEHIAZAR, MD; TRUC TRAN, MD

ABSTRACT

INTRODUCTION: Encapsulated papillary carcinoma (EPC) of the breast is a rare subtype of breast cancer, accounting for 0.5–2% of cases, and typically affects postmenopausal women. Characterized by well-circumscribed lesions lacking peripheral and central myoepithelial cells, EPC is associated with favorable prognosis due to its indolent behavior and high hormone receptor positivity. However, its potential association with ductal carcinoma in situ (DCIS) or invasive carcinoma necessitates thorough diagnostic evaluation.

CASE PRESENTATION: This study presents two cases of EPC—one in a 57-year-old and the other in a 39-year-old female—each with focal DCIS and strong estrogen and progesterone receptor expression. Both patients underwent breast-conserving surgery and were managed with hormone therapy.

CONCLUSION: Histopathological and immunohistochemical analyses confirmed the EPC diagnosis, and molecular insights revealed common mutations, particularly in the PIK3CA gene. This report underscores the importance of integrating clinical, histological, and molecular findings to guide diagnosis and management of EPC, which, despite its low invasive potential, shares genetic features with invasive ductal carcinoma.

KEYWORDS: papillary carcinoma; breast cancer

INTRODUCTION

Encapsulated papillary carcinoma (EPC) of the breast is a rare neoplasm and account for 0.5–2% of all breast cancer. EPC was first described in 1969,[1] and is typically characterized by a well-defined, slow-growing mass within the breast parenchyma. It predominantly affects postmenopausal women and often presents with favorable prognostic features, including low-grade histology and a high likelihood of hormonal receptor positivity, which can be treated with hormonal targeted therapy.[2] While EPC generally lacks invasive potential, its association with adjacent ductal carcinoma in situ (DCIS) or invasive carcinoma necessitates a comprehensive diagnostic and therapeutic approach.[1-3] A study suggested that the EPC capsule represents a reactive process characterized by increased collagen fiber width and density. This information supports the conclusion that EPC is an indolent invasive carcinoma based on the properties of its capsule.[3] Molecular analysis revealed that all invasive carcinomas associated with EPC exhibit recurrent hotspot mutations in the PIK3CA gene.[4]

This paper presents two cases of EPC, detailing its clinical course, diagnostic challenges. Additionally, we review the existing literature to provide insights into the histopathological and immunohistochemical (IHC) characteristics of EPC, with an emphasis on its molecular profile. By examining these two cases in conjunction with the current body of knowledge, we aim to enhance understanding of this uncommon entity and its implications for diagnosis, management, and prognosis.

CASE REPORT

Case 1

A 57-year-old woman with a medical history of morbid obesity and a prior hysterectomy for endometriosis presented with a slow-growing mass in the left breast, first noted four years ago. The mass was asymptomatic, with no associated pain or nipple discharge. She admitted to being noncompliant with routine mammography screenings during her 50s. Her family history was negative for breast carcinoma in first-degree relatives.

On physical examination, a 2.5 cm mass was palpated in the lower outer quadrant of the left breast. There were no signs of ulceration, edema, or axillary lymphadenopathy. Mammography revealed a high-density, oval-shaped mass with circumscribed margins, and ultrasonography (US) identified a hypoechoic lesion at the 5 o'clock position, 6 cm from the nipple, measuring 2.7 × 1.7 × 1.6 cm. An US-guided biopsy demonstrated carcinoma with papillary features. IHC staining was negative for p63, CD10, and calponin in the papillary fronds.

The clinical stage of the lesion was determined to be cT2N0Mx. Breast-conserving surgery was planned, and the patient underwent a left breast lumpectomy. Final pathological examination revealed a papillary lesion with a well-circumscribed border and a loss of both central and peripheral myoepithelial cells [**Figure 1**]. IHC staining showed negative expression for CD10 and p63 [**Figure 2**] and positivity for

Figure 1. Encapsulated Papillary carcinoma, H&E, 40x. Solid arrow shows thick fibrous capsule.

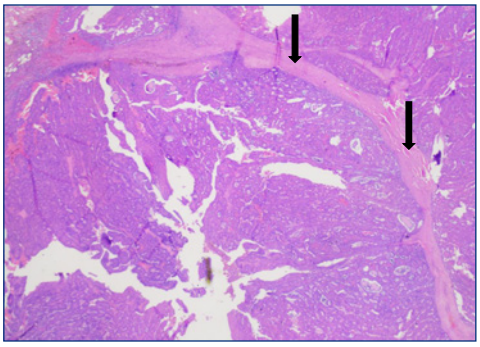


Figure 2. Encapsulated Papillary carcinoma, IHC stain, P63 negative on the papillae and periphery.

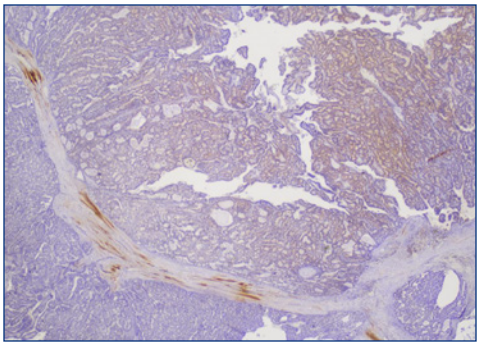
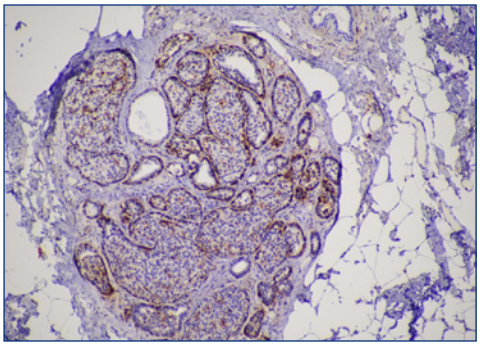


Figure 3. Ductal carcinoma in situ, IHC stain, CD10 highlights the myoepithelial cells.



CAM5.2, consistent with encapsulated papillary carcinoma (EPC). Additionally, focal areas of adjacent conventional-type ductal carcinoma in situ (DCIS) with low nuclear grade and no necrosis were identified and CD10 highlighted the myoepithelial layer [**Figure 3**].

The final staging was revised to pTisN(na)M(na). Due to the tumor's high estrogen receptor (ER) and progesterone receptor (PR) positivity (>90%) and HER2 negativity, the patient was initiated on adjuvant therapy with Anastrozole for a planned duration of five years.

Case 2

A 39-year-old woman with a medical history of obesity, hypertension, and uterine fibroids presented with a palpable, painless mass in the right breast. She reported no nipple discharge or skin changes. Her family history was negative for cancer among first-degree relatives.

On physical examination, a 2 cm mass was detected in the lower outer quadrant of the right breast. There were no signs of ulceration, edema, or axillary lymphadenopathy. Mammography revealed a mass with irregular borders, categorized as BIRADS 4b, and ultrasonography (US) identified a hypoechoic, irregular lesion at the 7 o'clock position, 4 cm from the nipple, measuring 2.2 × 2 × 1.5 cm. An US-guided biopsy confirmed papillary carcinoma, with IHCstaining negative for p63 and CK5/6.

The clinical stage was determined as cT2N0Mx. Breast-conserving surgery was planned, and the patient underwent a wide local excision of the right breast with sentinel lymph node biopsy. Final pathology revealed a papillary lesion with poorly circumscribed borders and a loss of central and peripheral myoepithelial cells [**Figure 4**]. IHC staining showed negative expression for CD10, calponin [**Figure 5**] and P63, consistent with EPC of intermediate nuclear grade. Additionally, focal areas of adjacent DCIS with intermediate nuclear grade and focal necrosis were identified; CD10 and calponin [**Figure 6**] highlighted the myoepithelial layer. All lymph nodes were negative for metastatic carcinoma.

The final pathological stage was revised to pTisN0M(na). Hormone receptor testing showed the tumor was positive for estrogen receptor (ER, 85%) and progesterone receptor (PR, 50%). Given the patient's young age, genetic counseling was recommended.

DISCUSSION

Encapsulated papillary carcinoma (EPC) is a rare subtype of breast cancer classified as a distinct entity by the World Health Organization (WHO). It is characterized by unique clinicopathological and molecular features and is often associated with a favorable prognosis. Representing 0.5–2% of breast cancers, EPC predominantly affects postmenopausal

Figure 4. Encapsulated Papillary carcinoma, H&E, 40x. Solid arrow shows thick fibrous capsule.

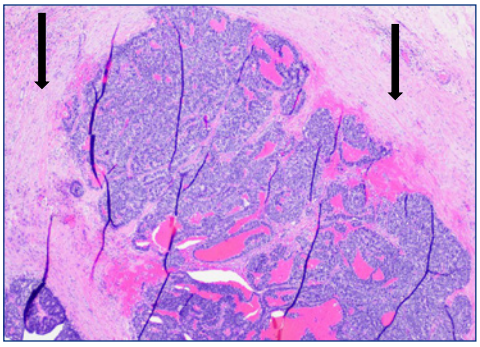


Figure 5. Encapsulated Papillary carcinoma, IHC stain, Calponin negative on the papillae and periphery.

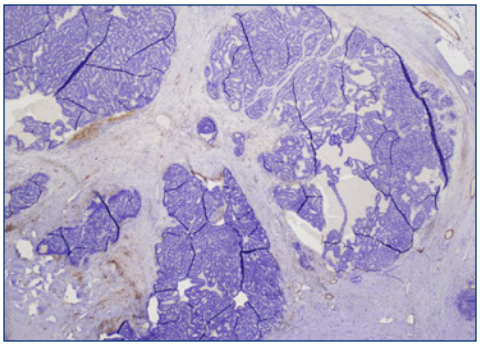
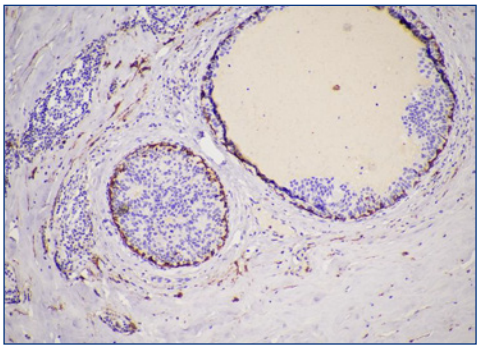


Figure 6. Ductal carcinoma in situ, IHC stain, Calponin highlights the myoepithelial cells.



women, with a median age at diagnosis of 65 years. Typically located beneath the nipple or areola, it presents as a retroareolar, painless lump or a solid-cystic mass, with diameters ranging from 0.3 to 6 cm and occasionally up to 15 cm, as reported in some studies. Symptoms may include nipple discharge or hemorrhage. Ill-defined margins are commonly linked to an invasive component.[1,2,4,6]

Histologically, EPC is characterized by a thick fibrous capsule, a solid-cystic structure, and papillary formations. A distinct histopathological feature is the absence of myoepithelial cells at the periphery and within the papillae.[1,2,3,6]

Imaging modalities like ultrasound, mammography, and MRI play a crucial role in diagnosing EPC. MRI offers superior visualization of lesion architecture and is particularly effective in identifying invasive components or associated DCIS. Ultrasound outperforms mammography in distinguishing between benign and malignant papillary lesions, with a sensitivity of 56% and specificity of 90%, compared to mammography's sensitivity of 69% and specificity of 25%.[1]

EPC is characterized by papillary structures enclosed within a fibrous capsule and an absence of myoepithelial cells. The tumor cells typically display low- to intermediate-grade nuclei, with occasional apocrine differentiation. Diagnosis relies on myoepithelial markers such as p63, CK5/6, and calponin, which help differentiate EPC from other papillary lesions, as these markers are negative at the papillae and periphery. The absence of myoepithelial cells suggests an invasive potential, despite the tumor's generally indolent behavior.[1,5]

Tumor cells in EPC demonstrate strong positivity for the estrogen receptor (ER) and variable expression of the progesterone receptor (PR). The Ki67 index indicates low proliferative activity in EPC. Human epidermal growth factor receptor 2 (HER-2) is almost always negative, though some studies have reported positive cases.[1,2,4,5] Approximately one-third of EPCs are found alongside conventional ductal carcinoma in situ (DCIS), while another third is associated with invasive ductal carcinoma (IDC). Despite some overlapping features, EPCs are typically staged as in situ lesions due to their encapsulated morphology and low metastatic potential.[4]

EPC is enclosed by a thick fibrous capsule, characterized by a higher content of collagen I and reduced collagen III compared to normal breast tissue and ductal carcinoma in situ (DCIS). Unlike the thin, organized basement membrane (BM) observed in normal tissue or DCIS, the EPC capsule displays a heterogeneous structure with straighter, shorter, and more disorganized fibers. The capsule consists of distinct inner and outer regions: the outer layer is denser and richer in collagen I, while the inner layer has a higher proportion of collagen III. These findings suggest that the capsule formation in EPC is a reactive process.[3]

Matrix metalloproteinases (MMPs) are molecular markers associated with invasiveness and tumorigenesis. The expression profile of MMPs in EPC falls between that of DCIS and IDC, suggesting that the invasive potential of EPC is intermediate between these two conditions.[1,4]

EPC exhibits genetic similarities with estrogen receptor-positive IDC, including PIK3CA mutations and chromosomal gains on 16p and 1q. Additionally, mutations in chromatin-remodeling genes, such as CREBBP and KMT2A, have been reported. Other mutations, like TP53 and GATA3, show more variability and occur in only a subset of cases.[1,4]

The standard treatment for EPC includes local excision or mastectomy. Sentinel lymph node biopsy (SLNB) is recommended for invasive EPC due to the possibility of lymph node involvement. Adjuvant therapies, including radiotherapy, are recommended for patients with associated DCIS or after breast-conserving surgery. Hormonal therapy is used for hormone receptor-positive EPC, while HER2-targeted therapies are applied in HER2-positive cases.[1,5,6]

EPC generally has an excellent prognosis, with low recurrence and metastasis rates. High-grade EPC, characterized by hormone receptor negativity and elevated Ki-67, shows more aggressive behavior and warrants systemic therapy. Long-term survival exceeds 90%, with similar outcomes for pure EPC, EPC with DCIS, and EPC with invasive carcinoma.[1,6]

When there is frank invasion arising from the papillary neoplasms, such as encapsulated papillary carcinoma, ductal carcinoma in-situ with papillary type, or solid papillary carcinoma, it is treated the same as other invasive carcinomas of the breast and the treatment approaches are similar to those. This is the same when there is metastasis. CDK4/6 inhibitors are FDA-approved to treat ER/PR positive/Her2 negative tumor.[7]

CONCLUSION

The findings from the literature, including data on genetic alterations, MMP levels, capsule characteristics, and the Ki67 index, suggest that this tumor possesses a low invasive potential. However, its shared genetic pathway with IDC grants it the capability to progress into invasive carcinoma and metastasize to lymph nodes.

Our case presents a classical ER- and PR-positive EPC with concurrent DCIS, managed through local excision with negative margins and hormone therapy. Follow-up demonstrated excellent outcomes, with no recurrence or metastasis, consistent with the prognosis for low-grade EPC.

References

1. Changrong W, Zhibo Z, Jufeng, Hongju Y, et al. Encapsulated Papillary Carcinoma of the Breast: A Review of Clinicopathologic Characteristics, Molecular Mechanisms, and Patient Management. Cancer Control. 2024 Jan-Dec:31. doi: 107327 48241299071
2. Tan HJ, Tan PH, Leong LCH, Tan VKM, et al. Encapsulated papillary carcinoma of the breast: An institutional case series and literature review. Cancer Med. 2023 May;12(10):11408-11416. doi: 10.1002/cam4.5855
3. Ghannam SF, Rutland CS, Allegrucci C, Mongan NP, Rakha E. Encapsulated papillary carcinoma of the breast: does it have a native basement membrane? Histopathology. 2023;83, 376–393. https://doi.org/10.1111/his.14939
4. Schwartz CJ, Boroujeni AM, Khodadadi-Jamayran A, Heguy A, et al. Molecular analysis of encapsulated papillary carcinoma of the breast with and without invasion. Hum Pathol. 2021 May:111:67-74. doi: 10.1016/j.humpath.2021.02.005
5. Kulka J, Madaras L, Floris G, Lax SF. Papillary lesions of the breast. Virchows Archiv 2022;480:65–84. doi: 10.1007/s00428-021-03182-7
6. Xu L, Mao Q, Gao Y, Luo L, et al. Encapsulated papillary carcinoma of the breast: A single institution experience. Oncol Lett. 2023 Sep 7;26(4):459. doi: 10.3892/ol.2023.14046
7. Wang X, Zhao S, Xin Q, et al. Recent progress of CDK4/6 inhibitors' current practice in breast cancer. Cancer Gene Ther. 2024;31:1283–1291(https://doi.org/10.1038/s41417-024-00747-x

Authors

Komeil Mirzaei Baboli, MD, Department of Pathology, Harbor-UCLA Medical Center, Torrance, CA.

Sara Salehiazar, MD, Department of Pathology, Yale School of Medicine, New Haven, CT.

Truc Tran, MD, Department of Pathology, Harbor-UCLA Medical Center, Torrance, CA.

Disclosures

Funding: Not applicable

Conflicts of interest/Competing interests: The authors declare that they have no conflicts of interest relevant to this study

Ethics approval: Not applicable

Consent to participate: Consented

Written Consent for publication: Consented

Correspondence

Komeil Mirzaei Baboli, MD
Department of Pathology, Harbor-UCLA Medical Center
1000 W Carson St, Torrance, CA 90502
424-306-66410
Fax 424-306-66400
KMirzaeiBaboli@dhs.lacounty.gov