

## Papillary carcinoma of breast: Minireview

Sachin B Ingle, Hemant G Murdeshwar, Saleha Siddiqui

Sachin B Ingle, Saleha Siddiqui, Department of Pathology, MIMSR Medical College, Latur 4132512, India

Hemant G Murdeshwar, Department of Pathology, Dr.V.M. Government Medical College, Maharashtra 413003, India

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**Correspondence to:** Sachin B Ingle, Professor, Department of Pathology, MIMSR Medical College, Ambajogai Road, vishwanathpuram, Latur 4132512, India. [dr.sachiningle@gmail.com](mailto:dr.sachiningle@gmail.com)  
Telephone: +91-2382-227424  
Fax: +91-2382-228939

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### Abstract

The term "intracystic papillary ductal carcinoma *in situ*" constitutes only 0.5% to 1% of all breast cancers. It is usually seen in postmenopausal age group. Herein, we are presenting a minireview about this unusual breast

malignancy usually difficult to diagnose on clinical grounds and highlighting modalities of diagnosis and management.

**Key words:** Papillary carcinoma breast; Intracystic; Solid; Diagnosis and management

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**Core tip:** The oncosurgeon and surgical pathologist should keep in mind this rare type of *in situ* carcinoma as a differential diagnosis in palpable breast lumps as it often mimics a benign lesion clinically. However, careful histopathological evaluation superadded by immunohistochemistry is an effective tool to arrive at the correct pathological diagnosis to avoid untoward complications related to under diagnosis and/over diagnosis.

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### INTRODUCTION

Papillary carcinoma (PC) of the breast constitutes 0.5% to 1% of all breast cancers<sup>[1-10]</sup>. PC can be either localized or diffuse<sup>[3,8,10-13]</sup>. In comparison with intracystic PC, solid PC is featured by mucin production exhibiting neuroendocrine features, and is usually multinodular<sup>[13,14]</sup>. Papillary ductal carcinoma *in situ* (DCIS) is characteristically surrounded by a myoepithelial cells<sup>[3,11]</sup>. Clinical presentation is either as subareolar mass and/or nipple discharge<sup>[11]</sup>. The newer entity encapsulated PC has been described<sup>[15-17]</sup> and solid papillary carcinoma<sup>[13,14]</sup> are well encapsulated and well circumscribed circumscribed with absence of myoepithelial cells.

## EPIDEMIOLOGY

### Age

Mainly seen in postmenopausal age.

### Sex predilection

Intracystic papillary carcinoma (IPC) is extremely rare in males<sup>[18-20]</sup>. The clinical presentation in males is similar to that in females except for a higher median age in males (60 vs 53 years)<sup>[19]</sup>.

### Incidence

Majority of the cases had localized involvement (89.6%). Approximately 7.8% had regional disease, with local spread, and (0.4%) presented with distant metastases<sup>[20,21]</sup>.

## PATHOPHYSIOLOGY

The contributing predisposing factors are risk factors are genetic predisposition, age, family history, dietary factors, alcoholism, weight gain and endocrine factors.

### Age

It had been observed that breast cancer the incidence gradually increases with age. By the age 90 one fifth of women are affected<sup>[22-25]</sup>.

### Gender

Males are affected less commonly as compared to females (incidence less than 1%)<sup>[22,26]</sup>.

### Genetic factors

Family history is an important contributing risk factor<sup>[22]</sup>. Women with one or more first degree relatives with breast cancer have more risk<sup>[23]</sup>.

### Diet and alcohol

The diet low in phyto-oestrogens and alcohol intake are predisposing factors for the disease<sup>[22]</sup>. Ingestion of dietary fibres is protective<sup>[25]</sup>.

### Obesity lifestyle and physical activity

Due to excess estrogen synthesis from adipose tissue, obesity is an important contributory factor<sup>[23,25]</sup>.

### Endocrine factors (endogenous)

Incidence of breast cancer is more in infertile females as the level of estrogen is lower in pregnancy and in women that had many children<sup>[22,23]</sup>.

### Exogenous factors

Hormone replacement therapy and oral contraceptives is associated with breast cancer<sup>[23,25]</sup>.

### Molecular genetics of breast cancer

Five to ten percent of breast malignancies arise due to germ-line mutations in genes such as *BRCA1*, *BRCA2*,

*p53* and *PTEN*<sup>[22,23,25,26]</sup>.

### Role of HER-2/neu antigen

HER-2/neu antigen is a growth factor protein, *i.e.*, over-expressed in breast cancers and is bad prognostic indicator<sup>[27-29]</sup>.

### Steroid hormones and their receptors

The adipose tissues forms estrogen from circulating cholesterol predisposing to breast cancer<sup>[30]</sup>.

Malignancies that depend on steroid hormones include breast, prostate, testicular, ovarian and endometrial cancer<sup>[24,31-33]</sup>.

## CLINICAL PRESENTATION

PC is commonly seen in postmenopausal age group. This form of breast cancer generally presents with painless breast lump hemorrhagic nipple discharge. Only few cases were reported below the age of 40 years<sup>[34,35]</sup>.

## DIAGNOSTIC EVALUATION

### Mammography

On a mammography usually revealed as a round, oval calcific opacity. The margin of the mass is usually well circumscribed, but may be indistinct at places indicating inflammation or invasion. The differential diagnosis includes colloid or medullary carcinoma, invasive ductal carcinoma, hematoma benign cyst or adenofibroma<sup>[35]</sup>.

### Sonography

On ultrasonography, it appears as cystic masses, with or without presence of septa<sup>[36,37]</sup>. Although some radiologic features, such as posterior acoustic enhancement and associated micro calcifications, are more frequently associated with malignancy, the radiologic appearance cannot accurately predict the behavior of papillary lesions, and histological evaluation is necessary<sup>[38]</sup>.

### Magnetic resonance imaging

Magnetic resonance imaging using contrast enhancement can give details of morphology, *i.e.*, enhancement of cyst wall, septations and mural nodules<sup>[39]</sup>.

### Cytology

Cytological diagnosis may be missing as we can aspirate the fluid only. Fine needle aspiration cytology (FNAC) reveals atypical cells in the smear<sup>[1]</sup> (Figure 1). Sonography-guided vacuum-assisted core biopsy is much better option over aspiration cytology<sup>[40]</sup>. The gun biopsy mainly hits the solid centre of tumor and the invasive component can only be recognized at the periphery of the tumor; so, excisional biopsy of B3 papillary lesions is an effective approach to demonstrate invasion<sup>[38]</sup>. Recently ductoscopy can be used as a valuable tool in diagnosing such lesions<sup>[41]</sup>.

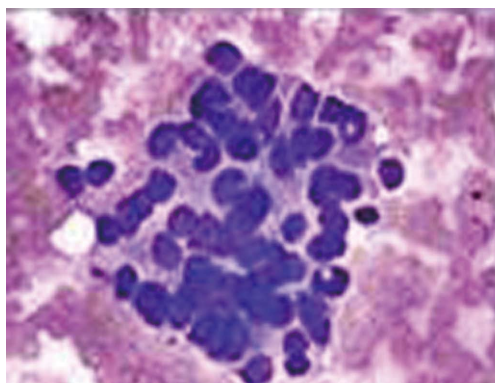


Figure 1 Fine needle aspiration cytology confirmed the presence of atypical cells.

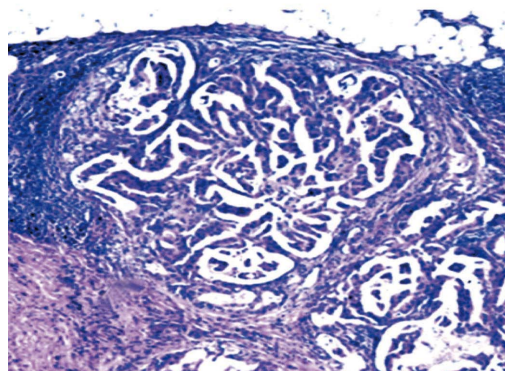


Figure 2 Low power view 10 × showing intraductal malignant cells arranged in papillary fronds exhibiting features of malignancy (*in situ* papillary carcinoma of breast).

### Histology

Prognostically IPC is a borderline lesion<sup>[42-44]</sup>. Microscopically *in situ* intracystic papillary tumor shows papillary, adenoid and cribriform structures lined by columnar cells exhibiting features of marked cytological atypia, *i.e.*, nuclear hyperchromasia, pleomorphism, abnormal mitosis and increased N:C ratio (nucleocytoplasmic ratio) with fibro vascular cores<sup>[1]</sup> (Figure 2). High nuclear grade and the presence of necrosis are bad prognostic indicators<sup>[43,45]</sup>.

A minority of the cases are associated with invasive component. The invasive areas rather exhibit histological features of an invasive ductal carcinoma not otherwise specified instead of usual papillary pattern<sup>[43]</sup>.

Usually it is difficult to differentiate between *in situ* and invasive lesions on FNAC and core biopsy, as invasion is often recognized at the periphery of the lesion. Hence, surgical excision is done for correct histological diagnosis and proper management<sup>[44,45]</sup>.

### DIFFERENTIAL DIAGNOSIS

Invasive features into the stroma, higher nuclear grade and necrosis differentiates the IPC from the intracystic (encapsulated) papillary breast which is usually of low or intermediate nuclear grade with no evidence of necrosis, strongly estrogen receptor (ER) positive, negative for C-erb2(Her2neu)<sup>[46]</sup>.

Differential diagnoses also include lesions like atypical ductal epithelial hyperplasia, lobular hyperplasia and DCIS<sup>[47,48]</sup>.

### Immunohistochemistry

Papillary carcinomas of the breast tend to be ER, progesterone receptor positive and Her2Neu negative<sup>[47,49,50]</sup>. Immunohistochemistry markers for myoepithelial cell layer (MCL) have an important role in invasion assessment with smooth muscle actin, p63, CD10, S-100, calponin, maspin commonly employed among which smooth muscle myosin heavy chain and p63 are more MCL specific<sup>[50,51]</sup>.

### TREATMENT

Treatment options are wide local excision, with or without adjuvant radiotherapy (RT), or mastectomy<sup>[9]</sup>. Tamoxifen is important drug as this cancer seems to be almost certainly hormonal positive and HER-2 negative<sup>[4,52]</sup>.

### RT

Adjuvant RT play role for invasive disease and or DCIS<sup>[4]</sup>.

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