



HISTOLOGICAL DIVERSITY OF BREAST CARCINOMA AT A TERTIARY CARE CENTER

Pathology

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ABSTRACT

Background- Breast carcinoma is comprised of distinct biological subtypes with varied natural history, clinicopathological features and molecular features with different therapeutic and prognostic implications. Thus a proper histological diagnosis and a special mention of the rare histological subtypes are required to formulate their treatment protocols.

Objective -The present study was designed to evaluate the frequency, clinical presentation and histological features of various types of breast carcinoma in a tertiary care center.

Materials and Methods-The present study was a prospective study, consisting of 43 cases of malignant breast tumours, conducted over a period of 2 years. The clinical, gross and microscopic features were studied in detail. Tumours were classified and graded.

Results - All the patients were female. Maximum number of patients (30.23%) were between 41-50 years. Lump in breast was the commonest presenting symptom. Upper outer quadrant was the most commonly involved region. Invasive ductal carcinoma – not otherwise specified (IDC-NOS) was the most common (79.06%) carcinoma. We found 9 cases of special subtypes which includes 2 cases of encapsulated papillary carcinoma, and a case each of invasive lobular carcinoma, carcinoma with medullary features, mucinous carcinoma, secretory carcinoma, low grade adenosquamous carcinoma, carcinoma with neuroendocrine features and invasive micropapillary carcinoma. Lymph node metastasis was seen in 14 cases (32.56%).

Conclusion- This study highlights the rarely encountered subtypes of breast carcinoma which differ in clinical presentation, outcome and has relevant prognostic implications.

KEYWORDS

Breast cancer, Breast lump, Special subtypes of breast cancer

INTRODUCTION

Invasive breast cancer is the most common carcinoma in women accounting for 23% of all cancers in women globally. The incidence of breast cancer increases rapidly with age. In India, breast carcinoma is the second most common malignancy in female next to uterine cervical carcinoma.(1)

A palpable mass is the most common clinical sign of invasive breast carcinoma. Patient may present with nipple retraction, nipple discharge, change in size of breast or enlargement of axillary lymph nodes. All these symptoms may be caused by benign breast lesions. So the evaluation with imaging and histological sampling are indicated to establish a definitive diagnosis.(1-3)

Invasive breast carcinoma exhibits a wide scope of morphological features, different immunohistochemical profile and unique histopathological subtypes. The morphological classification of invasive breast carcinoma is based upon features like architectural pattern, secretory products, cytomorphological types and growth pattern. The various histopathological subtypes have specific clinical course and outcome.-(4, 5)

Invasive carcinoma of no special type (IC-NST) or invasive ductal carcinoma not otherwise specified (IDC-NOS) is the most common type of invasive breast carcinoma. Special type of breast carcinoma comprises approximately 20-30% of invasive carcinoma.(1-3)

The wide histological diversity observed in invasive breast carcinoma has relevant prognostic implication and management of it is a real challenge. The histological type is one of the most useful pathological parameter in predicting breast cancer prognosis. Different histological subtypes have varied prognosis ranging from tubular carcinoma having indolent clinical course to metaplastic carcinoma generally having unfavourable outcome.(6)

The purpose of this study is to highlight histomorphological spectrum

of malignant breast tumours and distribution of various types of breast carcinomas.

MATERIALS AND METHODS

The present study was a prospective study of 43 cases undertaken at the department of pathology in our institute. The specimens were received in different forms such as modified radical mastectomy (MRM-33 cases), toilet mastectomy (4 cases), edge biopsy (2 cases), quadrantectomy (2 cases), lumpectomy (1 case) and simple mastectomy (1 case).

All relevant clinical data including patient's age, presenting symptoms, laterality and fine needle aspiration cytology (FNAC) findings if available were collected from requisition forms.

After overnight fixation in 10% neutral buffered formalin, thorough gross examination was carried out. The grossing was done according to standard protocol. The specimen size, tumour -size, colour, consistency, distance from margin, gross abnormality of skin and nipple areola were noted.

The representative sections including atleast three sections from tumour or 1 section/cm of tumour size, junction of tumour with adjacent tissue, margin, nipple areola complex, adjacent quadrant and axillary lymph node were taken.

These sections were further processed by routine paraffin embedding technique. The prepared blocks were cut in 3-5 micrometer in thickness and stained with hematoxylin and eosin. The histological features of 43 malignant breast tumours were studied and analysed.

RESULTS

In the present study all the patients were female and showed unilateral breast involvement. Right breast involvement was more common (51.16%) as compared to left breast (48.83%).

Age of the patient ranged from 31 to 96 years. The most common age

group of presentation was 41-50 years accounting for 13 cases (30.23%), followed by 51-60 years (20.90%). Age distribution of malignant breast tumours is given in Table 1.

Table 1: Age distribution of malignant breast tumours

Age group(in years)	No. of cases	Percentage
21 to 30	-	-
31 to 40	04	9.30%
41 to 50	13	30.23%
51 to 60	09	20.90%
61 to 70	07	16.27%
71 to 80	07	16.27%
81 to 90	02	4.70%
91 to 100	01	2.33%
Total	43	100%

The commonest presenting symptom was lump in breast, most frequently located in upper outer quadrant (25 cases) accounting for 58.13%, followed by upper inner quadrant 23.25%. We received specimens in various forms like MRM, simple mastectomy, lumpectomy etc.

On the basis of cell morphology, growth and architecture patterns, the tumours were classified according to World Health Organization (WHO) classification into different distinct histological types. In the present study, IDC-NOS was the most common histological type accounting for 79.06%(34 cases)(Fig 1)

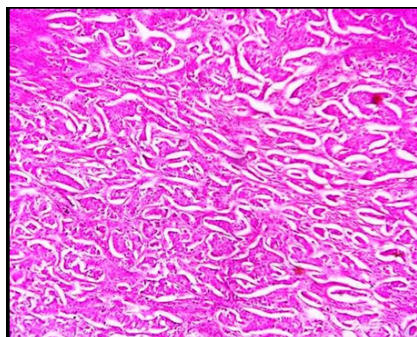


Figure 1: Photomicrograph of Invasive ductal carcinoma –not otherwise specified. HE x100

The frequency distribution of histological types of malignant breast tumours is given in Table 2.

Table 2: Distribution of histological types of malignant breast tumours

Sr No	Histological type of breast carcinoma	Number of cases	Percentage
1.	Invasive carcinoma-No special type	34	79.06%
2.	Invasive lobular carcinoma	01	2.33%
3.	Carcinoma with medullary features	01	2.33%
4.	Mucinous carcinoma	01	2.33%
5.	Secretory carcinoma	01	2.33%
6.	Encapsulated papillary carcinoma	02	4.62%
7.	Invasive micropapillary carcinoma	01	2.33%
8.	Metaplastic carcinoma (Low grade adenosquamous carcinoma)	01	2.33%
9.	Carcinoma with neuroendocrine features	01	2.33%
	Total	43	100

Lymph node metastasis were studied in 33 cases, out of which 14 cases showed lymph node metastasis. Fibrocystic change was the most common lesion in adjacent breast seen in 13 cases (30.23%). DCIS was found in 3 cases and ductal hyperplasia was seen in 1 case.

Invasive carcinoma of no special type and all other invasive breast carcinoma were graded by modified Bloom and Richardson's grading system. Grading were done in 40 cases majority were grade II accounting for 67.50%(27 cases). In the rest 3 cases grading was not

possible because of poor fixation of the specimens. Grading of various breast carcinomas is given in Table 3.

Table 3: Grading of breast carcinoma

Grade	Number of cases	Percentage(%)
Grade I	08	20.00%
Grade II	27	67.50%
Grade III	05	12.50%
Total	40	100

DISCUSSION

In the present study, we came across a variety of histological types of malignant breast tumours.

The most common age group affected was 41-50 years which is correlated with studies done by Qadri SK et al(7), Siddiqui et al(8) and Paul SN et al(9). Upper outer quadrant was the most common region involved which is in concordance with Paul SN et al.

IDC-NOS is the most common type of invasive breast carcinoma found in the present study. These findings were comparable with Dauda et al(10), Mudholkar et al(11), Njeze et al(12).

IDC-NOS represents the heterogenous group of tumours that fail to exhibit sufficient characteristic histology to classify as a specific histologic type. While some tumours having distinctive morphological features are classified as special subtype of breast carcinoma in which atleast 90% of a tumour should demonstrate the defining histologic characteristic.(1-3)

The distribution of histological type of invasive breast cancers has varied among published series. The frequency distribution of histological types of malignant breast tumors noted by different authors is shown in Table 4.

Table 4: Comparison of histological types of malignant breast tumours with different studies

Authors	Dauda et al (2011)	Mudholkar et al (2012)	Njeze et al (2014)	Present study
Total cases	165	125	28	43
Invasive carcinoma-NST	78.8	88	53.6	79.06
Invasive lobular carcinoma	6.7	0.75	-	2.33
Carcinoma with medullary features	3.6	0.75	10.7	2.33
Mucinous Ca	2.4	1.5	7.1	2.33
Secretory Ca	-	-	-	2.33
Encapsulated papillary Ca	4.2	0.75	7.1	4.62
Invasive micropapillary Ca	-	-	-	2.33
Metaplastic carcinoma	-	-	-	2.33
Ca with neuroendocrine features	-	-	-	2.33
Other	4.2	9.75	17.8	-

The most common lesion seen in the adjacent breast was fibrocystic change which is comparable with Mudholkar et al(11). Siddiqui et al(8), Lee et al(13), Truong et al(14), Vegt et al(15) found Grade II tumours as the most common grade which is correlated with the present study. The comparison of tumour grade with other studies is shown in Table 5.

Table 5: Comparison of grading of breast carcinoma with other studies

Sr. No.	Author	No. of cases in which grading was done	Grade		
			I	II	III
1	Siddiqui et al 2003	975	11.38	59.17	29.47
2	Lee et al 2006	736	23	40	36
3	Truong et al 2005	542	7.7	49.6	42.6
4	Vegt et al 2007	242	23.5	45.3	30.9
5	Present study	30	20.00	67.50	12.50

We found 34 cases of IDC-NOS and 40 cases of special subtypes of breast carcinoma. We studied these special subtypes in detail.

• Invasive lobular carcinoma

Invasive lobular carcinoma is composed of non-cohesive individually dispersed cells or cells arranged in a single file linear pattern in fibrous stroma. It accounts for 5-15% of invasive breast tumours. The mean age of presentation is 57-65 years slightly higher than IDC-NOS.

A 65 years old lady presented with lump in the left breast since 2 years. Left MRM specimen showed a grey white tumour in upper inner quadrant measuring 4.5x4x3.5cm. The microscopic examination showed tumour cells arranged in Indian file pattern (Fig 2) and at places arranged in targetoid pattern. As clinical and imaging features are equivocal the diagnosis rests solely on histopathological examination.

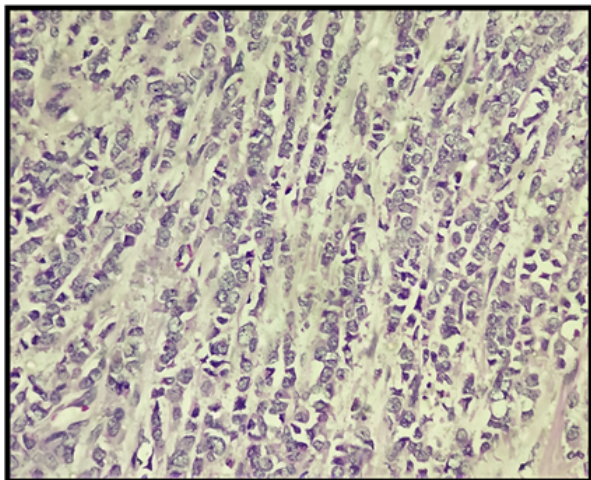


Figure 2: Photomicrograph of Invasive lobular carcinoma showing tumour cells arranged in Indian file pattern. HE x400

- **Low Grade Adenosquamous Carcinoma**

Low grade adenosquamous carcinoma of the breast is uncommon, comes under the family of metaplastic breast cancer which represents <1% of all breast carcinomas. Despite being a rare variant of metaplastic carcinoma, it has a more favourable prognosis. (17).

A 70 year old woman was referred with left breast lump since 4 months. She underwent left MRM. Microscopic examination revealed a tumour composed of glandular and squamoid elements set in a fibrous stroma. (Fig 3).

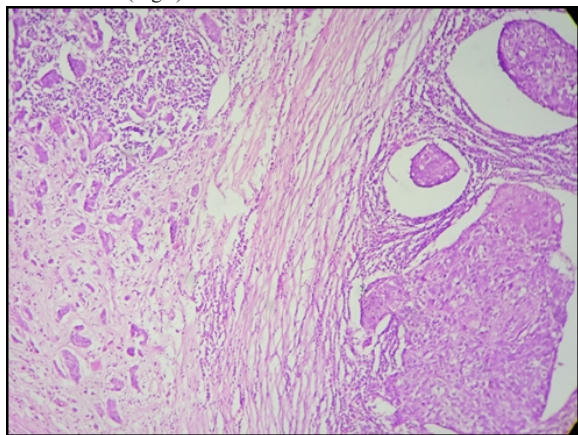


Figure 3: Photomicrograph of low grade adenosquamous carcinoma showing both squamous and glandular component. HE x100

- **Secretory carcinoma of breast**

Secretory carcinoma of breast is an extremely rare subtype of breast cancer accounting for <0.15% of all breast cancer. It is characterized by intracellular and extracellular secretion and granular eosinophilic cytoplasm of the neoplastic cells. (1) Secretory carcinoma generally has a favourable prognosis despite having a triple-negative phenotype. This tumour is frequently seen in children and adolescence but can also occur in elderly. (18).

A 71 years old female presented with slow growing, painless, well

circumscribed, mobile mass in right breast. The histological examination reveals features of secretory carcinoma and diagnosis of secretory carcinoma was given. (Fig 4) Immunohistochemistry and cytogenetic study were advised for confirmation of diagnosis.

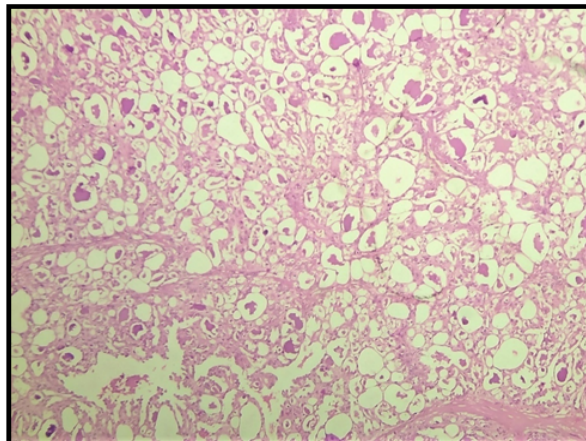


Figure 4: Photomicrograph of Secretory carcinoma showing abundant intra and extracellular eosinophilic secretions. HE x100

- **Invasive micropapillary carcinoma**

Invasive micropapillary carcinoma of breast is a clinically aggressive variant of ductal carcinoma. The poor prognostic significance of invasive micropapillary carcinoma holds true even for the minor component. Hence accurate diagnosis is pivotal.

A 69 years old woman presented with a lump in right breast. Microscopy showed a solid tumour composed of round to oval cells having vesicular nuclei, fine chromatin, and scant cytoplasm arranged in an inside-out pattern within clear stromal spaces (Fig 5). IDC-NOS was also seen. Deep surgical margin (DSM) was involved by tumour along with involvement of 9 out of 9 axillary lymph nodes.

Invasive micropapillary carcinoma is associated with a high rate of local recurrence and lymph node metastasis, which is seen in our case. Hence identification of micropapillary component, pure or mixed, is crucial for appropriate treatment.

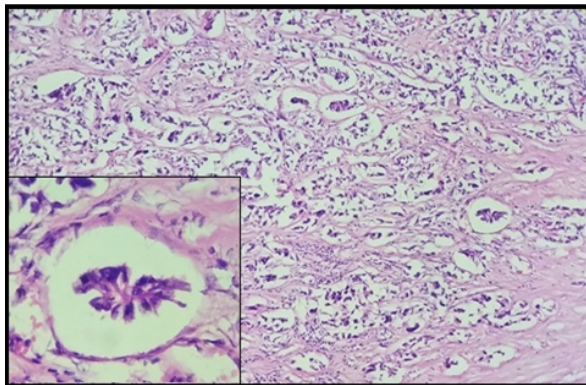


Figure 5: Photomicrograph of invasive micropapillary carcinoma. HE x100. Inset showing reverse polarity.

- **Encapsulated papillary carcinoma (EPC) of breast**

EPC is synonymous with intracystic papillary carcinoma. It is a variant of papillary carcinoma characterized by fibrovascular cores covered by neoplastic epithelial cells of low or intermediate nuclear grade and surrounded by a fibrous capsule (Fig 6). EPC is a rare breast cancer usually manifest in postmenopausal women. Clinically and radiologically EPC may appear like a benign lump, so it needs histopathology (19).

We had two cases of EPC, of which one was associated with multiple duct papilloma while the other was associated with IDC-NOS. EPC has an excellent prognosis. EPC lacks myoepithelial cell layer both in papillary structures and in fibrous capsule, which suggests invasive behaviour of the lesion.

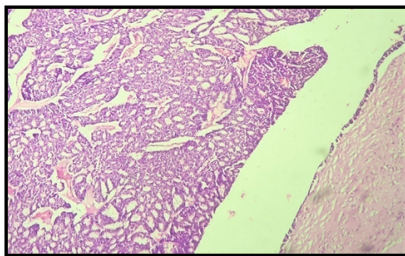


Figure 6: Photomicrograph of Encapsulated papillary carcinoma. HE x 100

• Mucinous Carcinoma

Mucinous carcinoma also known as colloid carcinoma or gelatinous carcinoma is a rare special subtype of breast carcinoma, accounting for only 2 % of total breast carcinoma. It prevails in postmenopausal women with median age of 70 years and has excellent prognosis when in pure form.

Clinically and radiologically it simulates a benign process. Microscopically, it is characterised by nest of tumour cells floating in lakes of mucin, separated by delicate fibrovascular septae. The mucin is almost entirely extracellular. Pure and mixed variant have been described. A pure form must be composed of >90% mucinous component(20).

An 84 year old lady presented with a circumscribed glistening gelatinous soft lump in upper inner quadrant. Microscopy was characteristic of pure mucinous carcinoma.(Fig 7) All lymph nodes were free of tumor.

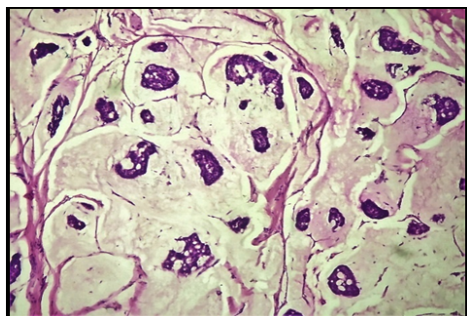


Figure 7: Photomicrograph of mucinous carcinoma- tumour cells floating in the pools of mucin. HE x100

• Invasive carcinoma with medullary features

It is a rare breast tumor accounting for < 5 % of invasive breast carcinoma. The histologic diagnostic criteria includes syncytial growth pattern (>75%), absence of glandular structures, diffuse lymphoplasmacytic infiltrate, grade 2 or 3 nuclei and complete histological circumscription(1, 21).

A 71 year old woman presented with a circumscribed mass in breast. The microscopy showed features of invasive carcinoma with medullary features(Fig 8). Despite it's highly malignant histopathological characteristic it has a favorable prognosis compared with invasive ductal carcinoma.

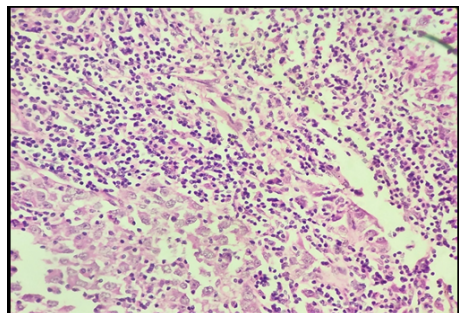


Figure 8: Photomicrograph of carcinoma with medullary features showing tumour cells arranged in syncytial pattern with dense lymphoplasmacytic infiltrate. HE x 400

• Carcinoma with neuroendocrine features

Carcinoma with neuroendocrine differentiation represents less than 1% of breast carcinomas. These tumors are usually seen in elderly women around sixth or seventh decade of life(22).

There was an elderly lady presented with lump in left breast since 6 months. Microscopic examination showed tumour cells arranged in solid nests and trabeculae. The cells have salt and pepper type of chromatin. It was diagnosed as carcinoma with neuroendocrine features(Fig 9) with involvement of seven out of eight lymph node. IHC was advised for confirmation.

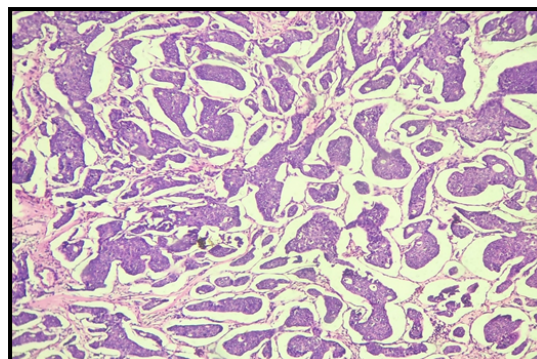


Figure 9: Photomicrograph of carcinoma with neuroendocrine features showing tumour cells arranged in nests and clusters. HE x 100

CONCLUSION

Invasive ductal carcinoma- not otherwise specified (IDC-NOS) is the most common subtype of invasive breast carcinoma. This study highlights the rarely encountered subtypes of breast carcinoma. These subtypes have distinct clinicopathological status and different treatment protocol. The histopathological type have distinct prognostic implication and it holds the ground even in the era of immunohistochemistry and molecular pathology.

REFERENCES

- Lakhani S. R. EIO, Schnitt S.J., Tan P.H., Van de Vijver M.J. . WHO classification of the tumours of the breast. 4 ed: IARC Lyon 2012.
- Fisher ER, Gregorio RM, Fisher B, Redmond C, Vellios F, Sommers SC. The pathology of invasive breast cancer. A syllabus derived from findings of the National Surgical Adjuvant Breast Project (protocol no. 4). Cancer. 1975 Jul;36(1):1-85.
- Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. Histopathology. 1992 Jun;20(6):479-89.
- Britta Weigelt FCG, and Jorge S. Reis-Filho Histological Types of Breast Cancer: How Special Are They? Molecular Oncology. 2010 June 4(3):192-208.
- Makki J. Diversity of Breast Carcinoma: Histological Subtypes and Clinical Relevance. Clin Med Insights Pathol. 2015;8:23-31.
- Kaur M, Tiwana KK, Singla N. Rare Breast Malignancy Subtypes: A Cytological, Histological, and Immunohistochemical Correlation. Niger J Surg. 2019 Jan-Jun;25(1):70-5.
- Qadri SK, Sejwal P, Priyadarshni R, Jaiswal M, Khandewal R, Khanna M, et al. Spectrum of Breast Diseases: Histopathological and Immunohistochemical Study from North India. Gulf J Oncolog. 2019 Jan;1(29):6-13.
- Siddiqui MS, Kayani N, Gill MS, Perviz S, Muzaffar S, Aziz SA, et al. Breast diseases: a histopathological analysis of 3279 cases at a tertiary care center in Pakistan. J Pak Med Assoc. 2003 Mar;53(3):94-7.
- Paul SN KS. A histopathological study of tumour and non-tumour breast lesions in Kolhan, Jharkhand. J Evid Based Med Healthc. 2018;5(36):2606-10.
- Dauda AM, Misauno MA, Ojo EO. Histopathological types of breast cancer in Gombe, North Eastern Nigeria: a seven-year review. Afr J Reprod Health. 2011 Mar;15(1):109-11.
- Mudholkar VG KS, Mashal SN. . Histopathological study of neoplastic lesions of breast. Ind Med Gazette 2012 sept;353-64.
- Njeze GE. Breast lumps: a 21-year single-center clinical and histological analysis. Niger J Surg. 2014 Jan;20(1):38-41.
- Lee AH, Gillett CE, Ryder K, Fentiman IS, Miles DW, Millis RR. Different patterns of inflammation and prognosis in invasive carcinoma of the breast. Histopathology. 2006 May;48(6):692-701.
- Truong PT, Berthelet E, Lee J, Kader HA, Olivetto IA. The prognostic significance of the percentage of positive/dissected axillary lymph nodes in breast cancer recurrence and survival in patients with one to three positive axillary lymph nodes. Cancer. 2005 May 15;103(10):2006-14.
- van der Vegt B, de Roos MA, Peterse JL, Patriarca C, Hilken J, de Bock GH, et al. The expression pattern of MUC1 (EMA) is related to tumour characteristics and clinical outcome of invasive ductal breast carcinoma. Histopathology. 2007 Sep;51(3):322-35.
- Jung SP, Lee SK, Kim S, Choi MY, Bae SY, Kim J, et al. Invasive pleomorphic lobular carcinoma of the breast: clinicopathologic characteristics and prognosis compared with invasive ductal carcinoma. J Breast Cancer. 2012 Sep;15(3):313-9.
- Senger JL, Meiers P, Kanthan R. Bilateral synchronous low-grade adenocarcinoma of the breast: A Case report with review of the current literature. Int J Surg Case Rep. 2015;14:53-7.
- Pohlodek K, Meciarova I, Grossmann P, Martinek P, Kinkor Z. Secretory carcinoma of the breast: A case report. Int J Surg Case Rep. 2019;56:74-7.

19. Reefy SA, Kameshki R, Sada DA, Elewah AA, Awadhi AA, Awadhi KA. "Intracystic papillary breast cancer: a clinical update". *Ecancermedicalscience*. 2013;7:286.
20. Bae SY, Choi MY, Cho DH, Lee JE, Nam SJ, Yang JH. Mucinous carcinoma of the breast in comparison with invasive ductal carcinoma: clinicopathologic characteristics and prognosis. *J Breast Cancer*. 2011 Dec;14(4):308-13.
21. Malyuchik SS, Kiyamova RG. Medullary breast carcinoma. *Exp Oncol*. 2008 Jun;30(2):96-101.
22. Murthy V, Geethamala K, Kumar B, Sudharao M. Primary neuroendocrine carcinoma of breast: a rare case report. *Ann Med Health Sci Res*. 2013 Nov;3(Suppl 1):S35-7.