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Case Series

Case series of pure mucinous breast carcinoma: A rare histopathological subtype

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ABSTRACT

Pure mucinous breast carcinoma (PMBC) is even rarer and accounts for about 2% of all primary breast carcinoma. It is composed entirely of tumour cells with abundant extracellular mucin and without admixing of infiltrating ductal carcinoma. We studied a total of ten cases of Pure Mucinous Breast Carcinoma. Here we describes each case of demographic features and histopathological features of PMBC. The results of immunohistochemistry of Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal growth factor receptor 2(HER-2neu) were also noted in this case series. All the cases were female and above 50 years of age. Out of 10 cases, 6 cases have the tumour's location on the left side of the breast and 4 cases have the tumour's location on the right side of the breast. All the cases belong to the lower grading and staging of the tumour. Only one case had positive lymph node status. Hormone receptor status of all the cases has ER & PR positive expression, HER-2neu negative expression and low Ki 67 labelling index. To conclude, PMBC was associated with lower-grade tumours, lower-stage, infrequent lymph node metastasis and luminal type A hormonal receptor status. These favourable findings suggest that PMBC has a better prognosis and may give a better response to hormonal therapy.

1. Introduction

Mucinous breast carcinoma (MBC) is a relatively rare histopathological type of breast cancer, accounting for about 4% of all breast cancers.[1] It is mainly present in women above 50 years of age.[2] It is histologically subtyped into pure mucinous breast carcinoma (PMBC) and mixed mucinous breast carcinoma (MMBC).[3] PMBC is even rarer and accounts for about 2%. It is characterised by the massive production of extracellular mucin.[4] PMBC may be subtyped into a hypocellular variant (PMBC-A) and a hypercellular variant (PMBC-B). The hypocellular variant is the most common subtype of pure mucinous breast carcinoma.[5] Pure mucinous breast carcinoma had favourable clinicopathologic features (lower histological grading & staging), better prognosis and infrequent lymph node metastasis compared to invasive ductal carcinoma of no special type.[6–8] PMBC had higher Estrogen receptor (ER) and Progesterone Receptor (PR) expression and less HER2/neu gene overexpression.[9] A recent study recommended axillary staging by sentinel lymph node biopsy and administration of adjuvant radiotherapy and hormone therapy after breast conservation for patients with Mucinous breast carcinoma.[3,6] It is important to differentiate PMBC from MMBC because patients with MMBC might be treated as guidelines for Invasive Ductal Carcinoma (No special type).[8,9] These cases aim to identify the rare histopathological subtype of invasive breast carcinoma that is pure mucinous breast carcinoma and their variants on histopathological features and also identified

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the hormonal receptor status of PMBC patients through Immunohistochemistry (IHC).

2. Materials and Methods

We are reporting the case series of 10 patients who were diagnosed with Pure Mucinous Breast Carcinoma on histopathology. These cases were retrieved in 5 years duration (April 2019 to March 2023) from two tertiary care centres. The demographic feature, gross & microscopic features, tumour grading & staging, lymph node status and hormone receptor profile status (ER, PR, HER-2neu) of these cases were retrieved. FNAC slides were stained with Haematoxylin and eosin (H&E) stain and Giemsa stain. H&E stain tissue sections were used for histopathological examination. To evaluate ER, PR, HER2/neu expression and Ki67 labelling index, immunohistochemistry was applied to the tissue section of formalin-fixed, paraffin-embedded tissue. The standard protocol used for the procedure of IHC. More than 1% nuclear expression of ER and PR in tumour cells was taken as positive. HER2-neu reactivity was assessed according to the College of American Pathologists (CAP) guidelines.

3. Case Presentation

4. Case 1

A 65-year-old female presented with a palpable left breast mass for 6 months. The swelling gradually increased in size. Positive family history of breast cancer. On examination, the mass was 5x4 cm in size, irregular border, soft to firm, immobile, non-tender and mass medial to areola of the left breast. The contralateral breast was normal. Sono mammography features showed suggestive of a malignant neoplastic lesion (BIRADS-5) on the left breast. Preoperative fine needle aspiration cytology (FNAC) smears showed clusters of atypical cells with a high nuclear-to-cytoplasmic (N:C) ratio, vesicular nuclei with prominent nucleoli and a scant amount of cytoplasm in the mucinous background (Figure 1 a, b). According to National Health Service Breast Screening Programme (NHSBP), the FNAC of the breast was categorized as C5 - malignant tumour. Subsequently, the patient underwent Modified Radical Mastectomy (MRM). On gross examination, the tumour measured 6x4x4 cm in size with an irregular border. Cuts firm. The cut surface of the tumour shows a solid grey-white along with a gelatinous area (Figure 2 a). All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 18 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells are arranged in clusters and solid nests which are floating in the pool of mucin in over 90% of tumour mass (Figure 2 b, d). Individual malignant epithelial tumour cells have round to oval nucleus, high nucleo-cytoplasmic ratio, vesicular nuclei, prominent nucleoli and a scant amount of cytoplasm (Figure 2 c, e). No evidence of perineural and lymphovascular invasion. All lymph nodes dissected out are free from tumour invasion. Histopathology confirmed the diagnosis of Pure Mucinous Breast carcinoma - Hypercellular variant (PMBC-B) with Grade I tumour (according to the Bloom-Richardson grading system). Immunohistochemistry (IHC) showed positive expression of ER and PR while negative expression of HER-2neu and low Ki67 index.

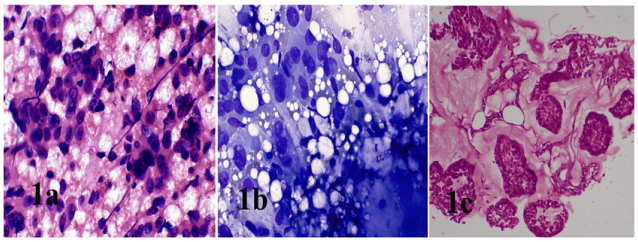

Figure 1: MBC: (**a**): H&E stain, 400X, (**b**): Giemsa stain, 400X. FNAC shows clusters of atypical cells with high N:C ratio in the mucinous background. (**c**): Core needle biopsy shows a cluster of malignant epithelial tumour cells floating in the pools of extracellular mucin. (H&E stain, 100X)

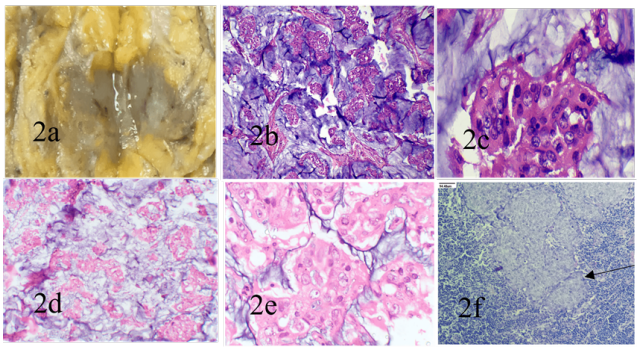

Figure 2:

4.1. Case 2

A 70 years old female presented with a right breast mass for 1 year. The swelling gradually increased in size. On examination, breast mass was measured 4 x 3.8 cm in size, firm, irregular border and non-tender. This fixed nodular mass is present on the upper quadrant of the right breast. Contra lateral breast was normal. Sono mammography features showed suggestive of a malignant neoplastic lesion (BIRADS-5) on the right breast. A preoperative core needle biopsy was performed which shows Invasive ductal carcinoma of the breast. Patients underwent MRM. On gross examination, the tumour measured 5x4x3 cm in size with a relatively circumscribed border. Cuts firm. The cut surface of the tumour shows a solid grey-white area along with intermixed gelatinous area. All surgical

resection margins are away from the main tumour area. In the axillary tail, a total of 15 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells are arranged in clusters and solid nests which are floating in the pool of mucin in over 90% of the tumour mass. Individual malignant epithelial tumour cells have round to oval nucleus, high nucleo- cytoplasmic ratio, vesicular nuclei, prominent nucleoli and a scant amount of cytoplasm. All lymph nodes dissected out are free from tumour invasion. Histopathology confirmed the diagnosis of Pure Mucinous Breast carcinoma - Hypercellular variant (PMBC-B). According to the Modified Bloom-Richardson grading system, she had a grade I tumour. IHC showed positive expression of ER and PR while negative expression of HER-2neu and low Ki67 index.

4.2. Case 3

A 59-year-old female presented with a right breast mass for 8 months. The swelling gradually increased in size. On examination, breast mass was measured at 2.8 x 1.8 cm in size, firm, irregular and non-tender. This fixed nodular mass is present on the upper outer quadrant of the right breast. Contra lateral breast was normal. Sono mammography features showed suggestive of a malignant neoplastic lesion (BIRADS-4) on the right breast. Preoperative breast FNAC smears were hypocellular and were categorized as C4 – suspicious of the malignant tumour. Patients underwent MRM. On gross examination, the tumour measured 3x2.5x2 cm in size with an ill-defined border. Cuts firm. The cut surface of the tumour shows a solid grey-white to gelatinous area (Figure 3 a-b. All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 12 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells are arranged in a cribriform pattern which is floating in the pool of extracellular mucin in over 90% of tumour mass (Figure 3 c). Individual malignant epithelial tumour cells have round to oval nucleus, high nucleo- cytoplasmic ratio, vesicular nuclei, prominent nucleoli and a scant amount of cytoplasm. All lymph nodes dissected out are free from tumour invasion. A diagnosis of Pure Mucinous Breast carcinoma - Hypocellular variant (PMBC-A) with Modified-Bloom-Richardson Grade I was made. IHC was positive for ER and PR while negative for Her2 neu and low Ki67 index.

4.3. Case 4

A 56-year-old female presented with a lump in the left breast for 1 year. The swelling was insidious in onset, gradually progressive, and painless. On examination, the breast lump was measured 2.0 x 1.8 cm in size, firm, and non-tender. This fixed nodular mass is present on the lower outer quadrant of the left breast. Contra lateral breast was normal. Sonomammography features showed

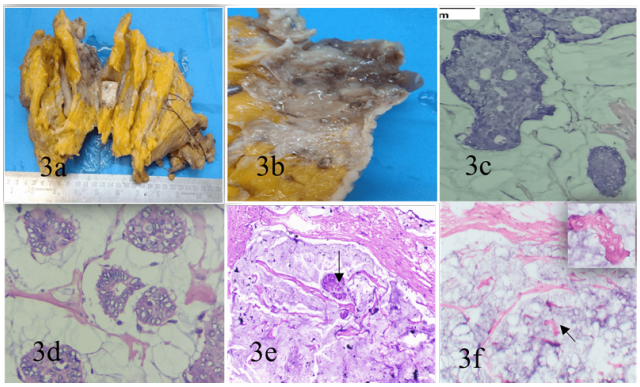

Figure 3: PMBC-A (**a, b**): Gross examination shows a solid grey-white area intermixed with a gelatinous area along with normal breast tissue. Histopathological examination shows tumour cells arranged in a cribriform pattern (**c**): micropapillary pattern (**d, e**): and cord-like pattern (**f**): floating in the abundant Pools of mucin. (H&E stain, 100X)

suggestive of a malignant neoplastic lesion (BIRADS-4) on the Left breast. Preoperative breast FNAC smears were categorized as C4 – suspicious of the malignant tumour. Patients underwent MRM. On gross examination, the tumour measured 1.8x1.5x1.0 cm in size with a relatively well-circumscribed border. Cuts firm. The cut surface of the tumour shows a grey-white gelatinous area. All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 12 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells arranged in a micropapillary pattern are floating in the pool of extracellular mucin in over 90% of the tumour mass (Figure 3 d). All lymph nodes dissected out are free from tumour invasion. A diagnosis of PMBC-A with Grade I tumour was made. IHC was positive for Estrogen receptor (ER) and progesterone receptor (PR) while negative for Her2 neu and low Ki67 index.

4.4. Case 5

An 85 years old female presented with a palpable left breast lump for 2 years. The lump was rapidly progressive in size over the last 6 months. On examination, the lump was 5.8x4.2 cm in size and located on the upper outer quadrant, firm in consistency, irregular border, non-tender and was fixed to the chest wall. The contralateral breast was normal. Sonomammography features showed suggestive of a malignant neoplastic lesion (BIRADS-5) on the left breast. Preoperative breast FNAC smears were categorized as C5 – malignant tumours. On gross examination, the tumour measured 5.0x4.5x4.0 cm in size with an ill-defined border. Cuts firm. The cut surface of the tumour shows a solid grey-white area with cystic mucin-filled areas. All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 11 lymph nodes were dissected.

On microscopic examination, malignant epithelial tumour cells are arranged in a solid pattern that is floating in the pool of extracellular mucin in over 90% of the tumour mass. Out of 11 lymph nodes, only one lymph node was positive for tumour invasion (01/11) without extranodal extension (Figure 2 f). A diagnosis of PMBC-B with Grade I tumour and positive lymph node (01/11) was made. IHC was positive for Estrogen receptor (ER) and progesterone receptor (PR) while negative for Her2 neu and low Ki67 index.

4.5. Case 6

A 64-year-old female discovered a slow-growing lump in his left breast over 1.5 years. On examination, breast mass was measured at 3.0 x 3.0 cm in size located in the lower quadrant of the left breast, firm in consistency, immobile, ill-defined border and non-tender. The contralateral breast was normal. Sono mammography features showed suggestive of a malignant neoplastic lesion (BIRADS-4) on the right breast. Preoperative breast FNAC smears were categorized as C4 – suspicious of the malignant tumour. Patients underwent MRM. On gross examination, the tumour measured 3.5x2.8x2.0 cm in size with no demarcated border. Cuts firm. The cut surface of the tumour shows a grey-white gelatinous area. All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 10 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells are arranged in a cribriform pattern which is floating in the pool of extracellular mucin in over 90% of the tumour mass. All lymph nodes dissected out are free from tumour invasion. A diagnosis of Pure Mucinous Breast carcinoma - Hypocellular variant (PMBC-A) with Modified-Bloom-Richardson Grade I was made. IHC was positive for Estrogen receptor (ER) and progesterone receptor (PR) while negative for Her2 neu and low Ki67 index.

4.6. Case 7

The patient was a 74-year-female with a lump in the right breast for 10 months. The lump progressively increased in size. On examination, the lump was 3.5x3.0x2.0 cm in size and located on the upper outer quadrant, firm in consistency, irregular border, non-tender and was fixed to the chest wall. The contralateral breast was normal. Sonomammography features showed suggestive of a malignant neoplastic lesion (BIRADS-4) on the right breast. Preoperative breast FNAC smears were categorized as C4 – suspicious of the malignant tumour. Patients underwent MRM. On gross examination, the tumour measured 3.8x3.5x2.0 cm in size with no clearly demarcated border. Cuts soft to firm. The cut surface of the tumour shows a mixture of solid grey-white area along with mucinous area. All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 12 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells arranged in a micropapillary pattern are floating in the abundant extracellular mucin in over 90% of tumour mass (Figure 3 e). All lymph nodes dissected out are free from tumour invasion. A diagnosis of Pure Mucinous Breast carcinoma - Hypocellular variant (PMBC-A) with Modified-Bloom-Richardson Grade I was made. IHC was positive for Estrogen receptor (ER) and progesterone receptor (PR) while negative for Her2 neu and low Ki67 index.

4.7. Case 8

The patient was a 67-year-female with a lump in the right breast for 8 months. The lump progressively increased in size. On examination, the lump was 5.5x4.5x3.2 cm in size and located on the central area of the breast, firm in consistency, irregular border, non-tender and was fixed to the chest wall. The contralateral breast was normal. Sonomammography features showed suggestive of a malignant neoplastic lesion (BIRADS-5) on the right breast. Preoperative breast FNAC smears were categorized as C5 – malignant tumours. Patients underwent MRM. On gross examination, the tumour measured 5.5x4.0x3.0 cm in size with no clearly demarcated border. Cuts soft to firm. The cut surface of the tumour shows a mixture of solid grey-white area along with mucinous area. All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 15 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells are arranged in a cribriform pattern which is floating in the pools of extracellular mucin in over 90% of the tumour mass. All lymph nodes dissected out are free from tumour invasion. A diagnosis of Pure Mucinous Breast carcinoma - Hypocellular variant (PMBC-A) with Modified-Bloom-Richardson Grade I was made. IHC was positive for Estrogen receptor (ER) and progesterone receptor (PR) while negative for Her2 neu and low Ki67 index. (Figure 4).

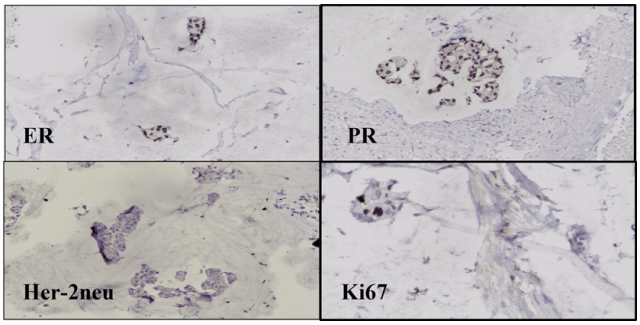

Figure 4: Immunohistochemistry. ER and PR show nuclear positivity in tumour cells. Her-2neu shows 1+ (negative) expression in tumour cells. Ki 67 labelling index <5%. (IHC, 100X)

4.8. Case 9

A 58-year-old female presented with a lump in the left breast for 1 year. The swelling was insidious in onset, gradually progressive and painless. On examination, the breast lump was measured 2.0 x 1.8 cm in size and located on the upper outer quadrant of the breast, firm, mobile, non-tender, ill-defined border. Contra lateral breast was normal. Sono mammography features showed suggestive of a malignant neoplastic lesion (BIRADS-5) on the left breast. Preoperative breast FNAC smears were categorized as C5 – malignant tumours. Patients underwent MRM. On gross examination, the tumour measured 2.0x1.5x1.5 cm in size with no clearly demarcated border. Cuts firm. The cut surface of the tumour shows a mixture of solid grey-white area along with mucinous area. All surgical resection margins are away from the main tumour area. In the axillary tail, a total of 10 lymph nodes were dissected. On microscopic examination, malignant epithelial tumour cells are arranged in cord-like patterns which are floating in the abundant pool of extracellular mucin in over 90% of tumour mass (Figure 3). All lymph nodes dissected out are free from tumour invasion. A diagnosis of PMBC-A with Grade I tumour was made. IHC was positive for Estrogen receptor (ER) and progesterone receptor (PR) while negative for Her2 neu and low Ki67 index

4.9. Case 10

The patient was an 87-year-female with a lump in the left breast for 1.5 years. The lump progressively increased in size. On examination, the lump was 5.8x5.5x4.2 cm in size and located on the central area of the breast, firm in consistency, irregular border, non-tender and was fixed to the chest wall. The contralateral breast was normal. Sonomammography features showed suggestive of a malignant neoplastic lesion (BIRADS-5) on the left breast. A preoperative core needle biopsy was performed. A diagnosis of Pure Mucinous Breast carcinoma with grade I tumour was made. (Figure 1 c) After that, the patient refused the treatment and lost follow-up.

5. Results

A total of 10 cases, all cases were female patients. The age of these patients was above 50 years. All the patients were postmenopausal females. In 6 cases, tumours were seen on the left side of the breast with only 4 cases having tumours on the right side of the breast. Nine patients underwent modified radical mastectomy and axillary lymph node dissection and one case lost follow-up after core needle biopsy was done. Grossly, the size of the tumour ranges from 3x2x2 cm to 6x4x4cm. (T1 in 2 patients, T2 in 5 patients, T3 in 2 patients, Tx in 1 patient). On histopathological examination, all cases were Pure forms of Mucinous carcinoma of the breast. All the cases had Grade I tumours according to the Modified Bloom-Richardson grading system. Only one case had positive lymph node status. No distant metastases were identified in any cases. The hormone receptor status of all the cases have ER positive, PR positive, HER-2neu negative and low Ki 67 index. All these features are summarized in Table 1.

6. Discussion

Mucinous breast carcinoma (MBC) is a rare histological type of invasive breast carcinoma accounting for a range of 1 to 7% of all breast carcinomas.[10,11] It is characterized by clusters of epithelial tumour cells floating in pools of extracellular mucin.[2] According to Zhang et al, MBC mainly occurs in postmenopausal women and usually affects older patients.[12] In our study, all women belong to the postmenopausal group. MBC is rarely diagnosed in younger women under 35 years of age (1%).[13] The mean age at diagnosis was 66 years compared to 60 years for invasive breast carcinoma (NST) patients.[1] In our study, the mean age at diagnosis is 68 years which is corresponding to various other studies.[1–4] A family history of breast cancer is the most important risk factor for breast cancer incidence. There is a twofold increase in the risk of developing the disease for women with breast cancer in their first-degree relatives.[14] In our study, 1 out of 10 patients had a positive family history of the breast cancer. In our study, most of the MBC is located on the left side of the breast. The results of the present study are in agreement with the findings of a similar study conducted by Dumitru et al and Hashmi et al.[2,7] But some studies are stating that MBC is located on the right side of the breast.[5] MBC is divided into two subtypes based on the quantification of its cellularity. These subtypes are pure mucinous breast carcinoma (PMBC) and mixed mucinous breast carcinoma (MMBC).[1] PMBC is more common than MMBC. The PMBC is composed entirely of tumour cells with abundant extracellular and intracellular mucin in over 90% of the tumour mass. Histologically, PMBC may be subtyped into a hypocellular variant (PMBC-A) and a hypercellular variant (PMBC-B).[5,7] PMBC-A shows a tubular, cribriform, cord-like, micropapillary or papillary growth pattern while PMBC-B shows only solid nests of tumour cells floating in mucin and often shows neuroendocrine differentiation.[15] The hypocellular variant (PMBC-A) is more common than the hypercellular variant (PMBC-B).[5,7] In this study, all the patients were diagnosed with Pure Mucinous Breast Carcinoma on histopathological examination and the hypocellular variant is more common than the hypercellular variant. This finding corresponds to existing literature.[1,3–7] The MMBC is composed of 50-90% of the area is mucinous and also admixing with infiltrating ductal epithelial component.[1,4,16] It can be divided into two groups based on the amount of mucinous components. It can be partial mixed mucinous breast carcinoma (pMMBC)

Table 1: Clinicopathological & immunohistochemistry profile of the patients

S.No.	Age/Sex	Location	HPE diagnosis	Modified Bloom Richardson grading	TNM staging	ER, PR, HER2-neu status	Ki 67Labelling Index
1.	65/F	Lt breast	PMBC-B	Grade I	T3N0M0	ER & PR +, HER-2neu -	Low
2.	70/F	Rt breast	PMBC-B	Grade I	T2N0M0	ER & PR +, HER-2neu -	Low
3.	59/F	Rt breast	PMBC-A	Grade I	T2N0M0	ER & PR + HER-2neu -	Low
4.	56/F	Lt breast	PMBC-A	Grade I	T1N0M0	ER & PR +, HER-2neu -	Low
5.	85/F	Lt breast	PMBC-B	Grade I	T2N1M0	ER & PR +, HER-2neu -	Low
6.	64/F	Lt breast	PMBC-A	Grade I	T2N0M0	ER & PR +, HER-2neu -	Low
7.	74/F	Rt breast	PMBC-A	Grade I	T2N0M0	ER & PR +, HER-2neu -	Low
8.	67/F	Rt breast	PMBC-A	Grade I	T3N0M0	ER & PR +, HER-2neu -	Low
9.	58/F	Lt breast	PMBC-A	Grade I	T1N0M0	ER & PR +, HER-2neu -	Low
10.	87/F	Lt breast	PMBC-A	Grade I	TxNxMx	Not done	Not done

and major mixed mucinous breast carcinoma (mMMBC). The pMMBC is composed of 30 -50% of mucinous components while mMMBC is composed of 50-90% of mucinous components.[4,11] In our study, we did not find any case of MMBC. In our study, the majority of MBC presented at the early stages (I and II) of cancer and low histological grade tumour (grade I). All the cases had Grade I tumours according to the Modified Bloom-Richardson grading system. This finding corresponds to various other studies.[13,16,17]

In most of the previous studies, MBC has been exhibited to have a very low rate of lymph node metastasis, positive expression of estrogen and progestogen receptors and negative expression of Her2-neu.[17,18] Axillary lymph node metastases occur in 12%-14% of the cases.[19] In our study, 1 out of 10 cases had lymph node metastasis and all the cases had ER/PR positive expression, HER2-neu negative expression and low Ki 67 index. This type of hormone receptor status of MBC belongs to the luminal type A molecular classification of breast carcinoma. These findings are similar to existing literature.[15–19] MBC is usually presented with a better prognosis than invasive ductal carcinoma (NST).[13,20] The pure type of MBC has a better prognosis than the Mixed type of MBC. The 5-year disease-free survival rates range from 81% to 94% (if lymph nodes are negative).[3] Management of MBC depends upon tumour size, lymph node status and hormone receptor profile status.[4,7,9] The treatment of mucinous breast carcinoma is based on surgical excision with post-operative hormone therapy in hormone-responsive (ER/PR) tumours. A recent study recommended axillary staging by sentinel lymph node biopsy and administration of adjuvant radiotherapy and hormone therapy after breast conservation for mucinous carcinoma.[3] Among patients with PMBC, "standard treatment" or "treatment for a histological type with a favourable prognosis" should be selected based on the presence or absence of lymph node metastasis in those with PMBC-B while in PMBC-A, "treatment for a histological type with a favourable prognosis" may be selected, regardless of the presence or absence of lymph node metastasis.[5]

7. Conclusion

MBC is a rare subtype of invasive breast carcinoma. In this study, we noted MBC was associated with lower-grade tumours, lower-stage, infrequent lymph node metastasis and luminal type A hormonal receptor status. These favourable clinicopathologic findings suggest that MBC has a better prognosis and may give a better response to hormonal therapy.

8. Source of Funding

None.

9. Conflict of Interest

None.

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