https://doi.org/10.29309/TPMJ/2024.31.05.8029

The Professional Medical Journal
www.theprofesional.com
2024, Volume, 31 Issue, 05

ORIGINAL ARTICLE

Clinicopathological characteristics of mucinous carcinoma of the breast.

Shireen Hamid[1], Muhammad Mudassar[2], Hafsa Tariq[3], Sadia Hameed[4], Tariq Mehmood[5], Saleha Tariq[6]

Article Citation: Hamid S, Mudassar M, Tariq H, Hameed S, Mehmood T, Tariq S. Clinicopathological characteristics of mucinous carcinoma of the breast. Professional Med J 2024; 31(05):704-711. https://doi.org/10.29309/TPMJ/2024.31.05.8029

ABSTRACT… Objective: To highlight clinicopathological differences between Pure Mucinous Carcinoma (PMC) and Mixed Mucinous Carcinoma (MMC) of the breast. **Study Design:** Descriptive Retrospective study. **Setting:** Private Lab in Faisalabad, Pakistan. **Period:** January 2017 to December 2022. **Methods:** FNAC smears diagnosed with Mucinous Carcinoma fulfilling the inclusion and exclusion criteria were carefully examined for features such as cellularity, extracellular mucin (ECM), nuclear pleomorphism, plasmacytoid cells, macrophages, and myxovascular fragments (MVFs). The diagnosis was confirmed by histopathology and were characterized in to PMC and MMC. Immunohistochemistry slides were evaluated according to established protocols. Statistical analysis was performed using SPSS ($p < 0.05$). **Results:** The study analyzed 16 FNAC cytological samples with subsequent histopathological confirmation. These cases were derived from a pool of 712 female breast carcinoma cytology cases over a five-year duration. The predominant age group was 40 to 50 years, with the left breast and upper outer quadrant being the most common site. Distinct cytological characteristics, particularly the significant presence of extracellular mucin in PMC, were observed. Tumor grade and lymph node involvement emerged as crucial prognostic factors. MMC exhibited a high Ki-67 index, indicating increased cellular proliferation. **Conclusion:** Pure mucinous carcinomas (PMCs) are uncommon breast tumors with distinguished cytologic features. It is clinically and genetically distinct from mixed mucinous carcinoma (MMC) and other types of breast cancer. An important prognostic factor is lymph node involvement, and PMCs often have a low proliferation rate and a more favorable long-term prognosis**.** Therefore, the identification of PMC through FNAC holds significant diagnostic and clinical importance.

Key words: Breast Cancer, Extracellular Mucin (ECM), Fine Needle Aspiration Cytology (FNAC), Mucinous Carcinoma (MC), Mixed Mucinous Carcinoma (MMC), Myxovascular Fragments (MVF), Pure Mucinous Carcinoma (PMC).

INTRODUCTION

Mucinous breast carcinoma is an uncommon subtype of ductal carcinoma, which accounts for 1-7% of breast cancers. It can be further characterized into Pure Mucinous Carcinoma (PMC) and Mixed Mucinous Carcinoma (MMC). PMC usually presents with abundant extracellular mucinous lakes, and are mostly circumscribed and have a gelatinous cut surface. PMC usually occurs in postmenopausal women and shows a more favorable prognosis than MMC. Therefore detection by fine needle aspiration cytology (FNAC) may influence treatment decisions. Although research is still ongoing, much remains to be discovered about this rare form of breast cancer, and research continues to improve our understanding of the underlying biology and refine treatment strategies. This study aims to correlate the cytomorphological features of PMC and MMC with histopathology, taking as gold standard.[1,2,3]

METHODS

This descriptive retrospective study was conducted in Faisalabad's private laboratory between January 2017 and December 2022. It was approved by ethical committee (MEZ/HISTO/PATH/126). It included all female breast cases of any age diagnosed with Mucinous Carcinoma (MC) on cytology in the last 5 years. The breast cytology cases diagnosed as MC but had no subsequent histopathology were excluded from the study. The demographic and clinical information were retrieved from the medical records. A total of 16

1. MBBS, FCPS (Histopath), Assistant Professor, Aziz Fatima Medical College, Faisalabad.
2. MBBS, FCPS (Histopath), Professor & Consultant Pathologist, Shahida Islam Medical College, Lodhran.
3. MBBS, FCPS Trainee, Senior Medical Officer, Evercare Eye Hospital, Lahore.
4. MBBS, M.PHil (Histopath), Professor (Retd) & Consultant Pathologist, UMDC & Meezan Lab, Faisalabad.
5. MBBS, M.Phil. FCPS (Histopath), Professor & Consultant Pathologist, Niazi Medical College, Sargodha.
6. MBBS, House Officer, CMH, Lahore.

Correspondence Address:
Dr. Muhammad Mudassar
Department of Pathologist,
Shahida Islam Medical College &
Teaching Hospital, Lodhran, Pakistan.
drmudassarmajeed@gmail.com

Article received on: 09/12/2023
Accepted for publication: 07/02/2024

cytology cases with subsequent histopathology were evaluated. The diagnosis was first made by cytology and then confirmed by histopathology. Cytological evaluation including semi percentile parameters including extracellular mucin (ECM), cellularity, pleomorphism, plasmacytoid appearance, macrophages, and myxovascular fragments (MVF). Two cytopathologists examined immunohistochemical slides for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2 Neu), and Ki-67. The clinicopathological features of PMC and MMC were compared and analyzed. Statistical analysis was done using SPSS 24; $p < 0.05$ was considered significant.

RESULTS

In this research, we analyzed 16 cytological samples diagnosed with Mucinous Carcinoma (MC) of the breast obtained through fine needle aspiration (FNA) and had histopathological confirmation. These cases were derived from a pool of 712 female breast carcinoma cytology cases over a five-year duration. The mean age is approximately 51.88 years, with a standard deviation of 14.62. The age range spans from a minimum of 30 years to a maximum of 80 years. The most common age group was 40 to 50 years. The left breast was the most commonly affected, with 11 cases, while 5 cases were identified in the right breast. The duration of the breast lump varied significantly, ranging from two weeks to a decade. The upper outer quadrant of the breast was the most frequently affected area, accounting for 12 cases.

The cytological assessment revealed distinctive features, marked by a significant presence of extracellular mucin. Within this mucin-rich material, clusters of tumor cells with relatively benign cytological features were suspended. Additionally, myxo-vascular fragments were observed in 6 cases. Dissociated tumor cells exhibited a plasmacytoid appearance, characterized by eccentrically located nuclei. In a minority of cases, mucin content was notably scarce, and in four instances, cellularity was significantly high, while in two cases, cellularity was extremely low.

Subsequent histological examination of excision or mastectomy specimens confirmed all 12 cases as pure Mucinous Carcinoma (PMC). Among them, 2 cases exhibited a micropapillary pattern, while 4 cases were identified as Mixed Mucinous (MMC). Pure Mucinous carcinoma (PMC) was characterized under the microscope by the presence of abundant mucinous areas and tumor cells with mild atypia, as illustrated in Figure-1. In contrast, Mixed Mucinous carcinoma (MMC) exhibited mucinous regions similar to those seen in PMC but also displayed solid areas featuring invasive ductal components adjacent to the mucinous areas, as depicted in Figure-2. All four cases of MMC in our study showed intraductal components.

While 4 cases have a “Positive” nodal status, one case of PMC and three cases of MMC demonstrated metastasis in the ipsilateral axillary lymph nodes. The presence of mucin was confirmed through Periodic Acid-Schiff (PAS) positive staining, as demonstrated in Figure-3.

Regarding tumor grading, 12 cases of PMC were categorized as Grade II. Among MMCs, two cases were classified as Grade II, while the remaining two were Grade III. Our study revealed that the tumor grade exhibited a statistically significant association with “Histopathology” (with a p-value of 0.009), indicating that the grade of the tumor (Grade II or Grade III) significantly differs between PMC and MMC cases.

On the other hand, variables such as “ER,” “PR,” “Her 2 Neu,” and “Ki 67” did not demonstrate statistically significant associations with “Histopathology” as their p-values were all above 0.05. In summary, “Grade of Tumor” was the only variable found to be significantly associated with “Histopathology,” while the others did not show such associations.

However, when considering the proliferative index, a notable distinction emerged. Among the Mixed Mucinous Carcinoma (MMC) cases, a high Ki-67 index was noted, indicating a high level of cellular proliferation. In contrast, Pure Mucinous Carcinomas (PMC) were characterized by a lower

proliferative tumor profile, with only one case exhibiting a Ki-67 index exceeding 20%.

	MMC	PMBC
Number of patients	04 (25%)	12(75%)
Mean age at diagnosis	36.75	56.91
Patients aged over 80	0	1
Median size	4.75 cm	6.35 cm

	Frequency	Percent
MPMC	4	25.0
PMC	12	75.0
Total	16	100.0

Table-I. Comparison of Mixed Mucinous Carcinoma (MMC) with Pure Mucinous Carcinoma (PMC). Histopathology

	MMC (%)	PMC (%)
ER−	2 (50)	1(6.8)
ER+	2 (50)	11 (91.6)
PR−	2 (50)	4 (33.3)
PR+	2(50)	8 (66.6)
HER2 0/1+	2 (50)	8(66.6)
HER2 2+	0	3 (25)
HER2 3+	2 (50)	1 (8.3)

Table-II. ER, PR, HER2neu Status

Tumor size (T) (no, %), MMC (%) PMC (%)		
T1a	0	0
T1b	0	4 (33.3)
T1c	0	3 (25)
T2	2 (50)	0
T3	1 (25)	5 (41.6)
T4	1 (25)	0
pN0	1 (25)	11 (91.6)
pN1	0	1 (8.3)
pN2	2 (50)	0
pN3	1 (25)	0
G1	0	0
G2	2 (50)	12 (100.0)
G3	2 (50)	0
Gx (necrosis/autolysis)	0	0

Table-III. TNM staging of mucinous CARCINOMA

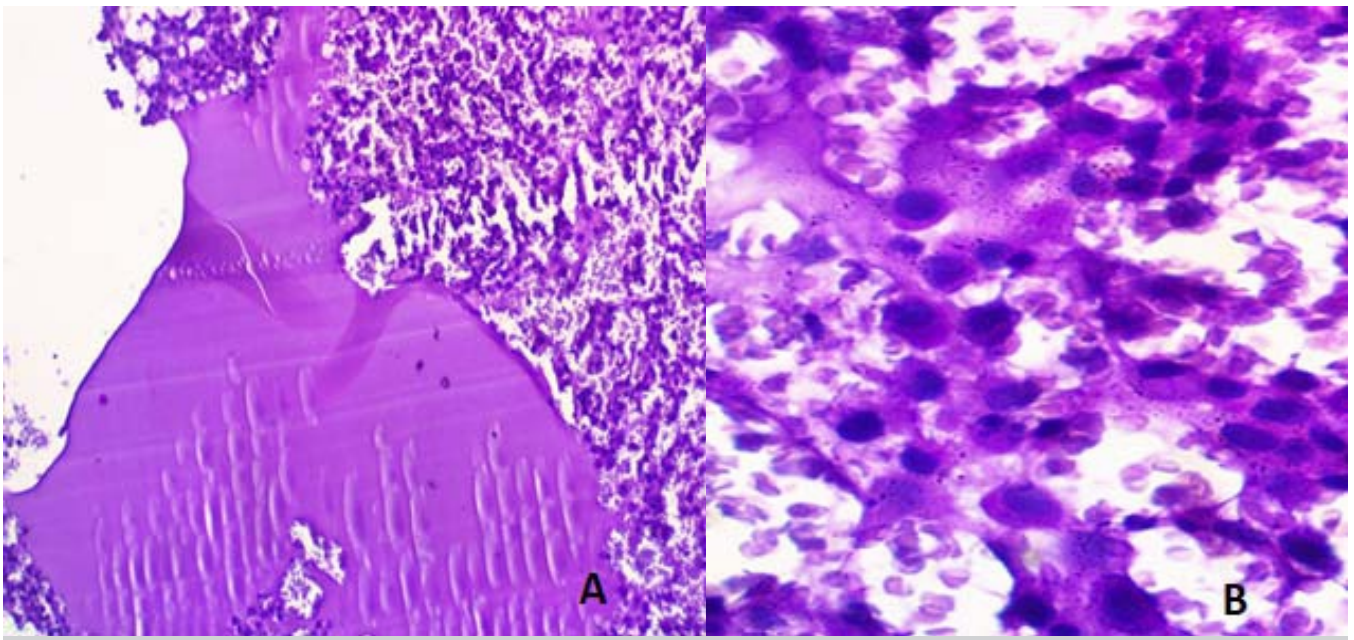

Figure-1. A microphotograph of cytological smear from a case of pure mucinous carcinoma, showing abundant extracellular mucin with clusters of floating bland tumor cells (A, Giemsa, 10×); Higher magnification of the same case showing macrophages (B,Giemsa, 40×)

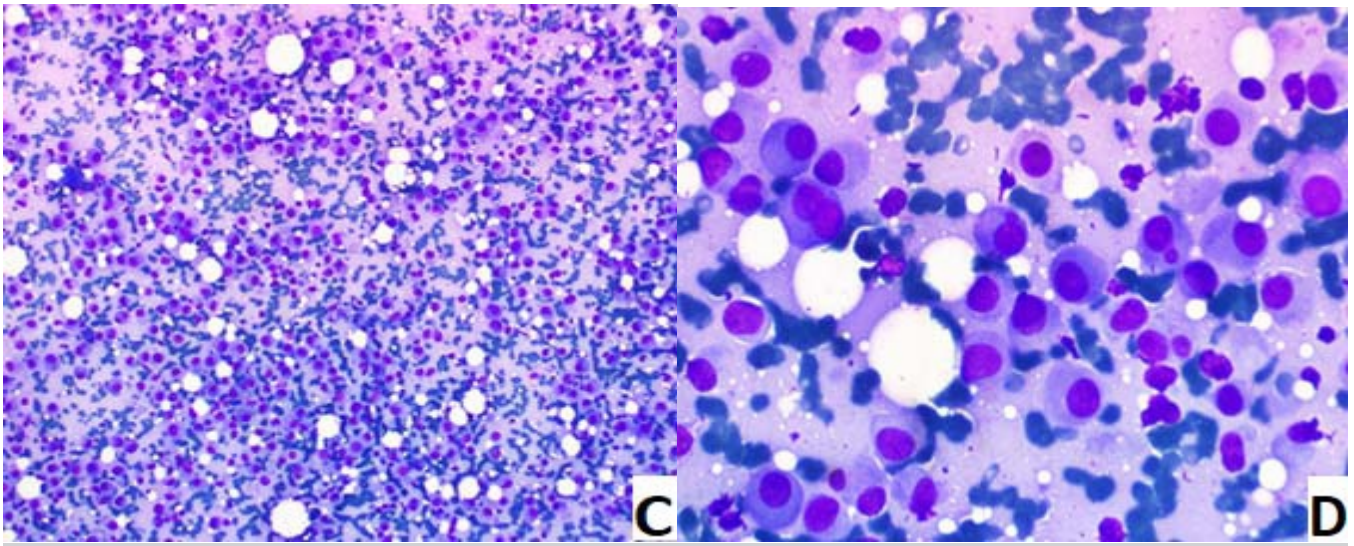

Figure-2. A microphotograph of cytological smear from a case of mixed mucinous carcinoma, showing focal extracellular mucin, high cellularity with mild plasmacytoid pleomorphic nuclei. (C, Giemsa10×); Higher magnification of the same (D, Giemsa, 40×).

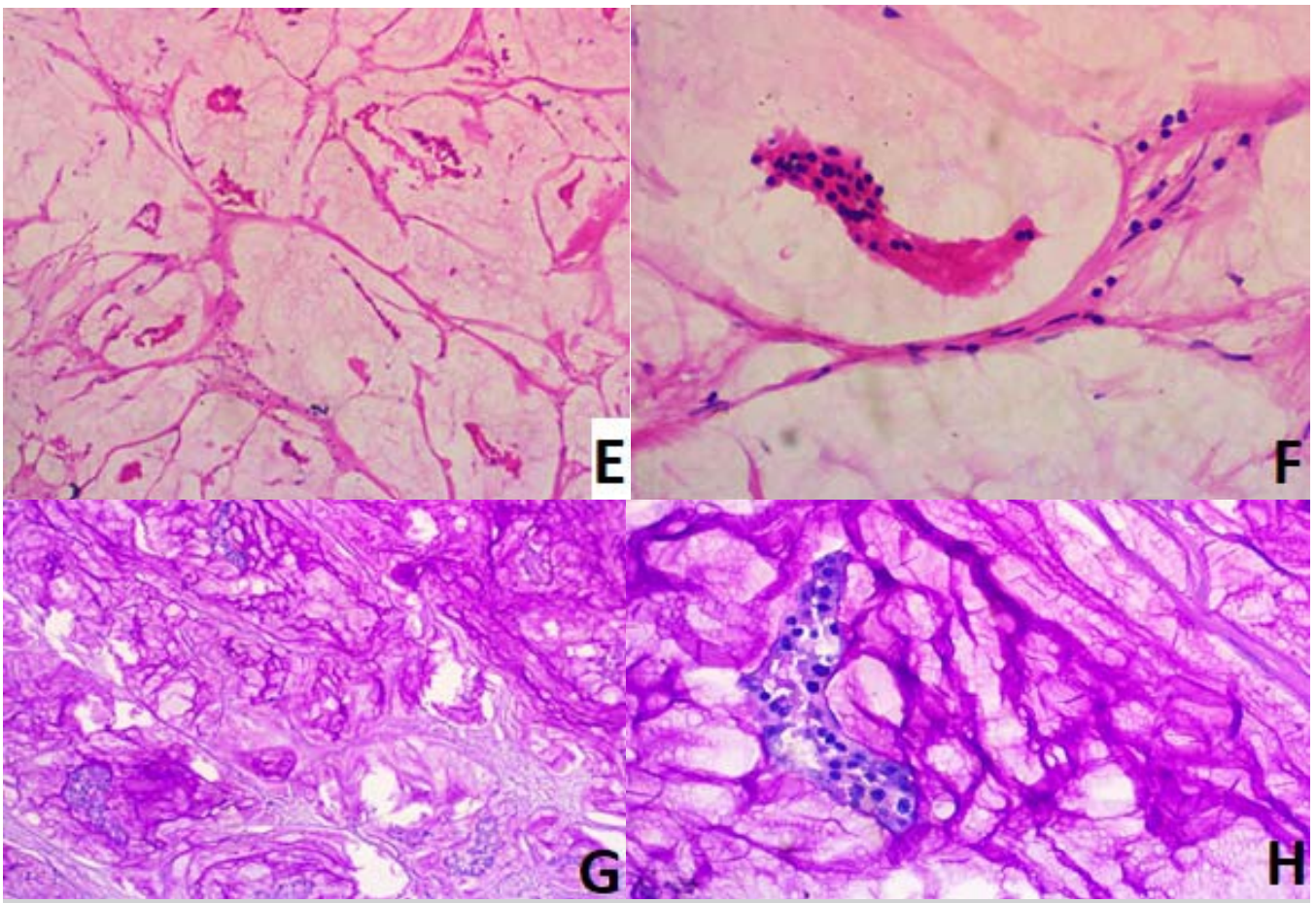

Figure-3. A microphotograph of pure mucinous carcinoma showing abundant extracellular mucin with clusters of bland floating tumor cells,(E) (, Hematoxylin and Eosin, [H&E] 10×); Higher magnification of the same case (H&E,40×); Periodic stain highlighting the mucinous areas(G, H) (Periodic acid–Schiff stain [PAS]10x and 40×).

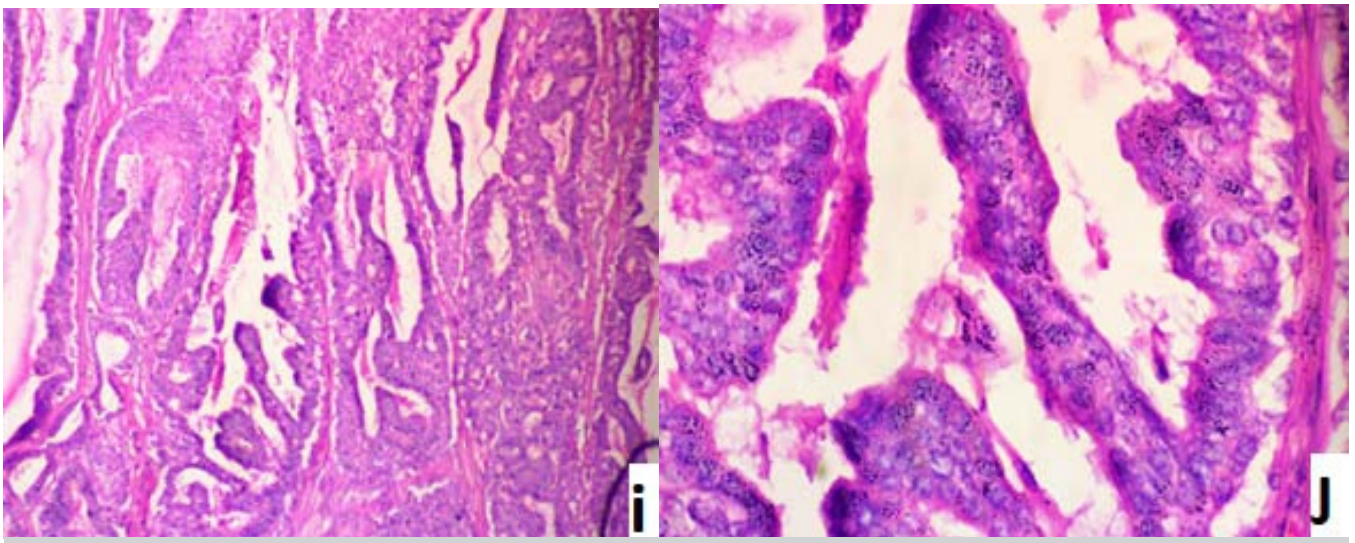

Figure-4. A microphotograph of mixed mucinous carcinoma illustrates alternating regions with focal extracellular mucin and clusters of tumor cells. The tumor cells exhibit pleomorphic nuclei. (I)(H&E, 10×). Higher magnification of the same (J) (H&E, 40×).

DISCUSSION

Our study found that mucinous carcinoma (MC) accounted for 2.2% of cases, consistent with existing literature. The worldwide prevalence of MC ranges from 2% to 7%, with 2.4% reported in China, 3.4% in Taiwan, and 3.3% in South India. Mucinous carcinoma (MC) primarily affects postmenopausal women, typically about ten years older than those diagnosed with invasive ductal carcinoma (IDC) in Western countries.[1,3] We observed cases in a wider age range, from 34 to 80 years. However, four cases were identified in individuals aged 60 and above. The mean age in our study was 51.9 years, with a standard deviation of 14.62 years.

The mean age in our study is consistent with the findings of Chikkannaiah P et al., who reported a mean age of 50.9 years. Upasana Joneja et al. observed a wider age range of 28 to 80 years (mean 55 years), with less than 50% of patients being peri- or premenopausal. In contrast, Budzik, M.P. et al. reported a mean age of 65.5 years, Tseng et al. found a mean age of 49.8 years, and Lei et al. stated an age of 63 (range 28-90).[4,12,13,15] This study found a significant difference in mean age presentation, PMC presents in an older age group. The average age for PMC was 56.1 years, whereas MMC cases exhibited a mean age of 36.75 years. This is consistent with a retrospective review by Sun, P et al. on 161 cases of mucinous breast carcinoma, where they found that mixed mucinous carcinomas occurred at a younger age and showed more aggressive features.[5] While in the study by Marrazz, E et al, the mean age at diagnosis was 64.4 years, and reported that PMC affects patients earlier than MMC.[10]

Cytological diagnosis of MC presents challenges. In this study, we identified distinguished features of PMC. These features are the presence of an abundance of mucin. relatively bland-looking monomorphic cells, plasmacytoid cells, and macrophages. While the MMC showed coexistent invasive ductal carcinoma component comprising sheets and nests of tumor cells with pleomorphic hyperchromatic nuclei and prominent nucleoli and mitosis. Most of these cytomorphologic features have been highlighted in previous studies. However, it is important to note that the existing data on cytological diagnosis of PMC comprises individual case reports, with only a limited number of comprehensive series available.[2,5,6,7,8,13]

Our study revealed that MMCs were slightly smaller than PMCs, which is consistent with the findings of Lei et al.[13] The difference in size can be attributed to the presence of invasive components in the MMC. However, some studies have suggested that MC tumors smaller than 5

cm have a favorable prognosis. This contrasts with the observations of Tseng et al., who found no difference in size between MCs and IDCs.12 Morphologically, PMCs are characterized by mucin in more than 90% of tumors, while MMCs contain solid components that often resemble IDC-NOS. A micropapillary pattern was observed in some cases, Upasana Joneja et al also documented that both pure mucinous and micropapillary (non-mucinous) carcinoma patterns can coexist.[3] similar to Budzik, M.P. et al. classify PMC tumors into hypocellular (PMC-A) and hypercellular (PMC-B) types, with micropapillary features seen in pure mucinous carcinoma.[5]

PMC exhibits distinctive clinicopathological features both morphologically and genetically. This study showed increased expression of ER, PR, and low expression of HER 2 Neu. This is in concordance with the study done by Sun et al. and Tseng et al. While there was no significant difference between PMC and MMC. This aligns with the existing literature.[14] The MMC cases showed a high proliferative marker Ki67, this is in concordance with Lei et al. They demonstrated increased P53 expression in MMC.[13]

Prognostic factors associated with mucinous carcinoma (MC) remain a matter of debate. However, there is consensus among researchers that lymph node status plays a key role as a prognostic factor. In our current study, we found that three cases of MMC had ipsilateral axillary lymph node metastases. These findings are consistent with research by Esmer, A.C. et al., who studied patients with mucinous breast carcinoma (MBC) and showed that PMCs had larger tumors and longer survival times, while MMC cases showed more advanced axillary dissection rates and higher N - phase.[8]

In addition, research by Zhou, X et al. suggested that patients with PMC had fewer cases of lymph node metastases, were diagnosed at an earlier stage, showed higher rates of hormone receptor positivity, and had lower rates of HER2 expression compared to patients with invasive ductal carcinoma (IDC). Furthermore, the study of Emiroglu S et al. involving 87 patients diagnosed with PMC found that most of these patients were in the luminal subgroups with an excellent prognosis and a lower incidence of lymph node metastases, illustrating the favorable tumor biology of PMC.[14,15]

A study by Khokher, S. et al. involving 6,718 registered breast cancer patients revealed that 91% had invasive ductal carcinoma (IDC), 2% had invasive lobular carcinoma (ILC), and 1% had mucinous carcinoma (MC). These data are consistent with the profile of breast cancer patients in Pakistan, which follows a similar pattern to other developing countries.[16]

CONCLUSION

Pure mucinous carcinomas (PMCs) are uncommon breast tumors with distinguished cytologic features. It is clinically and genetically distinct from mixed mucinous carcinoma (MMC) and other types of breast cancer. An important prognostic factor is lymph node involvement, and PMCs often have a low proliferation rate and a more favorable long-term prognosis. Therefore, the identification of PMC through FNAC holds significant diagnostic and clinical importance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Chikkannaiah P, Thangngeo D, Guruprasad C, Venkataramanappa S. **Clinicopathological study of mucinous carcinoma of breast with emphasis on cytological features: A study at Tertiary Care Teaching Hospital of South India.** J Lab Physicians. 2020 Mar; 12(1):68-75. doi: 10.1055/s-0040-1714935. Epub 2020 Aug 11. PMID: 32792796; PMCID: PMC7419167.

2. Cherie M Kuzmiak, Benjamin C Calhoun. **Pure mucinous carcinoma of the breast: Radiologic-pathologic correlation.** Journal of Breast Imaging. March/April 2023; 5(2):180-187. https://doi.org/10.1093/jbi/wbac084

3. Upasana Joneja, Juan Palazzo. **The spectrum of mucinous lesions of the breast.** Archives of Pathology & Laboratory Medicine. 2022; 147(1):19-29. https://doi.org/10.5858/arpa.2022-0054-RA.

4. Budzik, M.P., Fudalej, M.M. & Badowska-Kozakiewicz, A.M. **Histopathological analysis of mucinous breast cancer subtypes and comparison with invasive carcinoma of no special type.** Sci Rep 2021; 11:5770. https://doi.org/10.1038/s41598-021-85309-z

5. Sun, P., Zhong, Z., Lu, Q., Li, et al. **Mucinous carcinoma with micropapillary features is morphologically, clinically and genetically distinct from pure mucinous carcinoma of breast.** Modern Pathology. 2020; 33(10):1945-1960. https://doi.org/10.1038/s41379-020-0554-8

6. Dr. Unnimaya K S, Dr. Jaimie Anandan, & Dr. Lilarani Vijayaraghavan. **Micropapillary variant of invasive mucinous carcinoma - A case report and review of literature.** International Journal of Medical Science and Clinical Research Studies. 2022; 2(4):274-279. https://doi.org/10.47191/ijmscrs/v2-i4-04.

7. Irean Garcia-Hernandez, Carlos A. Lopez-Garcia, Servando Cardona-Huerta, Rocio Ortiz-Lopez, Nydia Paulina Herrera-Rios, et al. **Pure mucinous breast carcinoma in a 25-year-old female, A case report.** International Journal of Surgery Case Reports. 2018; 53:58-60. ISSN 2210-612, ttps://doi.org/10.1016/j.ijscr.2018.10.009.

8. Esmer, A. C., Tazeoğlu, D., & Dağ, A. **Comparison of clinical, histopathological, and survival outcomes of pure and mixed mucinous breast carcinoma.** Indian Journal of Surgery. 2023 Aug; 85(4):802-8. https://doi.org/10.1007/s12262-022-03573-3

9. Wu, Y., Shin, S. J., & Sahin, A. A. **Special histologic types and special morphologic patterns of invasive ductal carcinoma of no special type: Mucinous, Micropapillary, Mucinous Cystadenocarcinoma, Neuroendocrine Neoplasm, Cystic Hypersecretory, Glycogen-Rich Clear Cell, Carcinoma with Osteoclast-Like Giant Cells.** In A Comprehensive Guide to Core Needle Biopsies of the Breast. 2022; 575-614. Springer International Publishing. https://doi.org/10.1007/978-3-031-05532-4_13

10. Marrazzo, E., Frusone, F., Milana, F., Sagona, A., Gatzemeier, W., Barbieri, et al. **Mucinous breast cancer: A narrative review of the literature and a retrospective tertiary single-centre analysis.** Breast. Churchill Livingstone. 2020, February 1. https://doi.org/10.1016/j.breast.2019.11.002

11. Sun, Y., Gu, W., Wang, G. & Zhou, X. **The clinicopathological and prognostic characteristics of mucinous micropapillary carcinoma of the breast.** Histology and Histopathology. 2022; 37:691-698.

12. Tseng HS, Lin C, Chan SE, Chien SY, Kuo SJ, Chen ST, et al. **Pure mucinous carcinoma of the breast: clinicopathologic characteristics and long-term outcome among Taiwanese women.** World J Surg Oncol. 2013 Jun 14; 11:139. doi: 10.1186/1477-7819-11-139. PMID: 23768133; PMCID: PMC3689603

13. Lei L, Yu X, Chen B, Chen Z, Wang X. **Clinicopathological characteristics of mucinous breast cancer: A retrospective analysis of a 10-year study.** PLoS One. 2016 May 27; 11(5):e0155132. doi: 10.1371/journal.pone.0155132. PMID: 27232881; PMCID: PMC4883756.

14. Zhou, X., Zheng, Z., Li, Y. et al. **The clinical features and prognosis of patients with mucinous breast carcinoma compared with those with infiltrating ductal carcinoma: A population-based study.** BMC Cancer. 2021; 21:536. https://doi.org/10.1186/s12885-021-08262-0

15. Emiroglu S, Tukenmez M, Karakus S, Karanlik H, Onder S, Ozmen V, et al. **Pure mucinous breast carcinoma with a favorable tumor biology and clinical outcomes.** Eur J Breast Health. 2022 Oct 1; 18(4):353-359. doi: 10.4274/ejbh.galenos.2022.2022-8-1. PMID: 36248750; PMCID: PMC9521282.

16. Khokher, S., Qureshi, M. U., Riaz, M., Akhtar, et al. **Clinicopathologic profile of breast cancer patients in Pakistan: Ten years data of a local cancer hospital.** Asian Pacific Journal of Cancer Prevention. 2012; 13(2):693-698. https://doi.org/10.7314/APJCP.2012.13.2.693.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Shireen Hamid	Conception of study, Manuscript writing, Analysis, Discussion.	
2	Muhammad Mudassar	Critical review, Manuscript writing.	
3	Hafsa Tariq	Facilitated for reagents / Material analysis.	
4	Sadia Hameed	Critical review, Facilitated for reagents / material analysis.	
5	Tariq Mehmood	Critical review, Facilitated for reagents.	
6	Saleha Tariq	Data analysis.	