

Gray Lesions of the Breast and its Diagnostic Significance: A Retrospective Study from Rural India

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Abstract

Background: Breast lesions extend from benign to malignant ones. The National Cancer Institute recommended categories for the diagnosis of breast cytology. There are some lesions in the breast which are called intermediate or gray lesions. It includes C3 (atypical, probably benign) and C4 (suspicious, favor malignant) which needs to be evaluated. **Materials and Methods:** This study was conducted in the Department of Pathology, Uttar Pradesh University of Medical Sciences, Saifai, Etawah (Uttar Pradesh). Fine-needle aspiration cytopathology (FNAC) was the diagnostic tool. The present study was undertaken to determine the gray lesions of the breast and its correlation with histopathology and other associated parameters. Immunohistochemistry was applied where ever necessary. One hundred and fifty one cases of gray lesions of the breast were included. **Results:** C3 was seen in 85 (56.29%) and C4 in 66 (43.70%) patients. The maximum number of patients was of 31–40, (33.77%) years age group, the youngest patient was 12-year-old female, whereas the oldest was 86 years male. Histopathology evaluation confirmed malignancy in 35 (23.17%) cases, and infiltrating ductal carcinoma was the frequent malignancy (24 [68.5%]). Sensitivity, specificity, positive predictive value, and negative predictive value of C4 category for the diagnosis of malignancy were, respectively, 81.48%, 50%, 68.7%, and 64.2%. **Conclusion:** FNAC is an excellent diagnostic tool. It has some limitations, especially with the gray lesions, which may lead to miss interpretation in diagnosis, so a scope of mistake to the cytopathologist is always there. These lesions need to be evaluated because of the risk of malignancy. However, gray lesions can be reduced by cytology followed by histopathology examination along with ancillary radiological investigations such as mammography and ultrasonography.

Keywords: Breast, fine needle aspiration cytopathology (FNAC), gray lesions, histopathology

INTRODUCTION

Breast is a modified skin appendage which is functional in females during lactation and rudimentary in males. It develops in fifth or sixth intrauterine life from ectodermal thickening.^[1] Breast pathologies extend from inflammation to malignancy. It is one of the important organs which is routinely subjected to fine-needle aspiration cytopathology (FNAC) for the diagnosis of pathologies, especially malignancy, as carcinoma of the breast is the common malignancy in women after cervical malignancy in India.^[2] There are some lesions which are designated as gray lesions of the breast, in which diagnosis is difficult to appreciate. The National Cancer Institute had categorized five groups for the diagnosis of breast pathologies on FNAC which are inadequate C1, benign C2, atypical, probably benign C3, suspicious, favor

malignancy C4, and malignant C5.^[3] Categories C3 and C4 are included in gray lesions in which a definite diagnosis is difficult to interpret.^[4] Some authors use the term “equivocal” for such inconclusive C3 and C4 categories. The present study was conducted to evaluate the significance of FNAC in the diagnosis of C3 and C4 categories and to correlate it with histopathology and other associated parameters.

MATERIALS AND METHODS

This study was a retrospective study carried out in the Department of Pathology of Uttar Pradesh University of Medical Sciences,

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Received: 05-04-2020 Accepted: 04-07-2020 Published: 22-01-2021

Access this article online

Quick Response Code:



Website:
<http://www.jmau.org/>

DOI:
10.4103/JMAU.JMAU_19_20

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How to cite this article: Dayal S, Krishna M, Kannaujia SK, Singh S. Gray lesions of the breast and its diagnostic significance: A retrospective study from rural India. J Microsc Ultrastruct 2021;9:119-24.

Saifai, Etawah, from January 1, 2008, to September 2019. All the breast lumps who attended the outpatient department followed by FNAC were included. The cases which were C3 and C4 were obtained from departmental records, screened, and compared with histopathology and also in relation to age and sex. One hundred fifty-one cases were included in the present study. Inclusion criteria were all breast lumps with C3 and C4 criteria on cytology. Exclusion criteria- inconclusive fnac, other categories on fnac examination (C1, C2, C5). FNAC was done with 21-gauge 10 ml syringes. Aspirated material was stained with hematoxylin and eosin (H and E) and May–Grünwald/Giemsa stain. Surgically excised breast tissues including biopsies and mastectomies sent in 10% formal saline were fixed, grossed, and processed, and multiple sections were made at 3–4 μ and stained with H and E and studied. Immunohistochemistry wherever necessary was applied.

RESULTS

A total of 151 cases were studied. Males were 5 (3.31%), whereas females were 146 (96.68%). C3 was seen in 85 (56.29%) and C4 in 66 (43.70%) patients. The maximum number of patients was of 31–40 (33.77%) years age group, the youngest patient was 12 years female, whereas the oldest was 86 years male. Histopathology evaluation confirmed malignancy in 35 (23.17%) cases. C3 showed malignancy in 13 (37.14%), whereas C4 showed malignancy in 22 (62.85%). Infiltrating ductal carcinoma was frequent malignancy seen in 24 (68.57%) cases. Sensitivity, specificity, positive predictive value, and negative predictive value of C4 category in the diagnosis of malignancy were 81.48%, 50%, 68.7%, and 64.2%, respectively.

DISCUSSION

Breast pathologies range from mastitis to malignancy.^[2] India is facing a challenging situation due to an 11.54% increase in incidence and 13.82% increase in mortality due to breast cancer during 2008–2012.^[5] Clinical examination, ultrasonography, and FNAC are the excellent tools to diagnose breast lesions. Histopathological examination of lumpectomy or biopsy is required to confirm the diagnosis and also the way to management. Inflammatory conditions can be managed on medical treatment, but awareness and more emphases should be on malignancy and metastatic breast diseases. FNAC is an well established diagnostic tool in the diagnosis of various breast lesions and great significance is found to differentiate benign pathologies from malignant lesions^[6]. However, there exist some breast lesions in which this differentiation is quite difficult to diagnose which are called gray lesions. There are few recommendations given by the National Cancer Institute which includes different categories such as inadequate C1, benign C2, atypical C3, suspicious favor malignancy C4, and malignancy C5. Categories C3 and C4 poses challenges to the pathologist because there is no strict criteria for diagnosis^[4,7,8]. C3 is given when the aspirate shows benign characteristics, but some characters raise possibilities for malignancy such as

cellular crowd, nuclear pleomorphism, loss of cell cohesion, nuclear–cytoplasmic changes, or therapy-related nuclear–cytoplasmic changes, whereas C4 category is given when the morphology favors the possibilities of malignancy but microscopically there is scant cellularity, poorly preserved or spread and may be obscured by hemorrhage or inflammation to warrant a definitive diagnosis^[8]. It also includes samples which show features of a greater degree than seen in C3 without the presence of overtly malignant cells.^[4,6]

On FNAC diagnoses of these categories should not exceed 20% of the lesions and it is preferred if it remains below 15% as per the NHSBSP guidelines so as to prevent over use or abuse of the categories.^[7,8] In the present study, C3 and C4 categories constituted 4.37%, i.e., 151/3454 which was consistent with other studies which had given a range of 4%–17.7% for both.^[3,4] The age were ranging from 12 years to 86 years while most of patients were belonging to 31–40 (33.77%) years age group which was comparable with other researchers.^[3,4] Male breast cancer is a rare medical condition, accounting for only 0.7% of all breast cancers diagnosed,^[9] which was also confirmed in the current study [Table 1].

In the current research work, C3 was seen in 56.29% and C4 in 43.70% of the patients [Table 2]. Histopathology examination was performed in 46.35% of the cases, the possible reason for the less number of histopathology might be the rural population, and the patient does not come for follow-up because of unaware attitude toward health. Here, C3 cases which were diagnosed as malignancy on histopathology were 37.14% of the cases [Figures 1 and 2]. These results were found significantly similar to other authors literature which results in malignancy range from 8.6% to 52%.^[4,10]

In C4 cases, malignancy on histopathology was observed in 62.85% of the cases [Figures 3 and 4]. These obtained results were significantly low as compared with other literature in which malignancy ranges from 81% to 97%.^[4,10] This might

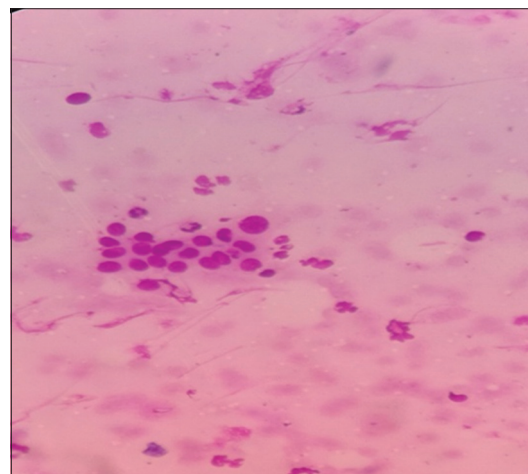


Figure 1: May Grunwald stain stained smear of C3 showing sheet of ductal cells with myoepithelial cells in the back ground. Some cells are showing enlarged cell with nuclear changes

Table 1: Age-wise distribution of patients with gray lesions

Age distribution	<21 years	21-30 years	31-40 years	41-50 years	51-60	61 and above	Total
Male	0	2	0	0	2	1	5 (3.31)
Female	17	32	51	23	16	7	146 (9 6.68)
Total (%)	17 (11.25)	34 (22.51)	51 (33.77)	23 (15.23)	18 (11.92)	8 (5.29)	151

Table 2: Distribution of fine-needle aspiration cytopathology and histopathology in the cases of gray lesions

	FNAC	Histopathology
C3	85	38 (n=13)
C4	66	32 (n=22)
Total	151	70 (n=35)

FNAC: Fine-needle aspiration cytopathology

happened because of proper screening of the cases clinically and on cytology also which results in less number of cases. However, the results also prove that changes to turn on malignancy are more in C4 in comparison to the C3 category, which recommends that every C4 category case must be followed by histopathological examination.

In both C3 and C4 categories on histopathology, infiltrating ductal carcinoma was the frequent malignancy observed in 68.5% of the cases, our results were similar to other studies.^[3,4] According to WHO classification, invasive ductal carcinomas is the most common cancer of breast among all breast cancers.^[11,12]

Among the FNAC cases for C3 and C4 categories fibroadenoma with atypia and proliferative breast disease were found common [Table 3]. Fibroadenoma is the most common benign breast lesion encountered on FNAC. Some degree of atypia, nuclear enlargement, and cellular dis cohesion is often seen in fibroadenoma, raising suspicion for low-grade adenocarcinoma. In present study 37.08% cases were of fibroadenoma which on histopathology examination diagnosed also as infiltrating ductal carcinoma and lobular carcinoma. The malignant transformation of fibroadenoma occurs either in ductal or lobular carcinomas.^[11] Another one had fibroadenoma with infiltrating ductal carcinoma. Although it is uncommon to find the combination of two pathologies, fibroadenoma with ductal carcinoma within the same breast, the possible causes for genesis might be a malignant transformation in preexisting fibroadenoma or simultaneous fibroadenoma and carcinoma arising in the same breast.^[11,12]

FNAC examination also reported fibroadenoma with mucoid changes which on histopathology diagnosed as mucinous carcinoma breast. The major differential of mucinous carcinoma breast is myxoid fibroadenoma and mucocele-like lesions.^[13] Similarly, gynecomastia has the same features as of fibroadenoma, but it is seen in males. It is not uncommon to found atypia in gynecomastia when seen raises the possibilities for malignancy. We could not access histopathology in gynecomastia as the patient did not come for follow-up.

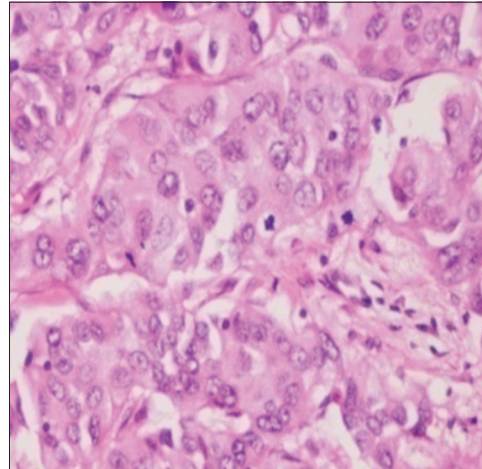


Figure 2: H and E-stained section of ductal carcinoma of the breast showing loosely arranged ductal cells. Cells are hyperchromatic, having vesicular nucleus, prominent nucleoli and some nucleoli are multiple in number, with frequent mitosis

Proliferative breast disease is the second most common group of grey zone lesions. Proliferative breast disease includes radial scar, complex sclerosing lesions and ductal hyperplasia.^[11,12] Ductal hyperplasia is common among proliferative breast disease, atypical ductal hyperplasia has an absolute risk for breast cancer. Atypical ductal hyperplasia cytological identification and its differentiation is quite difficult.^[8] In FNAC diagnosed cases of atypical ductal hyperplasia infiltrating ductal carcinoma was the common malignancy diagnosed on histopathology examination which justifies more chances of malignancy in atypical ductal hyperplasia.

The other grey lesions includes phyllodes tumor, mastitis, papillary lesions, fat necrosis and galactocele.^[4,8] Phyllodes tumor is diagnosed when epithelial components is broad and rounded as compared to angulated or staghorn pattern of fibroadenoma. Nuclear pleomorphism and the number of mitoses increase from mitosis borderline to malignancy. However, these features are subjective and difficult to access on cytology smears. Histopathology evaluation diagnosed four malignant phyllodes tumor and one scirrhous carcinoma [Table-4]. Malignant phyllodes tumors are differentiated by other breast tumors with the help of immunomarkers such as CD 34, CD 117, Ki-67, and vimentin.^[14,15] In the current study, these immunomarkers were also applied to differentiate and diagnose phyllodes tumor [Figures 5 and 6]. Scirrhous carcinomas are histologically characterized as hard, fibrous, and invasive carcinoma in which malignant cells occur singly or in small clusters in dense connective tissue.

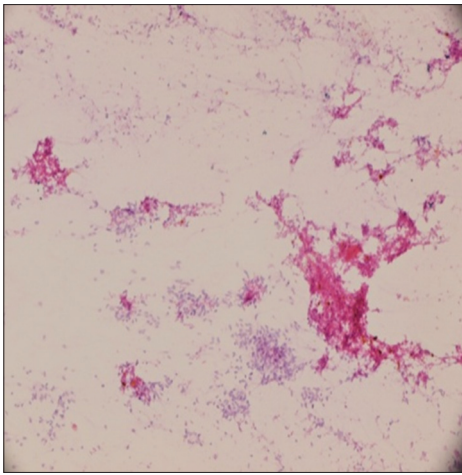


Figure 3: H and E-stained smear of C4 showing loosely and singly arranged spindle cells with enlarged hyperchromatic nucleus and prominent nucleoli

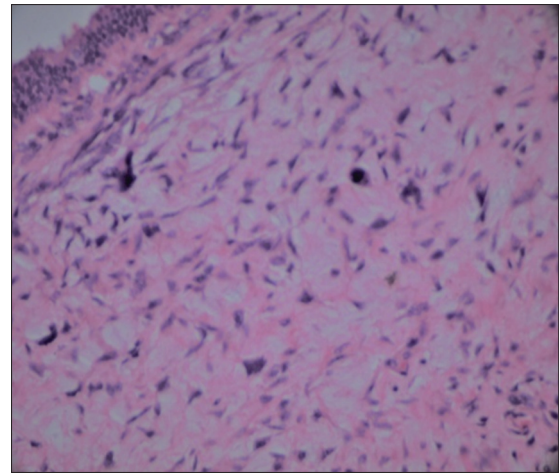


Figure 4: H and E-stained section of malignant phyllodes tumor showing spindle cells with elongated nucleus, prominent nucleoli, and mitosis

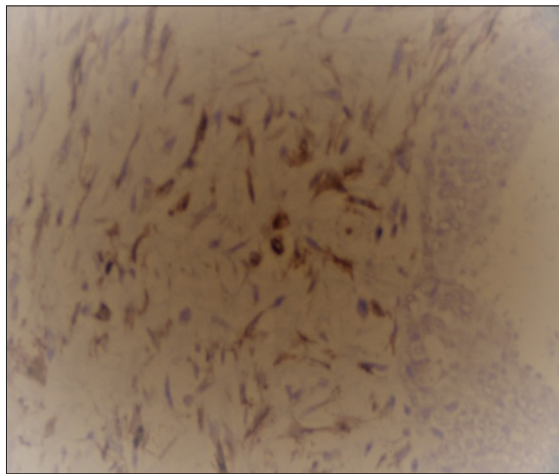


Figure 5: Section of malignant phyllodes tumor showing marked positivity for vimentin

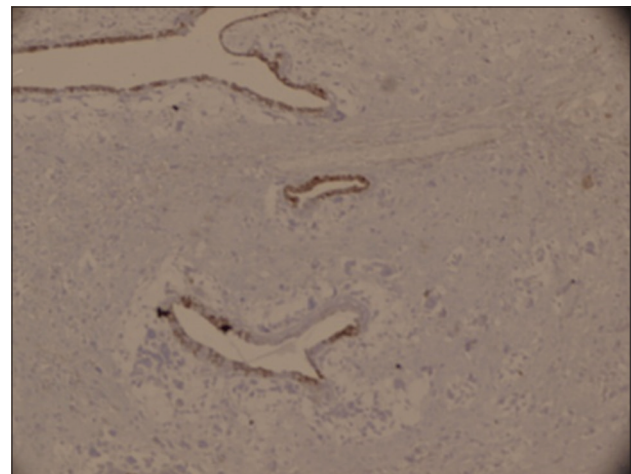


Figure 6: Section of malignant phyllodes tumor showing CD-117 positivity

Mastitis is inflammation of breast tissue in which breast tissue is surrounded and infiltrated with inflammatory cells. [16] Inflammatory cells may accelerate neoplastic processes by orchestrating the tumor microenvironment and sometimes, reactive atypia of the ductal epithelium in mastitis can cause problems in the categorization of the lesion. In such cases specially C3 we suggests repeat (FNA) after the inflammation subsides which is also supported by other authors.[4,8] We have found six cases which were shifted as a malignancy on histopathology, four as infiltrating ductal carcinoma and another as lymphoma and medullary carcinoma each, as it is common practice that sometimes malignancy is skipped and obliterated by over infiltrated inflammatory cells which leads to the miss diagnosis.

Papillary lesions of the breast are rare and constitute <10% of benign breast lesions and < 1% of breast carcinomas. It extends from central, peripheral, and atypical intraductal papilloma to papillary carcinoma.[17] It is always a diagnostic challenge

to differentiate benign from malignant because atypia may be appreciated in both, so it is not a discriminating feature. Similarly, of three atypical papillary breast lesions, two cases were diagnosed as papillary carcinoma on histopathology.

Fat necrosis, also known as “grand mothers disease,” usually presents in grandmothers who sustain trauma as a result of hanging their grandchildren. It usually presents as a breast lump or a radiological density, history of trauma is not available every time. On cytology examination, sometimes, there is reactive atypia in the ductal cells in the necrotic background which appears as malignancy.[7]

Galactoceles, on FNAC often poses diagnostic difficulties as there is possibilities of galactocoele, benign adenoma and carcinoma. In cytology smears having discohesive cells with round nuclei, coarse chromatin with prominent nucleoli raises suspicious for malignancy,[8] but proper clinical findings also helpful in proper diagnosis. However, it should be kept in mind that sometimes malignancy can be associated with lactation and lactation in such situation masks the evidence of

malignancy. In the present study, fat necrosis and galactocele were the components of gray lesions on cytology [Table 3], but we could not access histopathology in both.

In present study sensitivity, specificity, positive predictive value and negative predictive value of C4 category for the diagnosis of malignancy was respectively 81.48%, 50 %, 68.7 %, 64.2% which was comparable with studies done by Arul *et al*^[4], Yusuf *et al*^[6] and Goyal *et al*^[18] [Table 5].

False-positive and false-negative cases for malignancy are always a pit full of FNAC. In the current study, 25 in C3 and 10 in C4 were found false positive [Table 2] when compared with histopathology. The possible reasons for false-positive causes are inflammation, therapy, poor preservation, and poor preparation.^[18] False-negative cases are always more hazardous, the possible causes might be improper aspiration site, smaller

Table 3: Fine-needle aspiration cytopathology distribution of patients with gray lesions

FNAC	C3	C4	Total
Fibroadenoma	45	11	56 (37.08)
Proliferative breast ds	9	42	51 (33.77)
Phylloides tumor	6	3	9 (5.96)
Mastitis	9	8	17 (11.25)
Galactocele	4	0	4 (2.64)
Fat necrosis	4	1	5 (3.31)
Gynecomastia	4	1	5 (3.31)
Papilloma	1	2	3 (1.98)
Apocrine adenoma	1	0	1 (0.66)
Total			151

FNAC: Fine-needle aspiration cytopathology

Table 4: Variants of malignancy on histopathology with gray lesions

Type of malignancy	n (%)
Infiltrating ductal carcinoma	24 (68.5%)
Malignant phyllodes tumor	04 (11.42%)
Papillary carcinoma	02(5.71%)
Lobular carcinoma	01(2.8%)
Medullary carcinoma	01(2.8%)
Mucinous carcinoma	01(2.8%)
Scirrhous carcinoma	01(2.8%)
Lymphoma	01(2.8%)
Total	35

Table 5: Comparison of results of the present study with other studies

Study	Number of patients	Sensitivity	Specificity	PPV (%)	NPV (%)
Goyal <i>et al.</i>	40	60.8	88.2	87.5	62.5
Yusuf <i>et al.</i>	47	76.7	76.5	85.2	65
Arul <i>et al.</i>	93	84.8	66.7	86.2	64.3
Present study	151	81.48	50	68.7	64.2

PPV: Positive predictive value, NPV: Negative predictive value

tumor size, and scanty cellular, and some histopathology subtypes are low nuclear grade, scirrhous, lobular, and intracystic carcinoma which are possible reasons for false-negative results.^[18] In the current study, the results are depicted in Table 3. These cases can be reduced by triple tests that include FNAC, clinical examination, and radiological examination.^[18]

The significance of the gray lesions in the breast is that it identifies those cases which are having the possibilities of malignancy, thus help in rule out of malignant cases, finally resulting in early treatment before the complications arise.

CONCLUSION

In FNAC, gray lesions always have scope for malignancy. Hence, every FNA gray breast lesion is suspicious for malignant pathology that needs to be evaluated because of risk for malignancy. Although FNAC is an excellent diagnostic tool, histopathology examination must be done in these cases to rule out and exclude malignancy. Finally, gray lesions can be reduced by cytology followed by histopathology examination along with ancillary radiological investigations such as mammography and ultrasonography.

Ethical Approval

Ethical clearance was taken from university for research on breast lesions, Ethical committee with no. 230/2018 dated 27.2.19. Informed consent was taken wherever possible. Procedure follows guidelines laid down in declaration of Helsinki.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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