Section: Pathology

Original Research Article

MISMATCH REPAIR GENES IN BREAST CANCER

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ABSTRACT

Background: Breast carcinoma is one of the most common malignancies in the world. Every nine seconds, worldwide, a woman is diagnosed with breast carcinoma. Many patients will eventually develop resistance to hormone therapy due to several mechanism, one of which is mismatch repair dysregulation. The main objectives are to study the expression of MSH2, MSH6, MLH1 and PMS2. **Materials and Methods:** 34 modified radical mastectomy specimens received in the Department of Pathology, Victoria Hospital, BMCRI, Bengaluru were studied, which included cases of IBC- NST, Infiltrating Lobular Carcinoma and other histopathological subtypes. After routine processing, all cases were subjected to MSH2, MSH6, MLH1 and PMS2 IHC. These were evaluated on the basis of loss of nuclear staining in the presence of positive stromal control. **Results:** 1 case showed dMMR with loss of MSH6 expression and heterogenous pattern of expression seen in 3 cases of MSH2, 7 cases of MSH6, 5 cases of MLH1 and 4 cases of PMS2. MMR expression. **Conclusion:** MSH2, MSH6, MLH1 and PMS2 are the mismatch repair genes. From this study we have evaluated that MMR IHC though its deficiency is very rare in breast carcinoma, still IHC expression patterns serves as a clue to decide for further molecular testing and also helps us in identifying candidates appropriate for further check point inhibitor therapy, and also to some extent talks about the prognosis of the cancer.

INTRODUCTION

Breast cancer (BC) is one of the most common and deadly malignancy of women worldwide.[1] Every nine seconds, one woman is diagnosed with BC, hence most prevalent female tumor and most common cause of death due to cancer.[2] It has now replaced lung cancer as the foremost cause of global cancer incidence in 2020.[3] As per the Globocan data 2020, in India, breast cancer accounted for 13.5% (178361) of all cancer detected cases and 10.6% (90408) of all deaths.[4]

Approximately two-thirds of these patients have hormone receptor-positive (HR+) disease. For these patients, the main treatment approach involves endocrine therapy, either alone or combined with chemotherapy and/or targeted therapies. However, many patients with HR+ breast cancer (BC) eventually develop resistance to these therapies. This resistance can arise from various mechanisms, including changes in the tumor microenvironment and the downregulation of mismatch repair (MMR).[5] Acquiring of genomic instability is one of the characteristics of cancer cell. MMR acts as a natural defense mechanism. It is a system for recognizing and repairing genomic alterations during repair of DNA damage. Hence alterations in MMR system leads to cancer, tumor growth and progression and resistance to various therapies. Deficiency of this MMR could be due to somatic or germline mutation. Immune check point inhibitors, CDK4/6 inhibitors are used in all cases of refractory advanced solid tumors with MMR.[6] MMR alterations causing

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cancer in colon and endometrial carcinoma are well established.

However, our understanding of MMR deficiency in breast cancer is limited, particularly regarding its impact on patient outcomes and the role of cellular localization of MMR proteins in cancer phenotypes.[5]

MMR can be assessed by various methods. IHC, qPCR Based MSI analysis, NGS. IHC is used as a primary screening modality for evaluation of MMR status, and also, it's a good surrogate marker for MSI. Here we are using IHC of MSH6, MSH2, MLH1 and PMS2 MMR genes, because of its reliability, cost effectiveness and large availability.[5].Thus, the study of expression of MMR proteins in BC in Indian population is done by IHC. And thus help in proper treatment

Objectives: To evaluate MSH2, MSH6, MLH1 and PMS2 expression by Immunohistochemistry in breast cancer.

MATERIALS AND METHODS

It is a Cross sectional study from August 2022 to February 2024. All Breast cancer patients who underwent modified radical mastectomy, and the same specimens received in Department of Pathology at a Tertiary care centre were taken for the study. The total sample size was 34.

Inclusion Criteria

1. All cases of primary breast carcinoma who underwent modified radical mastectomy and those confirmed on histopathology
2. Patient willing to consent for study.

Exclusion Criteria

1. Cases of breast carcinoma post neoadjuvant therapy.
2. Trucut biopsy specimens are excluded.
3. Cores without internal stromal control on IHC.
4. Inevitable tissue loss during IHC handling.
5. Insufficient tumor sampling because of tissue depletion while sectioning.
6. Cases of breast carcinoma with poor tissue fixation and specimen.
7. Patients not willing to give informed consent.

The study was conducted after obtaining approval from Institutional ethical clearance.

After adequate fixation, appropriate sections are taken and paraffin embedded. 4-5 microns thick sections were cut from the paraffin blocks and then taken onto labelled slides for routine Haematoxylin and Eosin staining. MSH2, MSH6, MLH1 and PMS2 IHC staining was done subsequently on representative block of each case, by the immunoperoxidase method with the following antibodies: Monoclonal mouse antihuman antibody for hormone receptors, HER2, MSH2, MSH6, MLH1 and PMS2 (ER-clone 1D5 in a dilution of 1:200, PR-clone PR 88 in a dilution of 1:200 , HER-2/neu clone CB11 in a dilution of 1:100, MSH2- clone FE11 in a dilution of 1:100, MSH6-clone BC19 in a dilution of 1:100, MLH1- clone BC23 in a dilution of 1:100 and PMS2-clone A16-4 in a dilution of 1:100), colon is taken as positive control for MSH2, MSH6, MLH1 and PMS2 estimation, where colonic epithelial cells nuclear staining are considered positive. All the primary antibodies are from BIOCARE MEDICALS, USA and Secondary kit from Mach1 universal HRP from BIOCARE MEDICALS, USA.

The results were interpreted as Intact - When more than 90% tumour cells show nuclear positivity, Loss-Complete loss of nuclear staining in all the tumour cells (100%). The rest were considered as heterogenous. Complete loss of any of the above 4 IHC was taken as deficient MMR(dMMR), the rest were categorized as proficient MMR(pMMR)

RESULTS

Total of 270 specimens are received, in which 130 Trucut biopsy, 80 lumpectomy and 60 modified radical mastectomy specimens were received during the study period of 18 months i.e. August 2022 to February 2024. Out of 60 Modified radical mastectomy specimens, 6 were of post neoadjuvant therapy and those cases were excluded from the study. 54 specimens of modified radical mastectomy were diagnosed as Primary Invasive breast Carcinoma on histopathology. Only the first 34 Modified radical mastectomy diagnosed as invasive breast carcinoma were chosen in our study and these cases were subjected to MSH2, MSH6, MLH1 and PMS2 immunohistochemistry. Out of 34 cases, 31 cases (91.2%) showed MSH2 intact, 3 cases (8.8%) heterogenous MSH2 and 0(0%) cases with deficient MSH2. 26 cases (76.5%) showed MSH6 intact, 7 cases (20.6%) heterogenous MSH6 and 1 case (2.9%) with deficient MSH6. 29 cases (85.3%) showed MLH1 intact, 5 cases (14.7%) heterogenous MLH1 and 0 case (0%) with deficient MLH1. 26 cases (88.2%) showed PMS2 intact, 4 cases (11.8%) heterogenous PMS2 and 0 case (0.0%) with deficient PMS2. After interpreting individual expression, combined 1/34(2.9%) cases showed dMMR,and the rest were pMMR (97.1%).

Table 1: Distribution of cases according to MSH2, MSH6, MLH1 and PMS2 Immunohistochemistry status

	INTACT		HETEROGENOUS		DEFICIENT	
	Count	**Percentage**	**Count**	**Percentage**	**Count**	**Percentage**
MSH2	31	91.2 %	3	8.8%	0	0.0%
MSH6	26	76.5%	7	20.6%	1	2.9%
MLH1	29	85.3%	5	14.7%	0	0.0%
PMS2	30	88.2%	4	11.8%	0	0.0%

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Table 2: Combined MMR IHC expression in breast carcinoma

MMR STATUS	Number of cases	percentage
pMMR	33	97.1
dMMR	1	2.9
Total	34	100.0

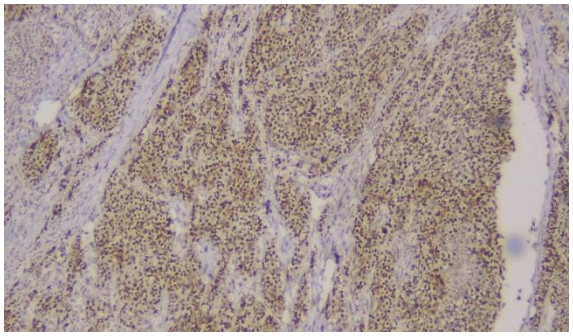

Figure 1: Staining pattern of MMR IHC marker: MSH2-intact with positive nuclear expression-10X

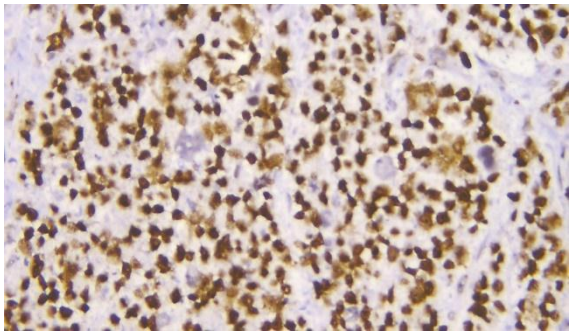

Figure 2: Staining pattern of MMR IHC marker: MSH6-intact with positive nuclear expression-40X

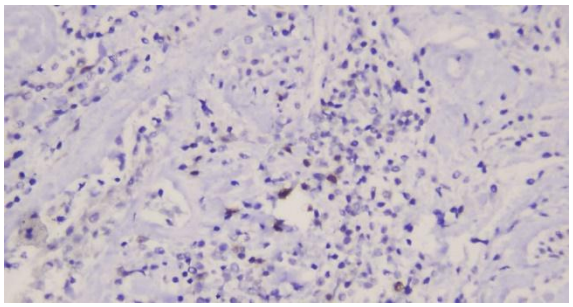

Figure 3: Staining pattern of MMR IHC: MSH6-deficient. - case of dMMR, 40X, showing loss of staining in tumour cells and positive internal control-lymphocytes

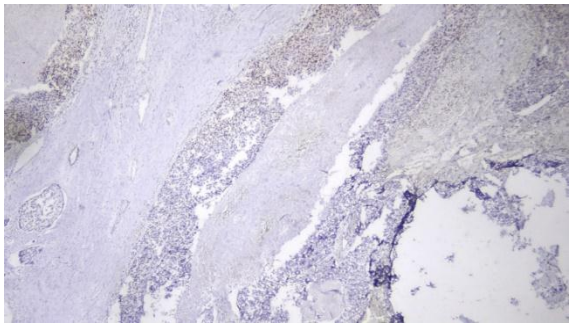

Figure 4: Staining pattern of MMR IHC marker: MLH1-Heterogenous (areas showing intact and areas with loss of staining in the same tumour). 4x

DISCUSSION

In the present study out of total 34 Cases, MSH2 IHC is intact in 31 cases, and 3 cases showed heterogenous staining pattern. MSH6 IHC is intact in 76.5% cases, and 20.6% cases showed heterogenous staining pattern. And 1 case (2.9%) with completely deficient pattern of expression was noted for MSH6. MLH1 IHC is intact in 29(85.3%) cases, and 5 cases (14.7%) showed heterogenous staining pattern. And none case with completely deficient pattern of expression. PMS2 IHC is intact in 30 cases (88.2%), and 4 cases (11.8%) showed heterogenous staining pattern. 97.1% (33 cases) showed proficient MMR and 2.9% (1 case) showed loss of expression of MSH2, hence 1 case was considered as dMMR. No cases of paired loss were noted in our study.

In study done by Cheng et al,[7] out of 2399 cases- 1.5% were MSH2 deficient, 1.9% were MSH6 deficient, 2.0% were MLH1 deficient and 2.0% were PMS2 IHC deficient. Rest all cases were reported as intact. 31 cases as MMR-deficient (1.9%). 25 cases had loss of a single MMR loss {11 cases- PMS2 loss only, 10 cases- MLH1 loss only, 3 cases- MSH6 loss only and 1 case- MSH2 loss only} and 6 cases had paired losses(4 cases- paired MLH1 and PMS2 losses, and 2 cases- MSH2 and MSH6 losses).

In Hacking S et al,[8] study, out of 994 cases, 1% were deficient for MSH2 IHC and rest 99% were intact for MSH2, 0.9% were deficient for MSH6 IHC, 0.9% were deficient for MLH1 IHC and 0.8% were deficient for PMS2 IHC. Rest all cases were reported as intact. dMMR was seen in 29(2.9%) cases.

In study by Fusco et al,[9] out of 444 cases, 12.3% were deficient for MSH2 IHC and heterogenous pattern of expression of MSH2 accounted for about 1.8%. MSH6 IHC 5.4% were deficient and 3% showed heterogenous expression. MLH1 IHC showed 9.4% were deficient and 1.3% showed heterogenous expression. PMS2 IHC showed 4.7% were deficient and 0.67% showed heterogenous expression. Rest all cases were reported as intact.

In study by Lopez et al,[10] out of 603 cases, 7.4% were deficient for MSH2 IHC, heterogenous pattern of expression, accounted for about 9%. MSH6 IHC - 9% showed deficient and 7% showed heterogenous pattern of expression. MLH1 IHC showed 13.6% were deficient and 7% showed heterogenous expression. PMS2 IHC showed 4.5% were deficient

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and 2.5% showed heterogenous expression. Rest all cases were reported as intact.

Limitations

A limitation of this study is the lack of a standardized quantitative and qualitative scoring system for MMR IHC, along with potential variability arising from the use of different primary antibodies. MMR IHC also demonstrates intratumoral heterogeneity, which may lead to misclassification of tumors as dMMR if only IHC-negative areas are sampled, potentially affecting therapeutic decisions. Additionally, molecular validation was not performed for cases showing heterogeneous MMR staining patterns. Finally, in our study, MSH6 loss on IHC appeared to correlate more closely with MMR functional status than with DNA mutational burden.

CONCLUSION

In this study of 34 invasive breast carcinoma cases, the expression of MSH2, MSH6, MLH1 and PMS2 was noted, out of which 1 case of MSH6 was completely lost and Heterogenous expression was seen in 3 cases of MSH2, 7 cases of MSH6, 5 cases of MLH1 and 4 cases of PMS2. These are the cases which have to be subjected for further NGS testing, to detect emerging subclones.

In recent years, many patients of breast carcinoma are developing therapy resistance by several mechanism, including MMR downregulation, tumor microenvironment alteration. Cases of MMR loss who don't respond to hormonal therapy, gets benefited with alternate check point inhibitors and may have better prognosis. Use of immune check point inhibitors like pembrolizumab are of great use in breast carcinoma also. The application of MMR IHC as a marker in the initial immunohistochemical panel of breast carcinoma may serve as an early marker to guide right therapeutic option.

The present study concludes that expression of MSH2, MSH6, MLH1 and PMS2 is very rare. However, MMR can be used as a marker for breast carcinomas and may be used as a marker to guide for cases where further molecular testing needs to be done. Further meta-analysis with a study on larger sample size needs to be considered and correlation with other genetic markers are required for validation of MMR in breast carcinoma. MMR IHC with genomic analysis is necessary for clinical assessment in breast carcinoma.

Conflict of Interest: Author doesn't have any conflict of interest.

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