Section: Pathology

Original Research Article

CYTOKERATIN 18 EXPRESSION IN INVASIVE BREAST CARCINOMA

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ABSTRACT

Background: Cytokeratin 18 (CK18) is an intermediate filament protein expressed in epithelial cells and has been implicated in epithelial–mesenchymal transition and tumor progression. Reduced CK18 expression has been associated with adverse prognostic factors in breast carcinoma. The objective is to evaluate the expression of CK18 in invasive breast carcinoma using immunohistochemistry (IHC).

Materials and Methods: A prospective cross-sectional study was conducted on 75 modified radical mastectomy specimens diagnosed as invasive breast carcinoma between April 2022 and May 2023. CK18 expression was assessed by IHC using a monoclonal anti-CK18 antibody. Expression was quantified using the H-score method (range: 0–300), calculated from staining intensity and percentage of positive tumor cells.

Results: The majority of cases were infiltrating duct carcinoma of no special type (86.7%). Most patients belonged to the 40–59 years age group (57.3%). CK18 expression was preserved in most tumors, with 53 cases (70.7%) showing an H-score >200 and 17 cases (22.7%) showing scores between 100 and 200. Only 5 cases (6.7%) demonstrated low CK18 expression with H-scores <100.

Conclusion: CK18 expression was maintained in the majority of invasive breast carcinomas, while a small subset showed downregulation. Since reduced CK18 expression has been linked to epithelial–mesenchymal transition and poor prognostic features, CK18 may serve as a potential prognostic biomarker. Further studies with larger sample sizes and clinicopathological follow-up are required to establish its prognostic significance.

Keywords: Cytokeratin, CK18, Breast cancer, Immunohistochemistry.

INTRODUCTION

Breast carcinoma is the most common cancer in women and is the 2nd most common cause of cancer deaths.[1] More than 1.7 million cases are reported worldwide annually.[2] In 2018, 1,62,468 new cases of breast cancer have been registered and 87,090 deaths have been reported.[3] Breast cancer among men is a rare with an estimated incidence rate of 0.5 to 1% among all breast cancers.[4]

Early diagnosis and treatment is necessary. There is a need to assess for new prognostic factors. One of the main features in the transition between normal and cancer cells is a change in cytoskeletal structure.[5] Cytokeratins are intermediate filaments which form the cytoskeleton of epithelial cells which are grouped into type I (acidic), and type II(basic).[6] Cytokeratin 18 is a type I intermediate filament. It is found in the epithelial tissues. It is located in cytoplasm and perinuclear region and is persistently expressed in adult epithelial organs such as breast, liver, lung, kidney, pancreas, GIT and also expressed by cancers arising from these tissues.[7,8] It performs the functions of intracellular scaffolding, apoptosis, mitosis, cell signaling and cell cycle progression.[7,9] Its down regulation has shown association with increased mitotic rate, higher histological grade and negative HER2/neu status.[10]

Only a few studies have been done in Indian population. This study is done to evaluate the

expression of cytokeratin 18 in invasive breast carcinoma.

Objectives of the study: To detect expression of cytokeratin 18 in invasive breast carcinoma by immunohistochemistry.

MATERIALS AND METHODS

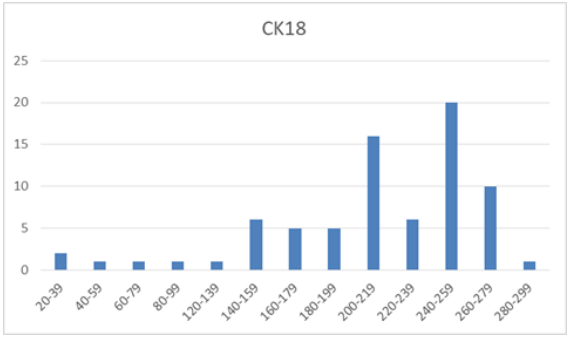
A Prospective cross sectional study with Modified radical mastectomy specimens diagnosed as Invasive breast carcinoma on histopathology in the Department of Pathology at a tertiary care centre during period of April 2022 to May 2023 were included. A total of 75 cases were studied. All cases of invasive breast carcinoma were included and tissues with poor fixation and poorly preserved, post neoadjuvant therapy were excluded from the study. Sample collection began after obtaining clearance from the ethical committee. Brief clinical history of the patient including name and age were noted. The specimens were received in a labelled container containing 10% formalin. 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 labeled slides for routine Hematoxylin and Eosin staining and CK18 IHC staining was done subsequently on representative block of each case. Anti-CK 18 mouse monoclonal antibody for CK 18 expression was used. Immunostaining of CK 18 was graded according to the study done by Aiad H A et.al10 CK 18 H score is given, which ranges from 0 to 300, calculated by the intensity of the staining multiplied by the percentage of cells (mild intensity x percentage of cells + moderate intensity x percentage of cells+ severe intensity x percentage of cells).

RESULTS

In the study period from November 2019 to May 2021, total of 64 trucut biopsy, 180 lumpectomy and 96 modified radical mastectomy specimens were received in the Department of Pathology. Out of 96 Modified radical mastectomy specimens, 6 were of post neoadjuvant therapy and those cases were excluded from the study. 90 specimens of modified radical mastectomy were diagnosed as Primary Invasive breast Carcinoma on histopathology. The first 75 consecutive cases Modified radical mastectomy diagnosed as invasive breast carcinoma were chosen in our study and these cases were subjected to IHC.

Invasive breast carcinoma was most commonly noted in the age group of 40-59 years with 43 cases (57.3%), followed by 61-70 years with 21 cases (28), 20-39 years with 10 cases (13.3%), 80-99 years with 1 case (1.3%). Among 75 cases, 65 cases (86.7%) were reported as Infiltrating duct carcinoma of no special type. 2 cases (2.7%) were reported as IDC with medullary features. 1 case (1.3%) of infiltrating lobular carcinoma, 1 case of Invasive papillary carcinoma (1.3%), 1 case (1.3%) of Metaplastic carcinoma, 3 cases (4%) of Mixed mucinous carcinoma and 1 case (1.3%) of Mucinous carcinoma were diagnosed.

Out of 75 cases, 20 cases (26.7%) showed CK 18 H score of 240-259. 16 cases (21.3%) showed CK 18 H score of 200-219. 10 cases (13.3%) showed CK 18 H score of 260-279. 6 cases (8%) showed CK 18 H score of 140-159. 6 cases (8%) showed CK 18 H score of 220-239. 5 cases (6.7%) showed CK 18 H score of 160-179. 5 cases (6.7%) showed CK 18 H score of 180-199. 2 cases (2.7%) showed CK 18 H score of 20-39. 1 case (1.3%) showed CK 18 H score of 40-59. 1 case (1.3%) showed CK 18 H score of 60-79. 1 case (1.3%) showed CK 18 H score of 80-99. 1 case (1.3%) showed CK 18 H score of 120-139. 1 case (1.3%) showed CK 18 H score of 280-299. Totally 5 out off 75(6.66%) cases showed H score less than 100.



Graph1: Distribution of cases according to ck18 H score

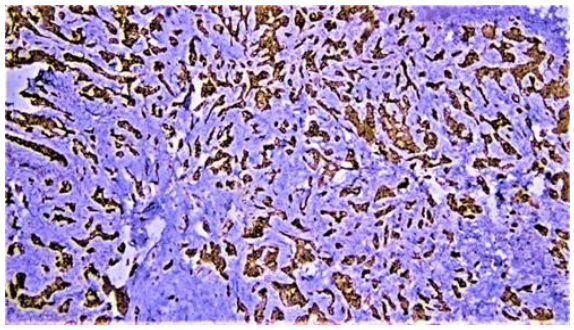


Figure 1: Invasive breast carcinoma CK 18 membranous positivity-, 10x

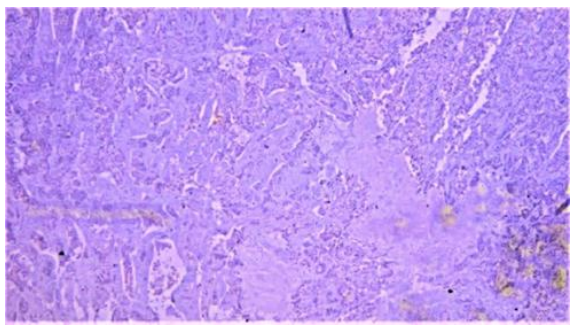


Figure 2: Invasive breast carcinoma CK 18 downregulation- 10x

DISCUSSION

Cytoskeleton is a cellular skeleton made up of proteins which gives the cell its structure and shape. Cytokeratins are of 20 different proteins belonging to 2 categories. Acidic type I group consisiting of cytokeratin 9 to cytokeratin 20. Neutral to basic type II group consisting of cytokeratin 1 to cytokeratin 8. Acidic type combines with the basic type in a ratio 1:1 to form hetropolymers which then form keratin filaments.[6,7,11]

The cytokeratin 18 gene is located on chromosome 12q13 and is 3,791 base pairs long. Cytokeratin 18 is expressed in many epithelial organs such as liver, lung, pancreas, kidney, breast and gastrointestinal tract and in the cancers arising from them7. In normal breast tissue cells adjacent to the basal membrane and myoethelial cells express cytokeratin 5,14, 17. Luminal cells express cytokerratin7, 8,18 and 19.[5] Cytokeratin 18 form cytoplasmic scaffold that emanates from the plasma membrane and spreads throughout the cytoplasm to provide shape and rigidity to the cells, therefore maintains the integrity of the cell and protects the cell against external stresses.[7,12,13] CK18 is also important for cellular processes such as apoptosis, mitosis, cell cycle progression, and cell signalling.[7,14]

Metastasis is one of the major poor prognostic factors in breast carcinoma. Epithelial mesenchymal transition is a critical mechanism involved in the aquisition of metastatic capacity by cancer cells. Cytokeratin 18 has been suggested as an epithelial specific marker of the epithelial mesenchymal transition. Some of the studies show that the downregulation of cytokeratin 18 is associated with metastasis and positive lymph node status. It is hypothesized that cytokeratin 18 downregulation causes epithelial mesenchymal transition and is associated with poor prognosis.[15]

In our study we studied about the expression of CK 18 by IHC and H scoring was given. 53 cases had CK18 H Score above 200, 17 cases with 100-200 and 5 cases with H score of less than 100. Though there is no standardized cut off value to tell downregulation, less number of cases showed H score of less than 100.

In a study done by Woelfle et al,[16] out of 1458 cases, downregulation was observed in 25.4% of ductal carcinomas and 17% in lobular carcinoma.

CONCLUSION

Metastasis is one of the major poor prognostic factors in breast carcinoma. Epithelial mesenchymal transition is a critical mechanism involved in the aquisition of metastatic capacity by cancer cells. Cytokeratin 18 has been suggested as an epithelial specific marker of the epithelial mesenchymal transition. Some of the studies shown that the downregulation of cytokeratin 18 is associated with poor prognostic factors.

In our study we have got 5 out off 75 cases with H score less than 100. The downregulation of CK18 was noted in these cases, which gives a clue towards the prognosis of the patient.

In recent years, wide clinical applications of radiotherapy and chemotherapy have significantly improved the prognosis of breast cancer patients. However metastasis is difficult to manage, since some of the studies show that the downregulation of CK18 play crucial roles in the regulation of metastasis which is helpful for prognosis assessment in breast cancer49. Further pre-clinical and clinical studies may be required to evaluate the role of CK18 as a potential predictor of breast cancer.

Limitations: Our analysis has certain limitations. First limitation is currently, no established standard system is available for CK 18 expression and H scoring. Multiple primary antibodies are available for staining and this can be the reason for variability in the rate of CK 18 expression. Second limitation was not correlating with other ER,PR, HER2 status and histopathological prognostic factors. And also long term followup of the patient was not done, which would have significant effect on the study.

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