CASE REPORT

Biomarker Profile Alteration in a Case of High-Grade Breast Carcinoma: Tumour Heterogeneity, Metaplasia or Chemotherapeutic Effect?

[1]Dr. Vaishali Yadav, [2]Dr. Kavita Gaur, [3]Dr. Kiran Agrawal

[1]Consultant Pathologist, Park Hospital, Faridabad, Haryana, India. [Ex: Post graduate Student, Department of Pathology, Lady Hardinge Medical College, New Delhi, India.]
[2]Assistant Professor, [3]Director Professor, Department of Pathology, Lady Hardinge Medical College, New Delhi, India.

Corresponding Author
Dr. Vaishali Yadav
Consultant Pathologist, Park Hospital, Faridabad, Haryana, India.

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ABSTRACT
Background: Neo-adjuvant chemotherapy is employed for patients with locally advanced breast carcinoma and in cases of metastatic or inoperable breast carcinoma to reduce tumor size and subsequently improve breast-conserving surgery rates. Biomarker studies performed on excisional specimens may be discordant with those performed on trucut biopsy, moreso after neo-adjuvant chemotherapy. There is paucity of data in the literature on whether the primary tumour characteristics, hormone receptors and HER2 expression change as a result of chemotherapy. The present case report shows biomarker profile alteration in a case of high-grade breast carcinoma.
Keywords: Neo-Adjuvant Chemotherapy, Breast Carcinoma,Trucut Biopsy.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women and is the leading cause of cancer-related death amongst women worldwide. Chemotherapy is an important treatment modality and has significantly improved the survival of breast cancer patients. In chemotherapy, neoadjuvant chemotherapy (NAC) has become a well-established approach to treat large-sized or locally advanced breast cancer.[1-3] The indications for neoadjuvant chemotherapy (NACT) in breast cancer have been implemented since 2006.[4] The introduction of neoadjuvant chemotherapy in locally advanced breast cancer offered us advantages like initiation of early systemic therapy, delivery of drugs through intact vasculature, down-staging of tumors, which makes inoperable tumors operable and renders tumors suitable for breast conserving surgery.[5,6]Biomarkers have been applied in the detection, screening, diagnosis, and monitoring of cancer treatment. Increasing evidence indicates that tumor biomarker levels can change following neoadjuvant chemotherapy.[7] Both NACT and adjuvant therapies are mainly based on the assessment of three biomarkers on tumor tissue from preoperative biopsies worldwide: estrogen receptors (ER), progesterone receptors (PR) and HER2 status.[8,9] Ki67 is implemented as a fourth biomarker by the majority of European countries in this setting to subdivide tumors into five surrogated intrinsic subtypes with different prognosis and treatment implications: Luminal A-like, Luminal B-like HER2 negative, Luminal B-like HER2 positive, HER2-positive non-luminal and triple-negative.[10]

CASE REPORT

A 45 year old female patient presented with complaints of lump in right breast since one year, progressively increasing in size and associated with pain and swelling in the right axilla. Multi-slice computed tomography showed carcinoma breast with extension and left axillary lymphadenopathy. Bone scan showed no evidence of skeletal metastases. Core biopsy findings were suggestive of an infiltrating ductal carcinoma, no special type with ER/ PR negative status.HER2/neu was 3+ and Ki67 was 90%. The patient subsequently received four cycles of paclitaxel neo-adjuvant chemotherapy before resection. We received a right breast specimen grossly

measuring 28x14.5x5cm. No skin changes were noted. Microscopy showed features of grade3 infiltrative ductal carcinoma with post chemotherapy changes. IHC profile of the tumour cells was triple negative and Ki67 was 10%, EGFR and CK5/6 was focal positive. The patient is currently on follow up and doing well.

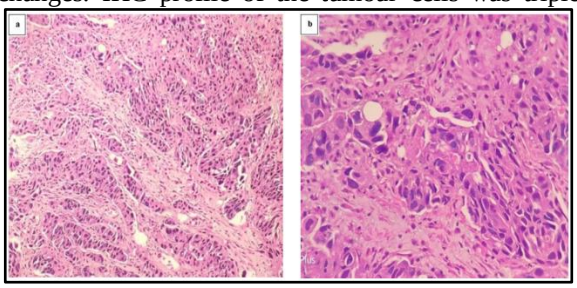

Figure 1: a and b: Microscopic examination(TRUCUT)10x and 40x

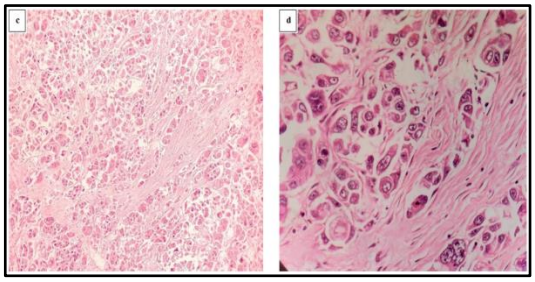

Figure 2:c and d: Microscopic examination (Tissue Section)10x and 40x

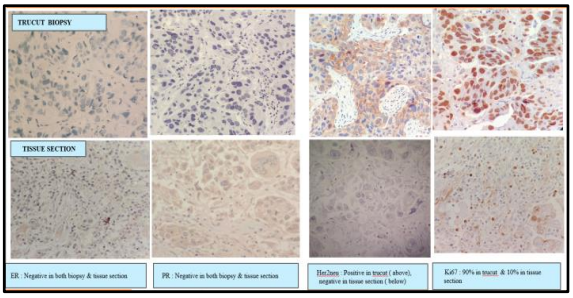

Figure 3: Immunochemistry

DIAGNOSIS

Infiltrative ductal carcinoma grade 3 with post chemotherapeutic changes

DISCUSSION

NAC is frequently utilized to treat patients with locally advanced breast cancer. Assessment of biomarker changes after NAC treatment is critical for evaluation of NAC efficiency and should be used to tailor the clinical management for breast cancer patients.[11,12]In 2015, recommendations from an international working group (BIG-NABCG) suggested indeed that a reassessment of hormone receptors and HER2 after neoadjuvant therapy should be considered only in some cases, such as negative results on pretreatment core biopsy and/or no response to therapy. Among a cohort of 83 cases, Xian et al. reported that 25 (30%) patients demonstrated changes in post-NACT biomarker status. Nevertheless, these changes impacted the patient management only in four (4.8%) patients that were hormone receptor and/or HER2 negative before NACT.[13]Zhou X et al did a study to study the effect of NAC on biomarker expression and explore the impact of tumor size and lymph node involvement on biomarker status changes. They collected 107 patients with invasive breast cancer who received at least three cycles of NAC. We retrospectively performed and scored the immunohistochemistry (IHC) of ER, PR, HER2 and Ki-67 using both the diagnostic core biopsies before NAC and excisional specimens following NAC. HER2 gene status was assessed by fluorescence in situ hybridization for cases with IHC result of 2+. We demonstrated that there was a significant decrease in expression of PR ($P = 0.013$) and Ki-67 ($P = 0.000$) in post-NAC specimens compared to pre-NAC core biopsies. In addition, cases with large tumor size (≥ 2 cm) and cases with lymph node metastasis were more frequently to have biomarker changes. Finally we studied cases with HER2 status changes after NAC treatments in detail and emphasized the nature of tumor heterogeneity.[14]Jin G et al did a study to assess the changes in estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 expression in breast cancer patients after various neoadjuvant chemotherapies. Data from 138 locally advanced breast cancer patients with histological diagnoses were reviewed. Seventy patients (group 1) were given 4 cycles of 500 mg/m^2 cyclophosphamide and 50 mg/m^2 pirarubicin every 21 days. Sixty-eight patients (group 2) were given 4 cycles of 500 mg/m^2 cyclophosphamide and 75 mg/m^2 docetaxel every 21 days. The biomarker changes of the operated tumor tissues were compared with the initial core biopsies. ER, PR, HER2 and Ki-67 expression changed by 28.6%, 22.9%, 17.1% and 54.3%, respectively, after neoadjuvant chemotherapy in group 1 and 16.2%, 22.1%, 13.2% and 70.6%, respectively, after neoadjuvant chemotherapy in group 2. There were significant differences between the groups regarding ER and Ki-67 status changes, and these changes can be used to inform treatment strategies.[15]

CONCLUSION

Biomarker expression profile may change after neoadjuvant chemotherapy because of intertumorand also because of intratumor heterogeneity. Careful marker profile is essential both for clinical and therapeutic prospective.

REFERENCES

1.Colleoni M, Goldhirsch A. Neoadjuvant chemotherapy for breast cancer: any progress? Lancet Oncol. 2014;15:131–132.
2.Thompson AM, Moulder-Thompson SL. Neoadjuvant treatment of breast cancer. Ann Oncol. 2012;10:x231–236.

3. Read RL, Flitcroft K, Snook KL, Boyle FM, Spillane AJ. Utility of neoadjuvant chemotherapy in the treatment of operable breast cancer. ANZ J Surg. 2015;85:315–320.
4. Kaufmann M., von Minckwitz G., Bear H.D., Buzdar A., McGale P., Bonnefoi H., Colleoni M., Denkert C., Eiermann W., Jackesz R., et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: New perspectives 2006. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2007;18:1927–1934. doi: 10.1093/annonc/mdm201.
5. Fisher B, Brown A, Mamounas EL. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from national surgical adjuvant breast and bowel project B-18. J. Clin. Oncol. 1997;15:2483–93.
6. Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: Findings from the national surgical adjuvant breast and bowel (NSABP) protocol B-18. Cancer. 2002;95:681–95.
7. Jin G, Han Y, Liu C, Chen L, Ding B, Xuan S, Liu X, Ma G, Gao J, Tian X. Evaluation of biomarker changes after administration of various neoadjuvant chemotherapies in breast cancer. Int J Clin Exp Pathol. 2015 Jan 1;8(1):914-21. PMID: 25755795; PMCID: PMC4348938.
8. National Comprehensive Cancer Network Breast Cancer (Version 8.2021) [(accessed on 13 September 2021)]. Available online: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
9. Cardoso F., Paluch-Shimon S., Senkus E., Curigliano G., Aapro M.S., André F., Barrios C.H., Bergh J., Bhattacharyya G.S., Biganzoli L., et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5) Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2020;31:1623–1649. doi: 10.1016/j.annonc.2020.09.010.
10. Goldhirsch A., Winer E.P., Coates A.S., Gelber R.D., Piccart-Gebhart M., Thürlimann B., Senn H.J. Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2013. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2013;24:2206–2223. doi: 10.1093/annonc/mdt303.
11. Cockburn A, Yan J, Rahardja D, Euhus D, Peng Y, Fang Y, Rumnong Sarode V. Modulatory effect of neoadjuvant chemotherapy on biomarkers expression; assessment by digital image analysis and relationship to residual cancer burden in patients with invasive breast cancer. Hum Pathol. 2014;45:249–258.
12. Zhang N, Moran MS, Huo Q, Haffty BG, Yang Q. The hormonal receptor status in breast cancer can be altered by neoadjuvant chemotherapy: a meta-analysis. Cancer Invest. 2011;29:594–598.
13. Xian Z., Quinones A.K., Tozbikian G., Zynger D.L. Breast cancer biomarkers before and after neoadjuvant chemotherapy: Does repeat testing impact therapeutic management? Hum. Pathol. 2017;62:215–221. doi: 10.1016/j.humpath.2016.12.019.
14. Zhou X, Zhang J, Yun H, Shi R, Wang Y, Wang W, Lagercrantz SB, Mu K. Alterations of biomarker profiles after neoadjuvant chemotherapy in breast cancer: tumor heterogeneity should be taken into consideration. Oncotarget. 2015 Nov 3;6(34):36894-902. doi: 10.18632/oncotarget.5050. PMID: 26384297; PMCID: PMC4742218.
15. Jin G, Han Y, Liu C, Chen L, Ding B, Xuan S, Liu X, Ma G, Gao J, Tian X. Evaluation of biomarker changes after administration of various neoadjuvant chemotherapies in breast cancer. Int J Clin Exp Pathol. 2015 Jan 1;8(1):914-21. PMID: 25755795; PMCID: PMC4348938.