JBUON 2015; 20(5): 1378-1381
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

LETTERS TO THE EDITOR

Breast cancer and high-grade glioma: link or coincidence?

Dear Editor,

Breast cancer is the most common type of cancer and the second leading cause of cancer death in women. The age-adjusted incidence rate is 124 per 100,000 women per year. High-grade gliomas are, however, relatively rare (incidence: ~4/100,000 person–years) [1]. Here, we report three cases and discuss possible links between these two distinct neoplasms.

Case 1: 39-year-old premenopausal woman was diagnosed with invasive ductal carcinoma of the breast (grade III; ER-PR+HER2+; T2N3M0).

Following modified radical mastectomy (MRM), she received radiotherapy, chemotherapy and hormone therapy. Nine months later, she had headache and memory deficits. A MRI of the brain showed a 48x50x45 mm left inferior temporal mass. She was operated and the biopsy revealed glioblastoma multiforme (GBM). She received concomitant chemoradiotherapy and 4 cycles of temozolomide. Despite stereotactic radiosurgery (CyberKnife) and irinotecan-cisplatin-cyclophosphamide chemotherapy for tumor recurrence 2 years postoperatively, the patient died at the 50th month of the follow-up.

Case 2: A 29-year-old premenopausal woman, having a cousin with colon cancer, was diagnosed with medullary breast carcinoma (grade III; ER-PR-HER2+; T2N3M0). Following MRM, she received radiotherapy and adjuvant chemotherapy. Three years later she was diagnosed with an early-stage endometrial carcinoma and underwent hysterectomy. On the 7th year of follow-up she underwent breast conserving surgery for another mass. Pathology showed invasive ductal carcinoma (grade III; ER+PR+HER2-; T2N0M0), and she received radiotherapy, chemotherapy and hormonal therapy. Three years later she developed progressive headache and dizziness and her brain MRI showed a 5 cm left parietal mass adjacent to the lateral ventricle. Partial excision was performed, and the pathology showed a GBM. She received radiotherapy followed by 6 cycles of temozolomide, and tumor volume regression was achieved. On the 11th year of follow-up she was diagnosed with tubulovillous adenoma on colonoscopy. She is still alive 14 years after the diagnosis of breast cancer with no intracranial tumor progression for a period of 4 years.

Case 3: A 51-year-old perimenopausal woman presented with a palpable lump in the left breast. Biopsy revealed invasive ductal carcinoma (grade II; ER% 10, PR% 10, HER2+). She received neoadjuvant chemotherapy with 6 cycles of docetaxel plus trastuzumab, and hormone therapy has been planned. Two months before the diagnosis of breast cancer, she had undergone an operation for a mass in the left frontal lobe. Pathological examination of the specimen showed an anaplastic oligodendroglioma (WHO grade III). Following diagnosis, she had received external radiotherapy and temozolomide. She is still alive 2 years after the diagnosis.

There are several reports in the literature describing breast carcinoma and glioma association. Maluf et al. reviewed 21 high-grade glioma cases with prior systemic malignancies, of whom 5 had breast cancer [2]. An Italian group reported on 11 cases of breast cancer and GBM [3]. It is not surprising that the CNS tumors detected in a breast cancer patient, especially if multicentric, can be easily confused with metastasis. Thus, a detailed radiological assessment and biopsy are warranted in suspicious cases.

Although several authors indicated that this association could be due to chance or related to the favorable long-term survival of breast cancer patients to allow them to develop glioma at a late age [2], there are some others who argue against the coincidence, proposing possible common etiopathogenetic mechanisms [3] such as hereditary cancer syndromes (e.g. Li Fraumeni's, Cowden's, BRCA1&2), hormonal factors and prior irradiation [3-5]. Tumors are usually considered and treated independently in the setting of two distinct neoplasms [2,3], which leads to overtreatment. In conclusion, long-term epidemiological studies of larger cohorts are needed to confirm the association and to establish the common risk factors, pathogenetic mechanisms and better treatment options for both tumors.

References

1. Ries LAG, Melbert D, Krapcho M et al (Eds): SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/ [Accessed 10 February 2015]
2. Maluf FC, DeAngelis LM, Raizer JJ, Abrey LE. High-grade gliomas in patients with prior systemic malignancies. Cancer 2002;94:3219-3224.
3. Piccirilli M, Salvati M, Bistazzoni S et al. Glioblastoma multiforme and breast cancer: report on 11 cases and clinico-pathological remarks. Tumori 2005;91:256-260.
4. Malkin D, Li FP, Strong LC et al. Germline p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233-1238.

5. Li J, Yen C, Liaw D et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997;275:1943-1947.

Sahin Hanalioglu[1], Elshad Hasanov[2], Kadri Altundag[2]

[1]*Department of Neurosurgery, Hacettepe University Faculty of Medicine, Ankara;*[2]*Hacettepe University Cancer Institute, Ankara, Turkey*

Correspondence to: Kadri Altundag, MD.
E-mail: altundag66@yahoo.com

Does eribulin mesylate cause recurrent transient diplopia?

Dear Editor,

Diplopia is commonly known as double vision caused by optic nerve damage or impaired function of the extraocular muscles. The most common causes of diplopia include conditions such as refractive, binocular vision disorder, ocular motor palsy, postoperative diplopia, posttraumatic diplopia, neurologic and myogenic conditions, and other causes. Although a structural cause is frequently present, an underlying structural disorder at times cannot be detected in the etiology of diplopia, particularly in transient cases [1]. Diplopia in breast cancer patients is usually caused by a metastasis to choroid plexus and iris. However, breast cancer patients may rarely present with transient diplopia due to drugs or paraneoplastic syndromes [2]. In clinical approach, transient diplopia is generally not a major concern to physicians as it does not cause any permanent damage and it is often a self-recovery process with no treatment required. Despite the fact that transient diplopia is reversible, it may cause avoidable accidents due to loss of depth perception [1].

Our primary aim in oncology is to provide a better quality of life for cancer patients as well as better outcomes and disease free survival. To this aim, we have to fight for the least mortality and morbidity of cancer patients as much as possible. With respect to this issue, visual side effects due to treatment in patients with advanced stage breast cancer hold an important place against a good quality of life.

Eribulin mesylate, a halichondrin B analog and microtubule inhibitor, is a relatively new drug in the treatment of breast cancer. It can cause neuropathic symptoms and pathology similar to the classical microtubule inhibitors (taxanes, vinca etc.) [3,4]. Other than these common side effects, we noticed a short duration of horizontal diplopia associated with eribulin. Most of the breast cancer patients with brain metastases receiving eribulin treatment complained of diplopia for about 10 minutes immediately after eribulin infusion. Brain metastases were also considered in these patients for a possible cause in the etiology of diplopia. However, diplopia is thought to be related to eribulin infusion due to its simultaneous occurrence with the drug infusion.

There is no information in the literature or in the drug manual regarding about eribulin and transient horizontal diplopia association [4,5]. On the other hand, breast cancer survivors receiving eribulin have stated that they encounter diplopia with the onset of eribulin infusion on some internet blogs or web sites, where breast cancer patients share their own personal complaints and experience.

On the basis of these clinical findings, it seems that eribulin mesylate causes transient neurotoxicity in the central as well as in the peripheral nervous system. This observation may indicate that eribulin crosses the blood-brain barrier with a higher concentration and that patients receiving eribulin may have better outcomes in terms of brain metastases.

References

1. Mashige KP, Munsamy AJ. Diplopia. South African Family Pract, 2015. Epub ahead of print.
2. Wickremasinghe S, Dansingani KK, Tranos P, Liyanage S, Jones A, Davey C. Ocular presentations of breast cancer. Acta Ophthalm Scand 2007;85:133-142.
3. Vahdat LT, Pruitt B, Fabian CJ et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2009;27:2954-2961.
4. Cortes J, Montero AJ, Gluck S. Eribulin mesylate, a novel microtubule inhibitor in the treatment of breast cancer. Cancer Treat Rev 2012;38:143-151.
5. US Food and Drug Administration. FDA labelling information-Halaven. FDA website [online], http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/201532lbl.pdf. 2010.

Fatih Karatas[1], Bekir Hacioglu[1], Serkan Akin[1], Taner Babacan[1], Ali R Sever[2], Kadri Altundag[1]

[1]*Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara;* [2]*Department of Radiology, Hacettepe University School of Medicine, Ankara, Turkey*

Correspondence to: Kadri Altundag, MD.
E-mail: altundag66@yahoo.com

May there be a role for hormonal manipulation for treatment of hormone receptor negative breast cancer?

Dear Editor,

Triple negative breast cancer constitutes about 15% of all invasive breast cancers. This subtype of breast carcinoma has tendency to recur and metastasize even when diagnosed at early stages1. Chemotherapy is the only effective systemic adjuvant and palliative treatment option. Moore and colleagues recently reported that pre-menopausal women with hormone receptor negative breast cancer treated with chemotherapy plus goserelin (for protection of ovarian function) had improved disease –free survival and overall survival2 when compared with chemotherapy-only group in the adjuvant setting. We believe that this interesting finding may be associated with several issues .Androgen receptor expression in tumor tissue has been shown in patients with breast cancer previously3. The androgen receptors have high affinity for testosterone and dihydrotestosteron. These receptors, particularly in apocrine subtype of triple negative breast cancer may be associated with disease progression and a promising therapeutic target in the near future, 4. İn women, % 50 of circulating testosterone is produced by the ovaries. Decreasing androgen levels to some extent via goserelin may have therapeutic effects in these subset of patients. Considering that the patients in the trial have hormone receptor negative breast cancer, some of the patients may be mutation carriers for BRCA 1 and BRCA 2. We know that hormonal manipulations such as tamoxifen use and bilateral oophorectomy are preventive strategies in BRCA mutation carriers5. Decreasing androgen levels via goserelin may also be effective in these group of patients. We believe that hormone dependency of some hormone receptor negative breast cancers deserves further consideration as a therapeutic target.

References

1. Budakoglu B, Altundag K, Aksoy S et al. Outcome of 561 non-metastatic triple negative breast cancer patients:multi-center experience from Turkey.J BUON. 2014 Oct-Dec;19(4):872-8.
2. Moore HC, Unger JM, Phillips KA et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015 Mar 5;372(10):923-32.
3. Robinson JL, Macarthur S, Ross-Innes CS et al. Androgen receptor driven transcription in molecular apocrine breast cancer is mediated by FoxA1. EMBO J. 2011 Jun 24;30(15):3019-27.
4. Lehmann BD, Bauer JA, Chen X et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011 Jul;121(7):2750-67.
5. Narod SA , Brunet JS, Ghadirian P et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet. 2000 Dec 2;356(92u45):1876-81.

Orhan Onder Eren, Ozlem Uysal Sonmez, Basak Oyan

Department of Clinical Oncology, Yeditepe University Hospital, Istanbul, Turkey

Correspondence to: Orhan Onder Eren, MD
E-mail: droneren@hotmail.com

Simultaneous genital & oropharyngeal HPV-related infection with Topoisomerase IIa overexpression

Dear Editor,

High risk (HR) HPV type persistent infection – involved in uterine cervix squamocolumnar (SC) junction epithelia or in squamous epithelia of upper aero-digestive tract– leads them progressively to cancerous transformation [1]. In the cervico-vaginal area precursor lesions include cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SILs) based on pathological and cytological microscopic morphological evaluation, respectively. Simple acquired HPV infection is not the crucial event during the carcinogenetic process. HR HPV DNA integration into the host chromosome -regarding HPV 16/18/31/33/35/39/45/51/52/56/58/59/66/68/82 subtypes predominantly - modifies the human epithelial cell DNA by inactivating p53 and Rb gene pathways [3]. Similarly, oral sex practice (mouth-genitalia) induces HPV transmitted infection leading to neoplastic and finally malignant cell modification [2].

A 44-year-old female with a known 3-year follow

up history of HPV (16/51 subtypes detected by HPV PCR arrays) infection attended a routine gynecological examination. Conventional and liquid based Pap test combined with colposcopy were applied. Pap test showed a HPV infection combined with focal high grade intraepithelial lesion (HGSIL, based on Bethesda 2001 classification for cervical lesions) with severe bacterial vaginosis. Abnormal colposcopy was followed by laser conization (LOOP) and the corresponding bioptic tissue specimens were analyzed. Pathology identified a CIN III-focal in situ carcinoma. Additionally, the patient complained for atypical symptoms inside her oral cavity. For this reason, an extensive oropharyngeal examination was performed detecting sporadic, specific white areas on the squamous epithelia, right tonsillar lodge and focally in other pharynx areas. Multiple biopsies were obtained and pathology showed a HPV infection with representative koilocytotic cell morphology. PCR examination was also performed in the corresponding tissue specimens and presence of the HPV 16 type was confirmed. Tissue sections were obtained for ki67 and Topoisomerase (Topo) IIa immunohistochemical (IHC) analyses, whereas p16 was analyzed on cytological slide. All of the markers were found to be overexpressed in the genital and oropharyngeal tissue slides, whereas Topo IIa expression demonstrated a higher intra-lesion activity focused on the genital tissues. The patient was put on a follow up protocol consisting of a rotated 4-month period with combined genital and oral examination. Therapeutic strategies including radiation and surgery were not assessed at the moment.

HR-HPV infection is a necessary but not sufficient condition for cervical carcinogenesis. But persistent infection leads the HPV E6/E7 overexpressed oncoproteins to inactivate the p53 and Rb pathways inducing also Topo IIa (gene locus: 17q21) activation. Simultaneous Topo IIa overexpression in genital and oropharyngeal tissues is correlated with an aggressive phenotype regarding HPV-related progression inside those epithelia [3]. In cervico-vaginal lesions, p16/ ki67 combined expression rates seem to be a reliable marker for evaluating HPV activity and are more sensitive than Topo IIa [4]. In contrast to this, interestingly, HPV positivity is related to Topo Iia over expression in atrophic oral lichen planus infected mucosa [5].

References

1. Martin CM, O'Leary JJ. Histology of cervical intraepithelial neoplasia and the role of biomarkers. Best Pract Res Clin Obstet Gynaecol 2011;25:605-615.
2. Ramirez N, Guerra F, Camporeale G et al. Expressions of E2 and E7-HPV16 proteins in pre-malignant and malignant lesions of the uterine cervix. Biotech Histochem 2015;8:1-8.
3. Santin AD, Zhan F, Bignotti E et al. Gene expression profiles of primary HPV16- and HPV18-infected early stage cervical cancers and normal cervical epithelium: identification of novel candidate molecular markers for cervical cancer diagnosis and therapy. Virology 2005;331:269-291.
4. Zhong P, Li J, Gu Y et al. P16 and Ki-67 expression improves the diagnostic accuracy of cervical lesions but do predict persistent high risk human papillomavirus infection with CIN1. Int J Clin Exp Pathol 2015;8:2979-2986.
5. Mattila R, Rautava J, Syrjänen S. Human papillomavirus in oral atrophic lichen planus lesions. Oral Oncol 2012;48:980-984.

Evangelos Tsiambas[1,4]*, Vasileios Ragos[2]*, Georgios E Metaxas[3], Grigorios Kyrousis[3], Theofania Theohari[3], Labros Bouzalas[3], Stavroula Antonopoulou[4]

[1]*Dept of Immunohistochemistry & Molecular Biology, 401 General Army Hospital, Athens;* [2]*Dept of Maxillofacial Surgery, School of Medicine, University of Ioannina;* [3]*Private Gynaecolosist;* [4]*Mycolab Private Lab, Athens, Greece*

**These authors contributed equally to this article*

Correspondence to: Evangelos Tsiambas, MD, MSc (ip), PhD.
E-mail: tsiambasecyto@yahoo.gr

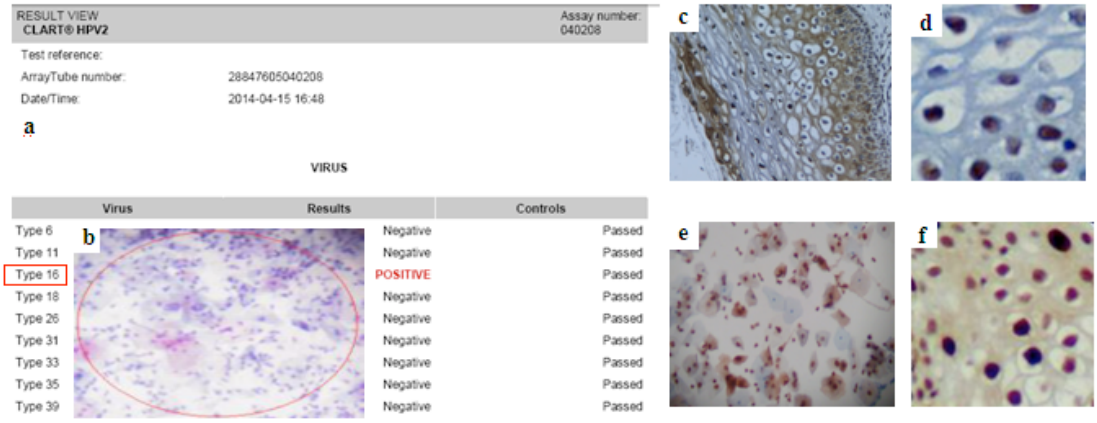

Figure 1. Molecular and immunohistochemical analysis of the current case. **a**: HPV PCR arrays detected HPV 16 type. **b**: Liquid based Pap Test identified HPV & focal HGSIL lesions (Pap stain). **c**: Topoisomerase IIa overexpression (nuclear staining pattern) in cervical biopsy (note the koilocytotic cell morphology). **d**: ki67 proliferation marker overexpression in the same tissue (note the koilocytotic cell morphology). **e**: p16 overexpression in liquid based cytological slide in cervical specimen. **f**: Topoisomerase IIa overexpression (nuclear staining pattern) in squamous oropharyngeal HPV infected tissue of the female patient (note the koilocytotic cell morphology). Original magnifications 10x, 40x.