ORIGINAL RESEARCH PAPER

Volume-7 | Issue-7 | July-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A CASE REPORT OF DOUBLE MALIGNANCY – INFILTRATING DUCTAL CARCINOMA BREAST AND EWING'S SARCOMA OF VAGINA

Pathology

Kodate Purnima M.* MD Pathology, Assistant Professor, Department Of Pathology, GMC, Nagpur *Corresponding Author

Quraishi Abdul Haque M MS, FRCS, DNB, Associate Professor, Department of Surgery, GMC, Nagpur

Quraishi Bushra Haque MS, Consultant Gyenecologist, Shantimohan Hospital, Nagpur

Kodate Madhusudanrao K MD, Consultant Pathologist, Shantimohan Hospital, Nagpur

ABSTRACT

The occurrence of multiple primary malignancies (MPM) is not uncommon. Genetic predisposition and the development of a second primary cancer after treatment of the first with radiotherapy or chemotherapy are well documented.

Case report: A 58 years old post menopausal female was diagnosed as infiltrating ductal carcinoma breast with metastasis in axillary lymphnodes and liver. During chemotherapy she noticed bleeding per vaginum with a vaginal mass which was initially diagnosed as metastasis of ductal carcinoma and finally confirmed as Ewing's sarcoma on immunohistochemistry and fluorescence in situ hybridization (FISH) analysis of the Ewing's sarcoma breakpoint region 1 (EWSR1).

This case reinforces the value of histomorphology and ancillary techniques in confirming the presence of specific sarcomas at unusual sites. Although rare the possibility of MPM should be considered with the presence of malignant tumors in two or more organs. This distinction between multiple primary or metastatic cancers is important for treatment as well as prognosis.

KEYWORDS

Ewing's Sarcoma, Immunohistochemistry, Multiple Primary Malignancy, Fluorescence In Situ Hybridization (fish), Ewsr1 Translocation And Metastasis

Introduction: The incidence of multiple primary cancers is rare about 0.3% and 4.3%.[1] In Indian literature, scant data is available regarding multiple primaries, most of them being case reports. The majority of MPMs may occur as a result of random chance and the reason remains obscure.[2] The second primary lesion is identified simultaneously with the first lesion within an interval of about 6 months (synchronous) or after a period of 6 months (metachronous).[3,4] After an exhaustive literature search we found a very unique and highly unusual presentation of two different synchronous malignancies i.e. infiltrating ductal carcinoma breast and Ewing's sarcoma in vagina.

Case Report

A 58-year-old post menopausal woman noticed a 3cms x 2cms lump in left breast since 15 days. On examination, there were two axillary lymph nodes palpable with mild hepatomegaly. Her family history revealed carcinoma breast in mother.

FNAC from left breast lump and axillary lymph node showed features of ductal malignancy with metastasis in axillary lymph node.

Patient underwent incisional biopsy of breast lump which confirmed the cytological diagnosis. Lymphovascular emboli were found without perineural invasion. As per modified Bloom and Richardson grading system (3+3+2=8) tumor was graded as grade III invasive ductal carcinoma(NOS). Immunohistochemical studies were negative for estrogen and progestrone receptor but were positive for HER-2neu.

Patient was further screened for metastasis. Computed tomography (CT) scanning of abdomen revealed mild hepatomegaly with extensive hepatic parenchymal discrete lesions which was suggestive of hepatic metastasis with ascitis. Gall bladder, spleen, pancreas and uterus with bilateral adnexae were normal. USG guided FNAC was performed from hepatic nodules revealed cytological features same as breast lesion, so diagnosis of metastatic deposits of ductal malignancy in liver was suggested. Bone scan and MRI brain showed no parenchymal lesion. As the patient was HER-2neu positive, a taxane-based regimen was planned. She underwent three cycles of chemotherapy consisting paclitexal.

After three months, patient complained of painless bleeding per vaginum. Local examination revealed a firm to hard friable growth in the lower one third of vagina. The cervix was free from the growth. Cervico-vaginal smear revealed atypical cells with highly dysplastic squamous cells. Provisionally the diagnosis was kept as metastatic ductal carcinoma. Biopsy from the growth taken.

Specimen revealed solid sheets of cells divided into irregular masses by fibrous strands. Individual cells were small and uniform with indistinct cell border. Nuclei were round with inconspicuous nucleoli.(Fig 1). The vaginal lesion was thought to be a metastatic lesion from the breast carcinoma. After three cycles of chemotherapy, breast lump and hepatic masses regressed in size but the vaginal nodule increased in size and the bleeding per vaginum became more profuse. So, diagnosis of small round cell malignancy was made and immunohistochemistry was advised for further sub typing.

The tumor cells were negative for pancytokeratin, epithelial membrane antigen, S-100 protein, alpha smooth muscle actin, myogenin, chromogranin, BCL-2, CD45, and CD31. The neoplastic cells contained glycogen and were positive for CD 99 and vimentin. (Fig 2). A diagnosis of Ewing's sarcoma was made after excluding all other possibility of small round cell malignancy.

The paraffin tissue block of tumor was subjected to molecular cytogenetic analysis by fluorescent *in-situ* hybridization (FISH) that showed characteristic EWSR1 translocation, confirming the diagnosis of ES/PNET.

The final diagnosis of double malignancy, infiltrating ductal carcinoma of breast with axillary lymphnode and liver metastasis and Ewing's sarcoma of vagina was made.

Six cycles of chemotherapy were given. She complained of bleeding per vaginum and protrusion of the vaginal mass.(Fig 3) She was not willing for a surgical treatment initially but finally she agreed. A wide excision of the mass was done. The patient developed liver failure and pulmonary complications to which she succumbed three months after the procedure.

Discussion:

The occurrence of multiple primary malignancies (MPMs) in an individual may occur due to following causes –

1. Incidental feature
2. By sharing an etiological factor
3. Treatment for one cancer may be related to the subsequent development of a second tumor
4. Genetic predisposition to multiple malignancy such as neurofibromatosis, Gorlin's syndrome, multiple endocrine neoplasia, Beckwith-Weidemann syndrome, retinoblastoma, Li-Fraumeni syndrome or to various cancer family syndromes.[2,6,7]
5. Genetic instability, microsatellite instability implicating impaired DNA repair mechanism.[3,4,6]

Here, we report an extremely rare case having infiltrating ductal carcinoma breast grade III with Ewing's sarcoma of vagina having ruled out all possibility of metastasis from one site to the other. Thus fulfilling all the criteria laid down by Werthamer et al. [8,9] to diagnose two separate synchronous malignant neoplasms in different organs.

Genitourinary cancers, especially cervical and ovarian cancers, bladder and prostate cancers were the common associated non-GI cancers, followed by cancers of lung and breast. Thus, attention should be paid to these sites during the period of post-operative follow-up of the first primary cancer.[3] Breast cancer patients often develop a 2nd primary malignant tumor; common sites being opposite breast, endometrium and ovary with rare primary cancer of cervix.[1,2,3,10] In gynecological neoplasia, the most common associations were endometrium and breast.[10] The rate of development of secondary soft tissue sarcoma after breast carcinoma was 0.15% and the relative risk was 2.2. Sarcomas of vascular origin such as angiosarcoma and lymphangiosarcoma were reported in breast carcinoma. Tamoxifen was reported to cause genital sarcomas in women.[11]

Detection of cancer at an early stage is possible with the development of more sophisticated invasive and non-invasive diagnostic tools. Patients which have diagnosed with a cancer, have a life time risk for developing another de novo malignancy depending on various inherited, environmental and iatrogenic risk factors. BRCA1 and BRCA2 breast cancer genes associated with multiple primary tumours including breast, colorectal, ovarian and other cancers. They may bestow a heightened sensitivity to carcinogenic effects of radiation.[12]

Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) of the genital tract of women is uncommon. Rarer still is its occurrence as double malignancy. The immunodeficiency after radio-/chemotherapy of hematological malignancies causes' impaired antitumor activity of the innate or adaptive immune system might represent critical factors that predispose to the failure of the system to detect and eliminate newly mutated cells carrying the Ewing sarcoma translocation, thus allowing for the initiation of secondary ES. [13]

Such undifferentiated malignancy presenting as a second malignancy possess a diagnostic problem for anatomical pathologists, therefore needs morphological skill, clinicopathologic correlation, and application of adjunctive laboratory studies. Table 1 showing literature review of cases of multiple primary malignancies.

The determination of a chimeric transcript translocation t (11; 22) (q24; q12) by RT-PCR and/or the gene rearrangement involved in a translocation by fluorescence *in situ* hybridization (FISH) is often required for validation of the diagnosis, especially at unusual sites where the index of suspicion is low.[14]

It is fundamental that patients who have been treated for cancers be carefully followed up . When symptoms and signs of tumour develop in a patient who has been treated for a primary cancer, it should not be assumed to be secondaries. The possibility of a localized and curable second primary cancer should be considered and evaluated. As advances in cancer therapy bring about a progressively large percentage of long-term survivors, the proportion of patients with subsequent primary lesions will increase. Early diagnosis of these lesions, based on an awareness of the possibility of second and third cancers, and multidisciplinary treatment will substantially increase the survival of these patients.[1,2]

Treatment strategies in case of double malignancy depend on treating the malignancy that is more advanced first, or sometimes both malignancies could be treated simultaneously, if chemotherapeutic agent is the same.[15]

CONCLUSION: Although these situations are relatively rare the possibility of MPM should be considered as it represents a challenging diagnostic and therapeutic problem. This distinction between multiple primary or metastatic cancers could be important for treatment as well as prognosis.

Table 1: literature review of cases of multiple primary malignancies

S. No.	Study	First malignancy	Second Malignancy	Interval between two malignancy	Outcome
1.	Ray et al[16] 2000	Infiltrating duct carcinoma Breast	Sqamous cell carcinoma cervix	3 months	Recovered
2.	Masood et al[1] 2005	Sqamous cell carcinoma lung	Rabdomyosarcoma scapula	Same time	Lost to follow up
3.	Sarkar et al [17] 2007	Non small cell carcinoma lung	Mixed germ cell tumor testis	Same time	Expired
4.	Singh et al[10] 2010	Sqamous cell carcinoma Oesophagus	Infiltrating duct carcinoma Breast	Same time	Recovered
5.	Park et al[7] 2011	Liposarcoma thigh	Ewing's Sarcoma Tibia	Two and half years	Received radio and chemotherapy
6.	Zhong et al[15] 2015	Infiltrating duct carcinoma Breast	Ewing's Sarcoma kidney	5 years	Declined treatment
7.	Plis et al[18] 2016	Ewing's Sarcoma liver	Adenocarcinoma Gall bladder	1 month	Survived after 3 years

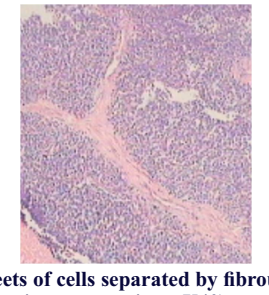

Fig:1 - Solid sheets of cells separated by fibrous strands, Ewing's Sarcoma(H&E stain, scanner view – X40)

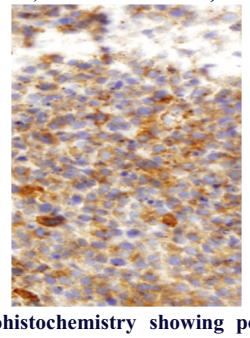

Fig:2 - Immunohistochemistry showing positive CD99 (IHC, X400)

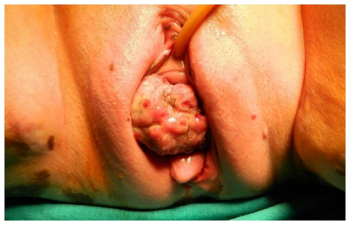

Fig:3: After six cycles of chemotherapy the cervico-vaginal mass protruding out from the vagina and covered with slough

References

[1]. Masood I, Bhargava R, Ahmad Z et al. A Case of Double Malignancy – Carcinoma Lung and Rhabdomyosarcoma – in a 90-year-old Male. JIACM. 2005; 6(2): 167-70.

[2] Hartley AL, Blair V, Harris M et al. Multiple primary tumors in a population-based series of patients with histopathologically peer-reviewed sarcomas. Br. J. Cancer. 1993; 68: 1243-1246.

[3] Cheng HY, Chu CH, Chang WH et al. Clinical analysis of multiple primary malignancies in the digestive system: A hospital-based study. World J Gastroenterol. 2005; 11(27):4215-4219.

[4] Jena A, Patnayak R, Yadagiri Lakshmi A, Manilal B, and Kumaraswamy Reddy M. Multiple primary cancers: An enigma. South Asian J Cancer. 2016 Jan-Mar; 5(1): 29–32.

[5] Olivier M, Goldgar DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P, Eeles RA. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. 2003;63:6643–50.

[6] Sardi I, Franchi A, Bocciolini C et al. Microsatellite instability as biomarker for risk of multiple primary malignancies of the upper aerodigestive tract. Oncol Rep. 2001; 8: 393-399.

[7] Park H.W, Jung S T, and Nah S Y. Double Primary Presentation of Liposarcoma and Ewing's Sarcoma: A Case Report. J Korean Bone Joint Tumor Soc. 2011 Dec;17(2):95-99.

[8] Warren S and Gates O. Multiple primary malignant tumors: A survey of the literature and statistical study. Am J Cancer 1932; 16: 1358-1414.

[9] Werthamer S, Jabush M and Schulman J: Multiple primary malignancies. JAMA 1961; 175: 558-562.

[10] Singh A, Khare IC, Dixit AK et al. Successfully treated synchronous double malignancy of the breast and esophagus: a case report. Journal of Medical Case Reports. (Serial online) 2010; 4:169doi:10.1186/1752-1947-4-169. Available from http:// www.jmedicalcasereports.com/content/4/1/169.

[11] Merimsky O, Kollender Y, Issakov J, Bickels J, Flusser G, Gutman M et al. Multiple primary malignancies in association with soft tissue sarcomas. Cancer 2001;91:1 363–71.

[12] Raymond J S and Hogue C J R. Multiple primary tumours in women following breast cancer, 1973–2000. Br J Cancer. 2006 Jun 5; 94(11): 1745–1750.

[13] Wolpert M A, Felix Niggli, Zimmermann D, Rushing E, and Lesniewska B. Ewing's Sarcoma as a Second Malignancy in Long-Term Survivors of Childhood Hematologic Malignancies. Sarcoma. 2016; 2016: 5043640.

[14] Gabriella Gamberi, Stefania Cocchi, Stefania Benini, Giovanna Magagnoli, Luca Morandi, Jennifer Kreshak, Marco Gambarotti, Piero Picci, Licciana Zanella, and Marco Alberghini. Molecular Diagnosis in Ewing Family Tumors The Rizzoli Experience—222 Consecutive Cases in Four Years. J Mol Diagn. 2011 May; 13(3): 313–324.

15. Jinjing Zhong , Ni Chen, Xueqin Chen, Jing Gong, Ling Nie, Miao Xu, And Qiao Zhou. Peripheral primitive neuroectodermal tumor of the kidney in a 51-year-old female following breast cancer: A case report and review of the literature. Oncol Lett. 2015 Jan; 9(1): 108–112.

16. Ray A, Mukundan H, Bahadur A k, Rantala R S, Naik SLD and Sharma BK. A rare case of two malignancies: Carcinoma of the breast and uterine cervix. Indian Journal of Clinical Biochemistry. 2000, 15(1);60-62.

17. Sarkar S, Kundu AK and Chakrabarti S. Lungs - victim of synchronous double malignancies. JAPI. 2007; 55: 235-37.

18. Plis A, Zygulska A, Püsküllüoğlu M, Szczepański W, Białas M, Krupiński M, Krzemieniecki K. Synchronous extraskeletal Ewing's sarcoma/PNET and gallbladder carcinoma: a case report and literature review. Contemp Oncol (Pozn). 2016;20(6):496-500.