Case Report

A rare case report of triple malignancy: Carcinoma urinary bladder, larynx, and breast in a single patient

Mukesh Kumar Singhal*, Akhil Kapoor*, Satya Narayan, Raj Kumar Nirban, Ramesh Purohit, Puneet Kumar Bagri, Harvindra Singh Kumar

Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India

*The first two authors contributed equally to the manuscript

ABSTRACT

Triple malignancy is a very rare occurrence. We report a case of transitional cell carcinoma of the urinary bladder (UB) that subsequently developed squamous cell carcinoma of the larynx after 2 months of diagnosis. He was given radiotherapy for both the primaries. However, after 3 years of completion of treatment, the patient developed a nodular lesion in the right breast just below the nipple. Excision biopsy of the lesion revealed invasive ductal carcinoma. Thus, triple malignancies with different histologies in all the primaries were established in the patient with UB cancer and laryngeal cancer developing synchronously followed by breast cancer metachronously.

Key words: Carcinoma breast, carcinoma larynx, carcinoma urinary bladder, transitional cell carcinoma, triple malignancy

INTRODUCTION

Cancer patients are at an increased risk for developing additional subsequent primary tumors. The reported incidence of multiple primary malignancies ranges from 0.734% to 11.3%, depending on whether the study is antemortem or postmortem.[1] Prevalence of multiple primary malignancies is slowly increasing due to prolonged survival of cancer patients with advances in diagnostic and therapeutic modalities. The reasons may be environmental modifications, genetic predisposition or therapy induced.[2] National Cancer Institute's Surveillance, Epidemiology and End Results Program reported that about one in six cancer patients develop second malignant neoplasm in their further lifetime.[3] Second and higher ordered primary cancers can be therapy induced, syndrome-related or by sharing common etiologic factors.[4] After the successful treatment or during the course of treatment of the urinary bladder (UB) cancer, multiple malignancies have been reported. Most commonly involved sites with second primary malignancies include lung, colon, breast, and skin. We are presenting an interesting case report in which a patient with UB cancer developed laryngeal cancer synchronously and then, breast cancer metachronously. To the best of our knowledge, such a combination of multiple malignancies has never been reported before in the literature.

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.142694

CASE REPORT

A 63-year-old male, nonobese farmer by occupation, presented with 2 months history of painless hematuria in March 2010. There was no family history of malignancy. The patient used to smoke one bundle of bidi/day and drink about 200 ml of alcohol/day for 30 years. However, he has gradually reduced the addictions now. There were no associated symptoms or co morbid conditions. The patient underwent routine baseline investigations (complete blood count, renal and liver function tests, and X-ray chest

Address for correspondence: Dr. Akhil Kapoor, Room No. 73, PG Boys Hostel, Bikaner - 334 003, Rajasthan, India.
E-mail: kapoorakhil1987@gmail.com

posterioranterior view), which were within the normal limits. Ultrasonography of the abdomen and pelvis with a full bladder revealed an intramural mass within the lumen of UB. Contrast-enhanced computed tomography scan of the pelvis revealed UB mass on its anterolateral wall without any pelvic lymphadenopathy. Transurethral resection of the bladder tumor was done, which on histopathology revealed transitional cell carcinoma (TCC) infiltrating muscularis propria [Figure 1a]. Thus, the stage assigned was T2N0M0. The bladder preserving approach was planned after counseling of the patient. Concurrent chemoradiotherapy with weekly cisplatin was delivered with telecobalt machine. In Phase I, 44 Gy to the whole bladder and pelvic lymph node and in Phase II, local boost to the dose of 66 Gy was given. After 2 months of completion of treatment, the patient developed progressive hoarseness of voice. On fiber optic laryngoscopy, ulcerative growth involving right vocal cord with its impaired mobility was found. Biopsy revealed moderately differentiated squamous cell carcinoma (T2N0M0) [Figure 1b]. Conventional radiotherapy on telecobalt machine was planned to deliver 66 Gy, 2 Gy/fraction, 33 fractions in 6.5 weeks. The size of the radiation field was 5 cm × 5 cm with superior border at the cranial edge of thyroid cartilage and inferior border at the caudal edge of cricoid cartilage. The patient was disease free for 3 years, after which he developed 1.5 cm × 2 cm nodular lesion in the right breast just below the nipple. Fine-needle aspiration cytology from the lesion was suggestive of malignancy. Axillary nodes were not palpable. Excision biopsy with wide local excision was performed, which revealed infiltrating ductal carcinoma [Figure 1c] (estrogen receptors, progesterone receptors positive and Her-2/neu negative). The patient refused further surgery or radiotherapy. As per the decision of tumor board considering patient's preferences and stage T1NxM0, six cycles of standard fluorouracil, doxorubicin, cyclophosphamide chemotherapy followed by hormonal therapy was planned. The patient is presently on chemotherapy.

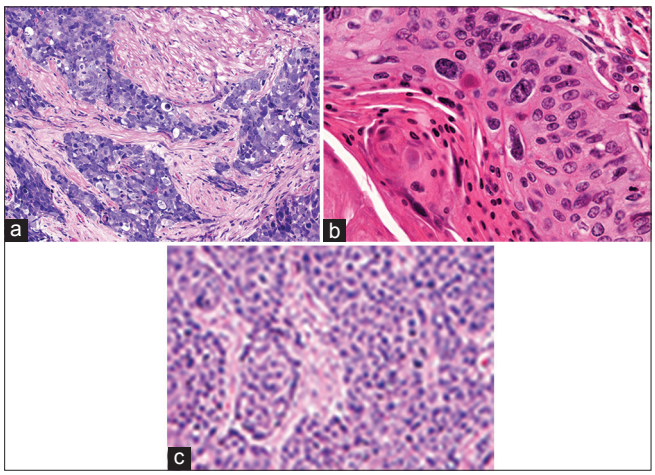

Figure 1: Photomicrographs demonstrating the microscopic picture of the three primaries: (a) Transitional cell cancer invading muscularis propria; (b) squamous cell carcinoma of the larynx; and (c) invasive ductal carcinoma of the breast

DISCUSSION

Several risk factors have been implicated in the development of subsequent primary malignancies, but the incidence and prevalence data with multiple malignancies are still lacking worldwide. The exact etiology of multiple malignancies is ill-defined; various factors include a genetic predisposition, environmental factors, gender, hormonal factors, previous medical treatment, and interactions of these factors. As per the Warren and Gates criteria, the probability of one being the metastasis of the other must be excluded before starting curative treatment of the new tumor.[5] In this patient, the common risk factors were smoking and alcohol that are established risk factors for various malignancies including UB, larynx and breast carcinoma. Numerous case reports have been reported in which TCC of UB occurs synchronously or metachronously with second malignancy, but triple malignancy of cancer UB associated synchronously with cancer larynx and metachronously with breast cancer is a very rare entity. Common second malignancies in patients UB cancer include renal cancer, prostate, lung, colorectal, malignant melanoma, and non-Hodgkin lymphomas.[6-10]

It is well-known that cancer therapy in the form of radiotherapy or chemotherapy may result in second malignancy, but these usually occur after 5 years. In this patient, radiotherapy was given to treat UB cancer, but the site of secondary malignancies were out of the radiation field area and occurred shortly after first diagnosis. Hence, this may not be a contributing factor in the development of multiple primaries in the case under discussion.

It has been observed that many patients, on detection of the new primary, deny any further treatment due to excessive psychological stress, social, and economic reasons. However, multiple malignancies may have a better overall prognosis as compared with their single malignant counterparts. It is hypothesized that there may be inherent difference in these patients' immune system or other genetic surveillance mechanisms that might confer improved survival. The case in reference has already survived two primary tumors. It should be stressed that rare appearance of breast cancer in male, rather than the presence of two malignancies related to smoke and alcohol such as bladder and larynx cancers was the most important feature in this patient.

The genetic changes may be associated with the multiple primary neoplasms. Confirming the importance of *p53* in controlling carcinogenesis, more than 70% of human cancers have a defect in this gene, and the remaining malignant neoplasms have defects in genes up-stream or down-stream

of *p53*.[11] Homozygous loss of the *p53* gene is found in virtually every type of cancer, including carcinomas of the lung, colon, and breast-the three leading causes of cancer deaths. In most cases, inactivating mutations affecting both *p53* alleles are acquired in somatic cells. Less commonly, some individuals inherit a mutant *p53* allele; this disease is called the Li-Fraumeni syndrome.[12] As with the *RB* gene, inheritance of one mutant allele predisposes individuals to develop malignant tumors because only one additional hit is needed to inactivate the second, normal allele. Patients with the Li-Fraumeni syndrome have a 25-fold greater chance of developing a malignant tumor by age 50 compared with the general population. In contrast to patients who inherit a mutant *RB* allele, the spectrum of tumors that develop in patients with the Li-Fraumeni syndrome is varied; the most common types of tumors are sarcomas, breast cancer, leukemia, brain tumors, and carcinomas of the adrenal cortex. Compared with sporadic tumors, patients with Li-Fraumeni syndrome develop tumors at a younger age and may develop multiple primary tumors. Individuals born with such inherited defects in DNA repair proteins are at a greatly increased risk of developing cancer. In general, genomic instability occurs when both copies of the gene are lost; however, recent work has suggested that at least a subset of these genes may promote cancer in a haplo-insufficient manner. A group of autosomal recessive disorders comprising Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia is characterized by hypersensitivity to other DNA-damaging agents, such as ionizing radiation (Bloom syndrome and ataxia-telangiectasia),[13] or DNA cross-linking agents, such as nitrogen mustard (Fanconi anemia). Their phenotype is complex and includes, in addition to predisposition to cancer, features such as neural symptoms (ataxia-telangiectasia), anemia (Fanconi anemia), and developmental defects (Bloom syndrome). As mentioned earlier, the gene mutated in ataxia-telangiectasia is *ATM*, which seems to be important in recognizing and responding to DNA damage caused by ionizing radiation. Evidence for the role of DNA repair genes in the origin of cancer also comes from the study of hereditary breast cancer. Mutations in two genes, *BRCA1* and *BRCA2*, account for 80% of cases of familial breast cancer.[14] In addition to breast cancer, women with *BRCA1* mutations have a substantially higher risk of epithelial ovarian cancers, and men have a slightly higher risk of prostate cancer. Similarly, mutations in the *BRCA2* gene increase the risk of breast cancer in both men and women as well as cancer of the ovary, prostate, pancreas, bile ducts, stomach, and melanocytes.

CONCLUSION

We conclude by recommending that every oncologist should be alert for identifying early symptoms of multiple primary malignancies in a known patient of cancer.

ACKNOWLEDGMENTS

The authors would like to thank consultants in Department of Oncology Dr. Ajay Sharma, Dr. N. Sharma and Dr. S. L. Jakhar and Dr. S. Beniwal. Also, they express gratitude to PG Students of the Department: Dr. D. Singh, Dr. R. K. Nirban, Dr. Sitaram, Dr. G. Singh, Dr. Murali, Dr. Tanya, Dr. Rajesh.

REFERENCES

1. Aydiner A, Karadeniz A, Uygun K, Tas S, Tas F, Disci R, *et al*. Multiple primary neoplasms at a single institution: Differences between synchronous and metachronous neoplasms. Am J Clin Oncol 2000;23:364-70.
2. Takalkar U, Asegaonkar BN, Kodlikeri P, Asegaonkar S, Sharma B, Advani SH. An elderly woman with triple primary metachronous malignancy: A case report and review of literature. Int J Surg Case Rep 2013;4:593-6.
3. Wood ME, Vogel V, Ng A, Foxhall L, Goodwin P, Travis LB. Second malignant neoplasms: Assessment and strategies for risk reduction. J Clin Oncol 2012;30:3734-45.
4. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, *et al*. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005;97:1428-37.
5. Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and statistical study. Am J Cancer 1932;16:1358-414.
6. Kantor AF, McLaughlin JK, Curtis RE, Flannery JT, Fraumeni JF Jr. Risk of second malignancy after cancers of the renal parenchyma, renal pelvis, and ureter. Cancer 1986;58:1158-61.
7. Rabbani F, Grimaldi G, Russo P. Multiple primary malignancies in renal cell carcinoma. J Urol 1998;160:1255-9.
8. Wegner HE. Multiple primary cancers in urologic patients. Audit of 19-year experience in Berlin and review of the literature. Urology 1992;39:231-6.
9. Czene K, Hemminki K. Kidney cancer in the Swedish family cancer database: Familial risks and second primary malignancies. Kidney Int 2002;61:1806-13.
10. Curtis RE, Freedman DM, Ron E, Ries LA, Hacker DG, Edwards BK, *et al*. New Malignancies among Cancer Survivors: SEER Cancer Registries, 1973-2000. Bethesda: National Cancer Institute; 2006. p. 05-5302.
11. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: Origins, consequences, and clinical use. Cold Spring Harb Perspect Biol 2010;2:a001008.
12. Chompret A. The Li-Fraumeni syndrome. Biochimie 2002;84:75-82.
13. German J. Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients. Am J Hum Genet 1969;21:196-227.
14. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer 2000;83:1301-8.

Cite this article as: Singhal MK, Kapoor A, Narayan S, Nirban RK, Purohit R, Bagri PK, *et al*. A rare case report of triple malignancy: Carcinoma urinary bladder, larynx, and breast in a single patient. Clin Cancer Investig J 2014;3:558-60.

Source of Support: Nil, **Conflict of Interest:** None declared.