Free full text available from
www.cancerjournal.net

Quadruple malignancy in a single patient: A case report and comprehensive review of literature

ABSTRACT

The occurrence of multiple primary malignant neoplasias (MPMN) is a rare but increasingly frequently reported event. Many theories have been proposed to explain MPMNs, but none have been proven. The key risk factors appear to be smoking and family history. While numerous studies have been published on the development of second malignancies following a first primary, the literature contains only few case reports and reviews of patients with three or more malignancies. We report a case of a young female who, over a period of 30 years, developed four different malignancies and was treated radically on each occasion.

KEY WORDS: Multiple primary malignant neoplasms, radiation exposure, tamoxifen, gene expression

Shabab L. Angurana, R. Kapoor, Pankaj Kumar, Divya Khosla, Narendra Kumar, S. C. Sharma, F. D. Patel
Department of Radiotherapy & Regional Cancer Centre (RCC), PGIMER, Sector-12, Chandigarh - 160012, India.

For corresponence:
Dr. R. Kapoor, Associate Professor, Department of Radiotherapy & RCC, PGIMER, Sector 12, Chandigarh - 160 012, India.
E-mail: drkapoor.r@gmail.com

DOI: 10.4103/0973-1482.65237

INTRODUCTION

As a result of improvements in diagnostic and therapeutic modalities in the field of oncology the number of patients who survive cancer over the long term – and thus run the risk of developing a second tumor – are on the increase.[1] This applies both to sporadic tumors and malignancies occurring within the framework of the hereditary cancer predisposition syndrome, which is also being diagnosed ever more frequently.

While numerous studies have been published on the development of second malignancies following a first primary, the literature contains only few reviews of patients who have developed three or more malignancies. As per our present state of knowledge roughly 2–12% of all patients with two metachronous or synchronous tumors go on to develop a third or fourth neoplasia.[1]

CASE REPORT

A 35-year-old premenopausal female patient presented with a lump in the right breast in the year 1978. Fine needle aspiration was done and revealed infiltrating duct cell carcinoma, stage $T_3N_0M_0$. The patient underwent total mastectomy with axillary clearance plus bilateral salpingo-ophorectomy. Postoperatively, the patient received external beam radiotherapy to the chest flap and regional nodal areas and systemic oral chemotherapy with melphalan for 2 years. Thereafter, the patient was on regular follow-up.

In the year 1995, she developed a lump in the left breast, for which she underwent lumpectomy with axillary clearance. "Histopathology showed early infiltrating duct cell carcinoma, stage $T_1N_0M_0$ [Figure 1], indicating a second primary." She underwent postoperative adjuvant radiotherapy to the breast and regional nodal areas, followed by chemotherapy with tamoxifen for 5 years.

In the year 2006, the patient presented with the complaint of bleeding per vaginum. Endometrial curettage was done and this was reported as adenocarcinoma endometrium [Figure 2A]. She underwent total abdominal hysterectomy and was found to have surgical-pathological stage IB grade 2 disease [Figure 2B]. In view of the two surgeries and early stage IB disease the patient was given the option of follow-up *vs* radiotherapy; she opted for follow-up

The patient was on regular follow-up. In the year 2008, she complained of difficulty in swallowing food, especially solids. On evaluation, endoscopy revealed an ulcerated, polypoidal, and friable growth at 20 cm in the upper esophagus. Biopsy revealed squamous cell carcinoma,, NK type [Figure 3]. CT scan could not reveal the esophageal growth. Barium swallow showed a 3 × 2 cm polypoidal mass lesion with an irregular outline in the posterior left lateral aspect of the proximal part of the esophagus. The patient was treated with two sessions of intraluminal brachytherapy of 6 Gy each, 1 week apart, and systemic chemotherapy with cisplatin and 5-FU for six cycles. She has been on regular follow-up till date.

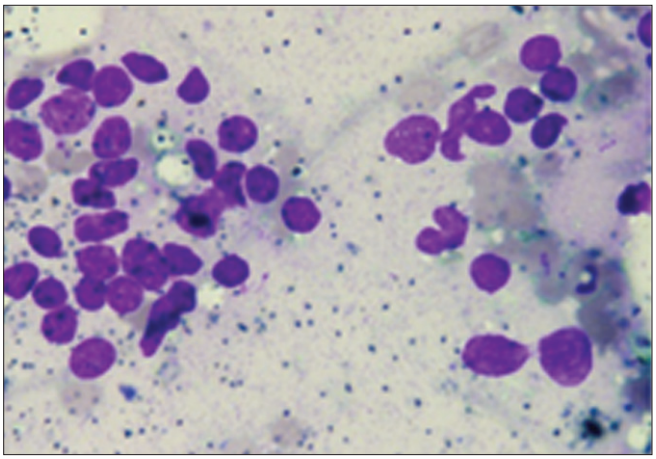

Figure 1: Left breast - infiltrating ductal carcinoma.

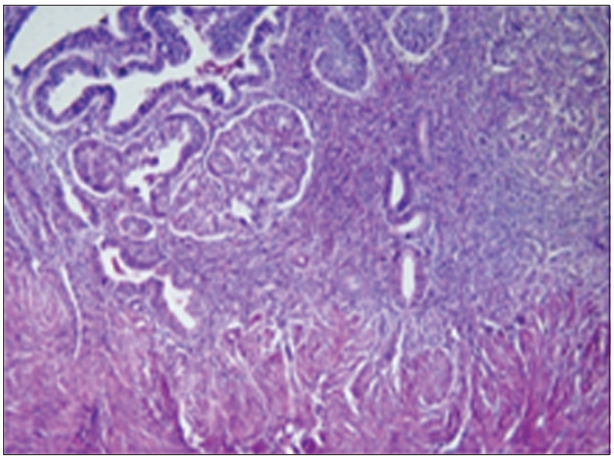

Figure 2A: Endometrial curettage - adenocarcinoma endometrium

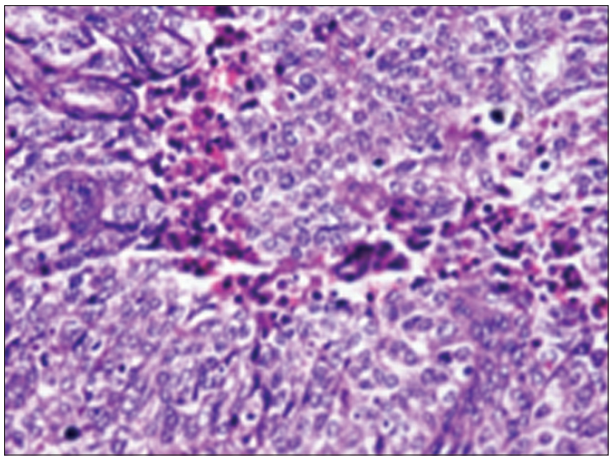

Figure 2B: Post-hysterectomy histopathology - adenocarcinoma endometrium

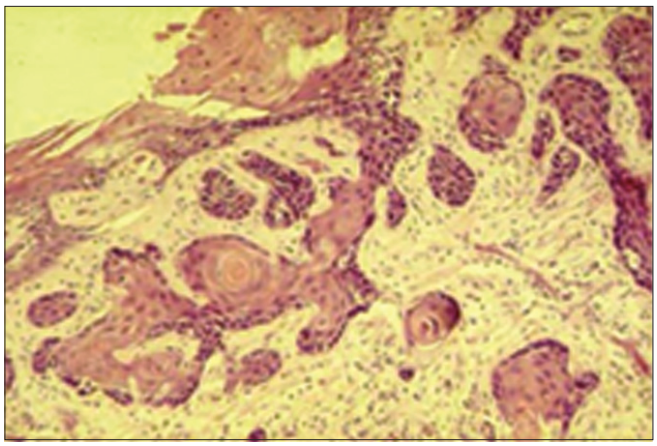

Figure 3: Biopsy upper esophagus: squamous cell carcinoma

DISCUSSION

The widely accepted criteria for diagnosis of MPMN were established by Warren and Gates.[2] According to this, each tumor must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded. Spratt and Hoag found that the reported prevalence varies from 0.7% to 11.7% and concluded that, empirically, persons living to extreme age can be expected to have multiple cancers with greater frequency.[3]

The majority of the patients with quadruple cancers present with breast and upper aero-digestive tumors.[4] In our patient, there was metachronous bilateral breast carcinoma with subsequent development of esophageal cancer.

In literature there has been evidence for moderately increased risk of squamous cell carcinoma of esophagus in patients being treated with postmastectomy radiotherapy for primary breast cancer, pointing toward the possibility of radiation-induced carcinoma of the esophagus developing after a substantial latency period.[5] The excess risk of carcinoma was mainly in the upper and middle third of the esophagus.

Several reports have described the occurrence of esophageal carcinoma after thoracic and neck radiation for various malignancies in these regions. However, the occurrence of a small number of cases of esophageal cancer among the huge number of patients treated with radiation for these conditions may not really indicate an excess risk, as is evident when the incidence is compared with that which would be expected on the basis of general population incidence rates.

Since the early 1980s, adjuvant tamoxifen therapy has been commonly used in the treatment of early-stage breast cancer to improve survival and to reduce the incidence of contralateral breast cancer among postmenopausal women.[6] However, the estrogenic effect of tamoxifen on the uterus has been reported to increase the risk of uterine corpus cancer by 2–3 fold.[7] Our patient was on tamoxifen for a period of 5 years. She developed carcinoma of the endometrium, which was confirmed on endometrial curettage, and subsequently underwent radical surgery.

Epidemiological data have indicated that in women taking tamoxifen there is an increased risk of endometrial cancer. In the studies of Rutqvist *et al*., involving > 4900 Scandinavian breast cancer patients, there was a 4-fold increase in endometrial cancers during a follow-up period of 8–9 years.[8] In the National Surgical Adjuvant Breast and Bowel Program (NSABP B-14) in the USA involving 2823 patients with node-negative, ER-positive, breast cancers, tamoxifen treatment over a 5-year follow-up period resulted in a relative risk of 7.5 over the placebo group.[9] Reviewing these data, it was concluded that there is sufficient evidence in humans that tamoxifen increases the risk for endometrial cancer.[10]

The occurrence of MPMNs is a rare but increasingly frequently reported event. Many theories have been proposed to explain MPMNs but none have been proven, even though the key risk factors appear to be smoking and family history. In the future, chemoprevention, more intensive surveillance, and appropriate cytogenetic and molecular studies should be developed in order to improve preventive strategies and the detection of MPMNs. Studies are needed to define the magnitude of the problem and determine the predisposing factors. Additionally, multidisciplinary treatment and conservative strategies are important to improve quality of life and survival in these patients.

REFERENCES

1. Feyerabend T, Richter E, Brandt A. Mehrfachmalignome – eine Analyse von 352 Patienten. Strahlenther Onkol 1991;167:214-9.
2. Warren S, Gates O. Multiple primary malignant tumours: A survey of the literature and a statistical study. Am J Cancer 1932;16:1358-414.
3. Spratt JS Jr, Hoag MG. Incidence of multiple primary cancers per man-year of follow up: 20-year review from the Ellis Fischel State Cancer Hospital. Ann Surg 1966;164:775-84.
4. Schottenfeld D. In: Schottenfeld D, Fraumeni JF Jr (eds) Cancer Cancer Epidemiology and Prevention. New York: Oxford University Press; 1996. p. 1370-87.
5. Ahsan H, Neugut AI. Radiation therapy for breast cancer and increased risk for esophageal carcinoma. Ann Intern Med 1998;128:114-7.
6. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet 1992;339:1-I5.
7. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994:86:527-37.
8. Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. J Natl Cancer Inst 1995;87:645-51.
9. Poirier D, Auger S, Mérand Y, Simard J, Labrie F. Synthesis and antiestrogenic activity of diaryl thioether derivatives. J Med Chem 1994;37:1115-25.
10. IARC Tamoxifen. In: Some Pharmaceutical Drugs. IARC: Lyon; 1996. p. 253-365.

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