Triple Malignancy Involving Breast, Ovary and Uterine Vault: A Case Report and Literature Review

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ABSTRACT

Introduction: The occurrence of two or more primary malignant neoplasms in the same person is rare. We have a case report of a 45-year-old woman with triple malignancy involving breast, ovary and uterine vault being managed at our center since 5 years.

Case Report: Our patient presented as a post operated case of two primary malignant neoplasms of carcinoma breast and ovary. For carcinoma ovary she underwent adjuvant chemotherapy and interval cytoreductive surgery. For carcinoma breast she received adjuvant locoregional radiotherapy and chemotherapy. After latent period of 42 months, patient was diagnosed with squamous cell carcinoma vault for which she received pelvic radiotherapy. After around one year she developed locoregional recurrence of vault carcinoma. She received six cycles of palliative chemotherapy and is on regular follow-up. Our patient presented with two synchronous primary malignancies and one metachronous malignancy. Two primary malignancies were carcinoma ovary and breast. She was diagnosed with the third malignancy (carcinoma uterine vault) when she was in regular follow-up and the two previous primaries were controlled. This emphasizes the importance of a regular follow-up and the need of a meticulous work-up for early diagnosis and prompt management of any metachronous malignancy.

Conclusion: Regular follow-up with suspicion of any metachronous primary malignancy and prompt diagnostic work-up to detect them at early stage is very crucial for better outcome. Moreover the choice of appropriate treatment strategy remains the cornerstone in management of patients with multiple primary malignancies.

Keywords: Multiple primary malignancies, infiltrating ductal carcinoma of breast, papillary serous cyst-adenocarcinoma of ovary, squamous cell carcinoma cervix.

INTRODUCTION

Warren and Gates first described multiple primary malignancies (MPM) in the same individual. When two or more malignancies with no relationship between them occur in the same individual, it is defined as MPM. In 1932, Warren and Gates defined three criterias for diagnosing multiple primary cancers, namely: (1) The histopathology of each tumor must have component of malignancy, (2) They must have different histopathology, and (3) Any one of the tumor must not be metastasis of the other malignancy.[1] It is of two types (a) synchronous in which all the malignancies occur at the same time or within six months of first malignancy (b) metachronous when the gap between second or high order malignancies and the previous one is at least six months.[2]

There are various but ill-defined risk factors for multiple primary malignancies, mainly including genetic predisposition, environmental factor and previous treatment history. Multiple primary tumors mainly involve respiratory, gastrointestinal and genitourinary tract.[3] According to various studies their prevalence is in the range of 3-5% among which triple tumors occur in only 0.5% of cases.[4] There is an increase in the incidence of MPM and one of the most important causes of this increasing trend is the gain in survival of cancer patients nowadays due to advances in diagnostic modalities, treatment and supportive care.[5] According to one report, about sixteen percent cancer patients in their further lifetime develop second malignant neoplasm.[6] There are several cases of MPM reported in literature. After thorough review of literature, it is concluded that this case report is the first one to describe three primary malignancies in a postmenopausal woman from India in which two malignancies involving breast and ovary are synchronous type and one involving uterine vault is metachronous type.

CASE REPORT

It is a case of a previously undescribed combination of coexistent triple primary malignant neoplasms. Each of the three lesions demonstrated the classical picture of a characteristic neoplasm of the structure involved, namely, infiltrating ductal carcinoma of breast, papillary serous cyst-adenocarcinoma of ovary and squamous cell carcinoma of uterine vault. No distant metastases to viscera were observed from

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any of the tumors, despite the clear-cut microscopic picture of malignancy and gross local invasiveness. A 45-year-old Indian woman with triple primary malignancy of carcinoma of breast and ovary followed by carcinoma of uterine vault over last five years is managed successfully at our center. In her medical history, she had no personal or family history of cancer or management related to it. She is an unmarried lady with age of menarche at 15 years and surgical menopause at 40 years. Our patient never received hormone replacement therapy and oral contraceptive pills in her lifetime. She is a known hypertensive since ten years and is on antihypertensive drugs. In January 2010 patient presented to our OPD as post operated case of carcinoma breast and ovary for adjuvant treatment. She had history of breast lump and ovarian cyst for which she got operated outside in a private clinic. She had undergone modified radical mastectomy for breast lump and bilateral ovarian cystectomy for ovarian cyst. Histopathology of mastectomy specimen revealed infiltrating ductal carcinoma breast (5x4x4 cm) with margin positive and all 5 resected axillary nodes positive for malignancy (Fig. 1). Ovarian histopathology was papillary serous cyst-adenocarcinoma of bilateral ovaries with involvement of external surfaces (Fig. 2). Both the hormone receptors (estrogen and progesterone receptors) and her2 neu were negative. She was planned for adjuvant chemotherapy followed by adjuvant radiation to chest wall and regional lymph nodes. She received three cycles of paclitaxel (260mg) and carboplatin (450 mg) every 21 days. Any chemotherapy induced serious adverse events were not reported during and after completion of chemotherapy. Following this her serum CA 125 level was within normal limit (15 IU/ml) but her CECT abdomen showed well defined hypodense pelvic lesion invading adjacent bowel loops and rectum with metastatic deposits over bowel loops and uterine fibroid. In May 2010, she was planned for interval debulking surgery. She underwent laparotomy with total hysterectomy, omentectomy, all metastatectomy and lymph-node sampling. Histopathology revealed metastatic deposits on omentum, chronic cervicitis with all the resected nodes showing reactive changes. After this she received three more cycles of same chemotherapy. Then she was treated with irradiation to chest wall and regional lymph nodes. Her treatment was completed in September 2010.

She was on regular follow up. During her follow up period she underwent thorough physical examination with regular monitoring of serum CA 125 level and radiological investigations as per requirement. In April 2012 she was admitted in gynecology ward for bleeding per vaginum and ultrasonography (USG) of abdomen revealed a 65 X 63 mm mass in uterine fossa with rich vascularity. All other organs were normal with no evidence of metastasis but her CA 125 level was raised to 1276 U/ml. She got symptomatic improvement following conservative treatment. She was again planned for chemotherapy and received 6 cycles of cyclophosphamide, adriamycin and cisplatin repeated every 21 days. After the completion of chemotherapy, radiologically the pelvic mass

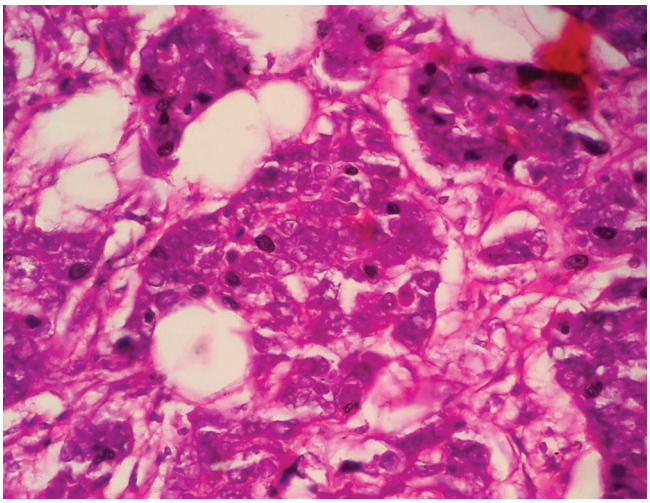

Figure-1: Histopathological features of infiltrated duct carcinoma of breast.

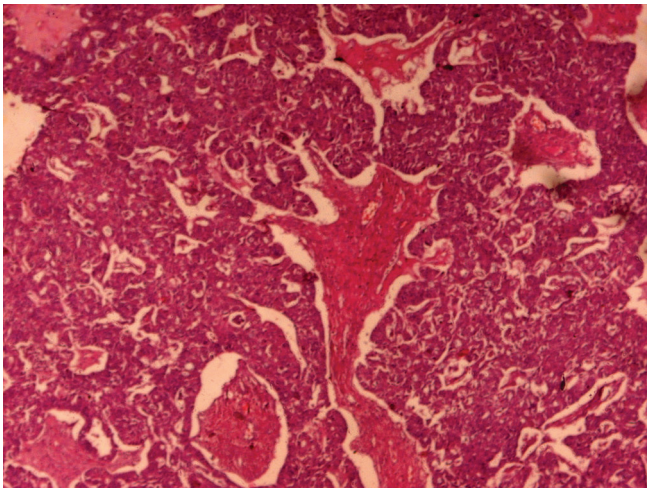

Figure-2: Histopathological features of serous papillary adenocarcinoma of ovary.

completely resolved and serum CA 125 level was within normal limit. In June 2013 she again presented with complains of bleeding per vaginum. Clinical examination revealed an ulceroproliferative growth involving uterine vault with induration of right sided parametrium short of pelvic wall. USG showed a heterogeneous hypoechoic mass in vaginal vault region. Vault biopsy was suggestive of squamous cell carcinoma (Fig.3). She received pelvic external beam radiotherapy (EBRT) dose of 50 Gray in 25 fractions along with concurrent weekly cisplatin based chemotherapy. It was followed by intravaginal brachytherapy dose of 3 fractions of 6.5 Gray each prescribed at vaginal mucosa. After radiotherapy there was complete response of vault growth with CA 125 level of 0.890 U/ml and USG abdomen showing normal scan. The patient was kept on regular follow up. In November 2014, she again had complain of whitish discharge per vaginum and on clinical examination there was recurrence of vault growth reaching upto introitus. Biopsy confirmed it as moderately differentiated squamous cell carcinoma. USG abdomen was suggestive of irregular mass in the pel-

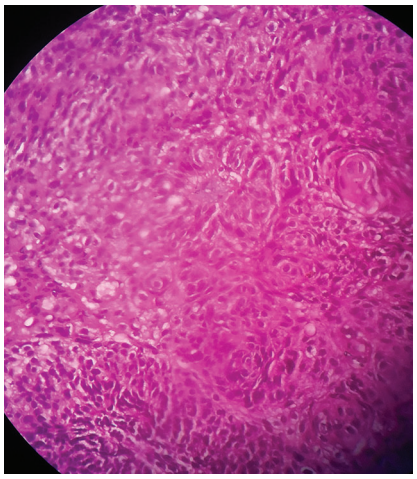

Figure-3: Histopathological features of squamous cell carcinoma of uterine vault.

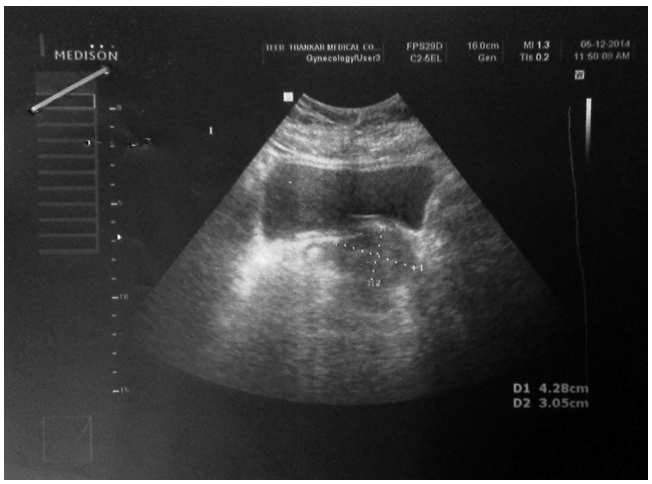

Figure-4: USG abdomen showing irregular mass in the pelvis posterior to the base of urinary bladder.

vis posterior to the base of urinary bladder (Fig. 4) and serum CA 125 level was 226.13 U/ml. She received six cycles of three weekly gemcitabine (1.4 gm) and carboplatin (450 mg) based chemotherapy. The pelvic disease responded to chemotherapy and the patient is kept on regular follow-up. Our patient tolerated all her treatment well with minimal side effects and without complications. In the last follow, all the three primary malignancies are well controlled with evidence of treatment related late toxicities. At present the patient is alive and disease free with no evidence of any recurrent or residual disease.

DISCUSSION

MPM are rare but now with increasing survival of cancer patients, the incidence of MPM is increasing. In 1879 Billroth, reporting the earliest recognized cases of true multiple malignancy, postulated that each tumor must have a different histologic appearance, must arise in a different location, and must produce its own metastases. Mercanton, in 1893, added that there must be no reappearance on removal. Warren and Gates pointed out that there was no significant difference in the age of female patients with one, two, or three cancers, and that the average duration of life in patients with multiple cancers is less than a year longer than the two-year average for a single malignant growth. The opposing contention of Hanlon, however, that patients with multiple malignant growths are generally several years older than those dying with a single new growth, somewhat confuses the issue. There is 20% higher risk of new primary cancer in same or different organ of a cancer survivor in comparison with general population. These newly developed primary cancers can be due to previous therapy, some syndrome related or some common etiologic factors.[7]

The most common cases of MPM involve hematological, lung, thyroid, breast, skin and genitourinary systems.[3] Because of embryological and hormonal factors, in MPM the most common organ to be involved is breast. The combined occurrence of carcinoma of breast and ovary is related to a familial carcinoma syndrome. In this case there are two primary synchronous malignancies namely carcinoma breast and ovary. There is no family history of any cancer in our patient. The patient is nulliparous and this is the only known risk factor for these malignancies. So it may be concluded that this case is an example of sporadic occurrence of theses malignancies which may be described by environmental modifications and polygenic model.[8] In a similar report, Soo-Kyung Noh described a case of four malignancies involving breast and rectum followed by ovary and endometrium.[9]

The third malignancy in this case is squamous cell carcinoma of the uterine vault. It fulfills the criteria of metachronous MPM as it occurred some time after the two synchronous varieties. This unusual occurrence of two synchronous MPMs namely, infiltrating duct carcinoma of breast and papillary serous cyst adenocarcinoma of ovary followed by one metachronous squamous cell carcinoma of the uterine vault, has not been reported among Indians. As the general condition of our patient was good, she underwent three surgical procedures, received 18 cycles of chemotherapy and two times irradiated at two different sites. But the choice of treatment and their sequencing was difficult task. Challenges faced in management of this case were due to differential diagnosis and diagnosis of onset of new malignant lesion with different histopathology. Through aggressive and systematic diagnostic approach, a clinician may resolve these problems. There are no standard recommendations and guidelines for management of MPM. The management should be based on general condition of patients, the types of malignancies, proper sequencing of treatment modalities and response to therapy. Curative lesions should be treated with radical approach. All other lesions are approached with palliative intent. After management of first malignancy, risk of development of subsequent higher order malignant lesions must be kept in mind. During follow up period of a cancer survivor, a clinician should not only focus on diagnosis of any recurrent or metastatic lesion from first malignancy, but also keep in mind

the occurrence of any second or higher order malignancies at the same or different site. The preventive and interventional strategies should be targeted for this high risk population. Among the cases of MPM, there are only about 10 per cent cases of true triple malignancies, with reporting of approximately 135 cases only. With this background, it is felt that this case warrants recording in the literature.

CONCLUSION

Suspicion, awareness, appropriate and aggressive diagnostic work up is crucial for detection of MPM at early stage to have better outcome. For the management of multiple primary malignancies, choice of appropriate treatments and their sequencing remains the cornerstone. It is a general tendency that if a patient with known malignancy develops new symptoms, it is correlated with recurrence of the previous one. In the follow-up period after successful management of first malignancy, a clinician should always keep in mind the development of second or, higher order primary malignancy, for detection at early stage with better outcome.

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