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Case Report

Triple Malignancy- Three different Histopathologies in a Single Patient. A Diagnostic Dilemma

Tejaswini M Pawar[1], Sreeramulu P N[2], Nipun A C[3]*, Kodaganur S, Gopinath[4], Manjunath G N[5], CSBR Prasad[6]

1. Post graduate, Department of General Surgery, Sri Devaraj Urs Medical College.
2. Professor and Head, Department of General Surgery, Sri Devaraj Urs Medical College.
3. Associate Professor, Department of Urology, Sri Devaraj Urs Medical College.
4. Professor, Department of Surgical Oncology, Sri Devaraj Urs Medical College.
5. Assistant Professor, Department of Radiooncology, Sri Devaraj Urs Medical College.
6. Professor, Department of Pathology, Sri Devaraj Urs Medical College, SDUAHER, Tamaka, Kolar.

ABSTRACT

The increasing effectiveness of cancer therapies and the improvement of diagnostic tools have led to better survival rates among cancer patients. This situation has made the problem of developing subsequent primary tumours more frequent. In our case we discuss about a 70 year old female with three different primary malignancies. Occurrence of malignancy of the cervix, rectum and bladder is very rare.

Key words: Triple malignancies, Bladder carcinoma, Cervical carcinoma, Rectal carcinoma.

INTRODUCTION

The increasing effectiveness of cancer therapies and the improvement of diagnostic tools have led to better survival rates among cancer patients. This situation has made the problem of developing subsequent primary tumours more frequent. 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 ante-mortem or post-mortem.[1] Prevalence of multiple primary malignancies is slowly increasing due to prolonged survival of cancer patients, 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 (SEER) 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]

According to the Surveillance, Epidemiology and End Results (SEER) cancer registries of the National Cancer Institute, cancer survivors had a 14% higher risk of developing a new malignancy than the expected general population. Females had a slightly higher relative risk than males for all subsequent cancers combined, and the most implicated sites were breast, colon, lung and melanoma of the skin.[7] Multiple primary cancers may be synchronous or metachronous depending on the interval between their diagnosis. Synchronous cancers are defined as malignant tumors that present either simultaneously or within a six-month period of identification of the original tumor, each of which must be distinct with no possibility of one being the metastasis of the other.[7]

***Corresponding Author**
Dr. Sreeramulu P N
Professor and Head, Department of General Surgery, Sri Devaraj Urs Medical College, SDUAHER, Tamaka, Kolar.
Mob No: 9845316361
E-mail: drsreeramulu@yahoo.co.in
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Cancers diagnosed beyond the six-month interval are referred to as metachronous cancer. Despite its low incidence, the association of two malignancies in a single patient has been widely reported in the literature, while only a few cases of three malignancies have been described.

CASE REPORT

A seventy-year-old woman presented with a 2-year history of mass per vagina associated with bleeding per vagina. She was evaluated for the above and was diagnosed to have differentiated squamous cell carcinoma of cervix stage IIA and on further evaluation was diagnosed to have carcinoma rectum (adenocarcinoma) stage T3N1M0. Fig 1 Patient received 25 fractions of radiotherapy following which she underwent abdominal hysterectomy 2 weeks later and was the treated with Neoadjuvant chemotherapy (FOLFOX regimen) which was given for six cycles Patient also underwent exploratory laparotomy with low Abdominoperineal resection for the Carcinoma of the rectum. Per op findings showed rectal thickening and a growth 8cms from the anal verge. Histopathology showed adenocarcinoma of the rectum (T3 N1 M0). Fig 1,2 Regular follow up was done and the patient was symptom free for 1 year. Patient came back after 1 year with complaints of haematuria. Patient was evaluated for the above and radiation cystitis was suspected as the median duration for onset of cystitis is around 1 year.

Patient was investigated and patient underwent Contrast enhanced Computer tomography abdomen and pelvis, Rectal mass on MRI Fig 3, Fig 4 and cystoscopy which showed a growth on the lateral wall measuring about 3 cm and a growth in the trigone measuring 3 cm and was diagnosed to have a bladder growth. The growth was seen involving the posterior wall of the bladder and the trigone of the bladder. Transurethral resection of the bladder tumour (TURBT) was done a sessile mass of around 2 x 2 cm on the left lateral wall and 4x 2 cm in the posterior and right lateral wall was seen, the growth was later resected and sent for histopathology. Histopathology proved it to be a transitional cell carcinoma of the bladder (low grade) Fig 5.Patient was planned for intravesical BCG therapy for 6 weeks advised for follow up and repeat cystoscopy after 6 weeks. The patient was subjected to genetic work up. The genetic work up revealed mutation in intron 9 at position g.19028 T>C.

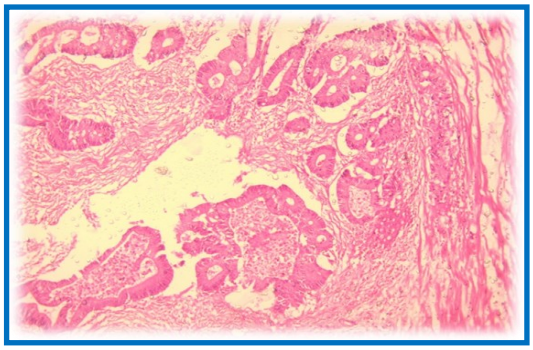

Fig 1. Microscopy of adenocarcinoma of the rectum. H & E Stain X 40

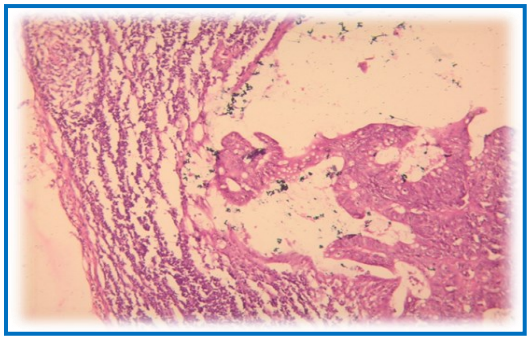

Fig 2. Microscopy of metastasis adenocarcinoma of the rectum. H & E Stain X 40

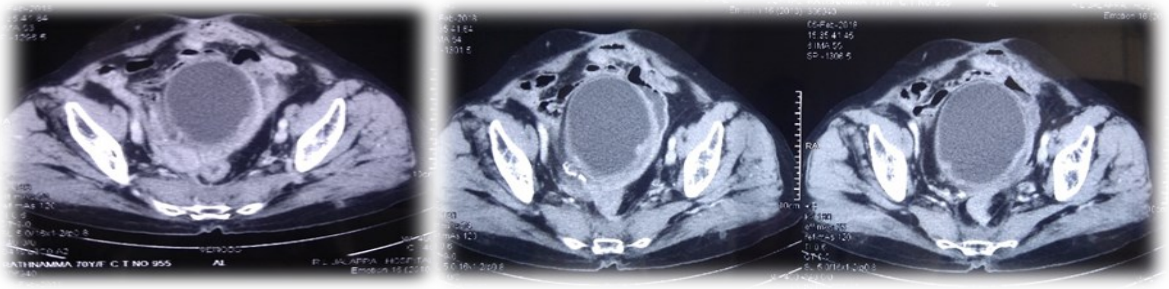

Fig 3. Bladder carcinoma on CT

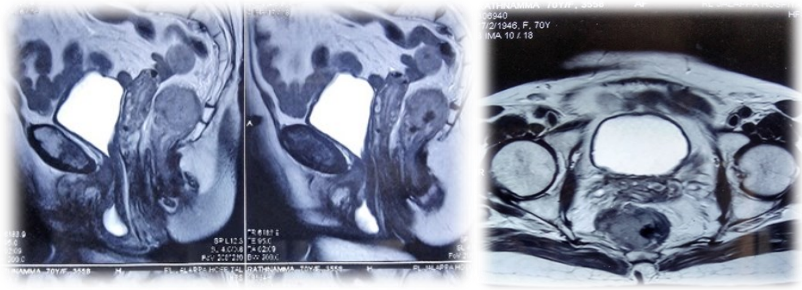

Fig 4. Rectal mass on MRI

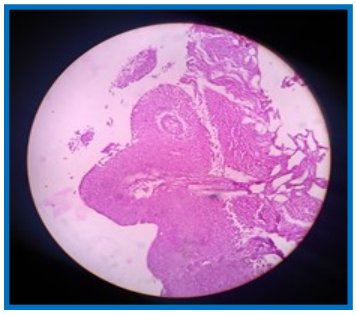

Fig 5. Microscopy of Transitional cell carcinoma

DISCUSSION

Several risk factors have been implicated in the development of subsequent primary malignancies, but the incidence and prevalence data in regard to this are still lacking worldwide. The exact aetiology of multiple malignancies is ill-defined. There are various factors including 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]

An association of multiple cancers in a single patient suggests common etiological factors, Patients with two synchronous or metachronous tumours have a higher risk of developing further malignancies. In a review covering 20 years at the Ellis Fischel State Cancer Hospital, suggested that, on the basis of the observed age-specific incidence cancers, persons living to extreme age can expect to have multiple cancers with great frequency. The above patient developed urinary bladder carcinoma 2years after the initial diagnosis of the synchronous described malignancies (carcinoma rectum and carcinoma cervix). It has been known to us that cancer therapy may result in second malignancy, but these usually occur after 10 years of treatment. It is hypothesized that there may be inherent difference in these patients' immune system or other genetic surveillance mechanisms that might confer improved survival. In the above case the patient presented with mass and bleeding per vagina which was diagnosed as carcinoma cervix and later on further evaluation carcinoma rectum was diagnosed. Patient received radiotherapy followed by hysterectomy and later low anterior resection was done for the carcinoma rectum. Cervical cancer is the fourth most common cancer in woman in the world. Given the good (67.2%) ten-year relative survival rate for cervical cancer patients treated with radiotherapy, develop subsequent primary carcinomas. Data from 104760 one-year survivors of cervical cancer of 13 population-based cancer registries were analysed. The risk of all second cancers was increased to a statistically significant extent (number = 12496; standardized incidence ratio [SIR] = 1.30; 95% confidence interval [CI] = 1.28 to 1.33). Cervical cancers patients treated with radiotherapy were at increased risk for all second cancers and cancers at heavily irradiated sites (colon, urinary bladder, ovary, rectum, anus and genital sites) as compared with general population. [11]

The diagnostic dilemma occurred when the patient presented with two operable carcinomas. Radiotherapy was planned for the carcinoma of the cervix. But the problem of radiotherapy was the loss of surgical plane of dissection if given at high doses and if the patient failed to follow up. Fortunately enough the above patient was compliant for the treatment that was planned and then underwent surgical resection of the rectal carcinoma, and was disease free for 2 years. There have been triple malignancies described in case of RCC (primary tumour). But triple malignancy involving the cervix, rectum and bladder has not been seen. The dilemma occurs in the treatment when the patient presents with multiple malignancies. The first primary is difficult to assess and treat. Individual treatment of the cancers can be done but coming up with a plan

to treat the multiple tumours is a task. 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.* Homozygous loss of the *p53* gene is found in virtually every type of cancer, including carcinoma 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 i.e. this disease is called the Li- Fraumeni syndrome. Other interpretations of this association of multiple cancers that are reported could be hereditary factors and genetic predisposition. Otherwise this unusual association could be due to a chance phenomenon. For identification of primary synchronous cancers, such as different histologic types (major criterion) or all the following minor criteria:[1] both tumours confined to primary sites;[2] no direct extension between tumours;[3] no lympho-vascular tumour emboli;[4] no or only superficial myometrial invasion; and[5] no distant metastases. MPC may be synchronous or metachronous depending on the interval between their diagnosis. A literature review on 1,104,269 cancer patients concluded that the prevalence of multiple primary malignancies occurs in 11.7% .In an other study mentioned that multiple primary malignancies are common, in a study encountered in 3–5% of malignant tumors which are most often secondary, triple tumors occur in only 0.5%, quadruple tumors in 0.3% of malignant tumors.

Conclusion

Triple malignancies are extremely rare in a single patient. The patient surviving 3 malignancies depends on the stage of the disease and the treatment modality. In the above case the malignancies were detected at an earlier stage and the appropriate an well planned management was executed, following which the patient is now symptom free.

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