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Multiple Primaries Rising Trend– a Case Series

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ABSTRACT

The last decade has clearly indicated a steady shift towards the rising trend of multiple primaries malignancies (MPM). These are not clinical curiosities anymore but very strong prevalent trends that is worthy of a closer scrutiny and study. This paper discusses a case series of 10 patients with MPM who came for their management to our hospital over 2 years

Keywords: Malignant thymic tumor, metronomic chemo

INTRODUCTION

The increase in smoking, alcoholism, obesity, sedentary habits, increasing geriatric population, increased environmental pollution, and familial incidence of cancer has not just increased the incidence of cancers but also to multiple primaries (synchronous or metachronous) in the same individuals. Second primary malignancies and multiple tumors are not uncommon. This case series was written because there are not many reported from Asia, specifically the Indian Sub continent.

CASE SERIES

CASE 1:

A middle aged, hypertensive and diabetic male of 57 years came with a history of colon cancer. He was a known smoker and alcoholic for 37 years. He had right hemicolectomy performed in 2011 and the histopathology showed growth in transverse colon with infiltration to muscle coat, Grade II Adeno carcinoma, 17 pericolic lymph nodes (LN) dissected without evidence of malignancy, lymphoid hyperplasia staged as pT2N0M0.

In Jan 2013, he had difficulty in talking and on investigation was found to have Cancer Glottis cT2N1M0. He was given chemo radiation 66 Gy @ 2.75 Gy in 24 fractions, with 3 cycles Carboplatin completed in April 2013 ,post chemo radiation , he was given 5 cycles of chemotherapy with Cisplatin and 5FU. In Jan 2017, CT scan in Jan 2017 showed lesion in the

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supraglottis with extension to the subglottis. In spite of the treatment the supraglottic growth was progressive, he had a tracheostomy. He continued to have difficulty in swallowing food and breathing for 3 months Upper Gastro intestinal (UGI) scopy showed 0.5 cm lesion at 30 cm, mid third esophagus. Biopsy of the lesion showed squamous cell carcinoma esophagus moderately differentiated. Physical examination was unremarkable except for his recent tracheostomy, neck hyperpigmented with loss of hair, mild induration of skin with subcutaneous fibrosis consistent with post radiation changes, Left middle jugular LN 2x2cm and a scar in the abdomen consistent with his previous abdominal surgery. Indirect laryngoscopy (IDL) scopy showed slough covered ulcero proliferative mass in the left aryepiglottic fold and ventricular band. He is a case of metachronous triple malignancy with cancer colon pT2N0M0 in 2009; cancer glottis cT3N1M0 in 2013, cancer middle third esophagus cT2NXM0 in 2017 along with recurrent growth of the glottis now extending to supraglottis and sub-glottis ryT3N0M0. The most probable causatives here are alcohol intake and smoking for over 37 years, it is a typical case of field cancerisation. He had been planned for concurrent chemotherapy with Cisplatin and 5FU with radiation for the oesophageal cancer, as this chemotherapy would be a salvage for the second primary as well. This patient is alive and is on follow up till September 2017.

CASE 2:

A 72 year old post-menopausal lady had cancer left fallopian tube St IIIB in 2009, TAH+ BSO+ Omentectomy was performed. Histopathology showed Left fallopian tube, poorly differentiated adeno carcinoma Grade III, omentum and nodule in the sigmoid mesocolon showed tumour deposits. Right fallopian tube, paracolic gutter, appendix were normal. Patient was given 2 cycles of Carboplatin and paclitaxel**.** In 2011, she was diagnosed to have cancer breast left Stage II A, ER +,PR +,Her 2neu 2+.She was given 2 cycles of adjuvant Adriamycin and Cyclophosphamide after which she defaulted. In 2012, she was diagnosed to have growth in the mesocolon-hepatic flexure and ascending colon, and 4 cycles of chemotherapy with Cyclophosphamide and Carboplatin was given. She was advised surgery but she defaulted not agreeing for the same. In 2013, CT scan showed a large mass 8x7x7cm in mesocolon abutting prominent one third of the transverse colon, hepatic flexure and ascending colon, she came with vomiting, abdominal pain, distension in April 2017. On examination, her performance status was 3 by ECOG score, left chest wall scar was normal consistent with post mastectomy status, per abdomen she had tenderness both iliac fossa left > right, bowel sounds were present. Colonoscopy showed intraluminal growth in the ascending colon, biopsy shows adeno carcinoma Grade 1. She was diagnosed to be a case of metachronous triple malignancies with cancer left fallopian tube Stage III B in 2009; cancer left breast cancer Stage II A 2011; third malignancy with cancer colon. The most probable cause would be genetic mutations? BRCA1 syndrome, we

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need genetic study to confirm the same. This patient is planned for surgery and chemotherapy with FOLFOX4 regimen. This patient is alive and was on treatment till October 2017.

Case 3:

A 44 year old pre-menopausal lady had difficulty in swallowing in June 2017. Her, indirect laryngoscopy revealed cancer hypo pharynx (post cricoid growth) with left vocal cord fixed. UGI scopy showed lesion in the cervical and upper third oesophagus also from 18 cm to 26 cm. Biopsy from hypo pharynx showed Squamous cell carcinoma Grade III, NG high; Biopsy from oesophagus showed Squamous cell carcinoma Grade II. She is a case of synchronous primary cancers with cancer hypo pharynx T3N1Mx and cancer Oesophagus upper cervical and thoracic oesophagus 18-26 cm. The causes for her malignancies were poor diet and chronic anaemia. This patient is planned for nutrition support followed by chemo radiation. This patient has completed her treatment but in poor general condition.

Case 4:

A 72 year old diabetic patient, a known smoker for 42 years had upper back pain with swelling. He had wheezing and altered bowel habits for 5 years. He came with recent complaints of difficulty in passing urine, loss of appetite and weight. His, MRI spine altered marrow signal changes C7 to D4 with near complete collapse of D2 with a possibility of myeloma/metastasis/ lymphoma. He was further investigated as an unknown primary with spine secondaries. CT guided biopsy of the upper thoracic D2 spine showed features consistent with metastatic adeno carcinoma. Physical examination was unremarkable PET-CT showed FDG avid metabolically active LN metastasis in bilateral supraclavicular, mediastinal, and bilateral, hilar LN. There was also metabolically active multiple lytic skeletal lesions involving the axial and appendicular skeleton (C7 to D4, D12, L4, right iliac bone, and scapula) and metabolically active enhancing nodule in the left submandibular gland. Prostate enlarged size of 48x44x43 mm, ultrasonogram (USG) neck showed right lobe thyroid multiple hypoechoic lesions 7x10mm, superior pole lesion 6x5 cm, left lobe 4x5mm hypoechoic lesion; PSA was 6.72ng/ml. He was diagnosed to have an unknown primary which latter was Prostatic adeno carcinoma with Gleason score of 7; papillary thyroid malignancy. The probable cause could be acquired germ line mutations. This patient had progressive disease and has succumbed to the disease.

Case 5:

A 58 old man a known case if CML diagnosed in 2014 , BCR ABL positive was started on Imatinib 400 mg everyday. Patient was on regular follow up and has achieved complete hematological remission in June 2017. As he was on follow up , he was diagnosed to have Cancer prostate in an investigation for increased urination. His PSA was 101ng/dl. He had no

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metastasis elsewhere. He was subjected to Bilateral orchidectomy and he was started on Bicalutamide and is doing well. This patient is on follow up regularly.

Case 6:

A 70 year old lady was diagnosed with cancer breast in 2012, had surgery modified radical mastectomy followed by chemotherapy 6 cycles FAC for pT2N0M0 Luminal A disease. On follow up with Letrozole, she had increased abdominal distension in 2015 May, On evaluation had Cancer Ovary with CA125 of 490 U and right adnexal mass, since ascitis was positive for malignancy, she was given neoadjuvant chemotherapy with Paclitaxol and Carboplatin 3 cycles followed by staging laprotomy and adjuvant 3 more cycles chemo. Now, patient is on regular follow up with a disease free status. For this case could be a genetic mutation such as BRCA , however mutation studies were not performed due to logistics. This patient has responded to treatment and is on follow up .

Case 7:

A 68 year old lady was diagnosed with cancer ovary in 2013 with CA125 of 990 U and right adnexal mass, since ascitis was positive she was given NACT with Paclitaxol and Carboplatin 3 cycles, staging laprotomy and adjuvant 3 more cycles chemo. On follow up in 2015, she had a mass in the right breast had surgery modified radical mastectomy followed by chemotherapy 8 cycles 4AC+4Taxol for pT2N2M0 Luminal B disease. On follow up patient had difficulty passing motion on investigation was found to have cancer sigmoid colon , she was taken up for surgery she had adenocarcinoma pT2N1MO, she has received 6 cycles of FOLFOX4 and has done well. However developed bone metastasis hence was given radiation to L3 spine she continues her hormonal treatment with zolendronic acid. This case also could be a genetic mutation such as BRCA , however mutation studies were not performed due to logistics. This patient is on follow up.

Case 8:

A 65 year old man a known case of cancer glottis post chemo radiation with progressive disease had tracheostomy and palliative chemotherapy with Cisplatin and 5 Fluorouracil. After 6 cycles the disease was under control. However there were new swellings under the right arm and right Inguinal region. On biopsy of the whole Lymph node from right axilla, patient was diagnosed to have Diffuse large B cell Lymphoma , Non Hodgkins Lymphoma. He was then started on R-COP regimen avoiding Anthracycline (Adriamycin) due to age and performance status. Cancer Glottis and NHL in this case are to different malignancies, there seems no common cause to both malignancies till now. This patient has succumbed to the disease.

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Case 9:

A 54 year man was diagnosed to have Malignant fibrous histiocytoma of the posterior left high with lung metastasis. It was inoperable and so he was given radical chemotherapy with MAID regimen and Local radiation. The lesion which was initially bleeding and uncontrollably growing became static and the patient was stable. On follow up for the metastatic disease patient started having breathlessness so with the impression that he is got worsening lung metastasis, he was investigated. The CT scan of chest showed a new left apical mass. Biopsy from the lesion showed Pancoast tumor. He is now on palliative chemo with Cisplatin and Etoposide and palliative Radiation to the left pancoast tumor. However disease progressed rapidly and the patient succumbed to the illness. In this case soft tissue sarcoma and lung cancer can probably be related to the exposure of insecticides and pesticides that this patient was exposed to as he was a farmer

Case 10:

A 54 year old post menopausal woman a known case of cancer cervix stage IIIB post chemo radiation in 2014, had constant headache on follow up. On further investigation with MR brain showed a solitary lesion in the right temporoparietal region. The neurosurgeon's opinion was sought, the lesion was removed . The histopathology revealed Anaplastic Astrocytoma. Patient was treated with Radiation and concurrent Temozolamide. There are case reports on cancer cervix with brain meningiomas but not with astrocytomas. This patient is on follow up.

DISCUSSION

One of the first reported statistical data on multiple primary malignancies was in 1889 by BIllroth [1], then by Burgher in 1934 and in 1932 Waren and Gates studied 1,259 patients with MPM [3]. First report case series was by Lt.Comdr et al in 1944, but the National cancer survey which first reported in 1938 and second in 1969-1971 gave no mention of MPM. The SEER (Surveillance Epidemiology and End results program) in 1979 gave first definition. NCI publications of 45 years of Cancer Incidence and the SEER data reported 5.9% of MPM between 1935 to 1982, 20% synchronous, 80% metachronous. MPM generally fall in to two categories. Synchronous cancers occur at the same time (SEER definition is within 2 months). Metachronous –cancers follow a sequence (more than 2 months apart). In 1977, Moertel defined "multicentric" when tumors occur simultaneously in the same anatomic site. Dr.Lynch said SEER data 1973-1999 2.7 million cancers across 9 registries around 10 % developed second primary by the US Workshop proceedings 2003[2].

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The aim of this presentation is to report our observation of increasing incidence of multiple primary cancers both synchronous and metachronous. Multiple malignancies in India are under reported. There is limited data on management of multiple malignancies more than 3 in number. There are up to 6 multiple synchronous and metachronous malignancies reported in the literature. Some of these cases were alive with treatment in spite of the disease. One patient survived 12 years and the other patient survived 18 years after 5 malignancies [6]. The pattern of incidence has risen from 0.73 to 11.3%, 36% cumulative incidence in 20 years, and 2-6 % per year incidence. There are few retrospective reviews on MPM 63 patients [7], 322 patients[8], 27 cases with 5 multiple primaries [6].

Mechanisms of causing multiple primaries are not explained fully. However the causes could be

(i) Host susceptibility – Diet, Infectious agents,
(ii) Immune function related,
(iii) Shared risk factors – Tobacco, Alcohol,
(iv) Family history,
(v) Medical conditions,
(vi) Genetic susceptibility,
(vii) Intense exposure to carcinogens,
(viii) Carcinogenic effects of Treatment, antecedent therapy [1] .

Warren and Gates Criteria, 1932 for diagnosis of multiple primaries, (i) each of the tumors should be malignancy confirmed by histology; (ii) each lesion must be geographically separate and distinct, these lesions must be separated by normal mucosa; (iii) the Probability of one being the metastasis of another must be excluded. The primary neoplasm are categorized as syndromic cancer (with inherited mutations of genes), cancer treatment related and shared exposure related.

The complete aero digestive tract is vulnerable to malignancies; there are few theories which elucidate the same. One is the mucosal involvement with multiple independent effects sub mucosal regions causing migration of tumor cells through saliva. The second is the intraepithelial migration of progeny of transformed cells. The third is distant spread through blood and lymph node [10].

Exposure of tobacco Smoking and alcohol might explain the elevated a bidirectional risks in various tumors. Chronic alcohol intake of > 45 gm per day that is > 3 drinks per day increases risk to 45% (Cho et al). Chronic ingestion of alcohol at a low daily intake of 10-40 g per day results in 1.5-3.5 fold risk in rectal and lesser in colonic cancer (Scheppach et al 1999). Oral cancer heavy drinker 300 fold risk (Zheng et al 2004). 2/7 genes encoding Alcohol

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dehydrogenease, i.e ADH 1B2 (40 times more active) and ADH 1C1 (2.5 times more active) show polymorphism causing increased Acetaldehyde this causes increased carcinogenic effect. Aldehyde dehydrogenase, ALDH 2/2 allele has low activity which causes less acetaldehyde conversion to acetate. This accumulation of acetaldehyde causes toxicity. Increased saliva and microbes causes more conversion of alcohol to acetaldehyde locally which has prolonged action on mucosa. Mutation of Cyt p450 2E1 can cause variation in accumulation of acetaldehyde. Acetaldehyde directly and by generation of Reactive Oxygen species causes DNA adducts disturbing DNA synthesis and division. There are several evident associations between cancer sites and the same risk factor. Alcohol and smoking affects cancer RR and molecular factors. Alcohol magnifies the effect of Tobacco. There is synergistic role between the two of them. The chemical solvent alcohol maximizes and prolongs the mucosal exposure to tobacco.

Genetic background study reveals Syndromic malignancies characterized by inherited mutations of genes are associated with high risk of malignancy which represents only a small proportion of all cancers. Relatives with germ line genetic predisposition are characterised by increased risk of second malignancy [14]. Genetics in multiple primaries seems to be noteworthy for future preventions and interventions. Field cancerization causes series of eventualities in the mucosal cells. These are aneuploidy and chromosomal aberration, Loss of Y chromosome in the smoking people in the Tumor Adjacent Mucosa (TAM). This leads to alteration in the CK expression 7, 8, 13, 16, 19; increased EGFR, TGF alpha mRNA. Change in Blood group ABH is also a reason for the cause. Cyclin D1 Expression increases – Chromosomal 11q13 amplification – protooncogene. Increased proliferation Lack of bcl2, negates apoptosis. Increased p 53 mutation and increased glutathione S transferase causes futility to the response to carcinogens of tobacco. Expression on proto oncogene product eiFGE Protein Tyrosine kinase phosphatase also increases cancer incidence. New technologies to assess genetic changes are X chromosome inactivation, Loss of heterozygosity, Microsatellite instability, P53 mutation, Polyclonality, Ki 67, viral markers. [14]

CONCLUSION

In case series three out of the ten succumbed to the disease, the rest are on follow up.There are not many articles on multiple primaries and its management from Asia. Younger people who develop cancer may be genetically predisposed and different from the older patients who may not have genetic predisposition. Multiple tumors need to be evaluated and staged individually. These tumors are to be treated aggressively to achieve maximum therapeutic benefit. If possible, 2-3 surgical procedures should be planned in the same sitting, to avoid mortality and morbidity. Strong suspicion during screening and follow up and thorough evaluation goes a long way in the management. According to the literature the prognosis of the patients with multiple primary

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malignancies could be determined independently in function of the stage of each cancer. There is also evidence that many of the metachronous multiple primary tumors have better survival almost matching to their age matched normal counterparts. Since, there is a rising incidence of multiple primary malignancies, it is worthwhile to have studies on this group of patients. This would help us learn better about the biology of the disease and its etiology helping us to be proactive to take prophylactic measures for prevention. In the event of an onset of such scenarios we would be in a better position to treat the patients effectively giving them the advantage of survival.

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