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Case Series

Oncology Section

Triple Malignancy: A Series of Three Cases

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ABSTRACT

Occurrence of Multiple Primary Malignancies (MPM) in an individual is an uncommon phenomenon. It can occur synchronously or metachronously, and the incidence ranges from 1 to 16%. There has been a dramatic increase in the incidence of multiple primaries in patients in the last few years. The diagnosis and treatment of these malignancies pose a clinical challenge as there is no consensus on the optimal management of this condition. It is important to distinguish this condition from the metastasis of an existing malignancy as it can alter the treatment and prognosis of these patients. So far, there have been few case reports published in the literature on triple malignancies, and to the best of authors knowledge, no series have been published yet. Here, authors report a series of three patients (one male and two females) who developed three primary malignancies either synchronously or metachronously. The management of all the patients was decided in a multidisciplinary board based on the stage of each disease and patient tolerance. Two of these patients are alive and on regular follow-up, while one patient was lost to follow-up during treatment. These cases highlight the importance of evaluating and closely following up patients, as well as considering histopathological examination of lesions in unusual sites of metastasis.

Keywords: Metachronous, Metastasis, Multiple primary malignancies, Synchronous

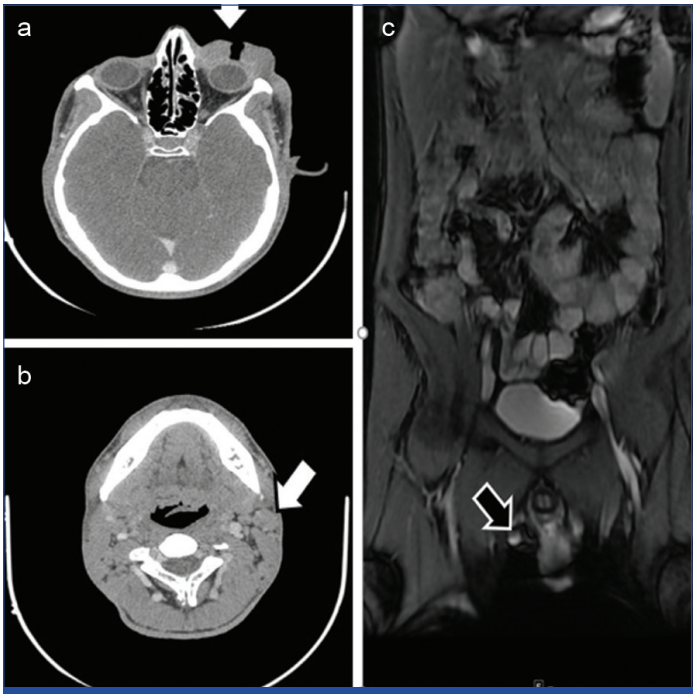
INTRODUCTION

The occurrence of Multiple Primary Malignancies (MPM) in a patient is not common. With advancements in screening methods, diagnosis, and treatment of malignancies, the number of patients with MPM is increasing [1]. According to Surveillance, Epidemiology and End Results (SEER) data, the incidence of MPM varies from 1 to 16% depending on the primary malignancy [2]. The management of these malignancies poses a clinical challenge as there is no consensus on their optimal treatment. Patients with a history of malignancy have a 14% increased risk of a second primary malignancy [3]. Two primary malignancies in a person are relatively more common, but three or more primary malignancies are exceedingly rare. Here, authors report the clinical characteristics and treatment of three patients with triple malignancies.

Case 1

A 29-year-old male with epidermodysplasia verruciformis has been receiving treatment since childhood. He presented with a rapidly enlarging swelling on the right eyelid, accompanied by ulceration lasting for two months. Examination revealed multiple verrucous lesions on the body and bilateral cervical lymphadenopathy. Histopathology {Haematoxylin and Eosin (H&E)} of the swelling confirmed cutaneous T-cell lymphoma. The diagnosis was T3N0M0 (stage IIB) disease. Cervical lymph node biopsy revealed Langerhans Cell Histiocytosis (LCH). The Computed Tomography (CT) images have been shown in [Table/Fig-1a-c] The patient underwent radiotherapy with 30 Gray in 15 fractions for the eyelid swelling and achieved complete remission. As he was asymptomatic for Langerhans Cell Histiocytosis (LCH), he was placed on follow-up.

One year later, he developed a scrotal ulcer measuring 5×5 cm and another ulceroproliferative lesion on the abdominal {Lower stage A2, Tumour Lymph node (TNM) stage III} wall measuring 8×7 cm. Biopsy from the scrotal ulcer indicated well-differentiated squamous cell carcinoma. He underwent wide excision of the ulcers along with right orchiectomy. Pathology confirmed the abdominal wall lesion as cutaneous T-cell lymphoma. Subsequently, he developed a new lesion in the interscapular region, which was biopsy-proven as cutaneous T-cell lymphoma. The patient was started on low-dose methotrexate, to which he initially responded, but later was lost to follow-up.

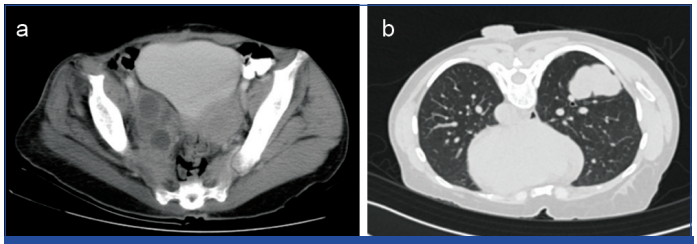


[Table/Fig-1]: Images of Case 1: a) CT image showing left eyelid swelling and ulceration; b) CT image showing enlarged neck node; c) CT image showing left abdominal wall ulceration (white arrow) and right scrotal ulceration (black arrow).

Case 2

A 46-year-old female with Neurofibromatosis (NF) was evaluated for a dull, aching pain radiating to her lower limbs, which had been present for six months. During the evaluation, a large pelvic mass was identified. She had multiple café-au-lait spots and neurofibromas. Her mother and brother also had NF. The Computed Tomography (CT) images have been shown in [Table/Fig-2a,b] The patient underwent

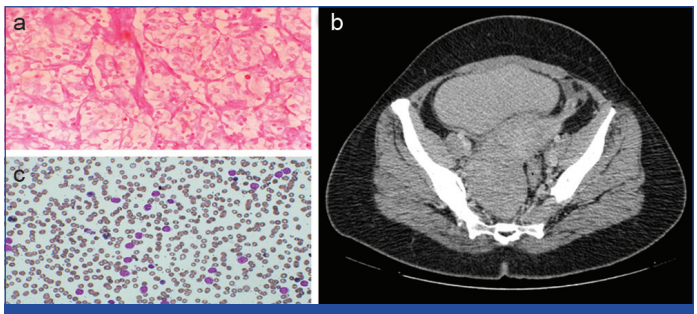
an incomplete resection of the mass due to its encasement of the femoral vessels and nerves. Intraoperatively, another mass lesion measuring 6×4.5 cm was found in the proximal jejunum, which was completely resected. The pelvic tumour was histologically confirmed as a Malignant Peripheral Nerve Sheath Tumour (MPNST) with rhabdomyoblastic differentiation (Malignant Triton Tumour), and the jejunal tumour was suggestive of a Gastrointestinal Stromal Tumour (GIST). Postoperative imaging revealed a residual right adnexal lesion fixed to the lateral pelvic wall. The patient received six cycles of adjuvant chemotherapy with ifosfamide and adriamycin. Subsequent re-evaluation showed regression of the adnexal lesion. Additionally, she received adjuvant Imatinib 400 mg daily for three years. After a period of seven years, a soft tissue lesion measuring 5×4 cm in the right lower lobe of the lung was detected. The patient underwent a right lung lower lobectomy, and histopathology confirmed a malignant spindle cell neoplasm with clear margins. Currently, she is in the third cycle of six cycles of chemotherapy with gemcitabine and docetaxel.



[Table/Fig-2]: Images of case 2: a) CT image showing pelvic mass; b) CT chest showing right lower lobe lesion.

Case 3

A 35-year-old unmarried lady underwent an evaluation for abdominal pain lasting two months. A CT scan revealed a 6×6×5.9 cm mass with necrosis in the lower pole of the right kidney, suggestive of renal cell carcinoma. She underwent laparoscopic right radical nephrectomy, and the histopathology confirmed clear cell renal cell carcinoma. The metastatic workup was negative, and she has been on regular follow-up. After six months, an ultrasound scan of the abdomen detected a right adnexal mass, leading to a right ovarian cystectomy. Histopathology showed an endometriotic cyst with marked atypia of the lining epithelial cells and stromal invasion, suggesting a diagnosis of borderline ovarian tumour [Table/Fig-3a,b]. Due to her preference against salpingo-oophorectomy, the patient was placed on close follow-up. After a disease-free survival of four years, she was investigated for right lower limb deep vein thrombosis and subsequently diagnosed with Philadelphia chromosome-positive acute B-lymphoblastic leukaemia [4]. She was started on chemotherapy with the BFM-95 protocol and achieved complete remission with minimal residual disease negativity following induction. Currently, she is undergoing the reinduction phase of chemotherapy.



[Table/Fig-3]: Images of case No.3: a) Haematoxylin and eosin stained nephrectomy specimen slide showing sheets of cells with abundant clear cytoplasm and distinct membrane and nucleus showing eosinophilic nucleoli with intervening network of arborising small, thin-walled vessels suggestive of clear cell renal cell carcinoma, grade 3 (40x); b) Computed tomography of pelvis showing an irregular fluid density area with peripheral enhancement in the left adnexa of size 2×1.5 cm histology of which was suggestive of borderline ovarian tumour; c) Peripheral smear slide stained with myeloperoxidase showing myeloperoxidase negative blasts with scanty cytoplasm, round nucleus, immature chromatin and 1 to 2 nucleoli suggestive of B lymphoblastic leukaemia (100x oil immersion).

DISCUSSION

It was Theodore Bilroth who first reported MPM about a century ago. In 1932, Warren and Gates analysed 1,259 patients from the literature with reasonably well-described MPMs [5]. MPM can be categorised into synchronous (the occurrence of tumours at the same time) and metachronous (the occurrence of tumours one after the other at an interval of more than six months) [6].

The occurrence of MPM can be due to genetic or other modifiable factors. There has been a dramatic increase in the detection of MPM in the last 50 years [7]. Better screening tests for cancers and advanced diagnostic imaging techniques have led to an increased detection of multiple primaries in patients. Increased exposure to radiation for diagnostic and therapeutic purposes may have also contributed to the increased incidence of MPMs [8]. Lifestyle changes, including increased use of alcohol and tobacco, are also contributing factors.

The major challenge in diagnosing MPM is distinguishing it from the metastasis of an existing primary tumour. This is important as it affects the patient's staging, treatment, and prognosis. Warren S and Gates D have established criteria for the diagnosis of MPM [5]: (1) Each of the tumours must be histopathologically confirmed; (2) each must be geographically separated and distinct, and the lesions should be separated by normal mucosa; (3) the probability of one being the metastasis of the other must be excluded. Hence, a biopsy from all the lesions is essential to confirm their nature.

The treatment of MPM poses a clinical dilemma as there is no consensus on its optimal management. It is usually decided in a multidisciplinary board based on the patient's age, performance status, and disease stage. Treatment modalities include chemotherapy, surgery, and radiotherapy, depending on the disease site and stage. Patients with MPM generally have a better outcome than those with metastatic disease [9].

Among authors' three patients, case 1 and 2 had synchronous primaries, while case 3 had a metachronous presentation. Two patients were females. Literature reviews of MPM also show a female preponderance. Case 1 had epidermodysplasiaverruciformis, which is prone to non melanoma cutaneous malignancies. The malignancy index in these patients is around 60% [10]. The patient had cutaneous T-cell lymphoma and squamous cell carcinoma, which are described associations of epidermodysplasiaverruciformis. LCH was an incidental diagnosis that could have been missed if the lymph node biopsy had not been performed. There has been a lot of debate on whether LCH is neoplastic or inflammatory. Identification of specific mutations, including those in the MAPK pathway, has established it to be malignant. The World Health Organisation included LCH in the group of histiocytic and dendritic cell neoplasms in the latest classification of haematologic malignancies in 2017 [11]. Case 2 had NF. Patients with NF-1 have a 6-7% increased chance of developing GIST [12]. While the most common site of GIST is the stomach in the general population, small intestinal GIST is common in NF-1 [13]. The incidence of MPNST is also dramatically increased in patients with NF-1 [14]. This case also highlights the importance of obtaining tissue diagnosis from all sites of disease, especially if the sites are unusual for metastasis. Both case 1 and 2 were prone to MPM, probably due to genetic predisposition. Genetic evaluation might have provided better insight into the pathogenesis of tumours in these patients.

Patient 3 was found to have metachronous lesions during regular follow-up. This case demonstrates the significance of regular imaging in detecting abnormalities early in patients with malignancy. This may sometimes lead to overdiagnosis and treatment; however, this patient developed another invasive malignancy later during the follow-up period.

All the patients' details were discussed in a multidisciplinary board, and the treatment was determined based on the stage of each disease. All except one patient are undergoing regular follow-up.

While there are numerous case reports on multiple malignancies, this is likely the first case series on triple malignancies. In the literature, all the reported patients were over the age of 45 years. Gastrointestinal malignancy was the most commonly reported type. Ten reported patients had three gastrointestinal malignancies, each diagnosed at a different site. Two patients had triple malignancies confined to the genitourinary system. Haematological malignancy was the least commonly associated type. All of them received treatment based on the stage of each disease [Table/Fig-4] [15-48]. A case summary of all the cases has been provided in [Table/Fig-5].

Author name	Year published	No. of cases	Age	Malignancies	Disease-free survival	Treatment
SaitohY et al., [15]	1995	1	64/M	Squamous cell carcinoma lung, adenocarcinoma rectum, moderately-differentiated squamous cell carcinoma trachea		Surgery, RT
Iioka Y et al., [16]	2000	1	60/M	Sigmoid colon cancer, early gastric carcinoma, oesophageal carcinoma	13 mnth DFS	Surgery, RT
Baba M et al., [17]	2002	1	64/M	Small cell carcinoma lung, poorly-differentiated adenocarcinoma prostate, scirrhous carcinoma breast	20 mnth DFS	Surgery
Oztopl et al., [18]	2008	1	76/M	Adenocarcinoma rectum, adenocarcinoma prostate and Chronic myeloid leukaemia	1 yr OS	Surgery, CT, RT, ET
Arikan-Sengul C et al., [19]	2009	1	70/M	Transitional cell carcinoma bladder, prostatic adenocarcinoma, renal cell carcinoma		
Kim JS et al., [20]	2013	1		Thyroid, breast, pancreas, stomach	8 mnth	Letrozole and imatinib
Takalkar U et al., [21]	2013	1	64	Small bowel carcinoma, ca ovary, ca breast	No mention of survival	
Okumura A et al., [22]	2013	1	73/M	Moderately-differentiated adenocarcinoma prostate, Grade 2 urothelial carcinoma bladder and grade 2 clear cell renal cell carcinoma		
Zargar Shoshtari MA et al., [23]	2013	1	71/M	Clear cell renal cell carcinoma, adenocarcinoma prostate, poorly-differentiated invasive ductal cell carcinoma breast	1 yr	Surgery, ET
Freeman HJ [24]	2013	1	72/M	Moderately-differentiated adenocarcinoma in the distal sigmoid colon, infiltrative moderately-differentiated colonic Adenocarcinoma in the descending colon, moderately-differentiated adenocarcinoma in the rectum	15 yr	Surgery
Chang HY et al., [25]	2013	1	67/M	Adenoid cystic carcinoma maxillary sinus, squamous cell carcinoma oesophagus, squamous cell carcinoma tympanic membrane	15 yr	Surgery, RT
Egashira A et al., [26]	2013	1	63/F	Oesophageal cancer, ascending colon cancer and jejunal cancer	10 mnth	Surgery
Nishikawa K et al., [27]	2014	1	37/M	Squamous cell carcinoma hypopharynx, oesophagus and tongue	10 yr	Surgery, RT, Chemotherapy
Grace S et al., [28]	2015	1		Glioblastoma, neuroendocrine tumour of ileum, schwannoma, sessile serrated adenoma, prostate cancer	No mention of survival	
Pastore AL et al., [29]	2015	1	70/M	Renal cell carcinoma, poorly-differentiated squamous cell carcinoma oropharynx, adenocarcinoma prostate		Surgery, RT, CT, Endocrine therapy
Meeks MW et al., [30]	2016	1	95	Adenocarcinoma colon, collission tumour, hamartoma and sessile serrated adenoma of appendix	No mention of survival	Palliative care
Elec FI et al., [31]	2017	1	78	Prostate adenocarcinoma, clear-cell renal carcinoma, papillary renal carcinoma and small-cell bladder cancer	4 yr	
Nanashima A et al., [32]	2017	1	67	Invasive pancreatic duct cancer, moderately-differentiated AC of the stomach, moderately-differentiated AC of the sigmoid colon, and NET G1 of the rectum	4 yr and 3 mnth	
Kataoka S et al., [33]	2017	1	72	Early pharyngeal squamous cell carcinoma, superficial and advanced oesophageal squamous cell carcinoma and early oesophageal adenocarcinoma		
Takada KH et al., [34]	2017	1	71	Duodenal papillary carcinoma, adenocarcinoma lung, breast cancer		
Katz H et al., [35]	2017	1	48	A granulosa cell tumour of the ovary, adrenocortical carcinoma and adenocarcinoma of the colon	Alive	Folfox chemotherapy
Gheoneal A et al., [36]	2017	1	75/M	Prostatic adenocarcinoma, small cell lung carcinoma, basal cell carcinoma	No mention	Endocrine therapy
Feng Y et al., [37]	2018	1	66/M	Adenocarcinoma prostate, adenocarcinoma lung and adenocarcinoma colon	4 months DFS	Surgery, Chemotherapy
Wang DD et al., [38]	2019	1	56	Endocervical adenocarcinoma admixed with neuroendocrine features, localised endometrial endometrioid adenocarcinoma, unilateral endometrioid ovarian carcinoma, and gastric adenocarcinoma	Lost to follow-up 1 yr after surgery	Surgically excised
Takada K et al., [39]	2019	1	89	Lung cancer, breast cancer, gastric cancer		
Jayarajah U et al., [40]	2019	1	63	Rectal cancer, invasive ductal cancer, renal cell carcinoma	6 mnth	
Tanaka S et al., [41]	2020	1	73	Gastric adenocarcinoma, prostatic adenocarcinoma, intrahepatic cholangiocarcinoma		
AlBaqmi KH et al., [42]	2020	1	63	Gastrointestinal stromal tumour, colon adenocarcinoma, and renal cell carcinoma		
Li G et al., [43]	2020	1	67/F	Moderately-differentiated endometrial adenocarcinoma, Ascending colon papillary adenocarcinoma and moderately-differentiated tubular adenocarcinoma colon, invasive ductal carcinoma breast	19 mnth	Surgery, RT, CT, Endocrine therapy
Sauri FM et al., [44]	2021	1	61	Colon cancer, oesophageal cancer, gastric cancer	Alive	5FU and cisplatin
Zhan X et al., [45]	2021	1	70	Oesophageal carcinoma, gastric cancer and colon cancer		

Peng WX et al., [46]	2021	1	39/M	Gastric adenocarcinoma, nasopharyngeal carcinoma, rectal adenocarcinoma	Alive	Surgery, chemotherapy and RT
JinC et al., [47]	2022	1	64	Moderately-differentiated gastric adenocarcinoma, adenocarcinoma rectum, poorly-differentiated adenocarcinoma rectum	Alive	Capeox chemotherapy as adjuvant
Huang R et al., [48]	2022	1	61	Non invasive urothelial carcinoma of the bladder, diffuse large B-cell lymphoma, and squamous cell carcinoma of the lung		

[Table/Fig-4]: Summary of the previously published cases of multiple malignancies [15-48].
DFS: Disease free survival; OS: Overall survival; RT: Rdiotherapy; CT: Chemotherapy; ET: Endocrine therapy

Summary	Case 1	Case 2	Case 3
Age in years	29	46	35
Gender	Male	Female	Female
Predisposing condition	Epidermodysplasia verruciformis	Neurofibromatosis (NF)	Nil
Clinical presentation	Rapidly enlarging right eyelid swelling with ulceration and cervical lymphadenopathy	Lower backache	Abdominal pain
Primary tumour	Cutaneous T-cell Lymphoma	Malignant Triton tumour	Clear cell renal cell carcinoma
Management	Radiation 30Gy* in 15#	Primary surgery, adjuvant IA#×6 cycles	Laparoscopic right radical nephrectomy
Treatment response	Complete remission	Partial response	Complete remission
DFS#	Synchronous	Synchronous	6 months
Second tumour	Langerhans Cell Histiocytosis (LCH)	GIST§	Borderline ovarian tumour with stromal invasion
Management	Regular follow-up	Complete resection, adjuvant Imatinib 400 mg OD‖ for 3 years	Laparotomy and right ovarian cystectomy
2nd DFS	1 year	7 years	4 years
Third tumour	Well-differentiated squamous cell carcinoma scrotum	Malignant spindle cell neoplasm	Ph**positive B - Acute lymphoblastic leukaemia
Management	Wide excision of scrotal ulcer with right orchiectomy	Right lung lower lobectomy, adjuvant gemcitabine+ docetaxel	BFM-95# protocol
Present status	Lost to follow-up	On chemotherapy with gemcitabine+ docetaxel	Reinduction phase of BFM-95 protocol

[Table/Fig-5]: Summary of all three patients.
*Gray, †Fractions, ‡Ifosfamide+Adriamycin, ‡‡Disease-free survival, §Gastrointestinal stromal tumour, ‖once daily, **Philadelphia chromosome, ††Berlin Frankfurt Munster 95

The present cases emphasise the importance of closely evaluating and monitoring patients, as well as considering histopathological examination of lesions in unusual sites of metastasis.

CONCLUSION(S)

Triple primary malignancies are uncommon, and only a few large studies describe this phenomenon. Regular surveillance and early suspicion are required in patients with a history of malignancy to promptly identify metachronous lesions. Biopsy from any unusual site of metastasis is also important in MPMs. Managing these patients poses a clinical challenge due to a lack of consensus. A multidisciplinary approach with patient-tailored treatment is necessary to achieve optimal outcomes.

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