World Cancer Research Journal WCRJ 2021; 8: e2129

CHALLENGES OF PATIENTS WITH A RARE COMBINATION OF MULTIPLE PRIMARY MALIGNANCIES: A SINGLE-CENTER EXPERIENCE AND A CASE SERIES STUDY

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Abstract – *Objective:* *When more than one primary tumor presents in the same patient, multiple primary malignancies (MPMs) are diagnosed. The incidence of MPMs has increased due to the progress in diagnosis and treatment of malignant tumors. MPMs are a clinical situation defined as the diagnosis of more than one histologically proven tumor within the same patient. The recent advances in diagnostic modalities, treatment, in addition to the cancer screening programs led to a substantial rise in the incidence of MPMs. Management of patients with MPMs is highly challenging and highlights the role of multidisciplinary tumor board management.*

Patients and Methods: *This report represents the clinicopathological features of 8 patients with MPMs from 2018 to 2021. We used Warren and Gate's criteria of classification of MPMs as synchronous or metachronous.*

Results: *A total of 2145 patients with malignant tumors presented to our Department from 2018 to 2021, while cases with histologically proven MPMs represented (0.37%) of the total cohort of patients. The mean age of the patients was 59.87 years. The male to female ratio was 1:1 (Figure 1). Solid tumors were the predominate in 6 cases (75%) as the first tumor, and as the second one in 7 patients (87.5%), while hematological tumors presented only in 2 cases (25%) as the first primary tumor and in 1 patient (12.5%) as the second tumor (Figure 2, 3). Hodgkin Disease (HD) and breast cancer represented the most common primary tumors in (50%) and (25%) cases, respectively, while breast cancer was diagnosed as a second tumor in (25%) of the patients. Metachronous MPMs constituted (75%) of cases, while 25% of cases were synchronous (Figure 4, 5).*

Conclusions: *The MPMs are proven not to be a rare diagnosis and is forecasted to show a steady increase in the incidence based on the progress in the diagnostic procedures. Meticulous follow up and the tackling of patients' symptoms are imperative in the early detection and proper management.*

KEYWORDS: *Case Series, Rare, Multiple primary malignancies (MPMs).*

INTRODUCTION

Multiple primary malignancies (MPMs) are defined as the presence of two or more histologically distinct malignant tumor that is not due to recurrence, metastasis, or local spread within the same patient. Miscellaneous reports about MPMs were found in the mid of the 19th century[1]. Billroth et al[2] were the first to report patients with double malignancies in 1860, while the clinical definition of MPMs was first defined in 1932 by Warren and Gates[3], who assumed that the unexpectedly high incidence of MPMs was not an accidental finding. The prerequisites of diagnosis of MPMs are as follows: each of the tumors must be histopathologically confirmed, each must be geographically separated and distinct, and the lesions should be separated by normal mucosa, with the exclusion

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of the probability of one being the metastasis of the other[4,6]. Moertel[7] divided the MPMs into two types, the synchronous MPMs was referred to tumor diagnosed within six months, while metachronous MPMs was defined as the lag time between the diagnosis of the primary and the second primaries was more than six months.

The incidence of MPMs has a steady increase due to the progress in diagnostic modalities as Positron Emission Tomography (PET) and novel cancer treatment modalities with the subsequent prolonged overall survival of patients[6,7] adding to this, the adoption of national screening programs in many countries worldwide.

MATERIALS AND METHODS

This retrospective study analyzed data from the hospital database of patients diagnosed with MPMs from 2018 to 2021 in the Department of Clinical Oncology at Assiut University (Assiut City, Egypt). We presented the following cases with the concordance of the "CARE reporting checklist" and Warren and Gate's classification of MPMs. Patients with no confirmed histopathology of double primary were excluded from the analysis.

RESULTS

A total of 2145 patients with malignant tumors presented to our Department from 2018 to 2021, while cases with histologically proven MPMs represented (0.37%) of the total cohort of patients. The mean age of the patients was 59.87 years. The male to female ratio was 1:1 (Figure 1). Solid tumors were the predominate in 6 cases (75%) as the first tumor, and as the second one in 7 patients (87.5%), while hematological tumors presented only in 2 cases (25%) as the first primary tumor and in 1 patient (12.5%) as the second tumor (Figure 2, 3). Hodgkin disease (HD) and breast cancer represented the most common primary tumors in (50%) and (25%) cases, respectively, while breast cancer was diagnosed as a second tumor in (25%) of the patients. Metachronous MPMs constituted (75%) of cases, while 25% of cases were synchronous (Figure 4). Table 1 summarizes the clinicopathological features of included patients.

CASES PRESENTATION - METACHRONOUS CASES

I) Hodgkin's disease followed by breast cancer

A 35-year-old female presented in 2008 with fever associated with cervical and para-aortic lymphadenopathy. A biopsy from the cervical lymph node revealed Hodgkin's disease (HD) with positive immunohistochemistry for CD15 and CD30. She received 6 cycles of ABVD (Adriamycin-Bleomycin-Vinblastine-Dacarbazine) regimen followed by involved-field local radiotherapy on the cervical lymph nodes resulting in complete response (CR).

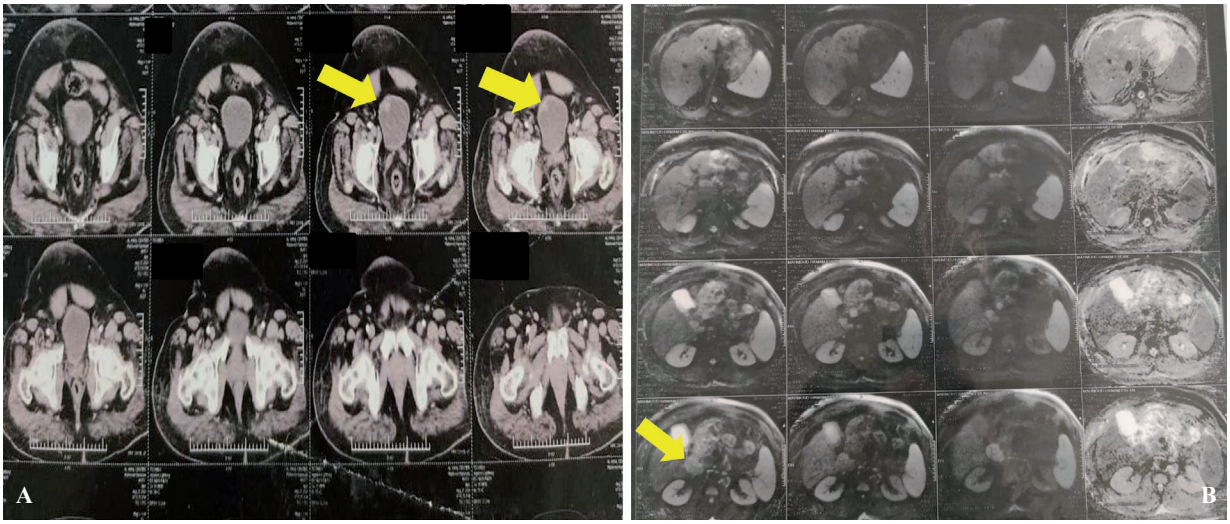

Fig. 1. The imaging studies of case two documenting the presence of double primaries as the CT pelvi-abdomen dated September 2020 showing the urinary bladder gross *(right)* while the MRI pelvi-abdomen on March 2021 showing the porta-hepatis mass with malignant features *(left)*. *A*, Multi-slice pelvi-abdomen axial view showing polypoid gross in the anteio-lateral aspect of the bladder. *B*, MRI pelvi-abdomen T2W1 with diffusion showing mass in the portahepatis 3*4 cm hyperintense with restricted diffusion and low ADC value. The liver is cirrhotic free of focal lesions with moderate splenomegaly and chronic calcular cholecystitis.

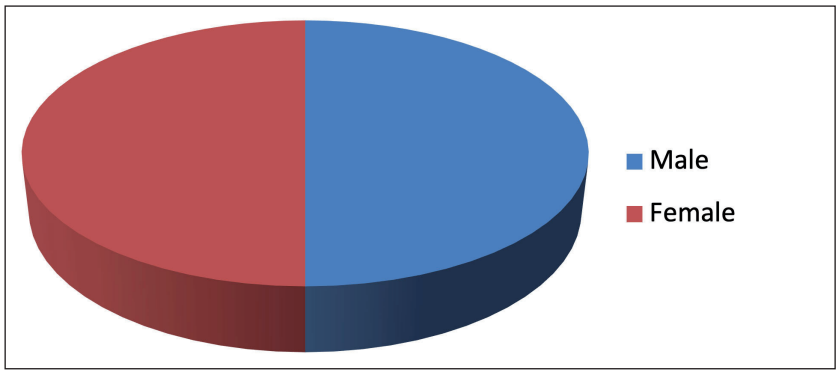

Fig. 2. Male to female ratio. The blue represents the males (50%), while the red represents the females (50%).

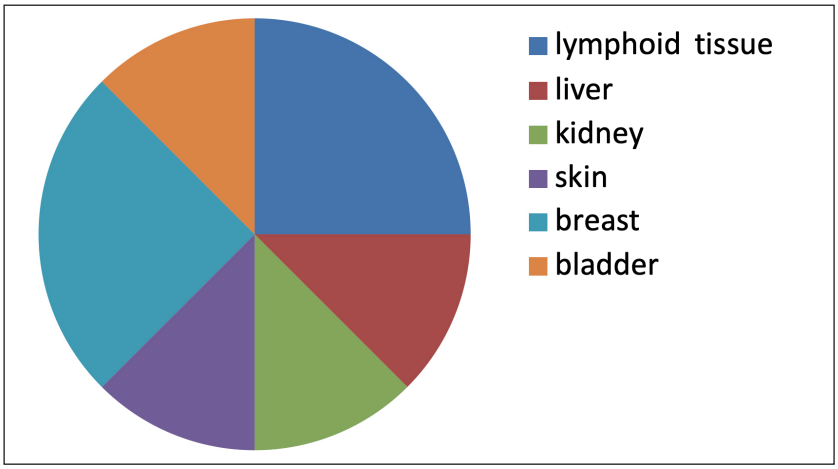

Fig. 3. Site of primary tumor. Lymphoid tissue represents 25%, liver 12.5%, kidney 12.5%, skin 12.5, breast 25%, and bladder 12.5%.

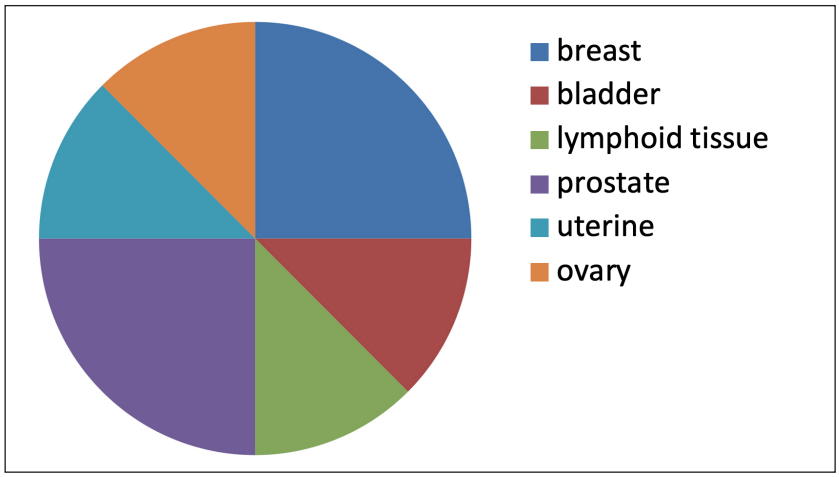

Fig. 4. Site of second tumor. Breast found in 25%, bladder in 12.5%, lymphoid tissue in 12.5%, prostate in 25%, uterine in 12.5%, and ovary in 12.5%.

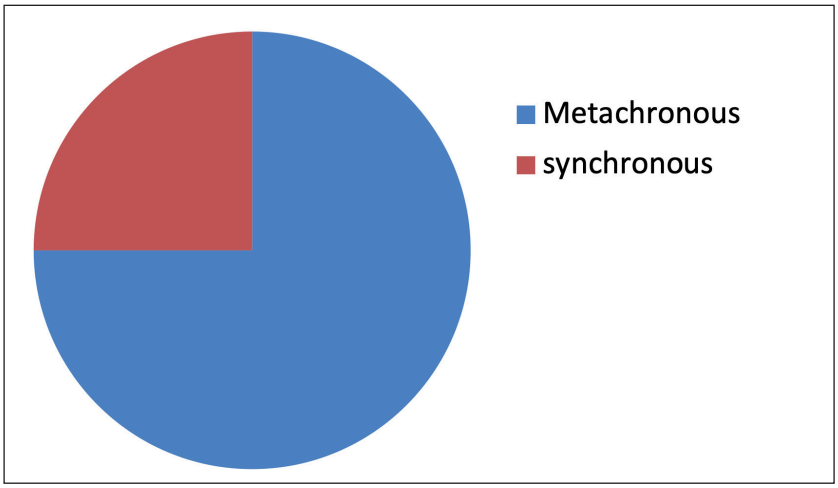

Fig. 5. Type of multiple primary malignancies. Metachronous type represents 75%, while synchronous type represents 25%.

TABLE 1. Summary of the cases of MPMs. Abbreviations: HD: Hodgkin's disease; IDC: Invasive ductal carcinoma; EBRH: external beam radiotherapy; HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; TCC: transitional cell carcinoma; NHL: non-Hodgkin lymphoma.

Case No.	*Age/ sex*	*Primary site*	*Histo pathology*	*Treatment*	*Second Primary Site*	*Histo- pathology*	*Treatment*	*Type of MPMs*	*Time from 1stto the 2nd tumor*
1	35/F	Lymphoid Tissue	HD	Chemotherapy	Breast	IDC	Surgery, Chemotherapy, EBRT, Hormonal Therapy	Metachronous	11 years
2	64/M	Liver	HCC	TACE	Urinary Bladder	TCC	Chemotherapy	Metachronous	3 years
3	54/F	Kidney	Clear cell type	Surgery	Breast	IDC	Surgery, Chemotherapy, EBRT	Metachronous	2 years
4	70/M	Skin	Basal cell carcinoma	Local radiotherapy	Lymphoid tissue	NHL	Chemotherapy	Metachronous	1 year
5	65/M	Lymphoid Tissue	HD	Chemotherapy	Prostate	Adeno- carcinoma	Local radiotherapy, Hormonal therapy	Metachronous	8 years
6	60/F	breast	IDC	Chemotherapy, EBRT, hormonal treatment	Uterine	Adeno- carcinoma	Surgery will be done	Metachronous	13 years
7	63/M	Bladder	TCC	Surgery, concurrent chemoradiotherapy	Prostate	Adenocarcinoma	Surgical	Synchronous	–
8	68/F	Breast	IDC	Chemotherapy, Surgery	Ovary	High Grade Serous cystadenocarcinoma	Chemotherapy, Surgery	Synchronous	–

The patient was kept under follow-up, ten years afterward; the patient came with a left breast lump and was diagnosed to have an invasive ductal carcinoma (IDC) grade II with hormonal-receptor positive, HER2/neu negative. A modified radical mastectomy (MRM) was done for a pT2pN1 tumor with no distant metastasis. The patient received Adriamycin, Endoxan and Taxol (AC-T) chemotherapy followed by local radiotherapy and hormonal therapy. Now she continues to be free from recurrence or metastasis on her third year of follow-up.

II) HCC followed by TCC of the urinary bladder

A 64-year-old male patient had a history of being diagnosed with HCC on top of liver cirrhosis treated with transarterial chemoembolization (TACE). Two years later, in May 2021, he presented with hematuria; therefore, a cystoscopy with transurethral resection (TUR) revealed high-grade transitional cell carcinoma (TCC) of the bladder with lamina propria invasion T2.

Multi-slice pelvi-abdominal computed tomography (MSCT) for staging purposes showed porta-hepatic and peri-hepatic lymph nodes, and ultra-sonographic (U/S) guided biopsy from the porta hepatic lymph node showed poorly differentiated adenocarcinoma. The immunohistochemical analysis was positive for Hep-Par so confirmed the diagnosis of recurrent hepatocellular carcinoma with an α-fetoprotein up to 3394.7 ng/ml. Now the patient is under neoadjuvant chemotherapy cisplatin - gemcitabine to bladder cancer with a partial response at mid-cyclic assessment. Regarding the progressed HCC, the patient was subjected to supportive care due to the unavailability of immunotherapy or biologics in our local treatment protocols.

III) Renal cell carcinoma followed by breast cancer

A 53-year-old female patient presented with an accidentally discovered left renal mass on MSCT pelvi-abdomen. The biopsy showed clear cell adenocarcinoma; therefore, left radical nephrectomy was carried out followed by surveillance. Two years later, on the annual follow-up, a right breast with multiple axillary lymph nodes were detected on clinical examination. Sono-mammography identified a mass 2x5 cm with micro-calcification and multiple ipsilateral axillary lymph nodes with malignant features. The histopathological analysis confirmed the diagnosis of IDC grade II with hormonal receptors and HER2/neu negative, right MRM was done for pT2pN2M0 tumor followed by adjuvant chemotherapy AC-T and local radiotherapy. The patient is free till the last follow-up visit while is kept under meticulous follow-up every three months for the breast cancer by the clinical examination with conventional imaging, and annually for the renal carcinoma using the abdominal MSCT.

IV) Basal cell carcinoma followed by Hodgkin's disease

A 70-year-old male patient presented with a skin lesion at the scalp; his clinical examination showed a malignant featuring ulcer which was confirmed to be basal cell carcinoma on histopathology treated by radical surgery followed by local radiotherapy. On his first annual follow-up visit, the patient presented with a history of persistent abdominal pain of two-months duration. MSCT pelvi-abdomen revealed abdominal lymphadenopathy in the para-aortic, porta-hepatis, and iliac lymph nodes. The biopsy revealed Non-Hodgkin lymphoma (NHL) positive for CD3, CD10 and CD20 with a whole-body CT showing cervical, abdominal, and inguinal lymphadenopathies. The patient has been treated as stage III NHL with six cycles Rituximab-CHOP chemotherapy with complete clinical response (CR). Now, the patient is under follow-up for around two years with his bi-annual whole body CT deemed to be free.

V) Hodgkin's disease followed by prostate adenocarcinoma

A 65-year-old male patient presented with a neck swelling; his clinical examination showed multiple enlarged lymph nodes. On biopsy, he was diagnosed as HD nodular sclerosis type case with CD15 +ve, CD30 +ve, and CD20 –ve. A whole-body CT showed lymphadenopathy on both sides of the diaphragm (stage III), so the patient received six cycles of ABVD chemotherapy resulting in complete clinical response. The patient was subjected to the standard surveillance strategy, showing during his eighth year of follow-up a history of urinary manifestation in the form of hesitancy and interrupted stream for six-month duration with recently developed acute urine retention for two days. The clinical examination was non-significant regarding the lymphadenopathy but enlarged both lobes of the prostate. Abdominal U/S showed an enlarged prostate with a hypoechoic

mass in the left lobe, subsequently, Prostatic Specific Antigen (PSA) showed more than 100 ng/ml, and a TRUS biopsy detected prostatic adenocarcinoma Gleason Score 8. The bone scan showed an increased tracer uptake in multiple osseous lesions which confirmed the diagnosis of metastatic hormone naive prostate cancer. The patient received local radiotherapy on the painful bony lesions and was commenced on androgen deprivation therapy in the form of anti-androgen for one-month duration followed by LH-RH agonist with serial follow-up of his testosterone and PSA levels. Following three months of treatment, the patient achieved the medical castrate level with PSA level approaches to the normal with maintained good objective and subjective response till the last follow-up visit.

VI) Breast cancer with a history of exposure to Tamoxifen for about ten years followed by an endometrial carcinoma

A 60-year-old female patient presented in 2021 with vaginal bleeding. Dilatation and curettage (D&C) and histopathology revealed high-grade endometrium adenocarcinoma. MRI pelvi-abdomen showed an endometrial thickening with enhancement in the myometrium but no enlarged pelvic or abdominal lymph nodes. The patient had a history of T2N1M0 right breast cancer dated 13 years backward. The patient had undergone MRM followed by chemotherapy in the form of 6 cycles of FAC regimen and local radiotherapy, then hormonal treatment in the form of Tamoxifen for ten years while being disease-free during her regular follow-up visits. Now the patient will be subjected for radical surgical resection of the uterine mass followed by adjuvant treatment when indicated.

CASES PRESENTATION - SYNCHRONOUS CASES

I) TCC of the urinary bladder and accidentally discovered prostate cancer

A 63-year-old male patient presented with hematuria and dysuria. Clinically the patient was free except for enlarged prostate on digital rectal examination. The cystoscopy showed multiple inter-vesical growths with enlarged prostate with a suspicious malignant mass within the left lobe, and the TUR biopsy revealed T3 high-grade TCC. MRI pelvi-abdomen detected the urinary bladder mass T3N1M0 along with malignant featuring enlarged prostate gland. Metastatic work-up was non-significant; following the patient counseling about different treatment options, radical cystectomy (urinary bladder, prostate, and seminal vesicles) was his preference. The postoperative histopathological analysis confirmed the diagnosis of synchronous MPMs in the form of TCC of the urinary bladder and adenocarcinoma of the prostate with Gleason score (GS) 7, positive for PSA by IHC. Following the radical surgery, the PSA became 0.05 ng/ml. Now the patient is under adjuvant concurrent chemo-radiotherapy for the bladder cancer

II) Breast cancer and high-grade serious carcinoma of the ovary

A 68-year-old female patient presented in November 2020 with a left breast lump. Sono-mammography showed a para-areolar mass heterogeneous hypoechoic with microcalcification with multiple axillary lymph nodes. The biopsy result was IDC grade II, hormonal receptors positive and HER2/neu –ve; the patient was diagnosed with T2N1 left breast cancer. On metastatic workup, the MRI pelvi-abdomin revealed peritoneal deposits and omental thickening, while other imaging workup showed normal. Tumor markers were shooting for both CA-125 and CA15-3, so a biopsy from the peritoneal deposit was taken and revealed high grade serious cystadenocarcinoma. The patient diagnosed to have synchronous stage III ovarian cancer and left breast cancer. The IHC evaluation of the peritoneal deposit biopsy did confirm the diagnosis of two primary tumors and excluded the Krukenberg tumor; it was WT1 +ve and GATA3 –ve. The patient received 6 cycles of chemotherapy in the form of carboplatin and taxol weekly as a common regimen for both breast and ovarian cancer in the neoadjuvant setting. Left MRM was done; biopsy showed complete pathological response and local radiotherapy was arranged while the patient was commenced on hormonal adjuvant treatment. Regarding primary ovarian cancer, on follow-up imaging there was partial response with a steady decline in the level of CA-125, so radical resection was arranged.

DISCUSSION

It has been thought that the incidence of MPMs is rare while recent reports[5,6] show that the diagnosis of MPMs is steadily increasing due to the recent advances in diagnostic modalities resulting in intensifying the ability to detect tumors at an early

stage. In addition to that, the improvements in cancer treatment led to prolonged survival of cancer patients; therefore, the chance of occurrence of multiple cancers rises. The etiology of second primary malignancy varies from the well-documented treatment-related secondary cancers as a complication of chemotherapeutic, hormonal, and radiation modalities to familial cancer syndromes that increase the probability of multiple primary cancer sites. It is imperative to highlight the underlying familial hereditary syndromes or the common etiologies for different tumors to triage high-risk patients and strictly follow up with them.

Having cancer by default increases the risk of MPMs by 14-20%[8,9]. The exact mechanism of development of MPMs has not been clarified despite many factors are related including non-modifiable risks like advanced age, genetic factors, and preventable ones as environmental pollutions, viruses, and smoking. Chemotherapy and radiotherapy, and possibly hormonal treatment used in the management of the previous tumor, are solely related to the metachronous MPMs as for our case of endometrial cancer following long term exposure to Tamoxifen in a postmenopausal woman. It prioritizes the thorough follow-up of cancer patients within a well-structured survivorship program and mandates the respectful approach to the patients' symptoms[10,12].

There are no standard guidelines for the MPMs treatment, so an individualized treatment approach should be applied according to the type, stage of each tumor, patient performance status, and previous response to the treatment. The radical strategy for curable tumors is indicated, while the palliative approach is another choice if the radical treatment is not feasible for one or both tumors[13,16]. In case of synchronous MPMs, it is recommended to start treatment of the most aggressive one, as it has shown that synchronous MPMs are associated with a significant reduction in the overall survival when compared to the metachronous MPMs[17,18]. That was true for our case series, as all cases presented with metachronous tumors were successfully treated for their primary tumor and continued to be free of disease till the appearance of the second primary. Thanks to the meticulous follow-up for our patients, the second primary tumors were detected in an early stage resulting in a feasible radical treatment with an excellent outcome. In both synchronous cases, they had presented with an advanced stage for one of the two primary tumors, which would jeopardize their survival outcome even in the best treatment scenarios. This case series represents the rare co-existence of liver and bladder cancer, kidney and breast, skin and NHL, HD, and prostate cancer. To our knowledge these presentations of MPMs were not described before in the literature. Having these rare second malignancies at a considerable high incidence clarifies the importance of tackling the clinical complaints of our cancer survivors as they are at an increased risk to develop tumors more than the general population and those secondary tumors have no anatomical preference. All cases were not associated with familial history of cancer, albeit the genetic testing for the possibility of hereditary cancer or the underlying germline mutations were not available, yet highly indicated. The fact that all patients were not metastatic for the primary or the second tumor highlights the importance of the meticulous follow-up of patients; therefore, the second primary tumor is to be discovered at early stages and treated on a radical basis. These results confirm that each tumor has its own behavior; although the primary tumor in most cases was not metastatic, not recurred a second primary tumor was diagnosed independently.

CONCLUSIONS

The incidence of second tumor is not a rare condition and can occur either metachronously or synchronously. The detection of second tumor increases due to the progress in diagnosis and treatment modalities. MPMs diagnosis should not be neglected and misdiagnosed as metastasis from the primary one. Therefore, a careful monitoring of patients with primary tumor is very important for early detection of second tumor at a curable stage.

Conflict of Interest:
There are no conflicts of interest.

Consent for publication:
A written informed consent was obtained from each patient for publication of either case.

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