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Case Report

Double Trouble: A Case of Synchronous Breast and Renal Malignancies Associated with ATM Gene Mutation in a 41-Year-Old Filipino Female

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Abstract

Introduction: While renal cell carcinoma is the most common malignancy of the kidneys, and breast canceris the leading type of malignancy in females, simultaneous diagnosis of both these malignancies in a patientis rare. In literature search, synchronous breast and renal malignancies were mostly presented in case reports due to its uncommon presentation.

Case Report: We report a case of a 41-year old Filipino female who initially complained of a right breastmass with nipple discharges. Breast ultrasound showed an irregular hypoechoic mass at the upper outer quadrant of the right breast measuring 7cm with equivocal/indeterminate features. Core needle biopsy was done revealing invasive mammary carcinoma, no special type, Black's Nuclear Grade 2, Luminal A ER/PR(+) Her2Neu(-). Upon metastatic work-up, an incidental finding of a large left renal mass on ultrasonography was seen and confirmed by whole abdominal computed tomography scan measuring 10.6x7.7x8cm. No urinary tract symptoms were experienced by the patient. Patient eventually had full course sequential neoadjuvant chemotherapy (4 cycles Doxorubicin/ Cyclophosphamide and 4 cycles Docetaxel) then underwent total mastectomy with axillary lymph node dissection (ALND) followed by leftradical nephrectomy in a single setting. Final histopathology report revealed Invasive Mammary Carcinoma PST IIIA (T2N2M0) no special type, Nottingham histologic Grade 3 and conventional Renal Clear Cell Carcinoma St II (T2aN0M0), Furhman Nuclear Grade 2. Genetic Testing was done with mutation in ATMgene.

Conclusion: The importance of holistic treatment in cancer patients cannot be over-emphasized. Complete history, physical examination and proper work up at the onset is of paramount importance in identification of possible synchronous malignancies. which may be treated simultaneously with curative intent.

Keywords: Breast Cancer, Renal Cell Carcinoma, Synchronous malignancy, Multiple primary malignancy

Introduction

Despite the increasing number of cases of multiple primary malignancies, synchronous breast and renal cancer remain rare. Synchronous malignancies are malignant tumors occurring atthe same time or within six months of diagnosis of the first tumor[1]. The identified tumors must present a definite picture of malignancy, each should be distinct, and the probability of one beinga metastasis should be ruled out.

In the Philippines, breast cancer remains the leading type of malignancy in females[2]. On the other hand, renal cell carcinoma is the most common tumor of the kidney. When taken individually, these two disease entities are common. However, renal and breast cancer occurring together in a patient is a rare disease entity. Most studies of synchronous breast and renal cancer were described in case reports or small series. Approach, treatment and outcomes of concurrent renal and breast cancer are still uncertain due to the rarity of the disease and limited reports in theliterature.

We report a case of a 41-year old female who presented with a right breast mass with findings of invasive mammary carcinoma on core needle biopsy with an incidental finding of a large left renal mass on whole abdomen ultrasound and computed tomography. Patient underwentright total mastectomy with axillary lymph node dissection (ALND) and left radical nephrectomy.Final histopathologic report of the left renal mass revealed renal clear cell carcinoma.

Case Report

A 41-year old G4P4(4004), 5 months post-partum, breast feeding mother noted a palpablebreast mass at the upper outer quadrant of her right breast. A month after, she noted progressive growth of the mass associated with breast discomfort and serosanguinous discharges from her right nipple. Patient then consulted with her Obstetrician-Gynecologist. Initial breast ultrasound was requested revealing multiple lesions seen from the 9 o'clock position all the way to the two o'clockposition of the upper outer quadrant of the right breast, the largest measuring 4.1x3cm, some with benign sonographic characteristics and some are categorized as equivocal/indeterminate. Ultrasound of the contralateral left breast was unremarkable. She was then referred to a breast surgeon for further management. The patient has no known co-morbidities, a non-smoker, non- alcoholic beverage drinker with no history of illicit drug use. There is a family history of hypertension on both maternal and paternal side and type 2 diabetes on the maternal side. However,no family history of malignancy was reported in her 1st and 2nd degree relatives. Oral contraceptiveuse for 1 month was documented years prior.

Upon examination, a breast mass was noted at the upper outer quadrant of the right breast,fixed, hard, approximately more than 5cms almost occupying the whole nipple areolar complex with sanguinous discharges from the nipple. No skin changes or ulcerations were noted. An accessory breast was palpated at the right axilla with multiple enlarged fixed matted nodes. Clinicalexamination on the contralateral left breast and axilla were unremarkable. No palpable mass or nodes noted. Bedside ultrasound was done showing a 7cm irregular hypoechoic mass at the upperouter quadrant of the right breast with equivocal/indeterminate features (Figure 1).

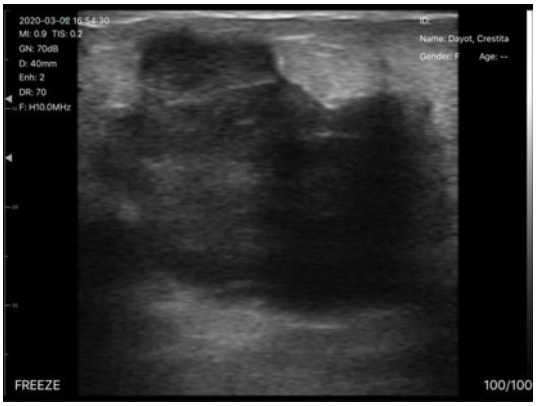

Figure 1: *Ultrasound of right breast mass prior to neoadjuvant chemotherapy showing a 7cm irregular hypoechoic mass at the upper outer quadrant of the right breast.*

Core needle biopsy of the right breast mass was done revealing invasive mammary carcinoma Stage cIIIA (T3N2M0), no special type, Black's Nuclear Grade 2, hormone receptor status Luminal A ER/PR(+) Her2Neu(-). Fine needle aspiration biopsy of the right axillary nodesshowed reactive lymphadenitis.

On metastatic workup, whole abdomen ultrasound showed an incidental finding of a largeleft renal mass. The patient had no associated urinary tract symptoms. Abdominal exam was also unremarkable with no palpable mass. Triphasic contrast enhanced computed tomography scan of the whole abdomen revealed a 10.6 x 7.7 x 8 cm well-circumscribed heterogenous left renal massconfined within the capsule extending to the central sinus and compressing the collecting system.Serum creatinine (0.62mg/dL) and other laboratories were normal.

Full course sequential neoadjuvant chemotherapy with 4 cycles of Cyclophosphamide + Doxycycline every 21 days followed by 4 cycles of Docetaxel every 21 days was done after referralto a medical oncologist. Partial response to therapy was noted (Figure 2).

Interval contrast enhanced computed tomography scan of the whole abdomen was done 2 months after showing no significant interval change in size of the renal mass 10.0 x7.8x7.5cm (previously 10.6 x 7.7 x 8 cm). (Figure 3)

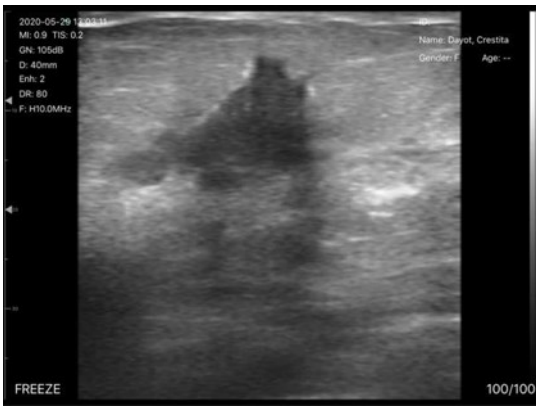

Figure 2: *Ultrasound of right breast mass during Neoadjuvant Chemotherapy showing a decrease in the size of the mass and partial response to therapy.*

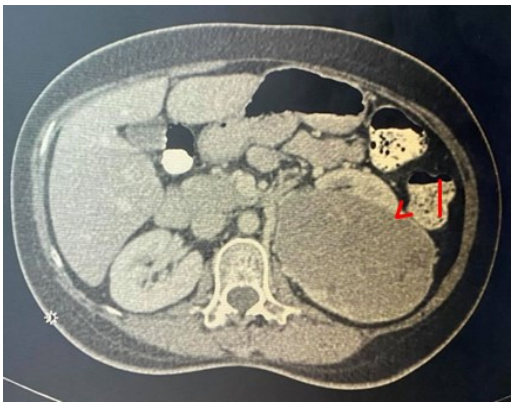

Figure 3: *Oral and triphasic intravenous contrast enhanced axial CT image of the whole abdomen showing a well-circumscribed, heterogenously enhancing left renal mass measuring 10x7.8x7.5cm.*

Patient was scheduled for right total mastectomy with axillary lymph node dissection andleft radical nephrectomy in one setting. She underwent surgery with no complications. Preoperatively, patient was given options for contralateral risk reducing surgery of the left breast but given the added operative time and risks, the patient did not consent.

Final histopathologic report showed right breast tissue post neoadjuvant chemotherapy with partial pathologic response, invasive mammary carcinoma pStIIIA(T2N2M0), no special type, tumor size 4.6cm in widest dimension, Nottingham histologic Grade 3 with peritumoral lymphovascular space invasion. Nipple and basal margin were negative for tumor involvement. 11of the 32 axillary lymph nodes were positive for metastatic carcinoma (Figure 4). Left kidney biopsy revealed conventional renal clear cell carcinoma StII (T2aN0M0), tumor size 9.7 in widestdimension, Furhman Nuclear Grade 2. No peritumoral lymphovascular invasion was noted.Ureteral line of resection and renal vessels were negative for tumor involvement (Figure 5).

Hormonal therapy with Tamoxifen was started 12 days after surgery and was referred to radio-oncology service one-month post-operation for 25 sessions of radiotherapy as adjuvant therapy for the breast cancer. Surveillance post nephrectomy for Stage II renal Cancer include baseline abdominal imaging (CT scan/ Magnetic Resonance Imaging) within 3-6 months for at least 3 years then annually up to 5 years. No adjuvant chemotherapy is warranted for the renal cancer in this case. Genetic testing was done revealing a mutation in the ATM gene.

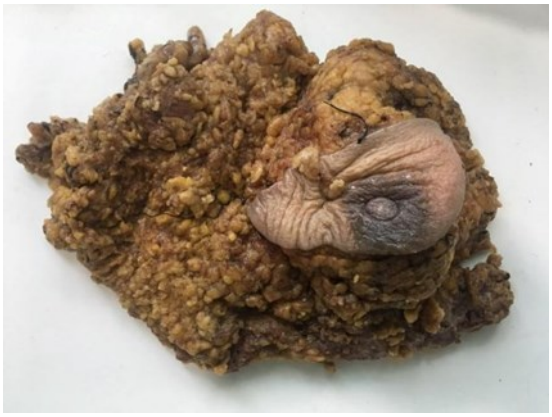

Figure 4: *Photomicrograph of patient's right breast with axillary tissue post mastectomy (soaked in formalin for 24hours).*

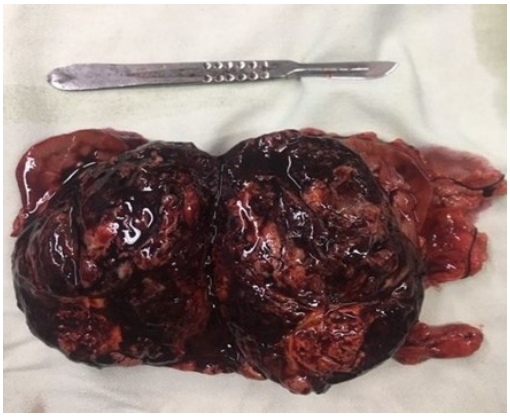

Figure 5: *Photomicrograph of the patient's left renal mass (11x10.5x7.4cm) post radicalnephrectomy.*

Guide 1
Invasive breast cancer stages

Stage 1	Stage 1A	• T1, N0, M0
	Stage 1B	• T0, N1mi, M0 • T1, N1mi, M0
Stage 2	Stage 2A	• T0, N1, M0 • T1, N1, M0 • T2, N0, M0
	Stage 2B	• T2, N1, M0 • T3, N0, M0
Stage 3	Stage 3A	• T0, N2, M0 • T1, N2, M0 • T2, N2, M0 • T3, N1, M0 • T3, N2, M0
	Stage 3B	• T4, N0, M0 • T4, N1, M0 • T4, N2, M0
	Stage 3C	• Any T, N3, M0

NCCN Guidelines for Patients®:
Invasive Breast Cancer, 2020 11

Table 1: Breast Cancer Staging based on National Comprehensive Cancer Network(NCCN) Guidelines.

T = Tumor Size		
	T1	Tumor is 2cm or less
	T1mi	Tumor is micrometastasis of 2 mm or less
	T2	Tumor is 2.1cm to 5 cm
	T3	Tumor is more than 5 cm
	T4	Tumor is of any size and has invaded nearby structures such as the chest wall and skin of the breast
	T4d	Inflammatory carcinoma
N – Regional Lymph Node Spread		
	N0	No cancer in the regional lymph node
	N1, N2, N3	Regional lymph node metastases are found
	N1mi	Micrometastases are found in the lymph nodes
M= Metastasis		
	M0	No distant Metastasis
	M1	Distant metastasis found

Table 2: American Joint Committee on Cancer (AJCC), TNM Staging for Kidney Cancer.

T = Primary Tumor		
TX		Primary Tumor cannot be assessed
T0		No evidence of Primary Tumor
T1		Tumor less than or equal to 7cm in greatest dimension, limited to the kidney
	T1a	Tumor less than or equal to 4cm in greatest dimension, limited to the kidney
	T1b	Tumor >4cm but less than or equal to 7cm in greatest dimension, limited tothe kidney
T2		Tumor > 7cm in the greatest dimension, limited to the kidney
	T2a	Tumor > 7cm but less than and equal to 10cm in greatest dimension, limitedto the kidney
	T2b	Tumor >10cm, limited to the kidney
T3		Tumor extends into major veins or perinephric tissues, but not into theipsi-lateral adrenal gland and not beyond Gerota's fascia
	T3a	Tumor extends into the renal vein or its segmental branches, or invades thepelvi-calyceal system, or invades perirenal and/or renal sinus fat but not beyond Gero-ta's fascia
	T3b	Tumor extends into the vena cava below the diaphragm
	T3c	Tumor extends into the vena cava above the diaphragm or invades the wallof the vena cava
T4		Tumor invades beyond Gerota's fascia (including contiguous extension intothe ipsi-lateral adrenal gland
N = Regional Lymph Nodes		
NX		Regional lymph nodes cannot be assessed
N0		No distant Metastasis
N1		Metastasis in the regional lymph node(s)
M = Distant Metastasis		
M0		No distant Metastasis
M1		Distant Metastasis

Table 3: AJCC Prognostic Groups.

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1-T2	N1	M0
	T3	Nx, N0-N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Discussion

Multiple primary malignancies (MPM) occurring concurrently in the same patient is an established phenomenon. It is defined as two or more malignancies with distinct characteristics occurring in the same or other organ of an individual patient[3]. Prevalence of multiple primary malignancies is about 4.5-11.7%, according to literature review on 1, 104 269 cancer patients[4]. MPM can be divided into synchronous malignancies and metachronous malignancies.Synchronous malignancies are malignant tumors occurring at the same time or within six monthsof diagnosis of the first tumor. The case reported fits this criteria since the renal mass was diagnosed within 6 months after the diagnosis of breast cancer. Those that do not fit the definitionare classified as metachronous malignancies[5]. The widely accepted criteria in diagnosing MPM was established by Warren and Gates. Each tumor must be histopathologically confirmed; each isgeographically separated, by normal mucosa, and distinct; and; the probability of one being a metastasis of the other must be omitted[1]. The presented case fulfilled the criteria and is classifiedas synchronous malignancies. For our patient, Tumors of the digestive system were the most common multiple primary malignant tumors (39.1%), followed by urogenital system and respiratory system tumor[6].

The co-existence of renal malignancy with synchronous or metachronous tumor of other organs have been reported[7 8 9], similar to the association of breast cancer with other malignancies[10]. On the other hand, studies and literature discussing synchronous breast and renal cancer have been presented mostly in case reports and small case series due to its rarity. In a report by ArjunanR et.al., a 45-year old female came in with complains of abdominal pain and loss of appetite. Examination of the abdomen and pelvis was unremarkable, however, a mass on the right breast and enlarged lymph node were noted on the breast exam. Imaging studies showed a right breast mass. Subsequently, a mass on the right kidney was incidentally identified in the metastatic workup for the breast mass. Right modified radical mastectomy with right radical nephrectomy was done in a single setting. Histopathology reports of the right kidney and breast revealed papillary Renal Cell Carcinoma (RCC) with aggregates of foamy macrophages, Fuhrman nuclear grade IIIand grade III invasive ductal carcinoma, no special type, respectively[5]. Another case was reportedby Üreyen O et. al., a 77-year old menopausal woman who complained of left breast mass with axillary lymphadenopathy. Work up, including ultrasono graphy, mammography and biopsy of theleft breast, revealed invasive ductal carcinoma. The same as the previous case, an incidental finding of a left kidney mass was seen in abdominal computed tomography scan for metastasis workup. In this case, breast conserving surgery and axillary lymph node dissection was performed first, followed by partial nephrectomy 4 weeks later. Histopathology report demonstrated invasive ductal carcinoma and clear cell-renal carcinoma[11].

In 2005, a study reported a 26% prevalence of synchronous breast cancer with renal cell carcinoma[9]. However, later study by Jiao F et. al reported eight cases of co-existing renal and breast cancer with lower prevalence of 13.1%[3]. In a study conducted by Sas-Korczyńska B et. al.,3 out of 112 breast cancer patients had concurrent renal malignancy[10].

In literature, the etiology of multiple primary malignant tumors includes genetic predisposition, previous medical treatment (radiotherapy or chemotherapy), environmental factors (tobacco, pollution, occupation,), gender-specific factors, hormonal factors, and interactions of these factors[9]. There were studies implicating the role of hormone-estrogen receptor complex in development of renal cancer. In a study by Di Silverio F et. al., 17 cases of renal cell carcinoma were associated with other primary tumors of steroid hormone target tissues such as breast, endometrium and ovary[12]. Close association of estrogen receptor genes with renal cell carcinomawas established in a study by Liu Z et. al.[13]. As investigated by Tanaka Y et. al., development ofrenal malignancy and aneuploidy in cells were seen in Syrian hamsters exposed to estrogen[14]. These studies recommend the need for further investigation of the role of endocrine manipulation in renal cell carcinoma that may bridge to the understanding of the occurrence of synchronous breast and renal malignancies such as in our case.

In this case, genetic testing was done reavealing a mutation in the ATM gene. The Ataxia-Telangiectasia Mutated (ATM) gene is an oncosuppressor found in chromosome 11q23. The ATMprotein encoded by the gene is involved in DNA repair and activates DNA damage pathways[15]. Ingeneral, the ATM gene is disregulated in a wide range of malignancies. The greatest prevalence include lung adenocarcinoma, colon adenocarcinoma, endometrial endometrioid adenocarcinoma, prostate adenocarcinoma, and bladder urothelial carcinoma. Other malignancies include breast, pancreatic, gastric, renal, and skin cancers[16].

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Conclusion

Patients diagnosed with any malignancy, may it be malignancy of the breast, kidney or other organs, should be properly worked up at the onset. The discovery of multiple primary malignancies, with any etiology, emphasizes the importance of holistic approach to cancerpatients. Synchronous malignancies may be treated simultaneously with curative intent. However,in cases that simultaneous treatment cannot be done, the more aggressive malignancy should be addressed first. In the case of this patient, a synchronous renal malignancy was diagnosed during metastatic work-up for her breast cancer. After full course sequential neoadjuvant chemotherapy showed partial response to treatment, total mastectomy with ALND and radical nephrectomy wasdone with no complications. Postoperatively, patient was managed accordingly with hormonal therapy, radiation therapy, and surveillance for recurrence of the renal cell carcinoma.

Conflict of Interest

The authors declare no conflict of interest.

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