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Concurrent treatment of metastatic breast and metastatic renal cell carcinoma: A case report

Sarah Jane Zardawi, Mathew Kattathra George

ABSTRACT

Introduction: Breast and renal carcinomas are common malignancies, with an increasing number of well-tolerated targeted therapies. Case Report: We describe a case of concurrent, synchronous, metastatic breast and renal carcinomas where diagnosis was achieved after biopsy of two incongruous metastatic sites. The patient has been successfully treated with targeted therapies, exemestane and sunitinib, and later anastrozole and pazopanib, with radiological improvement and resolution of symptoms. Conclusion: Literature review of cases of antecedent, synchronous and metachronous breast and renal cancers (multiple malignancies), did not reveal increased risk of developing renal cancer after breast cancer, or of breast cancer after renal cancer. Cases of multiple breast and renal cancers appear to occur at any time with out clear reasons for their occurrence. This case demonstrates the importance of appropriate investigation and accurate diagnosis of synchronous malignancies in patients who may be candidates for treatment targeted therapies. As clinical experience of concurrent use of targeted therapies grows, including trials for potential additive benefits of using targeted agents in combination, we will be able to offer improved treatment options for patients with both single and multiple malignancies.

Keywords: Multiple malignancies, Targeted therapies

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INTRODUCTION

Metastatic breast and renal carcinomas have an increasing number of well-tolerated, targeted therapies. This has made it possible to effectively treat patients whom otherwise might not have been considered for anti-cancer treatment, including patients with more than one advanced malignancy. This case report explores a patient with concurrent metastatic breast and renal carcinomas who has been treated successfully with two targeted therapies with radiological improvement and resolution of symptoms.

CASE REPORT

A 69-year-old female was incidentally noted to have a suspicious femoral lesion during elective right total knee replacement. This was on a background of a right breast carcinoma treated with mastectomy 35 years prior; a left breast carcinoma treated with partial mastectomy, adjuvant radiation and adjuvant tamoxifen

14 years prior; and a right clear cell renal carcinoma treated with nephrectomy nine years prior. The femoral lesion was biopsied, revealing metastatic oestrogen- and progesterone-receptor positive adenocarcinoma consistent with her prior hormone receptor positive left breast carcinoma (Figure 1 A-C). Staging computed tomography (CT) and FDG positron emission tomography (PET) identified multiple PET-avid lesions consistent with metastases in the pelvis, acetabulum, right femur, sternum, thoracic fifth and eighth vertebrae, and lumbar fifth vertebrae (Figure 2A). There was also a large, non PET-avid, pathological retro caval node, which was not in keeping with a diagnosis of metastatic breast carcinoma (Figure 2B). Biopsy of this node showed metastatic clear cell renal carcinoma consistent with her prior renal carcinoma (Figure 1 D-F).

The patient received palliative radiotherapy to the sternum, thoracic spine, lumbar spine, left ilium and retro caval lymph nodes. She was initially commenced on exemestane and sunitinib and subsequently changed to anastrozole and pazopanib due to gastrointestinal adverse effects.

Restaging CT scan, bone scan, and PET scan have shown radiological response with reduction in size and PET avidity of her metastases. This response was durable for 24 months and associated with good symptom control and functional status. At time of commencement of therapy there was no subsidized access to cyclin-dependent kinase 4/6 inhibitors.

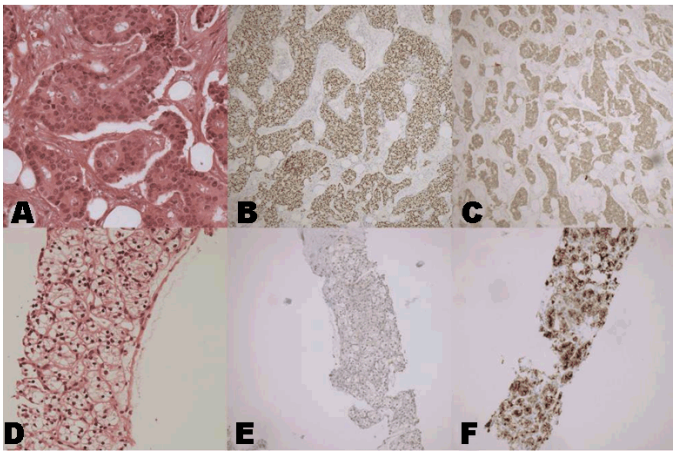

Figure 1(A–F): Histopathology of femoral lesion (A–C). (A) Haemotoxylin and eosin stain showing breast carcinoma metastasis, (B) positive ER stain, (C) positive Her-2 stain. Histopathology of retroperitoneal lesion (D–F). (D) Haemotoxylin and eosin stain showing renal cell carcinoma metastasis, (E) negative ER stain, (F) positive CD10 stain.

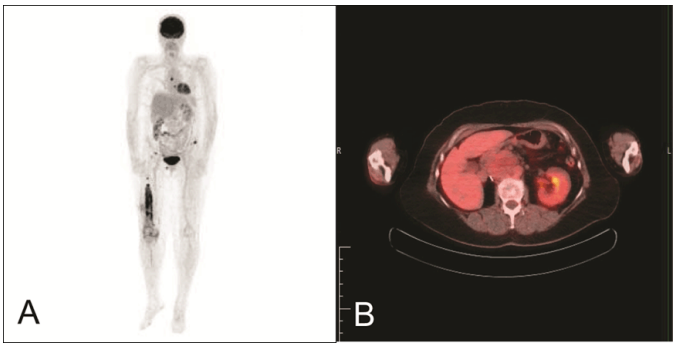

Figure 2(A–B): FDG PET images. (A) PET-CT image showing increased uptake at right femur. (B) PET-CT image showing low glucose avidity in enlarged retroperitoneal nodes.

DISCUSSION

Multiple malignancies are cases of multiple, pathologically distinct malignancies occurring in the one individual. The malignancies are described according to the time of diagnosis relative to the malignancy of interest. Antecedent malignancies occur at least 6 months prior to; synchronous malignancies are detected within six months; and metachronous malignancies are detected greater than six months after the malignancy of interest [1–4]. Antecedent, synchronous and metachronous malignancies are collectively referred to as multiple malignancies. Our case documents synchronous metastatic breast and renal carcinomas. The following discussion is based on a literature review using the PubMed database with the search terms breast carcinoma, breast cancer, renal carcinoma, renal cancer multiple malignancy, antecedent malignancy, synchronous malignancy and metachronous malignancy, as well as review of the references cited in articles retrieved through this search. Both full text articles and abstracts were included.

There are many instances of multiple malignancies involving breast and renal cancer, with previously reported case series listed in Table 1 [2–10]. However, despite these reported occurrences these series do not show an increased risk of developing renal cancer after breast cancer (standard incident ratio (SIR) 0.97–2.40 [2, 5]) or of developing breast cancer after renal cancer (SIR 0.47–2.53 [2–4, 6–9]) compared to the background population risk of developing either malignancy.

The time interval between malignancies in our patient was 26 years between right breast and renal cancer, and 5 years between the left recurring breast and renal cancer. This is similar to the median published time to the development of breast cancer after renal cancer of 5.5–24.2 years [4, 7]. Whilst this is the reverse order of malignancies to our case it highlights that metachronous malignancies can develop at any time.

Published case reports of patients with synchronous breast and renal carcinomas and are described in Table 2 [11–30]. Review of these cases show that it was more common to present with breast cancer (either early or advanced stage) and be diagnosed with a synchronous renal cancer [11–19]. When reported, the renal cell cancer was often a low grade and low stage cancer [11–17], or an incidental autopsy finding [18–19]. Interestingly, there were several cases of breast cancer metastasizing to a

Table 1: Published case series of multiple breast and renal cancers

Case series	Number patients	SIR (95% CI)
Metachronous renal cancer after breast cancer		
Hayat 2007 [2]	370,513 patients breast cancers; 136 cases metachronous renal cancer (antecedent and synchronous cancers renal cancers not reported).	SIR 0.97
Ricceri 2015 [5]	10,045 women breast cancer; 16 cases metachronous renal cancer (antecedent and synchronous cancers excluded).	SIR 2.40, (1.57-3.52)
Metachronous breast after renal cancer		
Kantor 1986 [9]	4,176 patients renal cancer; 18 cases metachronous breast cancer.	Not reported
Rabbani 2000 [8]	763 patients renal cancer; 25 case antecedent breast cancer, 3 cases synchronous breast cancer, 4 cases metachronous breast cancer.	SIR 2.53 (0.69-6.5)
Czene 2002 [6]	23,137 patients renal cancer; 123 cases metachronous breast cancer (antecedent and synchronous breast cancers not reported).	SIR 1.25* (1.04–1.48)
Sato 2004 [7]	319 patients renal cancer; 1 case antecedent breast cancer, 1 case metachronous breast cancer.	Not reported
Bleisland 2006 [3]	14,250 patients renal cancer; 12 cases antecedent breast cancer, 6 cases synchronous breast cancer, 8 cases metachronous breast cancer.	SIR 1.00 (0.43-1.98)
Hayat 2007 [2]	49,632 patients renal cancer; 353 cases metachronous breast cancer (antecedent and synchronous breast cancers not reported).	SIR 0.96
Murray 2015 [4]	3,066 patients renal cancer; 12 cases metachronous breast cancer (antecedent cancers excluded, synchronous breast cancers not reported).	SIR 0.47* (0.24–0.83)
Unspecified		
Jiao 2013 [10]	6,545 patients any malignancy; 5 cases synchronous breast cancer, 8 cases metachronous breast cancer, 1 case metachronous renal cancer.	Not reported

Abbreviations: SIR - standard incident ratio, CI - confidence intervals (when reported), * - $p<0.05$

Table 2: Case reports considering multiple breast and renal carcinomas

Case report	Presentation and treatment	Outcome
Sella 1987 [18]	62 year-old female presented with metastatic breast carcinoma (T2N2M1, IDC). RCC diagnosed at autopsy. Breast carcinoma metastasis to RCC. Further treatment not described.	Not reported
Piccinini 1996 [27]	2 patients with synchronous diagnoses breast carcinoma and RCC. Further treatment not described.	Not reported
Val-Bernal 2001 [19]	75 year-old female presented with metastatic breast carcinoma (T2N0M1, IDC, ER/PR negative, Her2 positive). RCC diagnosed at autopsy. Breast carcinoma metastasis to RCC. Further treatment not described.	Not reported
Van Wynsberge 2004 [15]	64 year-old female presented with recurrent metastatic breast carcinoma (ER positive). Synchronous RCC. Breast carcinoma metastasis to RCC. Further treatment not described.	Not reported
Sachdev 2005 [29]	56 year-old patient synchronous diagnoses breast carcinoma (ER/PR positive) and clear cell RCC (T1aNXMX). Further treatment not described.	Not reported
Moller 2006 [29]	62 year-old female presented with RCC (T1aN0M0, grade I, clear cell) treated with nephrectomy. Synchronous metastatic breast carcinoma (T4N3M1, IDC, ER/PR positive, Her2 negative), treatment of which not described.	Survival 10 months
Perrin 2011 [14]	Patient presented with metastatic breast carcinoma (T2NXM1, IDC, ER/PR/Her2 negative), treatment not described. Synchronous diagnosis RCC (clear cell) treated with nephrectomy.	Not reported
Kurlekar 2014 [13]	57 year-old female presented with breast carcinoma (T2N0M0, ILC, ER/PR positive) treated with modified mastectomy and adjuvant chemotherapy. Synchronous diagnosis RCC (T1bN0M0, grade III, clear cell) treated with nephrectomy.	PFS > 18 months
Ureyen 2015 [12]	77 year-old female presented with breast carcinoma (T2N1M0, IDC, ER/PR positive, Her2 negative) treated with modified mastectomy and axillary clearance, adjuvant radiotherapy and aromatase inhibitor. Synchronous RCC (T1aN0M0, grade III, clear cell) treated with nephrectomy.	PFS > 16 months

Table 2: *(Continued)*

Huo 2015 [16]		43 year-old female presented with metastatic breast carcinoma (IDC, ER/PR positive, Her2 negative) treated with palliative chemotherapy, GNRH agonist and aromatase inhibitor. Synchronous RCC (T1aN0M0, grade II, clear cell) treated with partial nephrectomy. Breast carcinoma metastasis to RCC.	PFS 3 months
Chen 2015 [17]		74 year-old female presented with breast carcinoma (pT2pN0M0, IDC, grade I, ER/PR/Her2 negative). Synchronous metastatic RCC to breast (pT3pN0cM1, grade II, clear cell). Further treatment not described.	Not reported
Mosholt 2015 [30]		71 year-old-female presented with RCC (clear cell). Synchronous metastatic breast carcinoma. Further treatment not described.	Not reported
Arjunan 2016 [11]		45 year-old female presented with breast carcinoma (T2N2Mx, grade III, IDC, ER positive) treated with modified mastectomy and adjuvant chemotherapy. Synchronous diagnosis RCC (pT1N0M0, grade III, papillary carcinoma) treated with nephrectomy.	Not reported
Urdiales-Viedma [20]	2016	71 year-old female presented with RCC (clear cell). Synchronous metastatic breast carcinoma. Breast carcinoma metastasis to RCC. Further treatment not described.	Not reported
Noguchi 2017 [21]		67 year-old female synchronous diagnosis metastatic breast carcinoma (T2N0M1, ILC) treated with hormonal therapy and RCC (T1aN0M0, clear cell) treated with nephrectomy. Breast carcinoma metastasis to RCC	PFS >5 months

Abbreviations: IDC - Invasive ductal carcinoma; ILC – Invasive lobular carcinoma; ER – Oestrogen receptor; PR – Progesterone receptor; Her-2 – human epidermal growth factor receptor 2; RCC – renal cell carcinoma; PFS – progression or disease free survival.

renal cancer, known as tumour-to-tumour metastases [15–21], but no cases of renal cancer metastasizing to a breast cancer. Further, there are no cases like ours that report synchronous metastatic breast and metastatic renal cancers.

Age is a known risk factor for multiple malignancies with one case series of renal cancers documenting that patients with synchronous or metachronous malignancies of any type were five years older than those without a second malignancy (P=0.0072) [8]. Otherwise, the development of second malignancies is thought to be dependent upon lifestyle factors, previous cancer treatments and genetic susceptibilities. For breast and renal cancers, there are common life style risk factors of cigarette smoking and obesity [5, 22–23] but the treatments used for breast and renal cancer are not associated with an increased risk of the other malignancy [24–26], nor are there common inherited genetic conditions. Despite an absence of clear causative reasons for multiple malignancies, as treatment of cancer and other diseases improves it is likely that the incidence of patients with multiple malignancies will increase.

Our patient was commenced on the targetted therapies, exemestane and sunitinib, and subsequently anastrozole and pazopanib for treatment of her metastatic breast and renal carcinomas. Exemestane and anastrozole are aromatise inhibitors that prevent the conversion of circulating oestrogen pre-cursors to oestrogen to reduce exposure of growth promoting oestrogen to breast cancer cells [31]. Sunitinib and pazopanib are tyrosine kinase inhibitors that prevent the activation of vascular endothelial growth factor receptors, platelet derived growth factors and stem cell factor receptor to affect the survival, proliferation, vascularization and metastasis of renal cancer cells [32]. Whilst these therapies have established efficacy for treatment of their respective malignancies, current phase II clinical trials are testing combined use of targeted therapies for potential increased efficacy in post menopausal breast cancer. These trials include the use of pazopanib with an aromatase inhibitor for the neoadjuvant treatment of stage II-III breast cancer [33], and with an aromatase inhibitor following development of resistance in metastatic breast cancer [34]. Such studies may explain why our patient has had such a significant response to treatment (noting that she also had palliative radiotherapy to most sites of disease), as well as offer improved treatment options for patients with both single and multiple malignancies.

Previously multiple malignancies have previously been associated with poorer outcomes. Two case series of renal cancers found that patients with antecedent or synchronous cancers had 5-year survival rates of approximately 30% compared with 50% for patients without a second malignancy [3]. Sato et al also demonstrated that an antecedent or synchronous tumour, like a high pathological stage, was a strong independent poor prognostic factor for overall survival in patients with renal cell cancer [7]. Further, the median survival time was vastly worse for synchronous cancers than for metachronous cancer (3.8 years versus 17.3 years, $p<0.05$) [7], potentially due to the challenges of treating two malignancies at the same time. Fortunately, our patient has had durable response to treatment for 24 months, which may suggest improved outcomes for these patients with targeted therapies.

CONCLUSION

This case demonstrates the importance of appropriate investigation and accurate diagnosis of synchronous malignancies in patients who may be candidates for treatment with multiple targeted therapies, which is a situation that is anticipated to become more common in the future due to improving health outcomes and cancer therapies. As clinical experience of concurrent use of targeted therapies grows, including trials for potential additive benefits of using targeted agents in combination, we will be able to offer improved treatment options for patients with both single and multiple malignancies.

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Conflict of Interest
Authors declare no conflict of interest.