

Metastatic Renal Cell Cancer Presenting as a Breast Mass

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Introduction

Metastases to the breast are uncommon, and demand an accurate and prompt diagnosis due to differences in prognosis and management from primary breast cancer. Here we describe a case of renal cell cancer metastasizing to the breast 10 years after nephrectomy for the primary tumor. Historically, the prognosis for such a patient has been extremely poor. In the era of novel therapies, however, we are now able to provide treatment with an oral agent and achieve an excellent response.

Case Study

A 64-year-old African American woman with a history of left-sided renal cell carcinoma that was treated with nephrectomy 10 years prior presented to us for management of ductal carcinoma in situ (DCIS) of the right breast. A routine mammogram performed 1 year prior revealed indeterminate microcalcifications of the right breast. Further work-up consisting of a stereotactic core biopsy on the right breast revealed the lesion to be DCIS, with a focus of microinvasion. It was estrogen-receptor positive. The patient then noticed a tender mass on the medial side of her left breast. An ultrasound revealed a 1.8-cm lesion consistent with a resolving hematoma versus fat necrosis. The patient recalled an incident involving a seat-belt injury to the left breast a few months prior, and therefore the lesion was considered to be a resolving hematoma.

The patient underwent a right partial mastectomy and sentinel lymph node biopsy. Although there was no node involvement by sentinel node biopsy, she required re-excision on the right side, because pathology revealed

a focus of residual DCIS extending to the lateral resection margin. The 2 sentinel lymph nodes examined were benign. Two weeks after her surgery, the patient complained of increased swelling on the medial side of the left breast. This swelling was re-evaluated by a repeat ultrasound, which showed an unchanged size of the oval mass and mixed echogenicity.

Preoperatively, a chest X-ray revealed a 6-mm right lung nodule, and a computed tomography (CT) scan was recommended for follow-up. The CT scan of the chest, which was performed approximately 3 months after the right lumpectomy, revealed multiple bilateral pulmonary nodules measuring 4–5 mm. Additionally, the lesion in the left breast had increased to 2.7 × 1.9 cm and was suspicious for metastatic disease (Figure 1). The patient then underwent an ultrasound-guided biopsy of the left breast mass (Figure 2), which revealed metastatic clear cell carcinoma compatible with metastases from a primary renal tumor (Figures 3 and 4). The patient had significant discomfort at the site of the left breast mass, so she underwent a left partial mastectomy. Surgical pathology confirmed the diagnosis, which was consistent with metastasis from the primary renal cell carcinoma. The original pathology report from 10 years prior was reviewed. It also revealed a clear cell tumor, Fuhrman grade 3, with negative surgical margins; there was tumor penetrating beyond the renal capsule.

The patient was subsequently started on pazopanib (Votrient, GlaxoSmithKline) as systemic therapy for her metastatic renal cell cancer, as well as anastrozole (Arimidex, AstraZeneca) as adjuvant hormonal therapy for breast cancer. Adjuvant radiation therapy was started 4 weeks after surgery on her left breast. She received 30 Gy in 10 twice-daily fractions to the left breast tumor bed and 38.5 Gy in 10 twice-daily fractions to the right breast. The total dose of radiation given to the left side was 3,000 cGy, and the total dose to the right side was 3,850 cGy. Her pain improved significantly after surgery and radiation. Four months after the initiation of pazopanib, an enhanced CT scan of the

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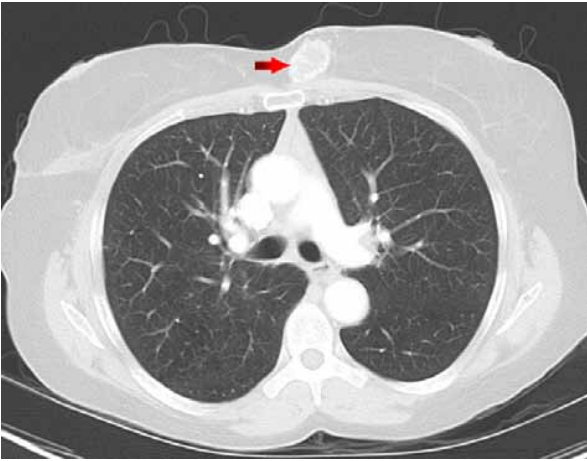


Figure 1. A computed tomography scan of the chest revealed that the lesion in the left breast had increased to 2.7×1.9 cm (arrow) and was suspicious for metastatic disease.

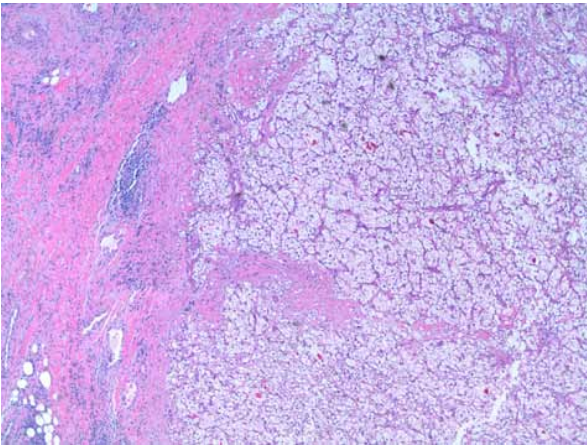


Figure 3. The metastatic clear cell carcinoma was compatible with metastases from a primary renal tumor (low power).

chest, abdomen, and pelvis revealed an interval decrease in size of the right lower lobe pulmonary nodule, resolution of previously seen smaller nodules, and no evidence of recurrent or metastatic disease elsewhere. The patient required 1 dose reduction of pazopanib due to diarrhea. Since then, she has been tolerating the therapy well.

Discussion

The breast is an uncommon site for metastatic deposits. Upon review of the literature, it appears that metastases account for 0.5–6.6% of all malignant tumors in autopsy series and 0.5–1.3% in clinical reports.¹ Approximately 80% of the cases occur in women.² The primitive neoplasms that most frequently metastasize to the breasts—after exclusion of contralateral breast cancer

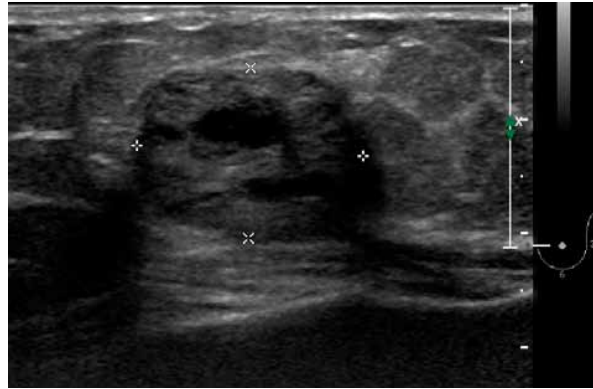


Figure 2. An ultrasound-guided biopsy of the left breast mass revealed metastatic clear cell carcinoma.

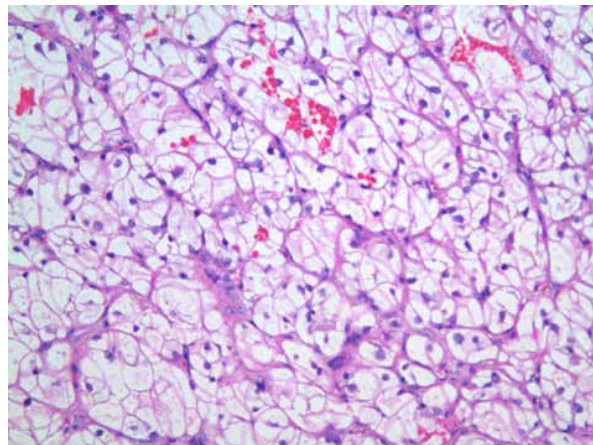


Figure 4. The metastatic clear cell carcinoma was compatible with metastases from a primary renal tumor (high power).

and lymphoma—are, in order of frequency: malignant melanoma, sarcoma, lung cancer, and prostate cancer.² Renal cell cancer has been previously reported to account for 3% of the cases.³ Due to the differences in prognosis and management of breast metastases when compared to primary breast cancer, accurate and prompt diagnosis is of utmost importance.

Metastatic tumors to the breast are frequently described as solitary, discrete, and asymptomatic. Patients tend to present with the typical picture of a rapidly enlarging, painless, palpable breast mass.⁴ Bilateral lesions are uncommon and account for 17% of cases.² The presentation of our patient was unusual because she experienced significant discomfort. Ultrasound scans of breast metastases typically show a heterogeneous, poorly defined, hypoechoic mass.⁴ Again, in the case of our patient, the initial ultrasound examination was nonspecific, and the corresponding history of trauma led to the initial misdiagnosis of a hematoma. This interpretation led to a delay in the diagnostic biopsy.

Summary

After discussion of this case at a multidisciplinary conference, the decision was made to perform a metastasectomy followed by adjuvant radiation therapy, due to the patient's significant discomfort from the metastatic breast mass.⁵ The patient had an excellent recovery after her surgery and tolerated the radiation therapy well. Her pain resolved after the radiation, and she was started on pazopanib.⁶ She has exhibited a good response to pazopanib therapy, with significant reductions in her pulmonary lesions, suggesting that these metastases were from the renal cell cancer as well. Thus far, the patient has done well and continues to tolerate her oral therapy.

Acknowledgment

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References

1. Bortnik S, Cohen DJ, Leider-Trejo L, Ron IG. Breast metastasis from a renal cell carcinoma. *Isr Med Assoc J*. 2008;10:736-737.
2. Forte A, Peronace MI, Gallinaro LS, et al. Metastasis to the breast of a renal carcinoma: a clinical case. *Eur Rev Med Pharmacol Sci*. 1999;3:115-118.
3. Alzarraa A, Vodovnik A, Montgomery H, Saeed M, Sharma N. Breast metastasis from a renal cell cancer. *World J Surg Oncol*. 2007;5:25.
4. Kannan V. Fine-needle aspiration of metastatic renal-cell carcinoma masquerading as primary breast carcinoma. *Diagn Cytopathol*. 1998;18:343-345.
5. Tunio MA, Hashmi A, Rafi M. Need for a new trial to evaluate postoperative radiotherapy in renal cell carcinoma: a meta-analysis of randomized controlled trials. *Ann Oncol*. 2010;21:1839-1845.
6. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061-1068.

Review

Late Recurrences of Renal Cell Carcinoma at Unusual Sites: Implications for Patient Management

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Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all malignancies; it is the 7th most common malignancy in men and the 12th most common malignancy in women.¹ Worldwide, the incidence of RCC is 209,000 cases per year, and it causes 102,000 deaths per year.

In addition, the incidence of RCC is rising at a rate of 2–3% per decade. Approximately 20–25% of patients with RCC are diagnosed with metastasis at initial presentation. Pulmonary, hepatic, and bone metastases are the most common.^{2,3} In metastatic RCC, conventional cytotoxic agents have been ineffective, and systemic cytokine therapies (interleukin 2, interferon) have a response rate of approximately 15–20%. Substantial advances in the field of molecular targeted cancer therapies and enhanced understanding of tumor biology have led to the approval of a number of novel agents that predominantly target the vascular endothelial receptor pathway (sunitinib [Sutent, Pfizer], sorafenib [Nexavar, Bayer/Onyx], pazopanib [Votrient, GlaxoSmithKline], bevacizumab [Avastin, Genentech]) or the mammalian target of rapamycin (mTOR) pathway (temsirolimus [Torisel, Pfizer], everolimus [Afinitor, Novartis]), which are dysregulated in RCC. These agents have significantly improved progression-free survival in patients with metastatic disease, who previously had limited therapeutic options. Consequently, it is important to establish whether or not metastatic deposits at unusual sites are from RCC origin, in order to optimally select therapeutic intervention.

Case Study Discussion

Pathe and colleagues report a case of a 64-year-old woman with ductal carcinoma in situ of the right breast

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who also noticed a mass in the left breast.⁴ The patient had a history of a left nephrectomy for RCC 10 years prior to presentation. Subsequent investigations demonstrated the presence of pulmonary metastases, and showed that the left breast mass was consistent with a metastasis from the renal primary. The patient underwent left mastectomy for palliation of her symptoms and was commenced on pazopanib, which she has continued to tolerate with good clinical response.

This case highlights a number of important points in patient management. Firstly, late recurrence of RCC with the development of metastases at unusual distant sites has been previously reported. With the advent of improved management of potentially curable early disease, there are more long-term survivors of RCC. This could potentially lead to an increase in late recurrence at more unusual metastatic sites. It is estimated that 30% of patients with RCC who undergo nephrectomy with a curative intent eventually develop local disease or metastatic recurrence. The chances of recurrence are considerably higher during the first 5 years following potentially curative treatment.⁵ However, there are now abundant reports in the literature of late recurrences of RCC—arbitrarily defined as recurrence at more than 10 years after nephrectomy—with reports of development of a solitary metastasis as late as 40 years after nephrectomy.⁶ Thus, these patients remain at lifelong risk of recurrence. The most common sites of metastases are similar to early recurrences and consist of pulmonary, hepatic, and bone metastases.⁷ However, late recurrence of RCC, including isolated (single-site) recurrence, have been documented in a number of more unusual sites, including the pancreas,⁸ small intestine,⁹ and breast.

Secondly, the article by Pathe and colleagues reinforces the importance of a histologic diagnosis in the management of patients who present with a breast mass, including those with a history of a contralateral in situ carcinoma.⁴ Metastasis to the breast from extramammary malignancy is rare. Published literature on intramammary metastases, predominantly from large, single-institution, retrospective reviews and case reports, has thus far reported fewer than 500 cases during the last century, and the incidence of intramammary metastases varies from 0.2–1.3% of all breast malignancies.^{10–13} These intramammary metastases are predominantly painless, discrete masses that are discovered incidentally. On mammography, intramammary metastases typically appear as well-circumscribed masses without any spiculation, and are located in the upper outer quadrant. Calcification is rare and noted only in ovarian papillary serous carcinoma.^{10,11,13} However, breast metastases with indistinct margins and spiculation have also been reported.¹⁴ Intramammary metastases usually do not have invasive ductal or in situ components on micro-

scopic examination.¹⁰ Although any malignant tumor can potentially metastasize to the breast, the most frequent solid malignancies that cause intramammary metastases are melanoma, small cell carcinoma of the lung, ovarian carcinoma, and squamous cell carcinoma. Approximately 1–5% of intramammary metastases originate from primary RCC.^{11–13} Histologic diagnosis should be sought in all patients; in cases where there is limited availability of tumor tissue, immunohistochemical diagnosis with validated immunomarkers should be used.^{13,15} A comprehensive clinical history alongside a review of histology from the previous malignancy is essential.

Conclusion

There has been considerable progress in the understanding of the biology of RCC. Nevertheless, many questions remain unanswered, including the appropriate duration of follow-up, the best method of risk stratification of patients for therapeutic intervention, the most appropriate criteria for surgical resection, the optimal choices for targeted agents and their sequencing, and how to overcome drug resistance. Clinicians should always consider that tumor deposits may be metastases from RCC, even if the primary tumor was treated with curative intent many years previously, and even if the metastatic disease arises at unusual sites. Establishing a histologic diagnosis is essential to plan appropriate treatment. The next challenge in cancer medicine is to further refine the selection of patients with a specific tumor type for a specific therapy based on the individual tumor molecular pathology. The development of predictive markers will be a crucial step toward this goal of a personalized medicine approach to patient treatment.

When describing the “soil and seed hypothesis of metastases,” English surgeon Stephen Paget elegantly wrote, “The best work in the pathology of cancer now is done by those who . . . are studying the nature of the seed. They are like scientific botanists, and he who turns over the records of cases of cancer is only a ploughman, but his observations of the properties of the soil might also be helpful.”¹⁶ Observations from the case report described by Pathe and colleagues may not be groundbreaking, but they will nevertheless add to our ever-expanding understanding of the complexities of cancer presentation and its management.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69-90.
2. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet.* 2009;373:1119-1132.
3. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev.* 2008;34:193-205.

4. Pathe N, Raymond J, Cintra AU. Metastatic renal cell cancer presenting as a breast mass. *Clin Adv Hematol Oncol*. 2012;10:124-126.
5. Skolarikos A, Alivizatos G, Laguna P, de la Rosette J. A review on follow-up strategies for renal cell carcinoma after nephrectomy. *Eur Urol*. 2007;51:1490-1501.
6. Shiono S, Yoshida J, Nishimura M, et al. Late pulmonary metastasis of renal cell carcinoma resected 25 years after nephrectomy. *Jpn J Clin Oncol*. 2004;34:46-49.
7. Breda A, Konijeti R, Lam JS. Patterns of recurrence and surveillance strategies for renal cell carcinoma following surgical resection. *Expert Rev Anticancer Ther*. 2007;7:847-862.
8. Kassabian A, Stein J, Jabbour N, et al. Renal cell carcinoma metastatic to the pancreas: a single-institution series and review of the literature. *Urology*. 2000;56:211-215.
9. Sadler G, Anderson M, Moss M, Wilson P. Metastases from renal cell carcinoma presenting as gastrointestinal bleeding: two case reports and a review of the literature. *BMC Gastroenterol*. 2007;7:4.
10. Lee AH. The histological diagnosis of metastases to the breast from extramammary malignancies. *J Clin Pathol*. 2007;60:1333-1341.
11. Surov A, Fiedler E, Holzhausen HJ, Ruschke K, Schmoll HJ, Spielmann RP. Metastases to the breast from non-mammary malignancies: primary tumors, prevalence, clinical signs, and radiological features. *Acad Radiol*. 2011;18:565-574.
12. Vaughan A, Dietz J, Moley J, et al. Metastatic disease to the breast: the Washington University experience. *World J Surg Oncol*. 2007;5:74.
13. Williams SA, Ehlers RA, Hunt KK, et al. Metastases to the breast from nonbreast solid neoplasms: presentation and determinants of survival. *Cancer*. 2007;110:731-737.
14. Noguera JJ, Martínez-Miravete P, Idoate F, et al. Metastases to the breast: a review of 33 cases. *Australas Radiol*. 2007;51:133-138.
15. Truong LD, Shen SS. Immunohistochemical diagnosis of renal neoplasms. *Arch Pathol Lab Med*. 2011;135:92-109.
16. Paget S. The distribution of secondary growths in cancer of the breast. *Lancet*. 1889;133:571-573.