

Enlarging Red Papulonodule on the Chest

Sheila Shaigany, MD; Cory L. Simpson, MD, PhD; Robert G. Micheletti, MD

Eligible for 1 MOC SA Credit From the ABD

This Photo Challenge in our print edition is eligible for 1 self-assessment credit for Maintenance of Certification from the American Board of Dermatology (ABD). After completing this activity, diplomates can visit the ABD website (<http://www.abderm.org>) to self-report the credits under the activity title "Cutis Photo Challenge." You may report the credit after each activity is completed or after accumulating multiple credits.



A man in his 60s presented with a subcutaneous nodule on the right side of the chest. Due to impaired mental status, he was unable to describe the precise age of the lesion, but his wife reported it had been present at least several weeks. She recently noted a new, bright red growth on top of the nodule. The lesion was asymptomatic but seemed to be growing in size. Physical examination revealed a 3-cm firm fixed nodule on the right side of the chest with an overlying, exophytic bright red papule. No similar lesions were found elsewhere on physical examination. A punch biopsy of the lesion was performed.

WHAT'S THE DIAGNOSIS?

- a. angiosarcoma
- b. bacillary angiomatosis
- c. Kaposi sarcoma
- d. metastatic renal cell carcinoma
- e. pyogenic granuloma

PLEASE TURN TO **PAGE 117** FOR THE DIAGNOSIS

Dr. Shaigany is from the Department of Dermatology, New York University Hospital, New York. Drs. Simpson and Micheletti are from the Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia. Dr. Micheletti also is from the Department of Medicine. The authors report no conflict of interest.

Correspondence: Robert G. Micheletti, MD, Department of Dermatology, Hospital of the University of Pennsylvania, 3600 Spruce St, 2 Maloney Bldg, Philadelphia, PA 19104 (Robert.Micheletti@uphs.upenn.edu).

THE DIAGNOSIS:

Metastatic Renal Cell Carcinoma

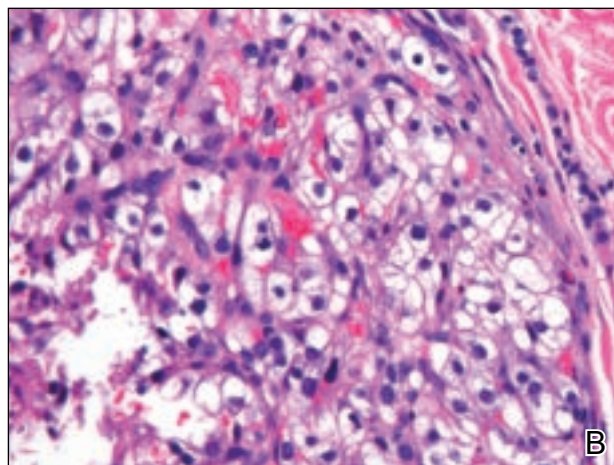
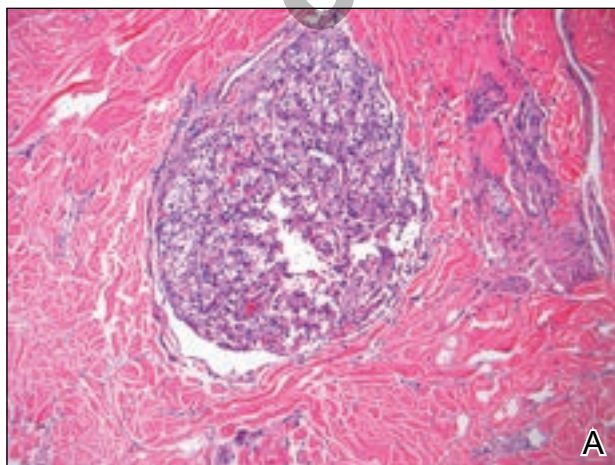
Histopathologic examination of the punch biopsy demonstrated epithelioid cells with abundant clear cytoplasm and numerous chicken wire–like vascular channels consistent with a diagnosis of cutaneous metastasis of renal cell carcinoma (RCC) (Figure). Collateral history revealed that 8 years prior, the patient had been diagnosed with clear cell RCC, stage III (T3aN0M0). At that time, he was treated with radical nephrectomy, which was considered curative. He remained disease free until several months prior to the development of the cutaneous lesion when he was found to have pulmonary and cerebral metastases with biopsies showing metastatic RCC. He was treated with lobectomy and Gamma Knife radiation for the lung and cerebral metastases, respectively. His oncologist planned to initiate therapy with the multikinase inhibitor sunitinib, which inhibits vascular endothelial growth factor (VEGF) signaling. Unfortunately, the patient died prior to treatment due to overwhelming tumor burden.

Clear cell RCC, the most common renal malignancy, presents with metastatic disease at the time of diagnosis in 21% of patients.¹ An additional 20% of patients with localized disease develop metastases within several years of receiving a nephrectomy without adjuvant therapy, which is standard treatment for stage I to stage III disease.^{1,2} Metastatic RCC most frequently targets the lungs, bone, liver, and brain, though virtually any organ can be involved. Cutaneous involvement is estimated to occur in 3.3% of RCC cases,³ accounting for only

1.4% of cutaneous metastases overall.⁴ The risk for developing cutaneous metastases is greatest within 3 years following nephrectomy.³ However, our patient demonstrates that metastasis of RCC to skin can be long delayed (>5 years) despite an initial diagnosis of localized disease.

Cutaneous RCC classically presents as a painless firm papulonodule with a deep red or purple color due to its high vascularity.⁴ Several retrospective studies have identified the scalp as the most frequent site of cutaneous involvement, followed by the chest, abdomen, and nephrectomy scar.^{3,4} The differential diagnosis includes other vascular lesions such as pyogenic granuloma, hemangioma, angiosarcoma, bacillary angiomatosis, and Kaposi sarcoma. Diagnosis usually is easily confirmed histologically. Proliferative nests of epithelioid cells with clear cell morphology are surrounded by delicately branching vessels referred to as chicken wire–like vasculature. Immunohistochemical studies demonstrate positivity for pan-cytokeratin, vimentin, and CD-10, and negativity for p63 and cytokeratins 5 and 6, helping to confirm the diagnosis in more challenging cases, especially when there is no known history of primary RCC.⁵

If cutaneous metastasis of RCC is diagnosed, a chest and abdominal computed tomography scan as well as serum alkaline phosphatase test are warranted, as up to 90% of patients with RCC in the skin have additional lesions in at least 1 other site such as the lungs, bones, or liver.³ Management of metastatic RCC includes surgical excision if a single metastasis is found and



Punch biopsy of the lesion revealed a mass of clear epithelioid cells filling the lumen of a lymphatic vessel within the dermis (A) (H&E, original magnification $\times 10$). Tumor histology demonstrated epithelioid cells with abundant clear cytoplasm and numerous vascular channels (B) (H&E, original magnification $\times 40$).

either immunotherapy with high-dose IL-2 or an anti-programmed cell death inhibitor. Patients with progressive disease also may receive targeted anti-VEGF inhibitors (eg, axitinib, pazopanib, sunitinib), which have been shown to increase progression-free survival in metastatic RCC.⁶⁻⁸ Interestingly, some evidence suggests severely delayed recurrence of RCC (>5 years following nephrectomy) may predict better response to systemic therapy.⁹

This case of severely delayed metastasis of RCC 8 years after nephrectomy raises the question of whether routine surveillance for RCC recurrence should continue beyond 5 years. It also underscores the need for further studies to determine the utility of postsurgical adjuvant therapy for localized disease (stages I–III). A randomized clinical trial showed no significant difference in disease-free survival when the multikinase inhibitors sunitinib and sorafenib were used as adjuvant therapy.¹⁰ The randomized, placebo-controlled PROTECT trial showed no significant difference in disease-free survival between the VEGF inhibitor pazopanib and placebo when used as adjuvant therapy.¹¹ However, trials are ongoing to investigate a potential survival advantage of adjuvant therapy with the VEGF receptor inhibitor axitinib and the mammalian target of rapamycin inhibitor everolimus.

REFERENCES

1. Dabestani S, Thorstenson A, Lindblad P, et al. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. *World J Urol*. 2016;34:1081-1086.
2. Ljungberg B, Campbell SC, Choi HY, et al. The epidemiology of renal cell carcinoma. *Eur Urol*. 2011;60:615-621.
3. Dorairajan LN, Hemal AK, Aron M, et al. Cutaneous metastases in renal cell carcinoma. *Urol Int*. 1999;63:164-167.
4. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Acad Dermatol*. 1993;29(2, pt 1):228-236.
5. Sariya D, Ruth K, Adams-McDonnell R, et al. Clinicopathologic correlation of cutaneous metastases: experience from a cancer center. *Arch Dermatol*. 2007;143:613-620.
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.
7. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:3584-3590.
8. Rini BI, Grunwald V, Fishman MN, et al. Axitinib for first-line metastatic renal cell carcinoma (mRCC): overall efficacy and pharmacokinetic (PK) analyses from a randomized phase II study. *J Clin Oncol*. 2012;30(suppl). doi:10.1200/jco.2012.30.15_suppl.4503.
9. Ficarra V, Novara G. Characterizing late recurrence of renal cell carcinoma. *Nat Rev Urol*. 2013;10:687-689.
10. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial [published online March 9, 2016]. *Lancet*. 2016;387:2008-2016.
11. Motzer RJ, Haas NB, Donskov F, et al; PROTECT investigators. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma [published online September 13, 2017]. *J Clin Oncol*. 2017;35:3916-3923.