A Case of Cutaneous Metastatic Renal Cell Carcinoma to the Scalp

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Abstract
Renal cell carcinoma (RCC) is the most common malignant genitourinary cancer in adults. It has been shown to be resistant to chemotherapy and radiation and can metastasize to virtually any organ site; however, cutaneous metastasis is rare. We present a case of cutaneous renal cell carcinoma metastatic to the scalp. It is important for the dermatologist to recognize the histopathologic and clinical features of cutaneous RCC in order to properly diagnose and treat patients and refer them for appropriate further management.

Introduction
Renal cell carcinoma (RCC) is among the top ten most prevalent cancers in adults, accounting for 2% to 3% of all malignant diseases. The American Cancer Society predicted about 62,000 new cases of kidney cancer in the United States in 2016. The average age at diagnosis is 65, and men have a higher risk for developing RCC than women. Renal cell carcinoma makes up the majority of kidney tumors, accounting for 80% to 90% of all malignant kidney cancers. The most common presenting symptoms of renal cell carcinoma are hematuria, abdominal pain, and a palpable flank mass, though fewer than 10% of patients present with all three symptoms. The greatest risk factors contributing to the development of RCC are cigarette smoking, high body mass index, and hypertension. RCC is known to present without early warning signs and has proved resistant to chemotherapy and radiation. With the frequent use of axial imaging, greater than 70% of RCC are found incidentally on imaging studies. At the time of presentation, metastatic disease is present in approximately 30% of patients, most commonly in the lymph nodes, lung, bone, liver, adrenal gland, contralateral kidney and brain. Metastatic disease typically occurs within the first five years after diagnosis, though cases have been reported of systemic spread decades after treatment.

Case Report
A 77-year-old Caucasian male presented to the dermatology office with a bleeding bump on his scalp. He reported the lesion had been present for a few years, and denied pain or rapid growth. The patient’s past medical history included atrial fibrillation, hypertension, and RCC status post nephrectomy in 2013. On physical examination, he was noted to have male pattern baldness and a 0.7 cm, crusted, brown-purple papule on the right posterior vertex of his scalp (Figure 1).

The clinical differential diagnosis included metastatic RCC, pigmented basal cell carcinoma, a vascular lesion and melanoma. A shave biopsy of the lesion was preformed, and histopathology revealed sheets and nodules of atypical clear cells with large vascular spaces filled with erythrocytes (Figures 2, 3). The tumor cells stained positive with RCCma (Figure 4), PAX-8 (Figure 5), PAX-2 and EMA, and negative for CK7 and CK20. A diagnosis of metastatic clear-cell renal cell carcinoma was made.

The patient had been following up with this urologist annually for computerized tomography scans, and none of his previous CT scans revealed evidence of RCC recurrence or metastasis. In light of the new evidence of metastasis, he was referred to his urologist and oncologist. A CT scan of his abdomen and pelvis revealed no evidence of recurrence or residual or metastatic disease, and his chest X-rays showed no evidence of metastasis to the lungs. The lesion on his scalp was the first indication of recurrence of his disease. The patient will continue to be managed by multiple specialists and receive screening imaging studies.

Discussion
Renal cell carcinoma is known for its aggressive nature and ability to metastasize to unique sites and mimic other cutaneous lesions. There are five types of kidney carcinomas distinguished histologically, including clear cell and papillary tumors (originating from the proximal tubule), oncocytic/chromophobe tumors (originating from the cortical collecting duct), and collecting duct tumors (originating from the medullary collecting duct). Clear cell carcinomas are the dominant tumor type, making up 75% to 85% of renal carcinomas. The clear cells are polygonal or round with abundant cytoplasm containing cholesterol, glycogen and phospholipids surrounded by a network of fibrovascular stroma. Most clear cell tumors are characterized by a deletion of the alleles of chromosome 3p25, the von Hippel-Lindau gene (VHL). VHL is a tumor suppressor gene, leading to inactivation of the VHL protein and increased expression of hypoxia-inducible factors (HIFs). The HIFs promote angiogenesis and tumor growth.

Figure 1. Papule on right posterior vertex of scalp.
Figure 2. Tumor nodule with large vascular spaces and lobules of clear cells.
Figure 3. Positive Pax-8 stain.
Figure 4. Positive RCCma stain.
Figure 5. Positive Pax-8 stain.
gene whose loss of function contributes to tumor development, including VEGF expression. There are genetic syndromes, such as von Hippel-Lindau syndrome and tuberous sclerosis, that predispose individuals to the development of clear-cell renal cell carcinomas. However, these syndromes make up a small proportion of clear cell RCC, and the majority occur without associated genetic disease.

Cutaneous metastasis of renal cell carcinoma is rare (3.4%). The four mechanisms for cutaneous metastasis are direct invasion from an underlying tumor, lymphatic extension, hematogenous spread and implantation of neoplastic cells from a procedural scar. Genitourinary malignancies' most common cutaneous metastasis site is abdominal skin, particularly for non-RCC tumor types. However, renal cell carcinoma more frequently affects the skin of the head and neck. The vascular nature of the tumor may contribute to RCC's ability to spread to distant sites, mostly via hematogenous extension. In one major retrospective study of patients with cutaneous metastasis, 4.6% of patients with metastatic RCC had cutaneous metastasis, with the majority spreading to the scalp. This finding supports previous studies showing a disproportionate number of cases of RCC metastasis to the scalp.

Most cutaneous metastases occur as nodules, typically multiple. Due to their red to purple color, the nodules of metastatic RCC are often mistaken for hemangiomas, pyogenic granulomas, or Kaposi's sarcoma on examination. The morphology of the lesions imitates that of cutaneous horns, lymphoma, abscesses and cutaneous cysts, similar to the findings in our case, establishing a broad differential and the need for histopathologic studies. A punch biopsy or excisional biopsy is recommended for diagnosis of metastatic RCC. As the carcinoma primarily involves the dermis, a superficial shave biopsy may be too shallow to provide sufficient tissue for diagnosis.

Histopathology

The histology of metastatic lesions typically maintains similarities to the primary lesion, but the presence of lymphatic and vascular infiltration, anaplasia and poor differentiation are clues that a lesion is metastatic. Immunohistochemistry (IHC) is an invaluable tool for differentiating clear cell tumors of similar morphology and unknown origin. IHC markers helpful in diagnosing metastatic RCC include RCC monoclonal antibody (RCCma), epithelial membrane antigen (EMA), PAX-2 and PAX-8. Both members of the human paired boxed gene family and important in the transcription of renal cell lines, are used most frequently due to their greater sensitivity and specificity in RCC. RCCma is well established and utilized as a marker for clear cell RCC, as it stains positive in approximately two-thirds of RCC cutaneous metastases. RCCma is highly specific and is not expressed in other clear cell malignancies of the skin (such as clear cell hidradenoma/carcinoma). The majority of RCC cells also express EMA. In our case, the tumor stained positive for PAX-2, PAX-8, EMA and RCCma, indicating clear cell RCC as the likely source of the tissue. In our study, we also utilized CK7, a marker for Paget's disease and non-G1 adenocarcinomas like lung, breast, bladder and pancreas, and CK20, a marker for Merkel cell carcinoma and gastrointestinal adenocarcinomas like colon cancer, to help rule out other potential sources of metastasis. Only 10% of RCC express either CK7 or CK20. Both markers were negative in our tissue sample.

Prognosis and Treatment

The mainstay of treatment for renal cell carcinoma is partial or radical nephrectomy dependent upon tumor size and stage. RCC has proved resistant to radiation and cytotoxic chemotherapy. The first five years after nephrectomy pose the greatest risk of RCC recurrence. Within the first year, about 43% of RCC will recur. Most recurrences are detected by follow-up laboratory and imaging studies, so it is important for patients to follow up with their urologists regularly for at least five years. The prognosis for patients who develop cutaneous metastasis from renal cell carcinoma is very poor. Most patients die within six months to a year of diagnosis. Survival rates increase with a longer disease-free interval from the time of initial diagnosis to the development of metastasis. Systemic therapy is typically recommended for metastatic disease after a period of observation. High-dose interleukin-2 and interferon-alpha were previously utilized as first-line treatments for systemic disease, but more-targeted therapies, using tyrosine kinase inhibitors and VEGF pathway inhibitors, have recently been approved for use in advanced RCC.

Conclusion

Cutaneous metastatic renal cell carcinoma poses a diagnostic dilemma in dermatology. Clinically, it can mimic many other tumor types and vascular lesions. A multidisciplinary approach to diagnosis and treatment is important, as patients will need referral to oncology and urology to manage the condition. It is important to be able to recognize the clinical and pathologic signs of metastatic cutaneous lesions, as they may be the first indication of underlying malignancy.

References