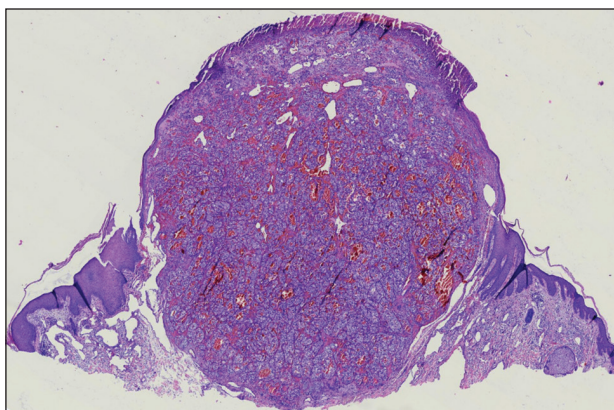


Bleeding Nodule on the Lip

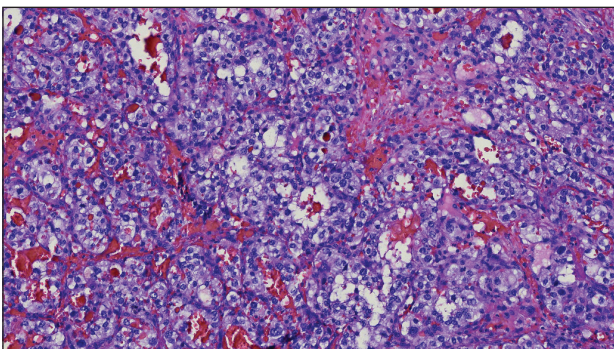
Crystal R. Lenz, DO; Morgan Arnold, DO; Nathan Cleaver, DO

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H&E, original magnification $\times 12.6$.



H&E, original magnification $\times 100$.

A 71-year-old man with no notable medical history presented with a bleeding nodule on the right lower cutaneous lip of 9 weeks' duration. The patient denied any systemic symptoms. A shave biopsy was performed.

THE BEST DIAGNOSIS IS:

- balloon cell nevus
- clear cell hidradenoma
- metastatic clear cell renal cell carcinoma
- pyogenic granuloma
- sebaceous carcinoma

PLEASE TURN TO **PAGE 262** FOR THE DIAGNOSIS

Dr. Lenz is from Centura Health Penrose Hospital-St. Francis Health Services, Colorado Springs. Dr. Arnold is from Northeast Regional Medical Center, Kirksville, Missouri. Dr. Cleaver is from Cleaver Medical Group, Cumming, Georgia.

The authors report no conflict of interest.

Correspondence: Crystal R. Lenz, DO, Penrose Hospital, 2222 N Nevada Ave, Colorado Springs, CO 80907 (CrystalLenz@Centura.org).

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THE DIAGNOSIS:

Metastatic Clear Cell Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a common genitourinary system malignancy with incidence peaking between 50 and 70 years of age and a male predominance.¹ The clear cell variant is the most common subtype of RCC, accounting for 70% to 75% of all cases. It is known to be a highly aggressive malignancy that frequently metastasizes to the lungs, lymphatics, bones, liver, and brain.^{2,3} Approximately 20% to 50% of patients with RCC eventually will develop metastasis after nephrectomy.⁴ Survival with metastatic RCC to any site typically is in the range of 10 to 22 months.^{5,6} Cutaneous metastases of RCC rarely have been reported in the literature (3%–6% of cases⁷) and most commonly are found on the scalp, followed by the chest or abdomen.⁸ Cutaneous metastases generally are regarded as a late manifestation of the disease with a very poor prognosis.⁹ It is unusual to identify cutaneous RCC metastasis without known RCC or other symptoms consistent with advanced RCC, such as hematuria or abdominal/flank pain. Renal cell carcinoma accounts for an estimated 6% to 7% of all cutaneous metastatic lesions.¹⁰ Cutaneous metastatic lesions of RCC often are solitary and grow rapidly, with the clinical appearance of an erythematous or violaceous, nodular, highly vascular, and often hemorrhagic growth.^{9,11,12}

Following the histologic diagnosis of metastatic clear cell RCC, our patient was referred to medical oncology for further workup. Magnetic resonance imaging and a positron emission tomography scan demonstrated widespread disease with a 7-cm left renal mass, liver and lung metastases, and bilateral mediastinal lymphadenopathy. The patient was started on combination immunotherapy as a palliative treatment given the widespread disease.

Histologically, clear cell RCC is characterized by lipid and glycogen-rich cells with ample cytoplasm and a well-developed vascular network, which often is thin walled with a chicken wire–like architecture. Metastatic clear cell RCC tumor cells may form glandular, acinar, or papillary structures with variable lymphocytic inflammatory infiltrates and abundant capillary formation. Immunohistochemically, the tumor cells should demonstrate positivity for paired box gene 8, *PAX8*, and RCC marker antigen.¹³ Vimentin and carcinoembryonic antigen may be utilized to distinguish from hidradenoma as carcinoembryonic antigen will be positive in hidradenoma and vimentin will be negative.¹⁴ Renal cell carcinoma also has a common molecular signature of von Hippel-Lindau tumor suppressor gene inactivation as well as upregulation of hypoxia inducible factor and vascular endothelial growth factor.¹⁵

Balloon cell nevi often clinically present in young patients as bicolored nevi that sometimes are polypoid

or verrucous in appearance with central yellow globules surrounded by a peripheral reticular pattern on dermoscopy. Histologically, balloon cell nevi are characterized by large cells with small, round, centrally located basophilic nuclei and clear foamy cytoplasm (Figure 1), which are thought to be formed by progressive vacuolization of melanocytes due to the enlargement and disintegration of melanosomes. This ballooning change reflects an

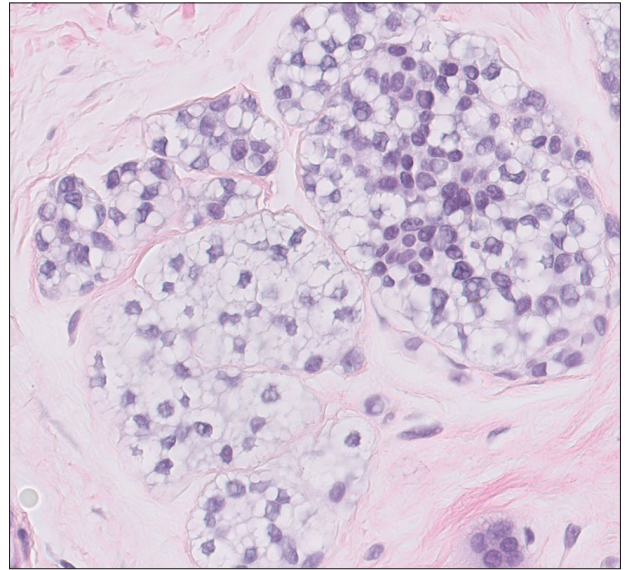


FIGURE 1. Balloon cell nevus. Dermal nests composed of altered melanocytes with vacuolated clear cytoplasm caused by defective melanogenesis (H&E, original magnification $\times 400$).

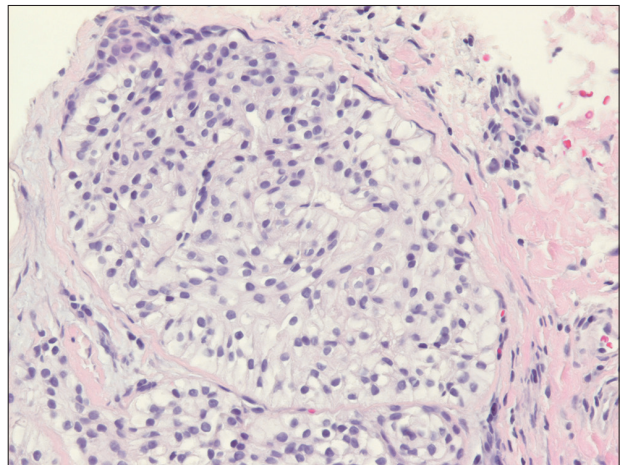


FIGURE 2. Clear cell hidradenoma. Nested polygonal cells with vesicular clear cytoplasm and eccentrically placed nuclei (H&E, original magnification $\times 200$).

intrinsic cellular degenerative process and also can be seen in malignant melanoma, in which case nuclear pleomorphism, atypia, and increased mitotic activity also are observed. The prominent vascular network characteristic of RCC typically is not present.¹⁶

Clear cell hidradenomas are benign skin appendage tumors that often present as small, firm, solitary dermal nodules that may extend into the subcutaneous fat. They have a predilection for the head, face, and arms and demonstrate 2 predominant cell types, including a polyhedral cell with a rounded nucleus and slightly basophilic cytoplasm as well as a round cell with clear cytoplasm and bland nuclei (Figure 2). The latter cell type is less common, representing the predominant cell type in less than one-third of hidradenomas, and can present a diagnostic quandary based on histologic similarity to other clear cell neoplasms. The clear cells contain glycogen

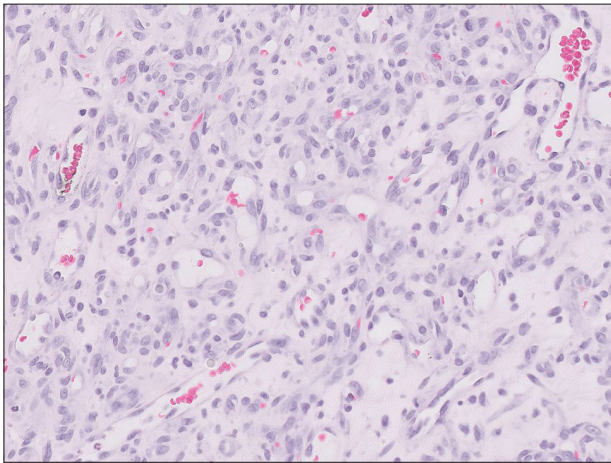


FIGURE 3. Pyogenic granuloma (lobular capillary hemangioma). Lobular pattern with prominent vascular proliferation and edema as well as pale staining but no true clear cells (H&E, original magnification $\times 200$).

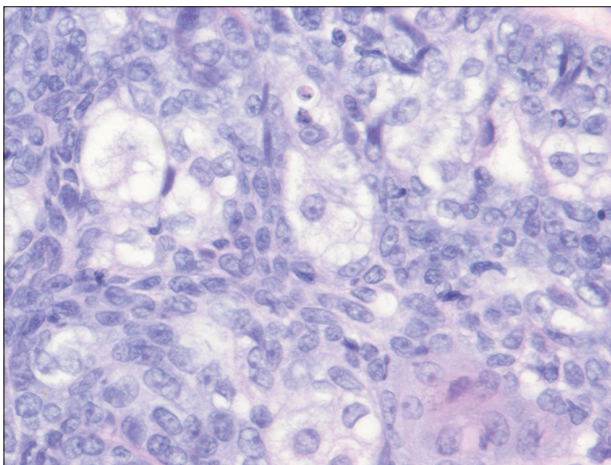


FIGURE 4. Sebaceous carcinoma. Dermal-based nodular aggregates of multivacuolated clear cells with surrounding poorly differentiated atypical basaloid cells (H&E, original magnification $\times 400$).

but no lipid. Ductlike structures often are present, and the intervening stroma varies from delicate vascularized cords of fibrous tissue to dense hyalinized collagen. Immunohistochemistry may be required for definitive diagnosis, and clear cell hidradenomas should react with monoclonal antibodies that label both eccrine and apocrine secretory elements, such as cytokeratins 6/18, 7, and 8/18.¹⁷

Pyogenic granulomas (also referred to as lobular capillary hemangiomas) are common and present clinically as rapidly growing, polypoid, red masses surrounded by a thickened epidermis that often are found on the fingers or lips. This entity is benign and often regresses spontaneously. Histologically, pyogenic granulomas are characterized by a lobular pattern of vascular proliferation associated with edema and inflammation resembling granulation tissue, with acanthosis and hyperkeratosis at the edges of the lesion (Figure 3).¹⁸

Sebaceous carcinoma is a locally aggressive malignant neoplasm arising from the cells of the sebaceous glands and occurring most commonly in the periorbital area. This neoplasm most often affects older adults, with a mean age at diagnosis of 63 to 77 years. It commonly presents as a solitary nodule with yellowish discoloration and madarosis, which is a key distinguishing feature to differentiate this entity from a chalazion or hordeolum. Histologically, sebaceous carcinoma is a dermal-based infiltrative, nodular tumor with varying degrees of clear cell changes—well-differentiated tumors show more clear cell change as compared to more poorly differentiated variants—along with basaloid or squamous features and abundant mitotic activity (Figure 4), which may be useful in distinguishing it from the other entities in the clear cell neoplasm differential.¹⁹⁻²²

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