

Ulcerated Nodule on the Lip

Georgianne Cornell, DO; Wei Su, MD; John Moesch, DO

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 79-year-old man with a medical history of type 2 diabetes mellitus, hypothyroidism, and atrial fibrillation presented with an enlarging lesion on the right side of the upper cutaneous lip of 5 weeks' duration. He had no personal history of skin cancer or other malignancy and was up to date on all routine cancer screenings. He reported associated lip and oral cavity tenderness, weakness, and a 13.6-kg (30-lb) unintentional weight loss over the last 6 months. He had used over-the-counter bacitracin ointment on the lesion without relief. A full-body skin examination revealed a firm, mobile, flesh-colored, nondraining nodule in the right axillary vault.

WHAT'S YOUR DIAGNOSIS?

- basal cell carcinoma
- cutaneous metastasis
- folliculotropic mycosis fungoides
- Merkel cell carcinoma
- paracoccidioidomycosis

PLEASE TURN TO **PAGE 44** FOR THE DIAGNOSIS

Dr. Cornell is from the Department of Academic Dermatology, Trinity Health, Ann Arbor, Michigan. Drs. Su and Moesch are from Midwest Center for Dermatology and Cosmetic Surgery, Clinton Township, Michigan.

The authors report no conflict of interest.

Correspondence: Georgianne Cornell, DO, Trinity Health Department of Academic Dermatology, Reichert Health Center, 5333 McAuley Dr, Ste R-5003, Ypsilanti, MI 48197 (georgiecornell@gmail.com).

doi:10.12788/cutis.0804

THE DIAGNOSIS: Cutaneous Metastasis

A shave biopsy of the lip revealed a diffuse cellular infiltrate filling the superficial and deep dermis (Figure 1A). Morphologically, the cells had abundant clear cytoplasm with eccentrically located, pleomorphic, hyperchromatic nuclei with occasional prominent nucleoli (Figure 1B). The cells stained positive for AE1/AE3 on immunohistochemistry (Figure 2). A punch biopsy of the nodule in the right axillary vault revealed a morphologically similar proliferation of cells. A colonoscopy revealed a completely obstructing circumferential mass in the distal ascending colon. A biopsy of the mass confirmed invasive adenocarcinoma, supporting a diagnosis of cutaneous metastases from adenocarcinoma of the colon. The patient underwent resection of the lip tumor and started multiagent chemotherapy for his newly diagnosed stage IV adenocarcinoma of the colon. The patient died, despite therapy.

Cutaneous metastasis from solid malignancies is uncommon, as only 1.3% of them exhibit cutaneous manifestations at presentation.¹ Cutaneous metastasis from signet ring cell adenocarcinoma (SRCA) of the colon is uncommon, and cutaneous metastasis of colorectal SRCA rarely precedes the diagnosis of the primary lesion.² Among the colorectal cancers that metastasize to the skin, metastasis to the face occurs in only 0.5% of patients.³

Signet ring cell adenocarcinomas are poorly differentiated adenocarcinomas histologically characterized by the neoplastic cells' circular to ovoid appearance with a flattened top.^{4,5} This distinctive shape is from the displacement of the nucleus to the periphery of the cell due to the accumulation of intracytoplasmic mucin.⁴ Classically, malignancies are characterized as an SRCA if more than 50% of the cells have a signet ring cell morphology; if the signet ring cells comprise less than 50% of the neoplasm, the tumor is designated as an adenocarcinoma with signet ring morphology.⁴ The most common cause of cutaneous metastasis with signet ring morphology is gastric cancer, while colorectal carcinoma is less common.¹ Colorectal SRCAs usually are found in the right colon or the rectum in comparison to other colonic sites.⁶

Clinically, cutaneous metastasis can present in a variety of ways. The most common presentation is nodular lesions that may coalesce to become zosteriform in configuration or lesions that mimic inflammatory dermatoses.⁷ Cutaneous metastasis is more common in breast and lung cancer, and when it occurs secondary to colorectal cancer, cutaneous metastasis rarely predates the detection of the primary neoplasm.²

The clinical appearance of metastasis is not specific and can mimic many entities⁸; therefore, a high index of suspicion must be employed when managing patients,

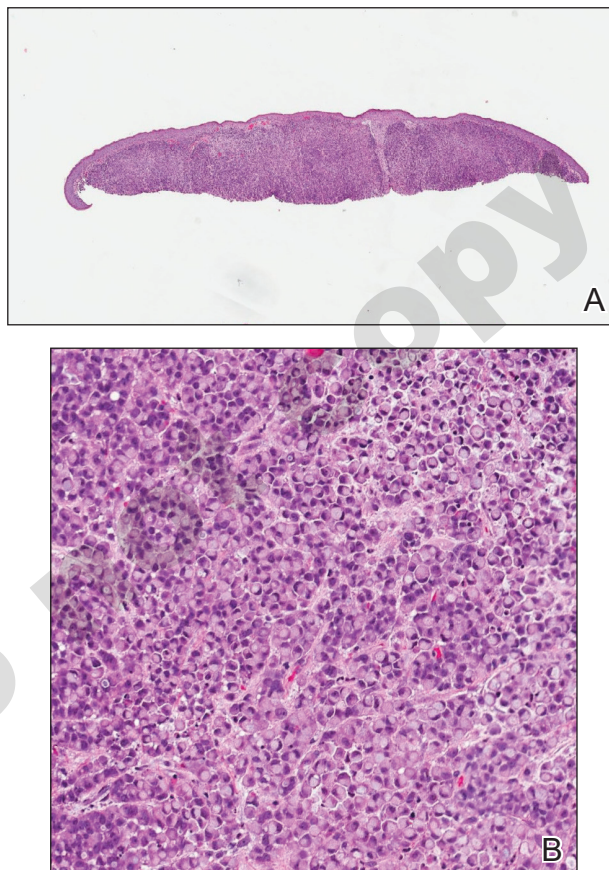


FIGURE 1. A, A shave biopsy of the lip demonstrated a cellular infiltrate filling the superficial and deep dermis (H&E, original magnification $\times 20$). B, The cells had abundant clear cytoplasm with eccentrically located, pleomorphic, hyperchromatic nuclei with occasional prominent nucleoli (H&E, original magnification $\times 200$).

even those without a history of internal malignancy. In our patient, the smooth nodular lesion appeared similar to a basal cell carcinoma; however, basal cell carcinomas appear more pearly, and arborizing telangiectasia often is seen.⁹ Merkel cell carcinoma is common on sun-damaged skin of the head and neck but clinically appears more violaceous than the lesion seen in our patient.¹⁰ Paracoccidioidomycosis may form ulcerated papulonodules or plaques, especially around the nose and mouth. In many of these cases, lesions develop from contiguous lesions of the oral mucosa; therefore, the presence of oral lesions will help distinguish this infectious entity from cutaneous metastasis. Multiple lesions usually are identified when there is hematogenous dissemination.¹¹ Mycosis fungoides is a subtype of cutaneous T-cell lymphoma and is characterized by multiple patches, plaques,

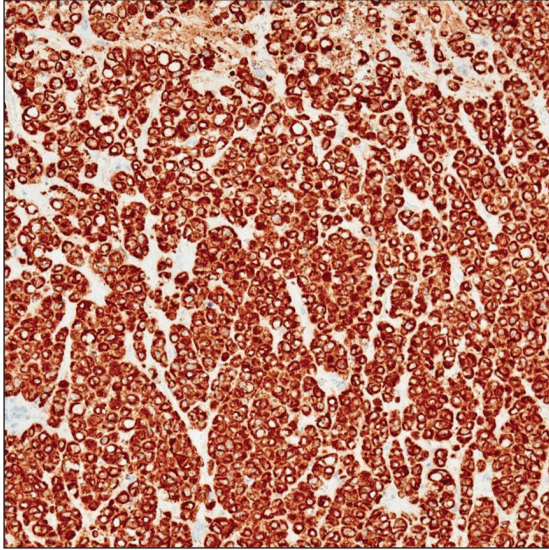


FIGURE 2. Immunohistochemistry revealed cells that stained positive for AE1/AE3 (original magnification $\times 200$).

and nodules on sun-protected areas. Involvement of the head and neck is not common, except in the folliculotropic subtype, which has a separate and distinct clinical morphology.¹²

The development of signet ring morphology from an adenocarcinoma can be attributed to the activation of phosphatidylinositol 3-kinase (PI3K), which leads to downstream activation of mitogen-activated protein kinase (MAPK) and the subsequent loss of intercellular tight junctions. The mucin 4 gene, *MUC4*, also is upregulated by PI3K activation and possesses antiapoptotic and mitogenic effects in addition to its mucin secretory function.¹³

The neoplastic cells in SRCAs stain positive for mucicarmine, Alcian blue, and periodic acid-Schiff, which highlights the mucinous component of the cells.⁷ Immunohistochemical stains with CK7, CK20, AE1/AE3, and epithelial membrane antigen can be implemented to confirm an epithelial origin of the primary cancer.^{7,13} CK20 is a low-molecular-weight cytokeratin normally expressed by Merkel cells and by the epithelium of the gastrointestinal tract and urothelium, whereas CK7 expression typically is expressed in the lungs, ovaries, endometrium, and breasts, but not in the lower gastrointestinal tract.¹⁴ Differentiating primary cutaneous adenocarcinoma from cutaneous metastasis can be accomplished with a thorough clinical history; however, p63 positivity supports a primary cutaneous lesion and may be useful in certain situations.⁷ CDX2 stains can be utilized to aid in localizing the primary neoplasm when it is unknown, and when positive, it suggests a lower gastrointestinal tract origin. However, special AT-rich sequence-binding protein 2 (SATB2) recently has been proposed as a

replacement immunohistochemical marker for CDX2, as it has greater specificity for SRCA of the lower gastrointestinal tract.¹⁵ Benign entities with signet ring cell morphology are difficult to distinguish from SRCA; however, malignant lesions are more likely to demonstrate an infiltrative growth pattern, frequent mitotic figures, and apoptosis. Immunohistochemistry also can be utilized to support the diagnosis of benign proliferation with signet ring morphology, as benign lesions often will demonstrate E-cadherin positivity and negativity for p53 and Ki-67.¹³

Cutaneous metastasis usually correlates to advanced disease and generally indicates a worse prognosis.¹³ Signet ring cell morphology in both gastric and colorectal cancer portends a poor prognosis, and there is a lower overall survival in patients with these malignancies compared to cancers of the same organ with non-signet ring cell morphology.^{4,8}

REFERENCES

- Mandzhieva B, Jalil A, Nadeem M, et al. Most common pathway of metastasis of rectal signet ring cell carcinoma to the skin: hematogenous. *Cureus*. 2020;12:E6890.
- Parente P, Ciardiello D, Reggiani Bonetti L, et al. Cutaneous metastasis from colorectal cancer: making light on an unusual and misdiagnosed event. *Life*. 2021;11:954.
- Picciariello A, Tomasicchio G, Lantone G, et al. Synchronous "skip" facial metastases from colorectal adenocarcinoma: a case report and review of literature. *BMC Gastroenterol*. 2022;22:68.
- Benesch MGK, Mathieson A. Epidemiology of signet ring cell adenocarcinomas. *Cancers*. 2020;12:1544.
- Xu Q, Karouji Y, Kobayashi M, et al. The PI 3-kinase-Rac-p38 MAP kinase pathway is involved in the formation of signet-ring cell carcinoma. *Oncogene*. 2003;22:5537-5544.
- Morales-Cruz M, Salgado-Nesme N, Trolle-Silva AM, et al. Signet ring cell carcinoma of the rectum: atypical metastatic presentation. *BMJ Case Rep CP*. 2019;12:E229135.
- Demircioğlu D, Öztürk Durmaz E, Demirkesen C, et al. Livedoid cutaneous metastasis of signet-ring cell gastric carcinoma. *J Cutan Pathol*. 2021;48:785-788.
- Dong X, Sun G, Qu H, et al. Prognostic significance of signet-ring cell components in patients with gastric carcinoma of different stages. *Front Surg*. 2021;8:642468.
- Marzuka AG, Book SE. Basal cell carcinoma: pathogenesis, epidemiology, clinical features, diagnosis, histopathology, and management. *Yale J Biol Med*. 2015;88:167-179.
- Nguyen AH, Tahseen AI, Vaudreuil AM, et al. Clinical features and treatment of vulvar Merkel cell carcinoma: a systematic review. *Gynecol Oncol Res Pract*. 2017;4:2.
- Marques SA. Paracoccidioidomycosis. *Clin Dermatol*. 2012;30:610-615.
- Larocca C, Kupper T. Mucositis fungoides and Sézary syndrome. *Hematol Oncol Clin*. 2019;33:103-120.
- Gündüz Ö, Emeksiz MC, Atasoy P, et al. Signet-ring cells in the skin: a case of late-onset cutaneous metastasis of gastric carcinoma and a brief review of histological approach. *Dermatol Rep*. 2017;8:6819.
- Al-Tae A, Almukhtar R, Lai J, et al. Metastatic signet ring cell carcinoma of unknown primary origin: a case report and review of the literature. *Ann Transl Med*. 2016;4:283.
- Ma C, Lowenthal BM, Pai RK. SATB2 is superior to CDX2 in distinguishing signet ring cell carcinoma of the upper gastrointestinal tract and lower gastrointestinal tract. *Am J Surg Pathol*. 2018;42:1715-1722.