Metastatic renal cell carcinoma presenting as multiple pyogenic granuloma-like nodules on the penis

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INTRODUCTION
Approximately 60,000 new diagnoses of renal cell carcinoma (RCC) are made per year, accounting for 90% to 95% of all malignant neoplasms arising from the kidney with an estimated mortality rate of 20%.1 Rarely, advanced RCC may exhibit cutaneous metastases, most often to the scalp, chest, arms, and fingers.1,2 We discuss an unusual case of cutaneous metastatic RCC involving the penis, presenting as multiple exophytic pyogenic granuloma-like lesions.

CASE REPORT
A 38-year-old man with clear cell RCC, diagnosed 9 months prior with metastases to the brain, lungs, and adrenal glands, was admitted to the hospital for worsening respiratory distress. His treatment at diagnosis included radical nephrectomy, left frontal lobe lesion resection, and whole-brain radiation. He then began treatment with targeted receptor tyrosine kinase inhibitor sunitinib but was transitioned to anti–PD-1 monoclonal antibody nivolumab after 5 months because of disease progression. The dermatology service was consulted for multiple painful penile growths, which had been increasing in number over 6 months. The patient denied dysuria, hematuria, urethral discharge, or history of trauma to the genitalia.
Physical examination found several tender, pedunculated flesh-colored and bright red vascular-appearing nodules on the corona of the penis (Fig 1) without regional lymphadenopathy. Results of laboratory evaluations for herpes simplex type 2, syphilis, HIV, gonorrhea, and chlamydia were negative. Clinical morphology strongly suggested pyogenic granuloma. Shave biopsy of a lesion found pleomorphic tumor cells with eosinophilic to focally clear cytoplasm embedded in a highly vascular stroma. The tumor cells of interest labeled with PAX-8, a finding consistent with that of cutaneous metastatic RCC (Fig 2). Unfortunately, the patient had respiratory failure caused by widespread metastatic lung involvement and died 2 days later.

DISCUSSION
The overall incidence of cutaneous metastases in patients with internal malignancy has been estimated to be around 5% to 10%.3,4 Skin lesions may be the first sign of extranodal metastatic disease in 7.6% of cases, often manifesting as solitary or multiple nodules and plaques.3 A retrospective study examining 4,020 patients with metastatic disease found that the most common primary tumor metastasizing to the skin was breast cancer in women and melanoma in men, whereas secondary spread to the penis was rare.4 In a review of the literature, Cherian et al identified 372 total cases of penile metastatic lesions, among which tumors of the kidney comprised only 8%.5 Our patient is among the few reported in the literature to exhibit an
uncommon pattern of localization of cutaneous metastatic RCC involving the penis.\textsuperscript{5,6}

The mechanism of cutaneous distribution closely depends on the route of spread via the lymphatics, bloodstream, or the peritoneum. Renal cell carcinoma has a propensity to spread hematogenously from the renal vein to the vena cava and vertebral veins to reach the central nervous system and the spermatic or ovarian vein to reach the pelvic organs.\textsuperscript{2,5} The latter mode of retrograde dissemination may explain the unusual presentation on the corona of the penis observed in our patient. Furthermore, RCC growth is associated with vascular endothelial growth factor, which explains its ability to disseminate widely and form highly vascular dermal metastasis.\textsuperscript{1,7}

Morphologically, cutaneous metastatic RCC can present as red, purple, black or flesh-colored intradermal or subcutaneous papules or nodules. Lesions are clinically challenging to diagnose, as they may resemble epidermoid cysts, fibromas, or vascular tumors such as Kaposi sarcoma, hemangioma, or pyogenic granuloma.\textsuperscript{1,7} Given the uncharacteristic location of the lesions in our patient, we initially considered pyogenic granuloma secondary to treatment with sunitinib as the leading differential diagnosis, as several receptor tyrosine kinase inhibitors were recently reported to be associated with this

\textbf{Fig 1.} A and B, Multiple raised flesh-colored vascular-appearing pedunculated nodules.

\textbf{Fig 2.} A, A biopsy specimen shows a polypoid fragment of skin. B, Beneath the areas of ulceration, pleomorphic tumor cells spanned the dermis with eosinophilic to focally clear cytoplasm embedded in a highly vascular stroma. C, Tumor cells labeled diffusely with PAX-8, supporting a diagnosis of metastatic renal cell carcinoma. (A and B, Hematoxylin-eosin stain; original magnifications: A, ×10; B and C, ×40.)
vascular lesion. However, histologically, RCC tumor nodules are composed of clear-staining tumor cells within a highly vascular stroma, as was seen in our patient.

The course and prognosis of patients with cutaneous metastatic disease is very poor. In a retrospective review of 130 patients with metastatic kidney cancer, the average time from biopsy-proven diagnosis to death was 21 months, as dissemination to the skin was usually a late finding. Thus far, tyrosine kinase inhibitors, anti–vascular endothelial growth factor inhibitors, and immune checkpoint inhibitors have been used to treat metastatic RCC with varying degrees of success as management is usually palliative.

Our report highlights that cutaneous RCC may masquerade clinically as a pyogenic granuloma-like lesion and may metastasize to the penis. Although penile involvement of metastatic disease is rare, it should be considered in the differential diagnosis in a patient with persistent painful penile nodules in the setting of known malignancy. Identification of spread of a primary tumor to the skin may serve as an indicator of disease progression and suggest a poor overall prognosis.

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