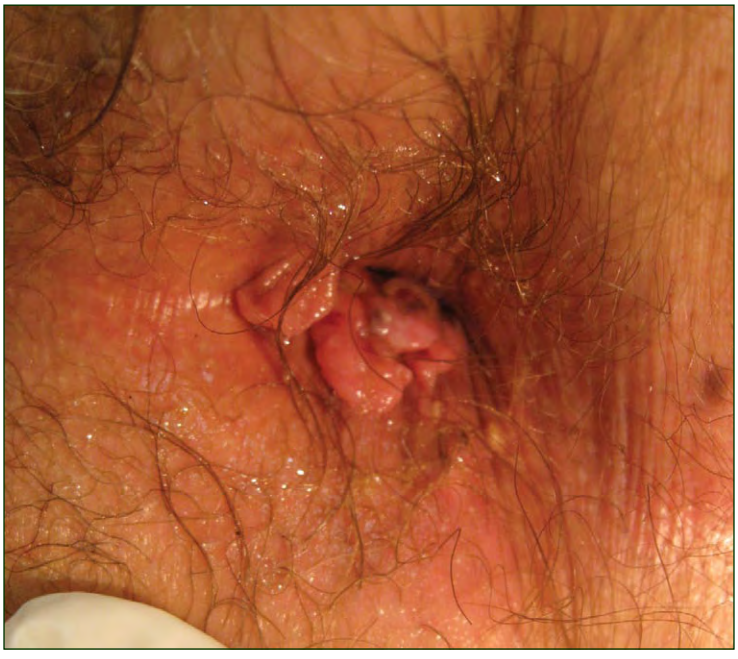
What Is Your Diagnosis?



A 67-year-old man presented to his primary care physician with a pink nodule on the perianal skin of 2 years' duration. This lesion initially had been treated with liquid nitrogen and remained asymptomatic for 1.5 years. Several months prior to presentation he noted blood-stained undergarments. There was no pain with this incident. The patient's medical history included a thin truncal melanoma, coronary artery disease, hypercholesterolemia, and hypertension.

PLEASE TURN TO PAGE 116 FOR DISCUSSION

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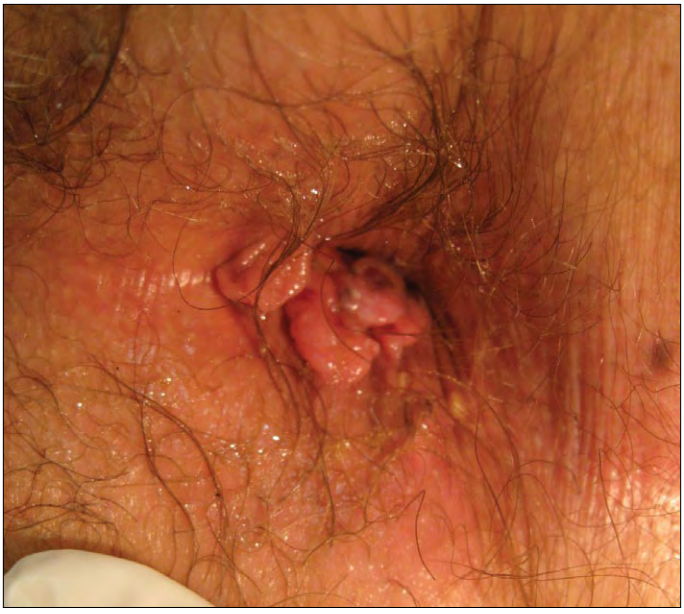
The Diagnosis: Anal Mucosal Melanoma



Mucosal melanomas (MuMs) are noncutaneous melanomas that occur in the nasal cavity, oral cavity, and anorectal and genital tracts; they account for 1.4% of melanomas.[1] Relative to cutaneous melanoma, the peak age of diagnosis is later (70–79 years), and the incidence has remained stable over the last 2 decades.[1,2] Because MuMs are rare, information regarding the presentation, pathogenesis, and epidemiology is scant. However, from the few reported studies, several trends have been noted.

Mucosal melanomas occur in several sites with the highest incidence in the female genital tract, followed by the anorectal tract and nasal and oral cavities. Anorectal melanoma accounts for 16.5% to 23.8% of reported MuM cases.[1,2] Mucosal melanoma is more common among women, with one study showing an 86.7% higher rate relative to men.[1] In women, they predominantly present on the vulva and vagina. For nongenital sites, however, there is no difference in incidence rates for males and females. In the head and neck, the most common site is the nasal mucosa followed by the oral mucosa.[2]

Within these various areas, patients may present with a mass and/or bleeding, with or without pruritus and pain. Nasal and sinus melanomas present with nasal obstruction or bloody discharge. Oral melanoma may present with a mass, an area of pigmentation, bleeding, or loosening of teeth. The morphology of these lesions can range from amelanotic or darkly pigmented patches and plaques to ulcerated papillomatous solitary or multiple nodules.[3]

Anal MuM is a rare disease accounting for less than 1% of melanomas and less than 1% of all anorectal cancers. Anal MuM is more common in men and the median age of diagnosis is 60 years with a second peak noted in human immunodeficiency virus–positive men in their mid-30s.[4] The majority of patients present with advanced disease due to lack of early symptoms. Despite aggressive surgical intervention and attempts at systemic treatment, these patients have a poor prognosis. One-third of patients present with mesenteric lymph node involvement; thus aggressive surgery, such as abdominoperineal resection with a radical groin lymph node dissection, has been advocated. Given the dismal survival, some physicians advocate for local excision, observation, or enrollment into a clinical trial.

Patients may report bleeding, change in bowel habits, pain, and sensation of a lump, raising the possibility of a hemorrhoid. Physical examination reveals a pink exophytic mass, usually polypoid, at or near the anorectal junction. Blue or black pigment can be detected to the discriminating examiner. In our patient, close inspection revealed macular blue and black pigmentation within the pink polypoid mass.

Regardless of the anatomic site, patients often are diagnosed at an advanced stage.[2] Staging for

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MuM currently follows the convention of measuring the Breslow depth of melanoma, as with cutaneous melanoma. The American Joint Committee on Cancer does not separate staging criteria based on the clinical subtype of melanoma. The prognostic significance of clinical nodal status in MuM remains controversial, though it clearly has prognostic significance in the setting of cutaneous melanoma. Another controversial topic is the uncertainty of a tendency for lymphatic versus hematogenous spread of tumors. Nodal disease appears to vary by site with one study revealing incidences of 26.6%, 23.0%, 61.0%, and 11.1%, for the head and neck, female genital tract, anorectal tract, and urinary tract, respectively.[2]

Current standard of treatment for MuMs varies by body region. Within the head and neck, the current standard of treatment is surgery with strong consideration given to postoperative radiotherapy. Within the genital and anorectal tracts, typically surgery alone, which may or may not include sentinel lymph node biopsy, may be adequate. These treatments aim at local disease control that then can be followed by adjuvant treatment and close clinical follow-up.

Despite the implementation of aggressive treatment, including surgery, radiation, and adjuvant therapy, the prognosis has remained poor, with 5-year disease-specific survival ranging from 17.1% to 50%, depending on the primary site.[2,5,6]

Systemic therapy for MuM has been disappointing. Although interferon alfa-2b was approved as postoperative adjuvant therapy for cutaneous melanoma in 1997, few adjuvant studies included MuM. Thus melanoma experts are divided on whether to advise interferon as adjuvant therapy for MuM. Chemotherapy with agents such as dacarbazine show little benefit, but there have been several reports of benefit using the combination of chemotherapy drugs with IL-2–based immunotherapy, termed *biochemotherapy*.[7-9] Bartell et al[7] reported 15 patients who received biochemotherapy for metastatic MuM; 4 (27%) patients experienced a complete response and prolonged cancer-free survival.

Curtin et al[10] found that 39% of patients with MuM have mutations and/or increased copy number in the v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog gene, *KIT*. Drugs such as imatinib have revolutionized the treatment of gastrointestinal stromal tumors because of their ability to inhibit the activity of the product of the *KIT* gene, the tyrosine kinase KIT receptor. Lutzky et al[11] reported that a complete response to therapy with imatinib was demonstrated in a patient with metastatic anal MuM and a mutation in the *KIT* gene at exon 13 (K642E). Our group has begun a study of the KIT receptor tyrosine kinase inhibitor sunitinib in patients with MuM and aberrations in the *KIT* gene. Thus therapy targeting abnormalities in the *KIT* gene and corresponding receptor protein hold promise for improved systemic therapy for some patients with MuM. Much research needs to be done to find the best method to identify patients with relevant abnormalities in the KIT receptor or *KIT* gene and find which of the receptor kinase inhibitors, many already approved for other cancers, will be helpful.

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