Successful management of malodor from fungating tumors using crushed metronidazole tablets

Jamie Katy Hu, BA,[a] Katherine Given Ligtenberg, MD, PhD, MBA,[b] Jonathan Leventhal, MD,[b] and Christopher G. Bunick, MD, PhD[b]
New Haven, Connecticut

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INTRODUCTION

Fungating tumors are associated with advanced cancers, including primary, secondary, and recurrent malignant disease.[1] They are characterized by rapid proliferation, ulceration, necrosis, and skin erosion, causing pain, hemorrhage, excessive drainage, and malodor.[1] In women, these tumors commonly arise from local cutaneous breast cancer metastases, whereas in men, they typically occur as cutaneous metastases of lung adenocarcinoma.[1] Fungating tumor prevalence ranges from 5% to 10% across all tumor types, but not all malignant wounds are fungating, and some malignant cutaneous lesions are slow to develop into wounds. This prevalence is underestimated because fear and embarrassment prevent many patients from seeking health care.[1]

Malodor is identified as the most distressing feature of fungating masses, causing substantial psychological distress for patients and families.[2] Malodor is associated with reduced quality of life, hopelessness, and social isolation,[2] yet malodor management remains suboptimal. The fetor of fungation often proves resistant to intervention, making odor elimination an important clinical challenge.

We report 2 cases of fungating tumors for which significant malodor was well controlled with topically applied crushed metronidazole tablets.

Abbreviation used:

MCC: Merkel cell carcinoma

CASE REPORTS

Case 1

An 87-year-old man with Merkel cell carcinoma (MCC) metastatic to his lungs presented to the hospital with significant bleeding from a large fungating tumor on his left thigh. He was admitted with dyspnea on exertion and a hemoglobin level of 8.8 g/dl in the setting of acute blood loss.

He received a diagnosis of MCC in 2014, which was managed by wide local excision and local radiation. His disease recurred in 2017 and progressed despite additional radiation, multiple wide local excisions, and combined ipilimumab and pembrolizumab therapy.

His tumors enlarged, causing significant bleeding, malodor, and reduced quality of life. Despite disease progression, his primary complaint was malodor from his tumors. He applied silver sulfadiazine to the lesions, which proved ineffective. Independent in all activities of daily living, the patient attended church and his weekly bowling league until a month before presentation, when children at church audibly complained about his smell, causing him to remain home in social isolation.

Upon admission, the dermatology department was consulted for wound care recommendations. At the examination, there was significant malodor upon entering the room. Distributed on the patient's left thigh and leg were dozens of 1- to 3-cm pink-red, semisoft, in-transit metastatic nodules, with a 5-cm plaque comprising clustered nodules

From the School of Medicine[a] and Department of Dermatology, Yale University, New Haven.[b]
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Correspondence to: Christopher G. Bunick, MD, PhD, 333 Cedar St, LCI 501, PO Box 208059, New Haven, CT 06520. E-mail: christopher.bunick@yale.edu.

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Fig 1. Fungating tumors in a patient with metastatic Merkel cell carcinoma. **A**, Dozens of in-transit metastatic nodules with (**B**) a larger plaque comprising clustered nodules with overlying malodorous exudate were distributed on the left thigh.

Fig 2. Fungating tumors in a patient with local cutaneous metastases from invasive ductal carcinoma of the right breast. Numerous violaceous, nodular, and ulcerative tumors were distributed on her right breast, axilla, and upper arm. Notably, there was significant exudate and weeping ulcerations on examination. Initial biopsy of her malignancy showed nuclear grade 3/histologic grade 3 cancer with focal ductal carcinoma in situ. She received several cycles of docetaxel and cyclophosphamide before right breast lumpectomy, axillary lymph node dissection, and radiation. Her disease, however, progressed, and further treatment with capecitabine, combination gemcitabine and carboplatin therapy, local radiation, a combined atezolizumab and MTIG7192A clinical trial, and paclitaxel and monopolar spindle 1 (MPS1) inhibitor combination therapy subsequently failed.

with overlying yellow malodorous debris on the lateral aspect of the left knee (Fig 1, *A*). A 9-cm plaque consisting of similarly clustered nodules with malodorous exudate was present on the upper medial portion of the left thigh (Fig 1, *B*). To ameliorate malodor, one 500-mg metronidazole tablet was crushed and sprinkled onto the 2 largest tumors twice daily (covering approximately 35 cm^2). No debridement or additional steps were required to prepare the tumors for the crushed tablet, and the patient denied adverse effects with application. After 24 hours, the smell completely abated. Subjectively, the patient reported improvement in tumor appearance and reduced exudate. Before malodor elimination, the patient resisted therapeutic interventions for his MCC. After improvement, the patient and his family reported an increased sense of hope and reopened conversations about treatment possibilities. After discharge, the patient attempted to control the malodor with 1% metronidazole gel rather than crushed tablets, but the fetor returned.

Case 2

A 70-year-old woman received a diagnosis of triple-negative invasive ductal carcinoma of the right breast with axillary node involvement in 2014. She received several cycles of docetaxel and cyclophosphamide preceding right breast lumpectomy, axillary lymph node dissection, and radiation. Her disease progressed, and multiple rounds of

Table I. Experiences with topical metronidazole use in patients with fungating tumors

Number of patients	Malignancy	Treatment	Dose	Time to improvement,* d	Year	Reference
32	32 breast, 22 other	Metronidazole gel (Metrotop; Ayrton Saunders, UK)	0.8%	1-30 (majority, 2)	1989	Newman et al[5]
20	Fungating tumors (not specified)	Metronidazole gel	0.75%	7 (initial not specified)	1996	Finlay et al[3]
16	Fungating wounds (not specified), 1 squamous cell carcinoma	Metronidazole gel	0.75%	1	2005	Kalinski et al[12]
9	9 breast, 1 ovarian, 1 lung	Metronidazole gel	0.8%	5-11 (initial not specified)	1992	Bower et al[9]
5	Breast	Metronidazole gel	0.8%	2-5 (median, 4)	1996	Kuge et al[10]
21	Breast	Metronidazole gel (Rozex; Laboratoires Galderma Z.I., France)	0.75%	7 (initial not specified)	2016	Watanabe et al[4]
1	Breast	Metronidazole tablet (crushed)	500 mg	1	2018	This report
1	Metastatic Merkel cell	Metronidazole tablet (crushed)	500 mg	1	2019	This report

*Initial time to malodor improvement was chosen as the parameter because our patients improved within 24 hours and therefore were not assessed at day 7 or day 14 after initiation of topical metronidazole treatment.

combination chemotherapy, immunotherapy, and radiation subsequently failed. In 2016, she developed weeping ulcerative tumors, for which the dermatology department was consulted. The patient complained of tumor malodor and pain.

On examination, there was prominent malodor from the fungating tumors. Distributed on her right breast, axilla, and upper portion of the arm were numerous violaceous, nodular, and ulcerative tumors, ranging from 1 to 5 cm, with irregular, well-defined borders and overlying yellow-brown crust (Fig 2). A 500-mg metronidazole tablet was crushed and sprinkled onto her tumors twice daily. There was immediate reduction in malodor and reduced tumor exudate after several days of therapy.

DISCUSSION

There is currently no standard management for malodor associated with fungating tumors.[1] These tumors are often colonized with mixed anaerobic microbes that thrive in moist and necrotic tissue.[3] Anaerobes produce foul-smelling fatty acids as metabolic end products, and anaerobe elimination correlates with odor improvement.[4] Although oral metronidazole has been used to combat anaerobe infection,[5] many cases resulted in incomplete odor eradication and immediate recurrence upon therapy cessation.[6] Furthermore, long-term oral therapy may not be feasible because of the risk of developing antimicrobial resistance and adverse effects such as nausea, neuropathy, and a disulfiram-like reaction with alcohol consumption.

Evidence shows that topical metronidazole has superior efficacy combating malodor compared with oral therapy[5]; hence, topical metronidazole is recommended by the World Health Organization[7] and the American Society of Clinical Oncology.[8] Topical metronidazole use has been described in trials (Table I[9,10]), although rarely with fungating tumors, and none used crushed metronidazole tablets.[11] Each trial describes odor improvement with metronidazole gel, but many patients experienced adverse effects, such as pain or burning, with application.[3] Malodor improvement after gel treatment ranged from 1 to 30 days (Table I) and was often accompanied by reduced patient-reported pain scores.[3]

In contrast, our patients denied adverse effects with the application of crushed metronidazole tablets. Sprinkling of crushed tablets circumvented painful manipulation of the tumors and eliminated the burning associated with a fluid-phase formulation. Both patients experienced complete resolution of malodor within 24 hours and reduced exudate. Crushed tablets effectively eradicated odor for our patient with MCC, whereas gel could not. The price of a 500-mg metronidazole tablet ranges from $0.20 to $0.65, making this a cost-effective

treatment compared with commercially available metronidazole gel, which 1 study estimated to cost $518.40 for 2 weeks of treatment.[12]

CONCLUSION

In the era of checkpoint inhibitors, patients with cancer live longer with more advanced disease; therefore, managing fungating tumors is clinically relevant. Malodor from fungating tumors dramatically affects the lives of patients and their families.[2] Crushed metronidazole tablets offer an efficacious, cost-effective, painless, and nontoxic therapy for malodor of fungation.

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