CASE REPORT

Treatment of refractory mycetoma by radiotherapy: a case study and review

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Abstract
Mycetoma is a localized chronic subcutaneous infection caused by fungi. It is clinically characterized by a triad of tumefaction, sinuses, and discharge containing typical grains. Eumycetoma, a subtype, is characterized by a low cure rate. Long-term medication and surgical excision are required to treat the infection. Radiotherapy, a less used modality of treatment, may provide a good salvage option for refractory eumycetoma. Herein, we present a case and a review of the literature of refractory eumycetoma of the foot where radiotherapy was used as a salvage treatment. In the present case, a dose of 17.5 Gy in five fractions was delivered, and the response was assessed as per the Response Evaluation Criteria in Solid Tumors 1.1, discharging grains status, and Dermatology Life Quality Index. The literature on the use of radiotherapy for mycetoma was found to be scanty. In the present case with radiotherapy, there was a partial radiological response, resolution of discharging grains, and improvement in the Dermatology Life Quality Index score. However, the benefit was short-lived, but re-irradiation and low-dose radiotherapy resulted in sustained benefits until 15 months of follow up. The antiproliferative and anti-inflammatory actions of radiotherapy can be exploited in the treatment of rare, medically difficult to treat mycetoma. This case report may serve as a basis for further evaluation.

KEYWORDS
benign disease, eumycetoma, low-dose radiotherapy, madura foot, mycetoma pedis, salvage radiotherapy

1 INTRODUCTION

Mycetoma is a localized chronic subcutaneous infection caused by eumycetoma (true fungi) or Actinomycetales (fungus-like bacteria).1 Mycetoma pedis, the most common form of mycetoma, is widely known as Madura foot.2 Although mycetoma is found worldwide, its exact incidence is unknown because of the slow, chronic nature of the disease, and late presentation by a majority of patients.3

The first reference to mycetoma dates back to the Byzantine era (300–600 AD), with evidence from a skeleton whose morphological bone changes were suggestive of a mycetoma infection.2,4 The first written reference to mycetoma is in the ancient Indian religious book, Atharva Veda, where it was mentioned as “pada valmikam” or “anthill foot”.5

The first description of mycetoma was attributed to John Gill, who reported the disease in a dispensary report of the Madras Medical

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Service of the British Army in India, in 1842. In 1846, Colebrook, who succeeded Gill, described further cases and introduced the term, Madura foot, after the region of Madurai in South India, where it was first identified. The first description in the medical literature was by Godfrey in 1846, who referred to the disorder as "morbus tuberculosis pedis". Carter recognized the fungal nature of the disease and introduced the name, mycetoma, or, fungus tumor, in 1860. In 1913, Pinoy et al. recognized the possibility of classifying mycetomas according to the causative organisms. The formal classification, which is still valid, was put into place by Chalmers and Archibald, who divided them into two groups: group 1, maduramycosis (eumycetoma), caused by true fungi; and group 2, actinomycosis (actinomycetoma), caused by Actinomyces belonging to a higher bacteria class.

Clinically, M. pedis (Madura foot) is characterized by a triad of tumefaction, sinuses, and discharge containing typical grains. Gradually, new nodules appear and may coalesce to form larger multilocular nodules or tumor-like masses. Over the next few months, the nodules soften at the surface and ulcerate, discharging purulent fluid containing characteristic grains. Occasionally, these ulcers and sinuses show exuberant granulation tissue and crusting. During the ensuing months, the lesion broadens and spread to the deeper tissues, such as muscles and bones. As new lesions appear, the older lesions heal, resulting in a depigmented and scarred skin. The diagnosis may involve radiology, ultrasonic imaging, cytology, culture, histology, and/or immunodiagnostics. Actinomycetoma is amenable to treatment with antibiotics, preferably by combined drug therapy for a long period. Eumycetoma is usually treated with aggressive surgical excision combined with antifungal medicines, such as ketoconazole, voriconazole, or itraconazole. Most mycetoma cases are painless, but it is a potentially serious, chronic, and devastating inflammatory pathology that may be refractory to multiple lines of antifungal and antibiotic treatment.

There is a longstanding tradition in Middle Europe, particularly in Germany, where radiotherapy (RT) is used for inflammatory and benign diseases. In some historic series from the kilovoltage era, successful treatments were reported for a variety of entities, such as paronychium, furuncles, lymphadenitis, abscesses, parotitis, soft tissue infections/phlegmon, hidradenitis suppurativa, and osteomyelitis. Historically, Heidenhain and Fried revealed that RT can be used for a spectrum of acute and chronic inflammation in clinical refractory stages, including acute lymphadenitis, hidradenitis suppurativa, soft tissue infections/phlegmon, osteomyelitis, pleuritis, and various abscesses (renal, gynecological, and perirectal). Successful radiation treatments for infectious skin disorders, such as actinomycosis and pneumonia, have also been reported. Studies conducted to investigate the immunomodulatory role of RT in alleviating symptoms of the coronavirus disease 2019 pneumonia have also shown to be beneficial.

Here, we present a case of refractory eumycetoma in which RT was used as a salvage treatment.

The patient was a 41-year-old male patient who had been well 9 years earlier when he developed single painless skin-colored papules on the lateral malleoli of the right foot. The papules progressed in 3–4 months to fluctuant swelling, and developed pus discharge and multiple sinuses with black grains.

The patient was diagnosed with eumycetoma based on microbiological culture (septate hyphae) and magnetic resonance imaging (dot in circle sign). He was initially treated with itraconazole 200 mg b.i.d. for 4 months, which resulted in a 30% improvement. Subsequently, he stopped the medication and developed sinus discharge progression and reappearance. Conventional radiography revealed no bony involvement. The patient was administered itraconazole, terbinafine, and voriconazole, with a 20% improvement in 6 months.

Within 3 months after discontinuation of treatment, the disease reappeared, but no treatment was initiated. After a gap of 18 months, the patient was administered itraconazole and terbinafine with no improvement. Surgical debridement was performed, and cotrimoxazole DS was added because of the mixed infection. An improvement of 30% was noted; however, the disease progressed within 6 months. Another surgical debridement was performed, and voriconazole was initiated. However, three months later, the medial, lateral, and posterior aspects of the foot became involved, presenting with multiple soft-to-firm tumorous growths ranging from 1 to 6 cm in diameter with multiple overlying sinuses (Figure 1). The tumorous growth infiltrating the calcaneal bone resulted in marked tenderness and edema. The Dermatology Life Quality Index (DLQI) score was 27.

Finally, only surgical amputation was considered as the ultima ratio treatment option. However, the patient refused amputation and was referred for RT.

Informed consent was obtained from the patient included in the study. Ethical approval was not required at our institution for publishing an anonymous case report. All procedures followed the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008.
FIGURE 2  (A) Planning computed tomography scan of the right foot showing the gross target volume (in red) and clinical target volume (in yellow); (B) Dose distribution

3  |  RT PLANNING

After a panel discussion, the patient was scheduled for salvage RT. A customized wax block of 15-mm thickness was individually made for the right foot (Figure 1). A computed tomography scan (Philips Brilliance Big Bore 16 slice computed tomography scanner) was performed for planning of the therapy (slice thickness of 3 mm), with the patient in a sitting position with the right foot slightly extended. It was tightly wrapped by bandages to prevent air gaps, and the computed tomography scan was imported to the Monaco 5.11 Planning system. The tumorous growth was delineated as the gross target volume and the right foot as the clinical target volume (Figure 2A).

Two sets of lateral opposing beams of 6 MV photons were applied. We decided to irradiate with a dose of 17.5 Gy in five fractions at 3.5 Gy per daily fraction to trigger antiproliferative and anti-angiogenic effects. The treatment plan was evaluated, and a plan with a hotspot of <107% and prescribed dose coverage of >95% was chosen (Figure 2B). The treatment was delivered in a linear accelerator (Elekta Versa HD). Treatment response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) V 1.1, the status of the sinuses, and discharge of grains. The DLQI is used to assess the impact of treatment on the quality of life of patients.

4  |  RESULTS

The patient had no treatment gap and had good tolerance to treatment. The DLQI score was 27 before RT (Figure 3A). One week after completing RT, he had stable disease as per RECIST v1.1, with a 10% decrease in the gross target volume, along with an improvement in the DLQI score to 22.

At 6 weeks after the completion of treatment, a partial response (30% reduction in the gross target volume) was observed with a complete resolution of sinuses and discharge grains (Figure 3B). Healthy granulation tissue appeared around it, and the DLQI further improved to 18. However, the improvement was short-lived, and 8 weeks after RT, the disease progressed again with an increase in edema and the appearance of sinus discharges with the DLQI worsening to 24 (Figure 3C).

Based on the initial good response, a hypofractionated RT plan with 15 Gy in five fractions at 3 Gy per daily fraction was repeated. This radiation treatment was applied in a similar manner as the first treatment. At the first follow-up visit after 6 weeks, the patient again showed a partial response (30% decrease in the original tumor volume) with partial resolution of the sinuses and discharge of grains with the DLQI improving to 18 (Figure 3D).

There was an increase in edema and discharge from the sinus, along with a burning sensation in the affected foot on further follow ups, for which the patient received non-steroidal anti-inflammatory drugs (a combination of diclofenac sodium and paracetamol) and a session of 0.5 Gy as anti-inflammatory low-dose RT. The patient was followed up with itraconazole antifungal treatment. Follow up at 9 months post-radiotherapy showed disappearance of edema and sinus discharge. In addition, there was a significant decrease in the size of the tumor-like mass and improvement in the quality of life, with the DLQI decreasing to 10 (Figure 3E). Furthermore, during the 15 months of follow-up, the response was sustained (Figure 3F).

5  |  DISCUSSION

Mycetoma is a disease commonly found in the tropics, such as Mexico, Sudan, Venezuela, and India. It is endemic in Africa, India, and Central and South America between latitudes 15°S and 30°N, the often so-called “mycetoma belt”. Men are more commonly affected; the most common site is the foot, as barefoot walking is common and is the leading cause of contracting the infection. The World Health Organization considers mycetoma as a neglected tropical disease. Eumycetoma has disappointing cure rates; long-term medication and surgical excision are required to treat the infection. Still, the cure rate is around 30%. The MycetOS (Mycetoma Open Source) project was launched to discover new drugs to find a cure for this debilitating disease.
In this medically problematic situation, in particular, in cases where the amputation of the foot is considered, other treatment approaches, such as RT, are justified. RT is being re-explored for its use in infectious diseases. RT was reported only as a treatment option to stop life-threatening hemoptysis in lung mycetoma. Falkson et al. treated five patients with 3.5 Gy administered once a week. Hemostasis was achieved in all the patients. Three patients required 7 Gy, one 10.5 Gy, and the fifth patient required a total dose of 14 Gy. With these encouraging results and a better understanding of the immunomodulatory effects of radiation, salvage RT was planned in this refractory case of mycetoma of the foot. The patient received two courses of an antiproliferative regimen, showing a regression each time. Subsequently, he received a very low dose of anti-inflammatory radiation against the inflammatory component.

The radiobiological mechanism of action of radiation in eumycetoma is unknown. Particularly because the pathogenetic and pathobiological background of the disease is not well known. Complement-dependent chemotaxis of polymorphonuclear leukocytes is induced by both fungal and actinomycotic antigens in vitro. Cells of the innate immune system attempt to engulf and inactivate these organisms; however, they ultimately fail to accomplish this goal. The persistence of the organism after an initial inoculation appears to be related to its ability to evade host defense through a variety of adaptations, such as cell wall thickening and melanin production. These mechanisms protect microorganisms against ultraviolet radiation and destruction by alveolar macrophages, enzymatic lysis, oxidants, and protection against antifungal drugs.

In animal models, it was suggested that the fractions of the microorganisms are chemotactic for granulocytes. The resultant influx of leukocytes to the site of inoculation is attributed to chemotactic activity-induced by-products of complement activation. T-cell responses also play an important role in the development of mycetomas. Th2-like responses (interleukin-10 and interleukin-4) were found in the primary lesions. Overall, the microorganisms induce both a pro-inflammatory and an anti-inflammatory environment. This results in macrophage polarization, which may be the basis for mycetoma presenting with severe inflammation, tissue damage, and proliferation. It can be hypothesized that low-to-intermediate-dose RT can have a positive influence on this pathogenetic action by anti-inflammatory effects on the immunocompetent cells and pro-inflammatory cytokines. On the contrary, radiation treatment has antiproliferative effects on hyperproliferative disorders, such as keloids and Dupuytren’s contracture, by interacting with cytokines, such as tumor growth factor-β and proliferative cell populations,
such as myofibroblasts. Thus, this can also play a role in mycetoma formation.24 Falkson et al. also postulated an effect of RT on the blood vessels and vasculature in mycetoma.25

6 CONCLUSION

To our knowledge, this is the first reported case of the use of RT to salvage refractory M. pedis. Nevertheless, the disease was not completely resolved, but there was a significant improvement in the quality of life of the patient, a decrease in sinus discharge, and reduced inflammation. Nevertheless, the disease was not completely resolved, but there was a significant improvement in the quality of life of the patient, a decrease in sinus discharge, and reduced inflammation. These results add up to the antiproliferative and immunomodulatory role of RT, which may serve as a basis for further evaluation of the value of RT in rare and medically difficult to treat fungal diseases.

CONFLICT OF INTEREST

The authors declare that they have read the article and there are no competing interests.

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How to cite this article: Gupta A, Sharma D, Gupta S, et al. Treatment of refractory mycetoma by radiotherapy: A case study and review. Prec Med Oncol. 2021;5208–212. https://doi.org/10.1002/pro6.1125