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Case Study

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Corresponding author:
Anupam Muraleedharan;
Email: anupamazhikode@gmail.com

Radiotherapy for refractory eumycetoma: another weapon in the antifungal armoury?

Sandip Kumar Barik, Anupam Muraleedharan, Avinash Badajena, Bikash Ranjan Mahapatra, Sk Soel Ahmed, Chandra Sekhar Sirka, Madhusmita Sethy, Deepak Kumar Das, Saroj Kumar Das Majumdar and Dillip Kumar Parida

All India Institute of Medical Sciences, Bhubaneswar, OD, India

Abstract

Introduction: Mycetoma is a chronic infection of the skin and the subcutaneous tissue caused by both bacteria and fungi. Eumycetoma, caused by fungus, requires prolonged use of antifungals and/or surgery.
Methods: In this scenario it has been attempted to treat a case of eumycetoma with an aim to improve the symptoms and to give an antifungal drug free period. Radiotherapy was delivered in two sittings. In the first sitting, 20 Gy in five fractions was given. Because of the excellent response to the radiotherapy, after 9 months, another 15 Gy was delivered in five fractions.
Results: The symptom-free period extended for another 11 months, making a cumulative effect of 21 months.
Conclusion: The use of radiotherapy in the salvage of refractory eumycetoma cases should be further explored.

Introduction

Radiotherapy plays a vital role in the multimodality management of cancers. Its utility in managing benign/non-oncological diseases is increasingly being explored. The groups of diseases include inflammatory, degenerative, hyperproliferative, functional and infectious diseases.[1] Many studies have been conducted to treat pneumonia, orthopaedic infections and otolaryngological infections with radiotherapy in the pre-antibiotic era.[2] Because of concerns about long-term toxicity, interest in using external beam radiotherapy had waned. With antibiotic and antifungal resistance development, there is a renewed interest in using radiotherapy as an alternative in refractory cases of infectious diseases.

Mycetoma is a chronic infection of the skin and subcutaneous tissue. The WHO declared it a 'neglected tropical disease' in 2016. Mycetoma is predominantly distributed in tropical and subtropical regions of the world. This includes countries such as Chad, Ethiopia, India, Venezuela, Mexico, Senegal, Sudan, Thailand and Yemen, collectively belonging to the 'Mycetoma belt'. The mode of infection is through traumatic inoculation of the fungi or bacteria. This usually affects manual labourers working in agricultural fields without protective gear such as footwear or gloves.[3]

Mycetoma can be broadly divided into two categories based on the causative agents.[1,4] Actinomycetoma is caused by bacteria, and eumycetoma is caused by fungi. The common bacterial agents include *Actinomadura pelletieri*, *Actinomadura madurae*, *Streptomyces somaliensis*, *Nocardia brasiliensis* and *Nocardia asteroids*, and the common fungal agents include *Madurella mycetomatis*, *Madurella fahalii*, *Madurella tropicana* and *Medicopsis romeroi*. Eumycetoma is commonly referred to as 'Madura mycosis'. This name comes from the name of the South Indian city of Madurai. It was from here that John Gill, in 1842, first reported about the disease that caused deformity of the foot associated with 'fungoid excrescences'.[4] The clinical features of mycetoma include painless plaques, discharging sinuses and characteristic granular grains or microcolonies.

The treatment of actinomycetoma includes using a combination of antibiotics, while prolonged use of antifungals and surgery is needed for eumycetoma. The long duration of use of antifungals such as triazole antifungals can also cause side effects such as hepatotoxicity, skin reactions, renal toxicity, CNS toxicity and cardiac toxicity.[5] In this context, attempts are being made to reintroduce radiotherapy in refractory eumycetoma cases.[6] Here, we present a case of refractory eumycetoma of the foot, which was treated by radiotherapy.

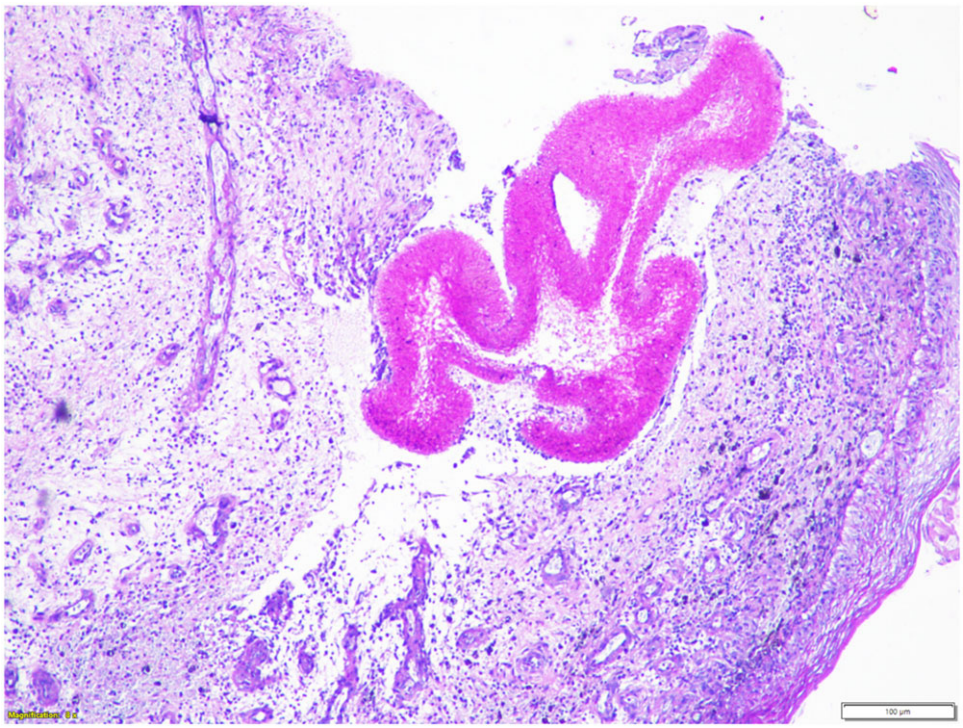

Figure 1. Periodic acid-Schiff staining of the wedge biopsy specimen from the foot showing the fungal colony along with infiltration of the dermis with lymphocytes, plasma cells, neutrophils and eosinophils.

Case Report

The patient, a 41-year-old male, presented to the orthopaedics outpatient department with a complaint of localised swelling with the discharging sinus of the left foot in 2016. A clinical diagnosis of fungal osteomyelitis was made, and a wedge biopsy was taken from the papule in the left foot, which showed that the dermis infiltrated with a dense inflammation consisting of lymphocytes, plasma cells, neutrophils and eosinophils and a large fungal colony in the superficial dermis (Figure 1). He underwent debridement of the lesion twice, in 2016 and 2018. He was on oral itraconazole, oral terbinafine, oral fluconazole and the modified Ramam regimen for varying periods before 2019. In January 2019, he was started on table itraconazole 200 mg twice daily for 18 months. The frequency of discharge of grains reduced from two to three episodes per month before starting itraconazole to one episode per month after beginning therapy. After that, the patient was started on tablet voriconazole 200 mg twice a day for 3 months. The discharge frequency was reduced from one episode per month to one episode per 3 months. The patient developed voriconazole-induced deranged liver function tests. Then, the patient was referred to the radiation oncology department for radiotherapy (Figure 2). (All images were taken with due permission from the patient.)

The patient was simulated in the feet-first supine position using a 1-cm-thick bolus made of dental wax (Figure 3). The CT simulator was GE & Optima CT580. A thermoplastic cast was used for immobilisation. Three-dimensional conformal radiotherapy was the treatment technique. Three beams (anteroposterior, right lateral and left lateral) were used to cover the target volume, which was the left foot (Figure 4). 20 Gy in five fractions at 4 Gy/fraction was given in December 2021 using the high-energy linear accelerator Elekta Versa HD with 10 megavolt photon energy. The tissue around the foot was softened with a reduction in the serosanguinous discharge and that of grains. This response was sustained till September 2022 (9 months) (Figure 5). Another course of radiotherapy was planned because of the excellent response to the first course. 15 Gy was delivered in five fractions at 3 Gy/fraction (September 2022). The response was sustained for another 11 months before the initial symptoms reappeared, and he was restarted on antifungals.

Discussion

The delay in diagnosis, the protracted course of treatment and the ignorance among the group of people who are more prone to develop this cancer all contribute to the tag of neglected disease to mycetoma. The use of radiotherapy in its management protocol has been rarely explored before this attempt. Only one case study stood as a guide to our treatment.[6] 17.5 Gy in five fractions at 3.5 Gy per fraction was used for the first course in that study. The response was short-lived (2 months). Another 15 Gy in five fractions at 3 Gy per fraction was delivered, which gave a sustained response for 15 months. The initial poor response could be attributed to the reduced dose, as evident from our experience. For the first course, the biologically equivalent dose was 23.6 Gy_{10} in that study compared with 28 Gy_{10} in our study. This could be a pointer toward the role of a higher dose in the first treatment phase for a longer response duration.

Radiation has been used to sterilise fungi in the agricultural/food processing sector at a much lower dose.[7,8] Most studies on treating eumycetoma treated haemoptysis caused by pulmonary

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Figure 2. The fungal osteomyelitis lesion on the left foot upon presentation at the radiation oncology department.

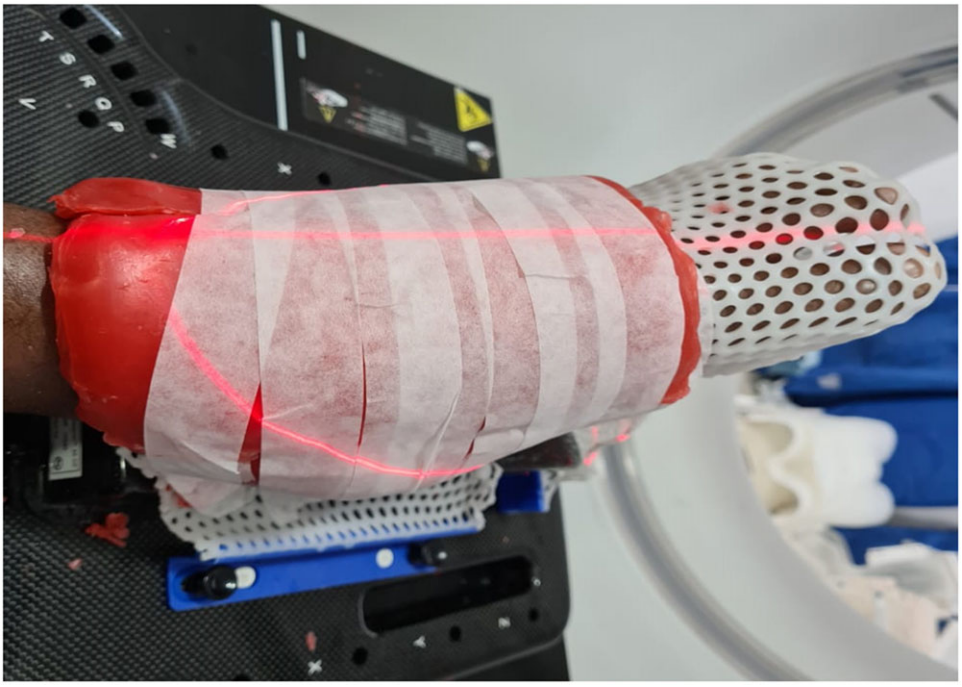

Figure 3. The image showing the immobilisation for CT (computed tomography) simulation of the left foot using bolus.

mycetoma.[9] They used a dose range from 7 Gy to 14 Gy, which gave a definitive relief from symptoms. Haemoptysis due to chronic pulmonary aspergillosis refractory to bronchial artery embolisation is being routinely treated by radiotherapy. The latest efforts at incorporating stereotactic body radiotherapy have also met with success. Because the intention of treatment is palliative, the dose fractionation ranged from 20 Gy in ten fractions to 16 Gy in two fractions.[10]

The haemostatic action of radiotherapy can be explained by its ability to cause obliterative endarteritis. However, the mechanism of antifungal action needs to be further investigated.

Conclusion

Radiotherapy can be used as a salvage treatment in the case of refractory eumycetoma. It can also be used in case of adverse

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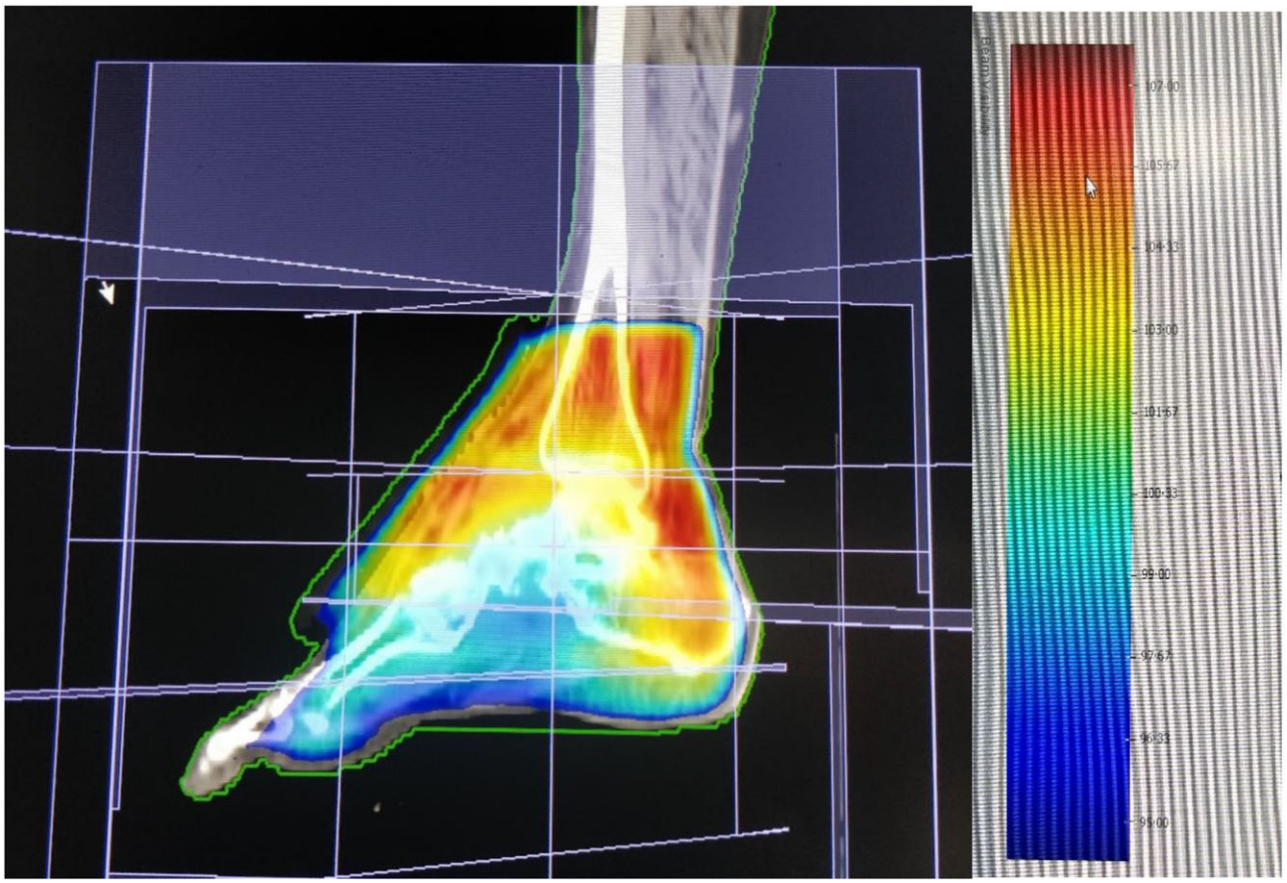

Figure 4. The dose colour wash of the three-dimensional conformal radiotherapy plan using anteroposterior, right lateral and left lateral beams.

Figure 5. The appearance of the left foot post 9 months of completion of radiotherapy course.

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reactions to antifungals. More studies are recommended to reach a consensus on the dose and fractionation.

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