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Case report

A rare case of candida osteomyelitis of the mandible associated with osteoradionecrosis and biofilm formation

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ABSTRACT

Candida osteomyelitis, in general, is a relatively rare manifestation compared to its bacterial counterparts. The mandible's involvement is rarer, lacking established management and fewer guidelines. Herein, we aim to illustrate the significant challenge in treatment, namely due to the persistent and resistant nature of *Candida albicans*-associated biofilm. A multidisciplinary approach involving adjunctive use of antifungals with surgical interventions is typically necessary and feasible in this case. However, surgical interventions may not always be possible in challenging instances in which the patient may be structurally (including osteoradionecrosis) and vascularly compromised, raising questions about the feasibility of standard-of-care as well as the success of alternative therapies aimed at disrupting biofilm formation. Clinicians should maintain a high index of suspicion for complicating, deep-seated Candidiasis in at-risk populations and endeavor to treat as aggressively as possible to limit recurrent disease owing to persistence.

Case

The patient is a 73-year-old female with a past medical history most remarkable for metastatic Squamous Cell Carcinoma of the left posterior tongue, status post multiple transoral laser micro resections, and left modified radical neck dissection followed by weekly radiation therapy (with carboplatin as a radiosensitizer) for six weeks. Her treatment course was complicated by mucositis, esophageal stenosis, and recurrent oral candidiasis. She eventually began experiencing increasing pain around the two left lower molars, which required extraction by an oral surgeon in the Spring of 2021, as well as multiple treatments with hyperbaric oxygen subsequently. Post-extraction jaw swelling prompted the initiation of two consecutive courses of amoxicillin-clavulanate for suspicion of associated, complicated soft tissue infection. A maxillofacial CT scan was performed in June 2021 and revealed diffuse osteitis of the mandible, which was attributed to prior radiation or osteomyelitis. As such, she was referred to our Infectious Diseases clinic for further evaluation in July 2021. Her complex course has been summarized in the attached Supplement-1.

An MRI of the face with and without IV contrast was obtained, and it appeared to favor osteoradionecrosis over frank osteomyelitis (Fig. 1). In late August 2021, she returned to the head and neck surgery clinic complaining of recurrent jaw swelling associated with two areas of visible drainage along the medial aspect of the left mandible, consistent with sinus tract formation. Biopsy of the exposed left mandible was performed in the operating room, and histopathology revealed features of osteonecrosis with Grocott's methenamine silver (GMS) stain highlighting fungal organisms. Subsequent left mandible tissue cultures were finalized at the end of September 2021. They were reported positive for fluconazole-sensitive *Candida albicans* and *Saccharomyces cerevisiae,* with a minimum inhibitory concentration (MIC) of 1 mcg/mL. Our service was alerted and felt that the patient's previous history of instrumentation, radiation, and associated osteoradionecrosis predisposed her to the development of Candidal osteomyelitis of the left mandible. Considering the significant bony deterioration, our institutional head and neck surgical colleagues (ENT) suggested resection and immediate reconstruction with an osteocutaneous fibular free flap. However, it was felt that compromised dermal integrity owing to significant scarring in her neck from prior surgeries and radiation therapy would likely fail the flap due to poor vascularization. Therefore, maximizing medical treatment with an extended course of antimicrobials was preferable before further surgical repair. Given the paucity of literature or established treatment protocol guidance, initiating the patient on a protracted course (> six months) of fluconazole 400 mg PO every 24 h was felt best.

Three weeks after initiation of therapy, she was re-admitted to our

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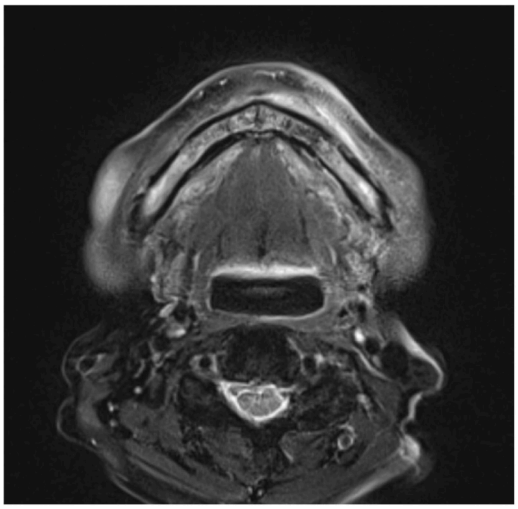

Fig. 1. MRI of the face showing osteoradionecrosis and chronic osteomyelitis of the mandible.

hospital on account of worsening facial pain and trismus. MRI of the brain with and without IV contrast did not show prominent drainable fluid collections; it demonstrated known osteoradionecrosis and osteomyelitis. She was transitioned to caspofungin 50 mg IV every 24 h for six weeks, followed by a resumption of fluconazole to complete a six-month course of therapy. Although she experienced progressive improvements throughout parenteral therapy with caspofungin, she was readmitted in mid-November 2021, three days before completing it, complaining of acute right jaw pain, swelling, and trismus. A maxillofacial CT scan was obtained and revealed a right masticator space abscess. Empiric piperacillin-tazobactam was initiated, followed by attempted, though unsuccessful, percutaneous aspiration. Piperacillin-tazobactam was ultimately discontinued in favor of empiric amoxicillin-clavulanate suspension (250 mg – 62.5 mg / 5 mL) 10 mL three times daily to complete a 6-week course of treatment in conjunction with previously outlined fluconazole 400 mg PO every 24 h targeting a six-month course for the latter agent. Liver function tests were obtained every two weeks while on antifungal therapy and remained within normal limits.

By December 2021, she returned to our clinic after completing the 6-week antibacterial course of amoxicillin-clavulanate, endorsing the resolution of swelling and trismus. MRI of the face with and without IV contrast was obtained at the end of March 2022 and demonstrated interval improvement of left mandibular osteomyelitis with a resolution of the right masseteric abscess. She completed the six-month course of PO Fluconazole in early April 2022 with continued improvement. However, during the May 2022 follow-up, the patient again complained of jaw fullness and discomfort, demonstrating the development of lower jaw pustular lesions reminiscent of previous sinus tracts. Because of underlying osteoradionecrosis, it was suspected that the remnant yeast colonies had most likely formed extensive deep tissue biofilms in the bone with lingering pockets of infection, and effective source control would remain a challenge. Unfortunately, an MRI of the mandible with and without IV contrast repeated in early June 2022 confirmed the presence of residual osteomyelitis of the jaw. Re-initiation of parenteral antifungal therapy with caspofungin was recommended until our ENT colleagues devised a definitive surgical plan. Due to unfortunate personal circumstances at the time, the patient expressed concerns about receiving daily intravenous infusions. In the interim, she was placed back on PO fluconazole 400 mg PO q24hrs until the day of surgery. In September 2022, she eventually underwent bilateral mandibulectomy and reconstruction with a composite left fibula free flap affixed with titanium plates and screws (Fig. 2), covered by a split-thickness skin graft from the left thigh. She was eventually discharged home in stable condition with plans to continue outpatient follow-up in our clinic

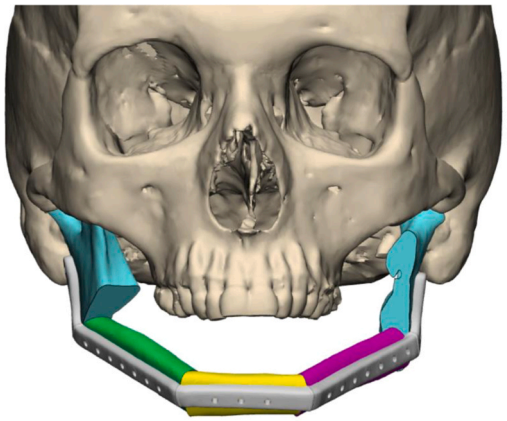

Fig. 2. 3D representation of the mandible reconstruction with a composite fibula free flap affixed with titanium plates and screws.

within four to six weeks postoperatively. Ultimately, the patient would demonstrate radiographic resolution of inflammatory changes suggestive of osteitis by October 2022, when her suppressive Fluconazole 200 mg PO q24hrs course was discontinued. Unfortunately, her malignancy would relapse, prompting re-initiation of adjuvant chemotherapy by early 2023.

Discussion

Candida osteomyelitis of the mandible is an infrequent and complex condition, with very few cases reported in the literature to provide clear therapeutic strategies. The 2016 Infectious Diseases Society of America (IDSA) clinical practice guidelines for management of candida osteomyelitis recommends the use fluconazole 400 mg PO for six to 12 months or two weeks of an echinocandin (caspofungin, micafungin, or anidulafungin) for at least two weeks followed by step-down fluconazole 400 mg PO for six to 12 months, as well as surgical debridement in certain cases. [1] Such recommendations are based on limited published case reports and case series. This case was particularly more challenging due to the propensity of *Candida albicans*, a commensal microbe of the native human microbiota [3–6], to generate deep-seated, biofilm-associated infections [3,4] especially in the setting of osteonecrosis with a history of multiple surgical instrumentations to include dental extractions. A recent literature review also favors fluconazole or echinocandins over amphotericin B due to its antibiofilm activity occurring at high concentrations, which is generally considered unsafe and toxic. [2,3,8].

Radiation-induced osteonecrosis of the mandible, a complication of the treatment this patient received for squamous cell carcinoma of the tongue, resulted in reduced production of mature bone tissue [7] and likely provided Candida albicans with an ideal biological surface to colonize and eventually infect by forming an extensive, intricate, deep-seated biofilm within the mandible, ultimately making this case of osteomyelitis, rarely linked to fungal infections [5], quite challenging to treat with the sole use of antifungals. It is important to note that abnormal microenvironmental conditions stemming from disrupted tissue architecture and fibrosis that exist even after completion of radiation treatment will perpetuate the tissue damage over time. [7].

Infections from *Candida albicans* often present with forming a biofilm [3,4], rendering eradication quite challenging. A review of the available literature suggests [1,2] that surgical debridement and resection would be the key to dislodging this infection. Unfortunately, concern for structural instability and the patient's reluctance to undergo an extensive reconstruction required the design of a treatment aimed at pharmacologically disturbing the composition of the existing biofilm initially, ultimately aiming to suppress its persistence/propagation.

Biofilms are the preferred growth state for Candida albicans and

most microorganisms [4], such as *Staphylococcal species*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. The National Institute of Health (NIH) estimates that approximately 80 % of chronic infections in the United States are associated with a biofilm etiology. [3,8] A biofilm is a highly organized network of microorganisms enrobed by an extracellular matrix (ECM) [2,8] and affixed to a biological or synthetic substrate. In this case, the ECM protects fungal cells against hostile environmental conditions by increasing their tolerance to antifungal agents and resisting the host's immune response. [3–5,9] As such, a biofilm greatly interferes with conventional pharmacological treatment approaches and, in turn, contributes to higher morbidity and mortality rates. [2,3,8].

Candida albicans biofilm formation generally takes 24 to 48 h [3,4] and can be partitioned into four phases: adherence, proliferation, maturation, and dispersal. [3,4,9] During the adherence phase, yeast cells attach to a biological or non-biological surface, the osteoradionecrotic mandible in this case, and form a basal layer that will harbor the biofilm. [3,4] Of note, *Candida albicans* antifungal resistance is increased within 15 min of cell adhesion. [5] The proliferation phase sees yeast cells changing their morphology to hyphae and pseudo hyphae [4], which elongate and commence invading the host surface by forming an intricately layered matrix responsible for the general hardiness of the biofilm. [3,4] A self-produced exopolymeric substance (EPS), an essential component of the ECM along with water, materializes during the maturation phase, blanketing hyphal layers, and is responsible for keeping the entire biofilm structure together. [3,4] Elongated yeast cells from the top hyphal layer are released during the dispersal phase, to colonize and establish new sites of infection [3,9] and initiate a new biofilm formation process. [4] A fully developed *Candida albicans* biofilm is ordinarily several hundred micrometers thick. [3].

The ECM of Candida albicans biofilms should remain a significant focus for future translational research on drug development. The ECM is a major contributor to resistance [3,4] due to its ability to trap antifungal molecules [3,4,9] and reduce the antifungal tissue concentration. [9] Such reduction, in turn, increases the biofilm's resistance to subsequent therapy, "[…]an outcome that may have serious clinical implications should mutated cells be dispersed from a recalcitrant biofilm." [9] Caspofungin displays excellent activity against Candida albicans biofilms at therapeutic concentrations [3]. Although biofilms are intrinsically resistant to Fluconazole and other azole derivatives [3,9], protracted courses, including lifelong suppression, may often be the best salvage therapy [2].

Gamaletsou MN [2] et al. provide an excellent literature review about Candidal Osteomyelitis cases in adults and children, highlighting the discordance in approach given the complexity of such presentations. Similarly, and more specifically, Attie et al. [6] reported the successful treatment of two cases of *Candida* mandibular osteomyelitis in marijuana and heroin abusers with fluconazole and surgical debridement. As in our case, medical management alone proved prone to recurrence, ultimately requiring mechanical removal of the deep-seated biofilm. In congruence with the evidence, we suspect that a multidisciplinary consensus involving medical and surgical therapy would be ideal for management, with timely surgical intervention as early as possible to disrupt the formation of deep-seated tissue Biofilm. Pharmaceuticals targeting critical components of the biofilm's ECM and the communication capabilities of yeast cells could represent a promising alternative to potentially unseat such Candida albicans biofilms when surgery is not an option.

Author contributions

Gabriel Godart wrote the paper. Sammer Elwasila supervised, reviewed, and edited the original draft. Ravindra Durvasula supervised and validated the manuscript. All authors read and approved the final manuscript.

Authors statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethics approval

Ethics committee approval was not required for this case report

Consent

Written informed consent was obtained from the patient to publish this case report and. accompanying images. A copy of the written consent form is available for review by the editor-in-chief of this journal upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.idcr.2024.e02029.

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