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Cover Page Footnote

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CASE REPORT

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ABSTRACT

Although thought to be uncommon, it is believed that cervicofacial actinomycosis is underreported due to frequent misdiagnosis. It has been called the "most misdiagnosed disease by experienced clinicians". A wide range of dental procedures or trauma, including tooth eruption, may precipitate actinomycosis by enabling microorganisms to penetrate the deeper tissue layers via an entry point. This infective disease is significant due to its potentially aggressive and locally destructive nature. This case describes a patient diagnosed with cervicofacial actinomycosis. Her history prior to this was significant for proliferative verrucous leukoplakia, and T4aN0M0 (AJCC 7th Edition) squamous cell carcinoma of the right hard palate for which she received surgery and post-operative radiotherapy. The mechanism of actinomycotic infection, its presentation, differential diagnosis, and management is discussed, with review of the relevant literature. This case highlights an unusual case of cervicofacial actinomycosis and demonstrates the complexities in reaching a definitive diagnosis in cases of osteomyelitis and osteoradionecrosis with significant bacterial burden.

Key words: actinomycosis, actinomycosis cervicofacial, osteomyelitis, osteoradionecrosis

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INTRODUCTION

Actinomyces are filamentous, branching, slow-growing, gram-positive anaerobic bacteria, and form a saprophytic component of the endogenous flora of the oral cavity.[1] In early childhood, the human mouth is colonized by different *Actinomyces* species, *and they* are a part of the normal oral flora.[2] Of the 30 A*ctinomyces* species, 8 may cause disease in humans, including *A. israelii, A. gerencseriae, A. viscosus, A. naeslundii* and *A. odontolyticus*.[3] The most of common of these is the strictly anaerobic species *Actinomyces israelii*.[3,4] *Actinomyces* species, while of low pathogenicity, can invade when there is a portal of entry, typically in the mucosa of the gastrointestinal tract.[5] This can present as suppurative abscesses or indurated masses, and are locally aggressive and destructive.[1,6] As suggested by Cope in 1938, this infection can be anatomically and clinically divided into three types; cervicofacial, pulmonary, and abdominopelvic.[1,7] Cervicofacial actinomycosis is the most common form of the disease, seen in up to 55% of cases.[5,8] *A. isrealii* and *A. gerencseriae* are implicated in almost 70% of cervicofacial actinomycosis.[1,9] *A. naeslundii* and *A. viscosus* are the next most encountered.[9] Clinical features include a peak incidence in the fourth and fifth decades of life, a male predilection (2.4:1) and predominance in immunocompromised individuals.[1,5-7] If females are affected, they tend to be younger, between 11 and 30 years of age.[9] Classic actinomycosis is characterized by a triad of localized abscesses or swellings with suppuration, tissue fibrosis, and sinus discharge of characteristic, but not pathognomonic, sulfur granules.[3] The sulfur granules are not pathognomonic as they are also produced by mycotic pathogens, *Nocardia*, and Botryomycosis, and even if present, may not be readily detectable.[10] Diagnosis of this condition, particularly in the oral cavity, is known to be difficult.[1,4,5,11] This may be complicated by its myriad presentations and the ability of this disease to mimic other medical conditions.[11-13] In addition to its classic presentation, it may also present as single or multiple of the following: ulcerations, sinus tracts, oroantral fistulas, midline palatal defects, osteoradionecrosis (ORN), osteomyelitis associated with bisphosphonates, osteomyelitis unrelated to radiation or bisphosphonates, periapical lesions, odontogenic cysts, peri-implantitis, lesion mimicking periodontal disease or subperiosteal swellings of the jaw.[6,8,10,14-16] Amongst the many

differential diagnosis, the less frequently encountered but significant conditions such as malignancies, lesions caused other bacterial organisms including *treponema pallidum* and *mycobacterium tuberculosis*, and a deep fungal infection should be considered.[17]

Actinomycosis is considered relatively rare nowadays and is so listed by the Office of Rare Diseases at the National Institute of Health, however it was common in the pre-antibiotic era.Its incidence in certain regions of the world appears to be decreasing.[9] Before the advent of antimicrobial therapy, it was considered a condition that was difficult to treat, frequently relapsing and life threatening when the infection was disseminated.[9] This infection is reported to be unusual in the oral mucosal membranes, and there are only a few cases reported in the literature of primary actinomycosis arising within the oral cavity.[1,5-7,11,12] It has been reported as the "most misdiagnosed disease by experienced clinicians".[1] Although rarely seen in everyday oral health practice, actinomycosis of the oral cavity is highly significant due to its potentially aggressive and locally destructive nature.[7] Rarely, it can lead to distant organ dissemination, including brain, lungs, and digestive tract.[19]

CASE REPORT

A 69-year-old female, a regular patient of the Oral Medicine Clinic, presented for her 3 monthly review appointment. She had been diagnosed with proliferative verrucous leukoplakia about 3 years ago, and about a year after, was subsequently diagnosed with T4aN0M0 (AJCC 7th Edition)[20] squamous cell carcinoma of the right hard palate. This was surgically resected, and she completed post-operative radiotherapy, for which she received 66Gy to the oral cavity. Chemotherapy was abandoned due to the side effects she experienced. Her medical history was also significant for hypothyroidism for which she was taking thyroxine, and hypertension for which she was taking telmisartan. She was an ex-smoker of 30 pack years who quit 12 years ago, and never consumed alcohol.

Her extra-oral examination was unremarkable. She suffered from xerostomia and salivary gland hypofunction. Examination of her oral cavity revealed non-homogenous leukoplakia involving her hard palate, bilateral buccal mucosa, and bilateral tongue. Of note, there was a thick, irregular white plaque involving her right hard palate on the background of a thinner, non-homogenous white plaque (Figure 1a), and an oroantral fistula involving her left hard palate (Figure 1b). The oroantral fistula had been present for several months. There was an area of exposed bone with suppuration adjacent to the cervical region of the left first premolar. This tooth was mobile, though otherwise asymptomatic. The patient was systemically well and reported no other symptoms.

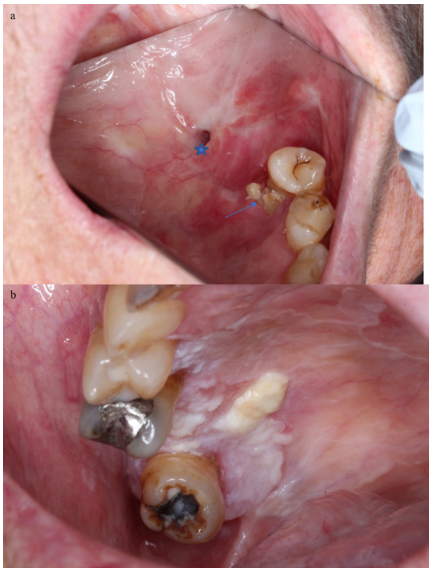

Figure 1. (a) An oroantral fistula involving the left hard palate (blue star), and an area of exposed bone adjacent to the cervical region of the left first premolar (blue arrow); (b) Proliferative verrucous leukoplakia of the oral cavity, extending from the buccal gingiva to the hard palate of the right maxilla.

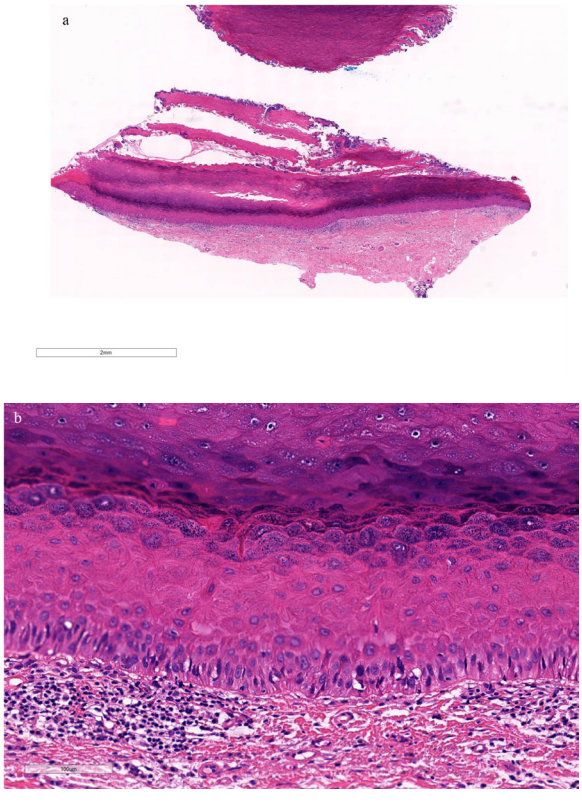

Figure 2. (a) Lower powered photomicrograph of a right hard palate biopsy showing marked hyperkeratosis with low grade dysplasia (H and E, x40); (b) Low grade dysplasia- A high powered photomicrograph showing mild architectural disorganization, with variation in nuclear size and shape, and hyperchromasia of some nuclei. (H and E, x100).

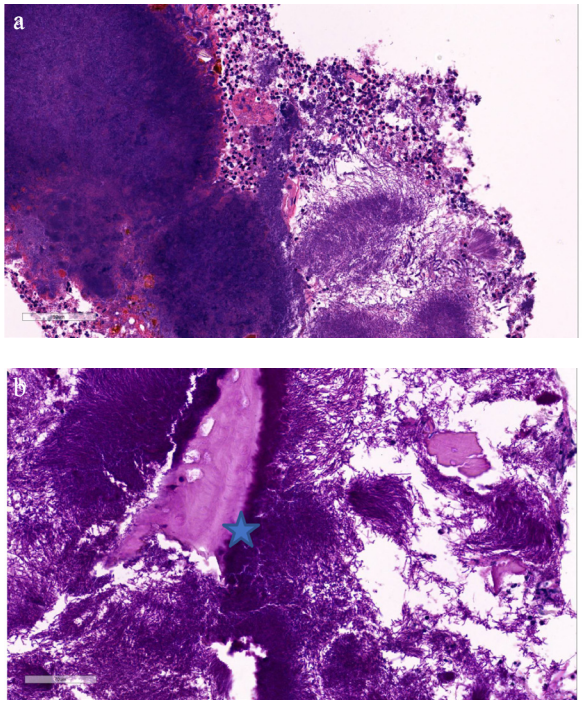

Figure 3. (a) Filamentous, branching actinomyces-like organisms (H and E, x100); (b) The necrotic bone is seen in (b, blue star). A concurrent microbiology report reported abundant growth of *Actinomyces naeslundii*.

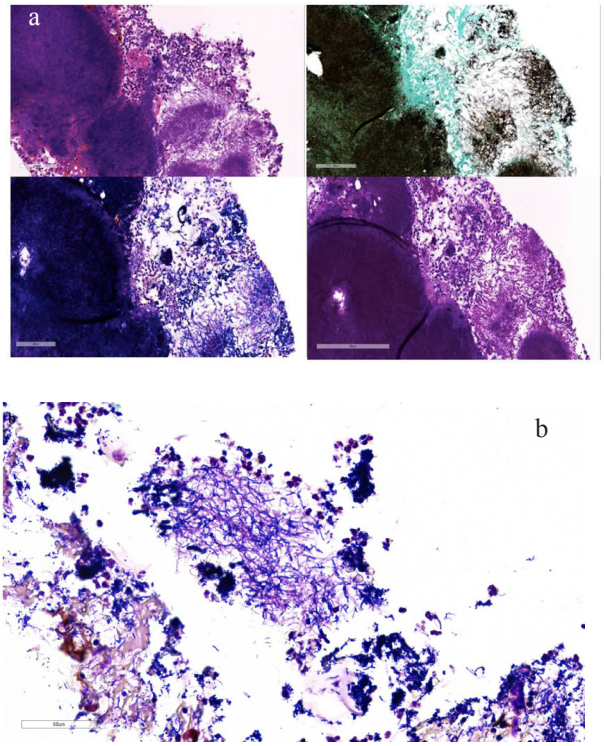

Figure 4. (a) L to R, top to bottom: Positive H and E, GMS, Gram and PAS stains showing filamentous, branching actinomyces-like organisms (x40); (b) A Gram positive high powered photomicrograph showing the organisms (x100). A concurrent microbiology report reported abundant growth of *Actinomyces naeslundii*.

The non-homogenous leukoplakia in Figure 1a was biopsied by a surgeon, and the histopathology report revealed this to be hyperkeratosis with low grade dysplasia (Figure 2a). There was mild architectural disorganization with crowding and overlapping of nuclei, with variation in nuclear size and shape, and hyperchromasia of some nuclei (Figure 2b). There was no invasive malignancy. A biopsy of the tissues surrounding the upper left second premolar was also performed when it was extracted, and this tissue and bone was submitted for histopathological evaluation. The histopathology report revealed necrotic and reactive bone and fibrous tissue, surrounded by filamentous actinomyces-like organisms, further highlighted by positive Gram, Periodic acid Schiff (PAS) and Grocott methenamine silver (GMS) stains (Figures 3 and 4). Most fungi can be readily demonstrated with the common special stains, of which GMS, Gridley's fungus (GF), and PAS are referred to as "broad spectrum" fungal stains.[21] There was no granuloma formation nor evidence of malignancy. A concurrent microbiology report reported abundant growth of *Actinomyces naeslundii*.

A positron emission tomography (PET) scan revealed an area of uptake in the left maxillary sinus, whose appearance was favoured to be reactive rather than a malignant (Figure 5). A computed tomography (CT) scan and orthopantogram (OPG) revealed subtle obliteration of the left maxillary sinus but

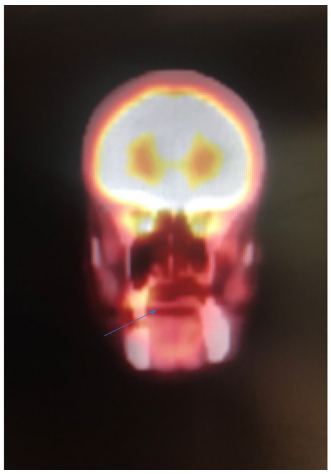

Figure 5. A positron emission tomography (PET) scan revealed an area of uptake in the left maxillary sinus, favoured to be reactive (blue arrow).

were otherwise non-contributory to the diagnosis. Radiographically, imaging findings are usually non-specific. A soft-tissue mass with inflammatory changes and an infiltrative nature may be seen, however the role of imaging lies principally in assessing bone involvement.[22] Bone involvement is observed in approximately 10% of cases.[19]

Based on the histopathology, culture, radiographic and clinical findings, the patient was diagnosed with actinomycosis osteomyelitis. Distinguishing between osteomyelitis and osteoradionecrosis with bacterial overgrowth can be difficult, however, osteomyelitis was favoured based on the marked degree of inflammation and the prominent infiltration of bone fragments by *Actinomyces*. She was treated with high-dose intravenous penicillin for 2 weeks, to be followed by oral amoxycillin for a period of 6–12 months. No randomized controlled trials exist regarding antibiotic regimens for cervicofacial actinomycosis, however isolates are susceptible to beta-lactams.[19] Early treatment regimes recommended a prolonged course of antibiotic treatment, however recent literature has supported a shorter course of less than 6 months in certain cases, such as when surgical debridement has been performed or with no bony involvement.[4,19] Close monitoring of the clinical and radiological response is necessary, and further surgical debridement is being considered pending the patient's response to antibiotics. On last review with Oral Medicine, she had completed her IV antibiotics and had commenced on oral antibiotics. She remains on regular recall for reviews in the Oral Medicine Clinic.

DISCUSSION

Proliferative verrucous leukoplakia (PVL) is a rare and recalcitrant form of leukoplakia, with a high malignant transformation rate of 50-90%.[23,24] Recurrence is common.[24] Unfortunately, PVL rarely regresses despite therapy, and there is a high rate of field cancerization.[25] A lifetime of close follow-up is necessary. In this patient's case, she subsequently developed oral squamous cell carcinoma, which was treated with surgery and post-operative radiotherapy.

Osteoradionecrosis (ORN) is a potential adverse effect of radiotherapy. The patient's diagnosis in this case was favoured to be that of osteomyelitis rather than ORN, in most part due to substantial inflammation and the prominent infiltration of bone fragments by *Actinomyces*, however reaching a definitive diagnosis is difficult. The differentiation between cervicofacial actinomycosis and osteomyelitis with actinomycotic superficial infection can be unachievable, and even with histopathological and imaging correlation. Thus, the condition can sometimes be enigmatic.

Actinomycosis may have arisen within the maxilla due to contiguous involvement of the sinus via an oroantral fistula, which provided an entry point for the microorganisms. A prerequisite for the development of this disease is pathogen transport into tissue layers via an entry point with an anaerobic environment.[10] Actinomycosis is typically polymicrobial, with synergism between *Actinomyces* and other fastidious organisms such as *Eikenella*, *Arachnia, Actinobacillus actinomycetemcomitans,* and *Fusobacterium* and *Bacteroides* species.[4,9,10] Association of these "companion organisms" facilitate infection by helping to establish a microaerophilic environment.[4]

Osteoradionecrosis with secondary *Actinomyces* colonisation remains a possible differential diagnosis. An opportunistic infection with *Actinomyces* in patients with ORN has been reported, and could be detected in 12% of 50 patients.[26] In another study, the presence of *Actinomyces* colonies itself in patients with ORN may be higher than previously thought; and was found in 20 (64.5%) of 31 patients.[27] Of relevance, median treatment duration of ORN was significantly longer in these patients with actinomycosis than those without, and is associated with a significantly higher risk of treatment failure.[26,28] It is also known that irradiated bone is highly susceptible to infections, mainly with Candida species and cariogenic bacteria.[27]

Indeed, to differentiate between osteomyelitis, medication related osteonecrosis of the jaw and ORN on the basis of histological and radiographic findings is difficult. The patient's history is of paramount importance. Radiographic findings are non-specific and can include osteolysis, sclerosis, persisting alveolar sockets, sequestrum, and involucrum formation.[29] While some authors have proposed histopathological patterns to differentiate between these entities, there is disagreement as to whether the results are reproducible.[29,30] A study, using 2 trained pathologists, attempted to identify distinct histological features of the three conditions and investigate if a diagnosis could be reached based on microscopic evaluation.[29] The presence or absence of necrotic bone, inflammation, reactive bone formation, bacteria and osteoclasts were evaluated, and no statistically significant differences were found between groups for any parameter.[29] The role of *Actinomyces* in ORN and osteomyelitis, is uncertain. Marx, when investigating the pathophysiology of ORN, observed that no organisms could be cultured or observed in deep bone, and were only observed in superficial bone.[31] This, coupled with his observation of no spread of ORN nor septic course, led to the conclusion that microorganisms play only a minor role in the pathophysiology of ORN.[31] Marx also suggested that in ORN, there is no interstitial infection, rather only a superficial contamination.[31] The role of *Actinomyces* in ORN is uncertain.

CONCLUSION

The diagnosis of actinomycotic infection can be elusive and managing clinicians should be aware of potential differential diagnoses and limitations of further investigation such as histopathology and imaging.

This case highlights an unusual case of cervicofacial actinomycosis and demonstrates the complexities in reaching a definitive diagnosis in cases of osteomyelitis and osteoradionecrosis with significant bacterial burden.

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The author wishes to thank the patient for her consent and other clinicians involved in her care.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this case report.

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