Title
Cervicofacial actinomycosis: a unique diagnostic challenge

Journal
Dermatology Online Journal, 27(7)

Authors
Fronek, Lisa
Brazen, Brett
Ross, Risa
et al.

Publication Date
2021

DOI
10.5070/D327754367

Cervicofacial actinomycosis: a unique diagnostic challenge

Lisa Fronek[1] DO, Brett Brazen[2] BS, Risa Ross[1] DO, Richard Miller[1] DO

Affiliations: [1]Department of Dermatology, HCA Healthcare/University of South Florida Morsani College of Medicine, Largo, Florida, USA, [2]Department of Dermatology, Broward Health, Fort Lauderdale, Florida, USA

Corresponding Author: Lisa Fronek, Department of Dermatology, HCA Healthcare/University of South Florida Morsani College of Medicine, 201 14th Street SW, Largo, FL 33770, Tel: 858-232-7382, Email: drlisafronek@gmail.com

Abstract

Actinomycosis is a rare, chronic bacterial infection caused by *Actinomcyes israelii*. This anaerobic filamentous gram-positive bacterium frequently colonizes the human mouth, digestive, and genital tracts. Cervicofacial actinomycosis infections have a proclivity for affecting the upper and lower mandibles and occur in 50% of cases. Most cases present in immunocompetent individuals and almost always involve some degree of pre-existing mucosal trauma through either recent dental procedures or poor dental hygiene. Herein, we present a 54-year-old man diagnosed with cervicofacial actinomyces infection in the absence of periodontal disease or recent dental procedures. The purpose of this testimony is to discuss the pathogenesis and clinical and histologic findings of actinomycosis. In addition, we review diagnostic techniques and the current breadth of treatment options. It is our hope that this manuscript will serve as a guide for physicians of all specialties in accurately recognizing and promptly treating actinomycosis.

Keywords: Actinomyces israelii, cervicofacial actinomycosis, infectious disease

Introduction

Actinomycosis is a rare bacterial infection caused by the *Actinomyces* spp, with roughly three new cases per 100,000 people per year [1]. There are three distinct clinical subtypes of actinomycosis: cervicofacial, pulmonary, and abdominopelvic [2]. Infection with *Actinomyces* results in granulomatous inflammation, which may lead to abscess or sinus formation [2]. The most common clinical presentation is that of cervicofacial disease, followed by pulmonary infection [1]. *Actinomyces israelii* is the pathogenic agent in approximately 70% of all cervicofacial actinomycosis cases [1]. A history of a recent dental procedure is frequently elicited upon questioning, as trauma is the most crucial predisposing factor to this infection; despite this fact, many cases occur spontaneously [3].

Case Synopsis

A 54-year-old man presented to our dermatology clinic for evaluation of a non-resolving plaque of 8-months duration on the left nasolabial fold (**Figure 1A**). He had previously been prescribed clindamycin 300mg twice a day for two weeks, resulting in a transient reduction in size. However, the plaque ultimately recurred promptly after the completion of treatment. The patient indicated that while the plaque was steadily increasing in size, the growth remained localized. He denied any tenderness to palpation, warmth to touch, drainage, discharge, or associated bleeding from the lesion. He denied any history of periodontal diseases, dental procedures, or recent dental cleanings. The patient was referred to the dentistry department and the examination corroborated the patient's history. Upon further questioning, the patient did endorse a history of mild jaw trauma during a sporting event as an adolescent. He otherwise denied fever, chills, fatigue, weight changes, chest pain, difficulty breathing, hemoptysis, abdominal pain, nausea, vomiting, diarrhea, or neurologic symptoms. The patient was a

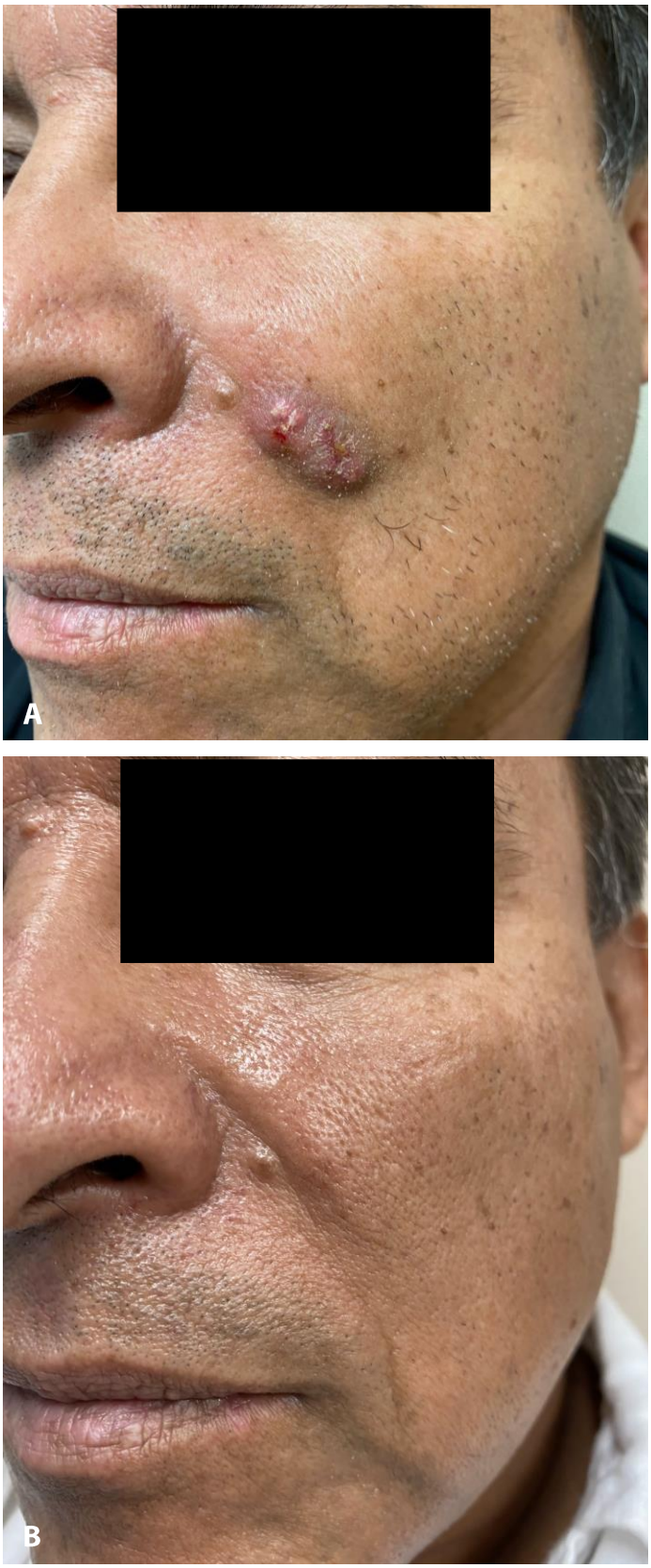

Figure 1. ***A)*** *A well-demarcated 1.0×2.0cm suppurative plaque on the left nasolabial fold of a middle-aged man.* ***B)*** *Complete clearance of cervicofacial Actinomyces infection following six months of doxycycline 100mg twice a day.*

lifetime non-smoker and his social history was unremarkable.

On physical examination, there was a 1.0×2.0cm pink-to-light brown indurated plaque with central purulent material over the left nasolabial fold (**Figure 1A**). Upon palpation, the plaque was entirely localized to the epidermis, dermis, and possibly subcutis. There was no palpable connection to the oral cavity, mandibular unit, mucosa, or gingiva. Prior to his referral to the dermatology department, the patient underwent facial computed tomography (CT) without contrast, which demonstrated a 3.0×3.0×1.7cm area of subcutaneous complex material surrounding the left upper canine with anterior cortical breakthrough, consistent with a periapical abscess. There was also evidence of extension of inflammation through the cortical defect into the subcutaneous soft tissues of the left face, lateral to the nose.

Two 3.0mm punch biopsies were performed; one was sent for H&E staining and the other was sent for aerobic, anaerobic, fungal, and mycobacterial culture.

The specimen submitted for H&E staining demonstrated an acanthotic epidermis with overlying neutrophilic and hemorrhagic crust (**Figure 2A**). In the papillary dermis there appeared to be significant erythrocyte extravasation and neutrophilic inflammation. Overlying the epidermis was a focus of central necrotic debris encased by a rim of neutrophils (**Figure 2B**). Basophilic-appearing gram positive filamentous rods were found within the center necrotic core (**Figure 2C**); this was further highlighted by gram stain (**Figure 3**). Both periodic acid-Schiff (PAS) and acid-fast bacilli (AFB) stains were negative. All appropriate cultures returned negative after six weeks. Given the combination of clinical and histopathologic correlation, a diagnosis of cervicofacial actinomycosis was made.

Upon completing this initial dermatologic consultation, we chose to empirically prescribe oral doxycycline at a dose of 100mg twice a day. This agent was chosen based on the patient's previous treatment failure to clindamycin and his allergy to penicillin-based medications. Additionally,

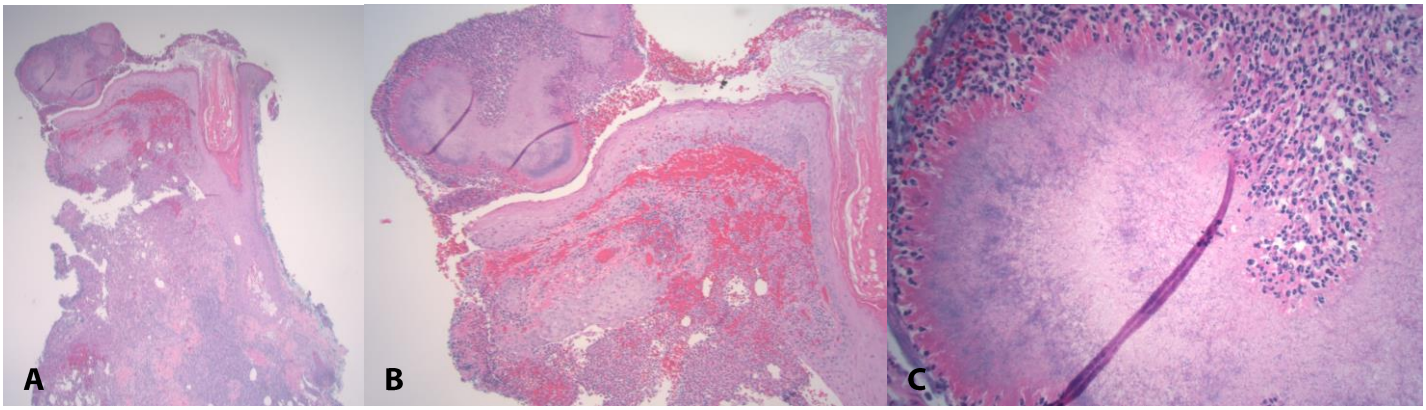

Figure 2. *A 3.0mm punch biopsy taken from the left nasolabial fold was submitted for H&E.* ***A)*** *On low power there is an acanthotic epidermis with overlying neutrophilic and hemorrhagic crust, 40×.* ***B)*** *In the papillary dermis there appears to be significant erythrocyte extravasation and neutrophilic inflammation, 100×.* ***C)*** *Overlying the epidermis was a focus of central necrotic debris encased by a rim of neutrophils; there is evidence of basophilic appearing filamentous rods, 400×.*

doxycycline has broad spectrum coverage including gram positive, gram negative, and atypical mycobacterial entities. The patient demonstrated impressive clinical improvement at his one month follow up appointment. Based on his positive response to doxycycline, we continued this regimen for a total of six months, resulting in complete clearance and no adverse side effects (**Figure 1B**).

Case Discussion

Actinomycosis is a rare, chronic, invasive bacterial disease with an annual incidence of approximately 0.00003% [1]. It is caused by *Actinomyces* spp., an anaerobic filamentous gram-positive bacterium. Actinomyces is known to be a frequent colonizer of the human mouth, digestive, and genital tracts [2]. Although more than 30 species of *Actinomyces* have been described, *Actinomyces israelii* is the most prevalent causative organism of human infection and is found in most forms of actinomycosis [2]. Typical presentations of actinomycosis vary widely, from cervicofacial actinomycosis, known colloquially as the "lumpy jaw syndrome," to pulmonary or abdominopelvic actinomycosis [2]. Cervicofacial infection is commonly seen after dental procedures or pre-existing dental infections, whereas pulmonary infection is associated with smoking and poor dental hygiene [2]. Most commonly, cervicofacial actinomycosis infections have a proclivity for affecting the upper and lower mandibles. The cheek and mental regions are affected at a much lesser rate of approximately 10-15%, respectively [1]. In addition, hematogenous spread of *Actinomyces* is rare; it occurs via direct or indirect extension to the thorax and can manifest as pulmonary actinomycosis [2].

Most cases occur in immunocompetent individuals and almost always involve some degree of pre-existing mucosal trauma, typically arising from poor dental hygiene or a recent dental procedure [3]. Despite our patient lacking a history of dental manipulation, it is presumed that his distant history of maxillofacial trauma as an adolescent may have predisposed him to develop the described infection. Similarly, Stájer et al. recount a case of *Actinomyces* infection preceded by an external trauma to the patient's jaw, also lacking a history of dental procedure. Immunosuppression certainly plays a role, as elucidated by Ayoade et al. reporting two separate cases of actinomycosis presenting with a periapical abscess. Although neither patient recounted a history of oral trauma or dental procedures, both had underlying immunosuppression in the forms of diabetes mellitus and multiple myeloma, respectively [4]. A thorough review of our patient's history failed to identify evidence of an immunosuppressive state. Cervicofacial actinomycosis characteristically presents as a chronic, indolent, fluctuating mass. Occasionally, the patient will endorse constitutional symptoms including fever. Lymphadenopathy and

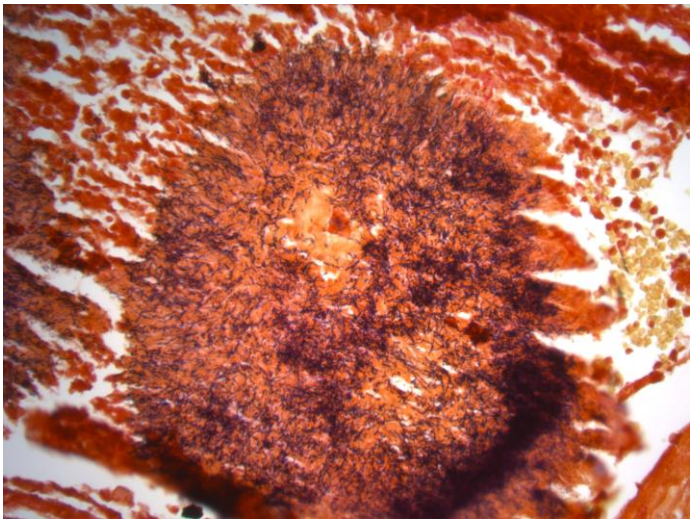

Figure 3. *Gram stain highlights branching filamentous rods within the center necrotic core, 400×.*

pain are typically absent [5,6]. Actinomycosis is known for the formation of sinus tracts producing foul-smelling yellow grains, often referred to as sulfur granules. Although these findings are essentially pathognomonic for the disease, they are only observed in approximately 40% of cases [5]. A hallmark of cervicofacial actinomycosis is the tendency to spread without regard for anatomical barriers, including fascial planes and sites of lymphatic drainage. This often leads to the development of the aforementioned sinus tracts and may complicate the disease course [7].

The gold standard for diagnosis of cervicofacial actinomycosis is histological examination and bacterial culture [8]. Histopathology of actinomycosis demonstrates suppurative inflammation with central necrosis and primarily a neutrophilic infiltrate. Additionally, histiocytes, plasma cells, and epithelioid cells may manifest in the periphery [6, 9]. An overlying hyperkeratotic and acanthotic epidermis can be seen along with gram-positive filamentous rods [10]. Another characteristic microscopic finding is the presence of an outer zone of granulation and central necrotic zone containing multiple basophilic granules representative of microcolonies of *Actinomyces* [7]. Precise bacterial culture, however, often proves challenging because of a high failure rate of culture. Valour et al. indicate that the difficulty in culturing is based on inadequate incubation time, inhibition of *Actinomyces* growth by other species, and prior antibiotic use [2]. Additionally, culture of actinomycosis requires thioglycolate or brain-heart-enriched agar at a temperature of 37 degrees Celsius [11]. For this reason, a gram stain is often the preferred initial diagnostic test of choice [2]. Diagnosis may often be delayed owing to the non-specific and indolent nature of the symptoms that may mimic other granulomatous infections, such as tuberculosis or nocardiosis [7]. As such, AFB and PAS stains provide helpful information in an effort to rule out other etiologies.

Depending on the severity of infection, penicillin V or G remains the treatment of choice for cutaneous *Actinomyces* [12]. For limited oral disease, it is recommended to initiate oral penicillin V, 2-4 grams daily divided into four doses per day [13]. Additional options include oral amoxicillin or amoxicillin-clavulanate. For patients who are allergic to penicillin, other effective choices include doxycycline 100mg twice a day or macrolide antibiotics such as erythromycin 500mg four times a day [14,15]. Doxycycline specifically has been reported to be one of the most efficacious oral antibiotics for treating *Actinomyces*, second only to amoxicillin, with a Minimum Inhibitory Concentration (MIC_{50}) of 0.064μg/mL [16-18]. This was deemed the most appropriate option in our penicillin-allergic patient who had previously failed a course of clindamycin. Clindamycin and fluoroquinolones may have some efficacy, but resistance to these agents has been increasing [19]. Of note, several reviews of antimicrobial susceptibility in regard to *Actinomyces* highlights the relative inadequacy of metronidazole, trimethoprim-sulfamethoxazole, penicillinase-resistant penicillins, cephalexin, ceftazidime, and antifungals [16,19]. The use of intravenous antibiotics in conjunction with surgical resection may be required for drainage of voluminous abscesses, marsupialization of sinus tracts, and debridement of necrotic bone tissue in the event of co-existing osteomyelitis [2].

When establishing a treatment protocol to treat *Actinomyces* it is important to take into account treatment duration and educate the patient appropriately. The recommendation is to continue

systemic treatment for an additional 1-2 months after the clinician observes resolution [14]. Typically, this accounts for a total duration of approximately 2-6 months. Longer duration of treatment may be required in complicated or invasive cases or in immunocompromised patients.

Conclusion

Actinomycosis is an unusual bacterial infection with three distinct clinical subtypes: cervicofacial, abdominopelvic, and pulmonary actinomycosis. *Actinomyces israelii* is the most frequently isolated pathogen of the approximately 30 pathogens belonging to the *Actinomyces* spp. Accordingly, *Actinomyces israelii* is the primary causative organism in cervicofacial actinomycosis, the most common of the three subtypes. Clinical and histopathologic characteristics are typically non-specific, often leading to delay in diagnosis and treatment. Bacterial culture with gram stain is the gold standard for diagnosis, albeit difficult to achieve with its specific growth requirements and susceptibility. Evidence of gram-positive filamentous rods on H&E in combination with an appropriate clinical picture aids in securing a diagnosis of actinomycosis. Current therapeutic regimens for localized cases include oral penicillin V or amoxicillin. Alternative treatment options include doxycycline and macrolides, which can be used in those with penicillin allergies. Dermatologists, infectious disease specialists, otolaryngologists, and dentists should work closely together in this type of interdisciplinary disease, as all components are essential in making a prompt, and accurate diagnosis.

Acknowledgements

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA affiliated entity. The views expressed in this publication represent those of the author(s) do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities. This work has not been submitted for publication elsewhere.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Gajdács M, Urbán E, Terhes G. Microbiological and Clinical Aspects of Cervicofacial *Actinomyces* Infections: An Overview. *Dent J.* 2019;7:85. [PMID: 31480587].
2. Valour, F, Karsenty, J, Breton, P, et. al. Actinomycosis: etiology, clinical features, diagnosis, treatment, and management. *Infect Drug Resist.* 2014;7:183-197. [PMID: 25045274].
3. Bonnefond S, Catroux M, Melenotte C, et al. Clinical features of actinomycosis: A retrospective, multicenter study of 28 cases of miscellaneous presentations. *Medicine.* 2016;95:e3923. [PMID: 27311002].
4. Ayoade F, Olayiwola A, Li A. "Holes" in the Jaw-A Report of Two Cases of Periapical Actinomycosis. *Diseases.* 2018;6:79. [PMID: 30200654].
5. Volante M, Contucci AM, Fantoni M, Ricci R, Galli J. Cervicofacial actinomycosis: still a difficult differential diagnosis. *Acta Otorhinolaryngol Ital.* 2005;25:116-119. [PMID: 16116835].
6. Bolognia JL, Schaffer JV, Cerroni L. Dermatology. 4th edition. Philadelphia, PA: Elsevier; 2018.
7. Moturi K, Kaila V. Cervicofacial Actinomycosis and its Management. *Ann Maxillofac Surg.* 2018;8:361-364. [PMID: 30693266].
8. Stájer A, Ibrahim B, Gajdács M, Urbán E, Baráth Z. Diagnosis and Management of Cervicofacial Actinomycosis: Lessons from Two Distinct Clinical Cases. *Antibiotics.* 2020;9:139. [PMID: 32218154].
9. Lo Muzio, L, Favia, G, Lacaita, M. *et al.* The contribution of histopathological examination to the diagnosis of cervico-facial actinomycosis: a retrospective analysis of 68 cases. *Eur J Clin Microbiol Infect Dis.* 2014;33:1915–1918. [PMID: 24870370].
10. Kura MM, Rane VK. Cervicofacial actinomycosis mimicking lymphangioma circumscriptum. *Indian J Dermatol.* 2011;56:321-323. [PMID: 21772599].
11. Oostman O, Smego RA. Cervicofacial actinomycosis: Diagnosis and management. *Curr Infect Dis Resp.* 2005;7:170-174. [PMID: 15847718].
12. Moghimi M, Salentijn E, Debets-Ossenkop Y, Karagozoglu KH, Forouzanfar T. Treatment of cervicofacial actinomycosis: a report of 19 cases and review of literature. *Med Oral Patol Oral Cir Bucal.* 2013;18:e627-e632. [PMID: 23722146].
13. Bonifaz A, Tirado-Sánchez A, Calderón L, et al. Treatment of cutaneous actinomycosis with amoxicillin/clavulanic acid. *J Dermatolog Treat.* 2017;28:59. [PMID: 27151779].
14. Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I. Treatment of skin disease: comprehensive therapeutic strategies. 5th edition. Philadelphia, PA: Elsevier; 2017.
15. Martin MV. Antibiotic treatment of cervicofacial actinomycosis for patients allergic to penicillin: a clinical and in vitro study. *Br J Oral Maxillofac Surg.* 1985;23:428-434. [PMID: 2933063].
16. Smith AJ, Hall V, Thakker B, Gemmell CG. Antimicrobial susceptibility testing of Actinomyces species with 12 antimicrobial agents. *J Antimicrob Chemother.* 2005;56:407. [PMID:

15972310].
17. Bennhoff DF. Actinomycosis: diagnostic and therapeutic considerations and a review of 32 cases. *Laryngoscope.* 1984;94:1198-1217. [PMID: 6381942].
18. Wong VK, Turmezei TD, Weston VC. Actinomycosis. *BMJ.* 2011;343. [PMID: 21990282].
19. LeCorn DW, Vertucci FJ, Rojas MF, et al. In vitro activity of amoxicillin, clindamycin, doxycycline, metronidazole, and moxifloxacin against oral Actinomyces. *J Endod.* 2007;33:557. [PMID: 17437871].