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CASE REPORT

Actinomycosis osteomyelitis of the jaws: Report of four cases and a review of the literature

Bahar Sezer [a*], B. Güniz Akdeniz [b], Sevtap Günbay [a], Süleyha Hilmioğlu-Polat [c], Gülçin Başdemir [d]

[a] Department of Oral Surgery, School of Dentistry, Ege University, Izmir, Turkey
[b] Department of Oral Diagnosis and Radiology, School of Dentistry, Ege University, Izmir, Turkey
[c] Department of Microbiology and Clinical Microbiology, Ege University, Izmir, Turkey
[d] Department of Pathology, School of Medicine, Ege University, Izmir, Turkey

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Abstract Actinomycosis osteomyelitis of the jaw bones, particularly in the maxilla, is an extremely rare disease. This report presents two cases of maxillary and two cases of mandibular actinomycosis osteomyelitis, with the diagnosis particularly based on histological procedures. The highly diversified pathogenicity of the phenomenon and the absence of solid diagnostic criteria are discussed. Laboratory challenges are emphasized, and a comprehensive overview of the entity including treatment alternatives is given along with a review of the relevant literature.

Introduction

Actinomycosis of the jaws is a relatively uncommon infection that produces abscesses and open draining sinuses. The principle cause of cervicofacial actinomycosis is *Actinomyces israelii*. However, *Actinomyces naeslundii*, *Actinomyces viscosus*, and *Actinomyces odontolyticus* are occasionally identified. *Actinomyces* produces chronic, slowly developing infections, particularly when normal mucosal barriers are disrupted by trauma, surgery, or a preceding infection.[1] A break in the integrity of the mucous membranes and the presence of devitalized tissue can result in invasion of the deeper body structures and cause illness.[2]

Actinomyces strains resemble both bacteria and fungi, thus, they were often considered to be transitional

* Corresponding author. Ege Üniversitesi, Dişhekimliği Fakültesi, Ağız Diş Çene Hastalıkları Cerrahisi, Bornova, Izmir 35100, Turkey.
E-mail address: baharsezer@yahoo.com (B. Sezer).

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between the two groups of microorganisms. However, most of the fundamental characteristics of *Actinomyces* indicate that they are, in fact, bacteria. They are anaerobic or facultative in contrast to pathogenic fungi, which are uniformly aerobic. In addition, *Actinomyces* does not contain sterols in its cell walls, and is sensitive to antibacterial chemotherapeutic agents.[3]

Actinomycosis is generally a polymicrobial infection requiring the presence of companion bacteria, most frequently anaerobic streptococci, fusiform or Gram-negative bacilli, and *Haemophilus* species. The associated flora form a kind of symbiosis with *Actinomyces* species and may cause an anaerobic environment which furthers the growth of this species.[4] Hence, these associated bacterial species act as copathogens and participate in the production of infection by elaborating a toxin or enzyme or by inhibiting host defenses. Furthermore, these accompanying species enhance the relatively low invasive power of *Actinomyces* by eliciting early manifestations of the infection and by treatment failure.[4–6]

Involvement of bone is rare, but osteomyelitis sporadically occurs, secondary to the primary infection at primary sites. The infection progresses by direct extension into adjacent tissues. Unlike other infections, actinomycosis does not follow the usual anatomical planes but rather burrows through them and becomes a lobular "pseudotumor".[7]

The purpose of this report was to present four cases of *Actinomyces* osteomyelitis and review the possible pathogenesis of the disease along with the outcomes after proper treatment modalities. A review of the literature on clinical sites, diagnostic methods, and treatment procedures is also included.

Case reports

Case 1

A 37-year-old woman was admitted to the Department of Oral Surgery Clinic in May 2002. The patient's medical history was noncontributory. Root-canal treatment had been completed in her left upper first premolar 2 years previously. This was followed by progressively increasing swelling in the oral vestibular region adjacent to the tooth. The swelling also mildly involved the left buccal area. She also described a continuous pain in her tooth. The patient was empirically treated by her dentist with oral administration of ampicillin/sulbactam (50 mg/kg), but after 1 week of gradual and partial recovery, the swelling returned. Because her pain was still present, she asked for her tooth to be extracted and the extraction was performed 2 months prior to her admission to the Department of Oral Surgery Clinic. The patient reported that she had been prescribed oral spiramycine for 20 days after the extraction, but the treatment failed to resolve her pain and swelling. She described a sense of "itching" on her cheek, and an ongoing sensation of pressure and intermittent discomfort around the tooth. She also described pain in the neighboring molar tooth with a gross amalgam restoration (Fig. 1B). Clinical examination revealed an unhealed tooth socket. The color of the adjacent gingiva showed slight erythema resembling desquamative gingivitis (Fig. 1B). Additionally, exposed sequestra were present. On an X-ray examination, the maxillary bone adjacent to the tooth socket showed destruction of the alveolar bone (Fig. 1A). As a result of the clinical and radiological findings, the patient underwent surgical intervention with a preliminary clinical diagnosis of actinomycosis infection.

Local infiltration anesthesia was induced, a full mucoperiosteal flap was elevated, and the defect was curetted. The right maxillary first molar adjacent to the area of the lesion was extracted due to the extensiveness of the lesion and complaints of the patient. Curetted tissue from the surgical site was submitted for histopathological and microbiological examination [Fig. 1A(i)]. In hematoxylin-and-eosin (H&E)-stained sections, fragments of bone and granulation tissue were observed. Hard-tissue specimens included trabeculae of woven bone enclosing marrow tissue and a number of partly resorbed bony sequestra with extensive involvement of microorganisms. For the histological differential diagnosis, sections were also stained with tissue Gram, Giemsa, periodic acid Schiff (PAS), Gomori methenamine silver (GMS), and Ziehl Neelsen stains. The histological appearances were consistent with those of osteomyelitis in association with infection by *Actinomyces* organisms (Fig. 2A and B).

Culture of the involved tissue did not demonstrate the presence of *Actinomyces*. Similarly, no *Candida* colonies were observed. However, cultures were positive for Gram-positive microorganisms that are common inhabitants of the oral cavity.

Case 2

A 24-year-old otherwise healthy man was referred to the Department of Oral Surgery Faculty Clinic because of an unhealed extraction socket in the region of the lower left first molar that had been extracted 2 years prior to referral. The tooth had been asymptomatic, and the patient could not recall ever experiencing pain. However, on clinical examination, the socket seemed like a freshly extracted one [Fig. 1B(i)]. A panoramic radiograph of the area revealed ill-defined bony changes with osteolytic and osteosclerotic areas (Fig. 1B). There was no soft-tissue involvement.

Actinomycosis was suspected in accordance with clinical and radiological findings; therefore, the patient underwent surgical intervention with a preliminary clinical diagnosis of actinomycosis. Necrotic tissue curetted during the surgical intervention [Fig. 1B(ii)] was submitted for histopathological evaluation, and sections were primarily stained with H&E, and then similar staining procedures were performed with each of the stains used in Case 1. On histopathological examination, trabeculae of necrotic woven bone enclosing *Actinomyces* granules with bone marrow and a number of partially resorbed bony sequestra, nonspecific inflammatory cell infiltrates, vascular proliferations, and granulation tissue were seen. Within the granulation tissue were granules surrounded by polymorphonuclear leukocytes (Fig. 2B). The periphery of the *Actinomyces* granules showed radiating, basophilic filaments and eosinophilic, club-shaped ends (Fig. 2B and C). However, culture of the tissue was

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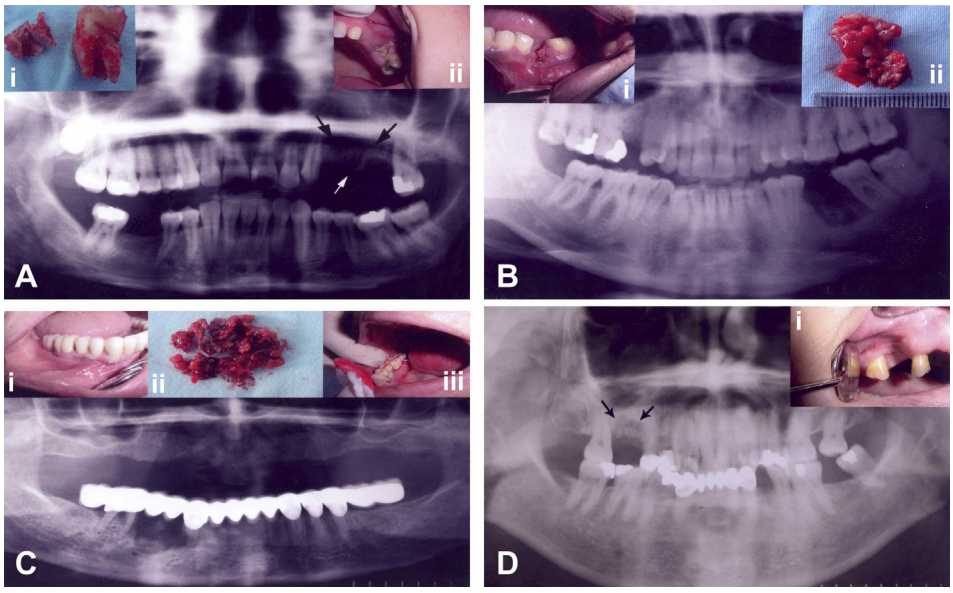

Figure 1 (A) Preoperative panoramic radiograph showing an extensive radiolucent lesion in the left maxillary premolar region (arrows). (i) Excised sequester and extracted neighboring molar tooth. (ii) Clinical view showing sequester and erythema of the gingiva in the maxillary premolar region. (B) Preoperative panoramic radiograph with radiolucent and sclerotic areas of the lesion in the left mandibular molar region. (i) Clinical view of an unhealed alveolar socket. (ii) Excisional biopsy material consisting of soft tissue and sequester. (C) Preoperative panoramic view showing radiolucent and radiopaque areas in the right mandibular premolar region below the prosthetic restoration. (i and iii) Preoperative clinical views showing gingival erythema and swelling of the right mandibular premolar region. (ii) Biopsy material. (D) Preoperative panoramic X-ray showing the right maxillary molar area with osteolytic and sclerotic lesion (arrows). (i) Clinical view of unhealed tooth socket and gingival erythema.

not positive either for *Actinomyces* or *Candida*. By contrast, Gram-positive cocci were observed on cultures of the involved tissue.

Case 3

A 67-year-old woman had her lower right first premolar tooth extracted due to severe pain. Extraction of the tooth was performed without complications 5 months prior to referral to the Department of Oral Surgery Faculty Clinic. A fixed prosthetic restoration had been applied to the area, but her pain did not resolve. She had also been empirically treated by her dentist with oral administration of amoxicillin/clavulanate potassium for 2 months. She was referred to our clinic with the complaint of a partially healed extraction socket and gingival swelling accompanied by mild pain [Fig. 1C(i) and C(iii)]. The patient's medical history was noncontributory. A radiographic examination showed a large periapical osteolytic area and sequestra (Fig. 1C).

A typical clinical picture with a long-lasting infection and gingival swelling strongly suggested actinomycosis; therefore, the patient underwent surgical intervention with a preliminary clinical diagnosis of actinomycosis.

The periapical defect was curetted, and the sequestra were surgically removed [Fig. 1C(ii)]. Curetted tissue from the surgical site was submitted for histopathological and microbiological examinations. The histopathological examination of the curetted tissue revealed that there were reactive bone and chronically inflamed granulation and fibrous tissues. *Actinomyces* was identified primarily on H&E-stained sections (Fig. 2D). Additionally, tissue sections were stained with Giemsa, PAS, GMS, and Ziehl Neelsen stains, as similarly done with the previous two cases. The attempts to grow *Actinomyces* from the cultures taken at the time of the operation were not productive. However, cultures were positive for Gram-positive cocci.

Case 4

A 60-year-old woman was referred to our clinic with a complaint of mild pain in her right maxillary molar area. The patient's medical history was noncontributory. Root-canal treatment had been completed in her right upper first molar 2 years previously. The continuous pain in her tooth had not subsided, therefore, she had asked for the tooth to be extracted 1 year after completion of her endodontic treatment. Meanwhile, the patient had been empirically treated by her dentist with oral administration of various antibiotics, but she could not recall either the type or duration. She still described ongoing pain, particularly on pressure, on her admission to the Department of Oral Surgery Faculty Clinic in January 2003. Her clinical examination revealed an unhealed tooth socket, and the adjacent gingiva showed slight erythema [Fig. 1D(i)]. On X-ray examination, the maxillary bone adjacent to the tooth socket showed destruction of the alveolar bone (Fig. 1D). Based on the clinical and radiological findings, the patient underwent surgical intervention with a preliminary clinical diagnosis of actinomycosis.

Necrotic tissue curetted during the surgical intervention was submitted for histopathological and microbiological

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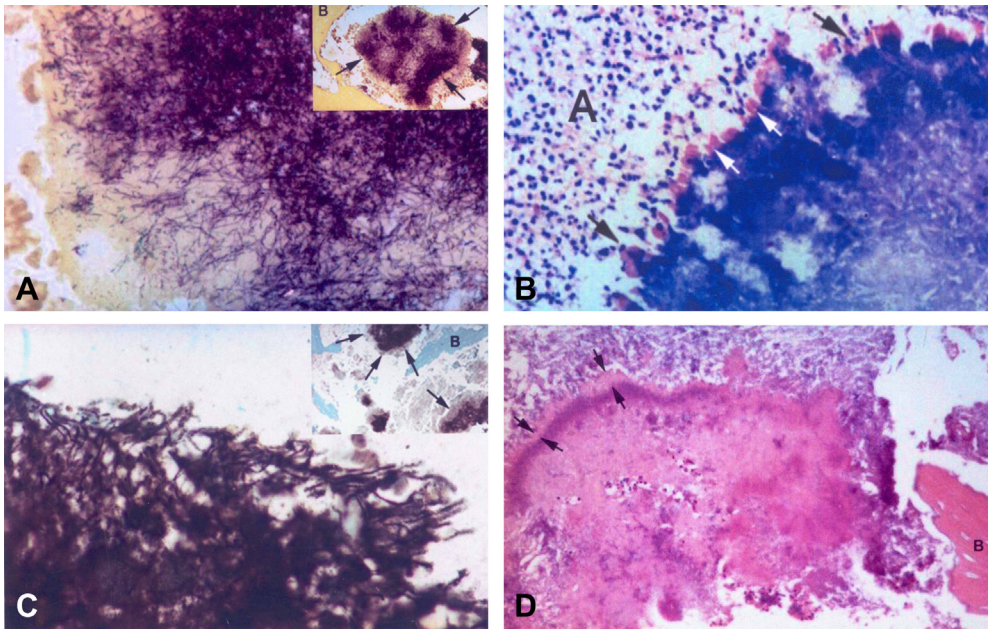

Figure 2 (A) Photomicrograph of peripherally radiating filaments of the actinomycotic granule (i), (tissue Gram stain, 100×). (ii) Granule is surrounded by trabecular bone. Note the deep-purple Gram-positive filaments (arrows), (tissue Gram stain, 20×). (B) Photomicrograph of deeply stained basophilic actinomycotic granule with prominent peripheral cubs (white arrows) surrounded by polymorphonuclear leucocytes (black arrows) embedded in an abscess (A), (Giemsa stain, 40×). (C) Periphery of actinomycotic granule (i). Note the branching filaments and cocoid elements. (ii) Gomori methamine silver stain of actinomycotic granule (arrows) embedded in an area of suppurative necrosis between bone trabeculae (10×). (D) Photomicrograph of an actinomycotic granule bordered by eosinophilic Splendore—Hoeppli material (between arrows), embedded in fibrino-purulent exudate and surrounded by trabecular bone (B). Note the numerous polymorphonuclear leucocytes within the matrix of the granule (H&E stain, 20×).

examinations. Histological sections were prepared and primarily stained with H&E due to the diagnosis of actinomycosis, and then similar staining procedures were done with each of the stains used in the above-described cases.

In the histopathological examination, trabeculae of necrotic woven bone enclosing *Actinomyces* granules with bone marrow and a number of partially resorbed bony sequestra, and granulation tissue were observed. The

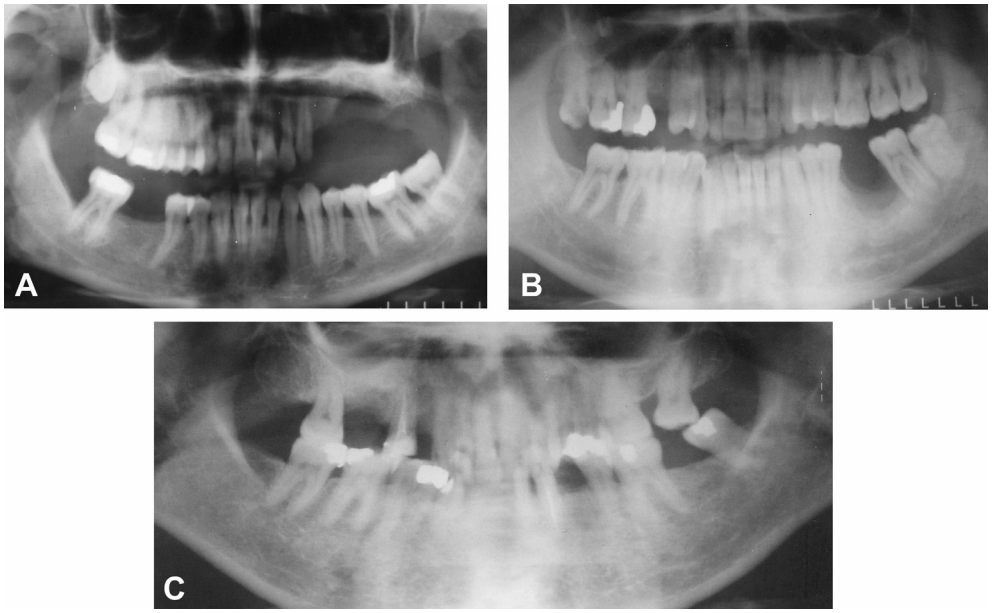

Figure 3 Postoperative panoramic radiographs showing the healing of bone in the (A) left maxillary premolar, (B) left mandibular molar, and (C) maxillary molar regions of Case 1, Case 2, and Case 4.

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periphery of the *Actinomyces* granules had radiating filaments with club-shaped ends. However, culture of the tissue was negative for *Actinomyces*. *Peptostreptococcus* species were present in the culture of curetted tissue.

The histopathological characteristics were typical of actinomycosis for all four cases, thus, treatment proceeded accordingly. Treatment with 2 g oral penicillin was initiated and continued for 2 months in all patients. Postoperative healing was uneventful, and no recurrence of the lesions occurred during 1 year follow-up of the presented cases (Fig. 3A–C).

Discussion

A systematic search of the MEDLINE database(1952–2011) was performed using the terms "osteomyelitis, jaw", "actinomycosis, mandibular", "actinomycosis", and "osteomyelitis". Cases among children younger than 18 years old (i.e., pediatric cases) were omitted (Table 1). As can be seen from Table 1, 10 of 30 reports were made during the past 11 years, whereas 20 reports were made during the previous 48-year period.[6,8–35] This is believed to be due to modern diagnostic techniques used to identify the involved *Actinomyces* species. Almost all of the reported cases resolved after proper surgical treatment and antimicrobial therapy.

A chronic, persistent, purulent, localized infection associated with unhealed tooth sockets characterized all four of the actinomycosis cases presented in this report. A jaw fracture, oral surgery, an infected tooth socket, deep periodontal pockets, and a root canal may serve as points of entry for microorganisms, with the consequent development of actinomycosis. Therefore, the prerequisite for the development of endogenous disease is the transport of pathogens into tissue layers with an anaerobic environment.[32,36] These organisms lack tissue-decomposing enzymes (hyaluronidases), therefore, they require the aid of other accompanying bacterial flora to achieve pathogenicity.[37] The presence of accompanying bacteria in all of the presented cases revealed by microbiological culture adheres well to the accepted concept of the combination of *Actinomyces* with other bacteria, particularly streptococci

Table 1 Reports of actinomycosis osteomyelitis affecting jaws.

Authors (y)	Location of bone infection	Diagnostic method	Therapy
Garg et al[8] (2011)	Palatina		Surgery + IV antibiotics
Vigliaroli et al[9] (2010)	Mandible	PR + CT	Surgery + IV + local antibiotics
Finley & Beeson[10] (2010)	Mandible	CT + MRI + nuclear scan + hematology	Oral antibiotics
Kaplan et al[11] (2009)	60% mandible 40% maxilla	Histomorphometry	Surgery + IV antibiotics + Hyperbaric oxygen
Vazquez et al[12] (2009)	Maxilla + mandible	Culture + PR + nuclear scan	Surgery + IV antibiotics
Sharkawy[13] (2007)	Mandible	Histomorphometry + culture	Surgery + IV antibiotics
Hansen et al[14] (2007)		Histology + PCR + SEM evaluation	Not performed
Tarner et al[15] (2004)	Maxilla	MRI + histology + hematology	Not performed
Curi et al[16] (2000)	Maxilla + mandible	Histology + microbiology	Surgery + systemic antibiotics
Liu et al[17] (1998)	Maxilla	NA	NA
Bartkowski et al[18] (1998)	Mandible	Bacteriology + histopathology	Surgery + systemic antibiotics
Sakellariou[19] (1996)	Mandible	Histopathology	Surgery + systemic antibiotics
Rubin & Krost[20] (1995)	Maxilla	NA	NA
Watkins et al[21] (1991)	Mandible	Bacteriology + histopathology	NA
Nuss et al[22] (1989)	Mandible	NA	NA
Saxby & Lloyd[23] (1987)	NA	NA	
Gupta et al[24] (1986)	Mandible	Bacteriology + smear + sensitivity tests	NA
Yenson et al[25] (1983)	Mandible + maxilla	NA	Surgery + systemic antibiotics
Price et al[26] (1982)	Mandible	Bacteriology + histopathology	Surgery + systemic antibiotics
Walker[27] (1981)	Mandible	NA	NA
Fergus & Savord[28] (1980)	Maxilla	Histopathology	Surgery + systemic antibiotics
Pinzur[29] (1979)	Maxilla + mandible	NA	NA
Yakata et al[30] (1978)	Mandible	Culture + Gram stain	Systemic antibiotics
Oppenheimer et al[6] (1978)	Mandible	Bacteriology + histopathology	Surgery + systemic antibiotics
Ermolov[31] (1975)	Mandible	NA	NA
Stenhouse[32] (1975)	Intraoral	Histopathology	Surgery + systemic antibiotics
Stenhouse & MacDonald[33] (1974)	Maxilla + mandible	NA	NA
Goldstein et al[34] (1972)	Maxilla	PAS + Brown–Brenn stain	NA
Gold & Doyne[35] (1952)	Alveolar process	NA	NA

CT = computed tomography; MRI = magnetic resonance imaging; NA = not available; PAS = Periodic acid–Schiff; PCR = polymerase chain reaction; PR = panoramic radiography; SEM = scanning electron microscopy.

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and staphylococci, having a synergistic effect in the pathogenicity of cervicofacial actinomycosis.[38] As a soft-tissue infection progresses, it penetrates by direct extension to adjacent tissues, that is, bone. However, it was not clear in the present cases whether the actinomycosis was the primary infection or a secondary infection to a pre-existent nonspecific local osteomyelitis of the alveolar bones.

Only a few cases of actinomycosis osteomyelitis have been reported in the literature.[20,39] Although the pathomechanism of actinomycosis osteomyelitis is unclear, it is suggested that inflammation begins when the normal composition of the microbial flora is disturbed, and chronic inflammation leads to localized pathological changes in the bone. It is assumed that the mandibular predominance of the disease stems from the relatively poor vascularization of the condensed cortical bone in the mandible with a similar mechanism that predisposes it to osteoradionecrosis.[40] Although two of the cases reported here had mandibular involvement, Case 1 and Case 4 were noteworthy in that the actinomycotic osteomyelitis was of maxillary origin, which is extremely rare compared to mandibular actinomycotic osteomyelitis, probably because of the good blood supply of the face, which provides more oxygen and better circulation.[34] Hence, the present cases may serve as a reminder to consider actinomycosis as a possible cause of osteomyelitis in the maxilla in persistent infections.

An actinomycotic infection was not confirmed in the cultures of any case reported here. The diagnosis of actinomycosis was based upon morbid anatomical, radiological, and microscopic evidence, particularly H&E-stained preparations rather than bacteriological culture and identification. Major difficulties in bacteriological identification of the present cases may have been due to the possible suppressive effect of prior antimicrobial therapy that was blindly used for persistent infections and/or concomitant aerobic and anaerobic bacterial overgrowth.[28,40] A diagnosis of actinomycosis is best made by culture, but $<$50% of cases are positive due to numerous problems associated with culturing these organisms.[41] The necessity for special handling of specimens in order to obtain positive cultures of anaerobic organisms was highlighted.[6] For this reason, a histopathological examination is also highly recommended.[34,40,42] Herein, the diagnosis depended upon the morphology and staining characteristics of the microorganism. *Actinomyces* species strongly stain positive for H&E, PAS, and Giemsa. Additionally, GMS staining is also useful for demonstrating the filaments.[43]

Actinomycosis is difficult to diagnose based on typical clinical features and direct identification, and/or isolation of the infecting organism from a clinical specimen may be laborious, therefore, nucleic acid probes and polymerase chain reaction (PCR) methods have been developed for rapid and accurate identification. Actinomycosis is generally considered a polymicrobial infection.[14] For a diagnosis involving osteomyelitis of the jaws, molecular testing is considered a suitable method. In a study by Hansen et al,[44] a PCR was used to detect A. israelii in bone specimens, which were decalcified in trichloroacetic acid, and a remarkable reduction in sensitivity was reported. In a subsequent study by the same group, it was confirmed that a PCR analysis of A. israelii resulted in a higher sensitivity if milder decalcification, such as with ethylene diamine tetraacetic acid (EDTA), was applied.[14] Thus, this molecular diagnostic approach was recommended even for bone biopsies that were primarily used for histology.[14]

Current PCR research in the bacteriological laboratory focuses on applying this technique to detect pathogens directly in clinical samples. It is clear that this approach has several advantages over culture techniques for slowly growing or noncultivable bacteria. However, comparing PCR to conventional identification procedures, PCR is more expensive and requires experienced research personnel.

After arriving at a sound diagnosis, it is recommended that treatment of actinomycosis infection should be vigorous. After removing the foci of infection, including resection of the sequestrated bone and excision of all granulation tissue until healthy tissue is exposed, prolonged administration of antibiotics, preferably penicillin, is recommended.[40,45] It has been concluded that additional exposure time to antibiotics is necessary because lysis of *Actinomyces* species occurs at a slow rate compared to most other bacteria.[46] As demonstrated in all four of our present cases, the prognosis for satisfactory resolution is excellent, and recurrence after adequate treatment is rare.[47]

A clinical diagnosis of actinomycosis may be difficult because the condition might not provoke pain at any or in later stages, and the cause is frequently not recognized on presentation.[48] However, any unidentified mass, facial swelling, or persistent infection particularly after endodontic therapy or tooth extraction, regardless of its nontraumatic history is suggestive of actinomycosis.[45,49] Diagnosis of this infection should be actively attempted in all instances of persistent oral infections because progressive actinomycosis, particularly in the maxilla, is likely to have relatively serious consequences if it is not diagnosed.[34] It is reasonable to assume that early diagnosis can significantly improve outcomes.

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