IDCases xxx (2019) xxx–xxx

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

A case series of actinomycosis from a single tertiary care center in Saudi Arabia

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ARTICLE INFO

Article history:
Received 22 January 2019
Received in revised form 24 February 2019
Accepted 6 March 2019

ABSTRACT

Actinomycosis is an uncommon but curable chronic infection caused by *Actinomyces* spp. The cervicofacial region is the most susceptible to infection; however, other sites may also become infected. Data on the current prevalence of this rare disease in Riyadh, Saudi Arabia is lacking. We herein report a case series of four patients with actinomycosis from a single tertiary care center in Riyadh, Saudi Arabia.

Three patients presented to us with slowly progressing actinomycosis and one patient developed an acute abdomen, secondary to viscus perforation. Two of the patients had cervicofacial disease, including hard palate actinomycosis. Tissue cultures were sent for three patients; however, tests for actinomycosis were negative. Subsequently, the diagnosis was made through histopathological examination. Therapy involved a combination of surgical resection and debridement and prolonged antimicrobial treatment tailored to each patient.

The cases reported in this series highlight the difficulty in diagnosing actinomycosis. For most patients, the diagnosis was delayed or accidentally discovered on histopathological examination. We conclude that increased awareness among physicians is needed for early diagnosis and treatment of actinomycosis.

Introduction

Actinomycosis is a rare chronic disease caused by Actinomyces spp., which are anaerobic gram-positive facultative bacteria that colonize the human mouth, digestive, and genital tracts. The bacteria can infect the skin and mucosal sites, such as the face, odontogenic and cervicofacial regions, respiratory tract, genitourinary tract, and digestive tract [1]. Diseases associated with Actinomyces spp. may also resemble malignancies, tuberculosis, and nocardiosis, often leading to a misdiagnosis [1–3]. Generally, actinomycosis has a peak incidence in the fourth to sixth decade of life, with a slight male predominance, but is uncommon in children [4].

Several risk factors can predispose patients to actinomycosis; these include male sex, poor oral hygiene, diabetes mellitus, immunosuppression, alcoholism, and malnutrition. A breach of the skin and mucosa facilitates the spread of infection to other organs, which can result in co-infections with other local bacteria [5]. On rare occasions, the bacteria can disseminate to distant sites, including the brain and musculoskeletal system [1].

Case reports

Case 1

A 71-year-old woman from Southern Province, Saudi Arabia presented with a 2-year history of a painless mid-palate ulcer with occasional pus discharge. She denied having weight loss, night sweats, or fever. Her temperature, heart rate, and blood pressure were 37.0°C, 98 beats/minutes, and 131/82 mmHg, respectively. There was a 2.0-cm mid-palate ulcer, located towards the left. The ulcer's margins were erythematous and deep, which exposed the underlying bone. The area contained black spots, with necrotic areas, and there was a communicating fistula between the base of the ulcer and the nasal cavity. Laboratory examinations, including complete blood count (CBC) and chemistry panel, revealed normal findings. Head and neck contrast computed tomography (CT) showed a hard palate defect with a left-sided oro-nasal fistula. Soft tissue thickening

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https://doi.org/10.1016/j.idcr.2019.e00521

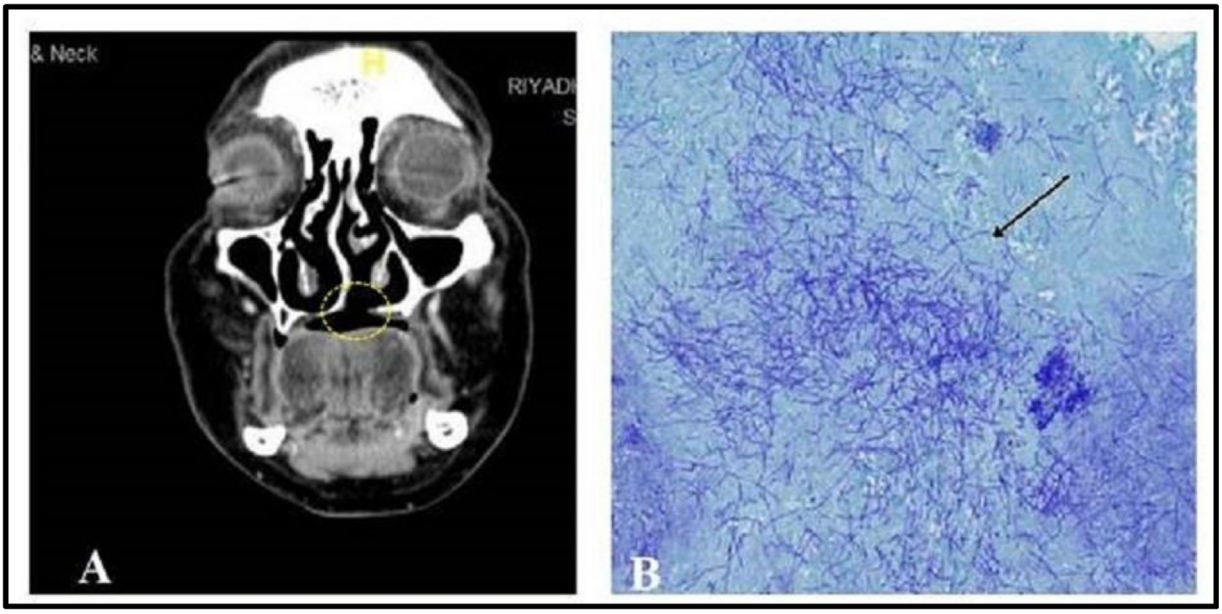

Fig. 1. (A) CT scan of the head and neck showing defect at hard palate with left side oroantral fistula (white circle). B. Clumps of gram-positive filamentous bacteria seen on gram stain of the bone biopsy.

surrounded this area; however, no evidence of osteomyelitis, bony erosions, or lymphadenopathy was detected (Fig. 1A).

The biopsy indicated a mass of hard white-brown tissue approximately 1.0×1.0 cm in size. Microscopic examination revealed necrotic bone, acute inflammation, and gram-positive branching filamentous bacteria, consistent with actinomycosis. *Enterobacter cloacae* and *Pseudomonas aeruginosa* were isolated through a routine culture; however, the culture was negative for actinomycetes. No granulomas were identified, and AFB staining showed negative findings (Fig. 1B).

Ceftriaxone (2 g) was administered intravenously every 24 h for 6 weeks, followed by oral amoxicillin (1 g) every 8 h for 6 months. She showed remarkable improvement and was subsequently offered a palate obturator to close the oro-nasal fistula, which she refused, and was then lost to follow-up.

Case 2

A 52-year-old man from Western Province, Saudi Arabia was referred for a possible right-hand palm tumor. He had a history of uncontrolled diabetes mellitus and a 5-year history of a recurrent painless mass involving his right middle finger, extending proximally to the palm, progressing in size over 6 months prior to presentation. The mass started as a tiny painless nodule that subsequently enlarged, thereby restricting hand motion. A trial surgical excision 2 years prior to presentation was successful in removing the mass, which did not recur for almost a year. However, the mass subsequently enlarged and began producing a whitish discharge.

Multiple sinuses were noted (Fig. 2A). Initial laboratory examinations, including a CBC and chemistry panel, revealed normal results. HIV test results were negative.

Plain radiography and magnetic resonance imaging (MRI) of the right hand showed multi-lobulated enhancing soft tissue conglomerated masses at the base of the middle finger, extending along its volar proximal aspect, circumferentially surrounding the finger and its tendons. No signs of tenosynovitis or osteomyelitis were observed (Fig. 2B).

The patient underwent an incisional biopsy and mass debridement. Tissue Gram staining and culture showed negative findings. AFB smear and polymerase chain reaction (PCR) findings were also negative for tuberculosis. Macroscopic examination of the sample revealed a mass approximately 2.0×1.5 cm in size and pinkish tan in color. Microscopic examination revealed skin with underlying tissue showing heavy infiltration by actinomycetes (positive results for the gomori methanamine silver [GMS] and periodic acid-Schiff [PAS] tests) that caused a severe inflammatory reaction and tissue destruction (Fig. 3C and D).

The patient was treated with oral amoxicillin/clavulanic acid (1 g) every 12 h and then discharged home. During the follow-up 2 months later, a whitish discharge was observed. He was referred for further debridement. After six months of treatment, he showed marked improvement.

Case 3

A 49-year-old man presented to us after undergoing right hemimandibulectomy and right neck dissection in July 2011, followed by chemoradiation for submandibular cystic adenocarcinoma (T4N2M0). Following the surgery, he developed trismus and difficulty in brushing his teeth. Five years later, he developed chronic right sided facial pain associated with recurrent purulent skin discharge and fever. Multiple trials of antibiotics including ciprofloxacin failed to achieve complete recovery. A dental assessment showed multiple decayed teeth. Dental treatment could not be administered due to his markedly reduced ability to open his mouth (8 mm). His temperature, heart rate, and blood pressure were 37.1°C, 95 beats/minutes, and 131/82 mmHg. A small right sided submandibular fistula draining a minimal amount of pus was observed on examination. His CBC, ESR, and CRP laboratory results were all normal. Enhanced head and neck CT did not reveal any underlying fluid collection, and no apparent fistula was observed on radiological evaluation. The right mandible bone biopsy was negative for AFB, TB-PCR, and bacterial cultures. Another biopsy taken from the right upper alveolar edge consisted of yellowish tan colored soft tissue. The bacterial culture was negative; however, heavy growth of mixed candida species was noted on tissue culture. Histopathology revealed necrotic tissue with positive PAS and GMS staining, suggesting actinomycosis

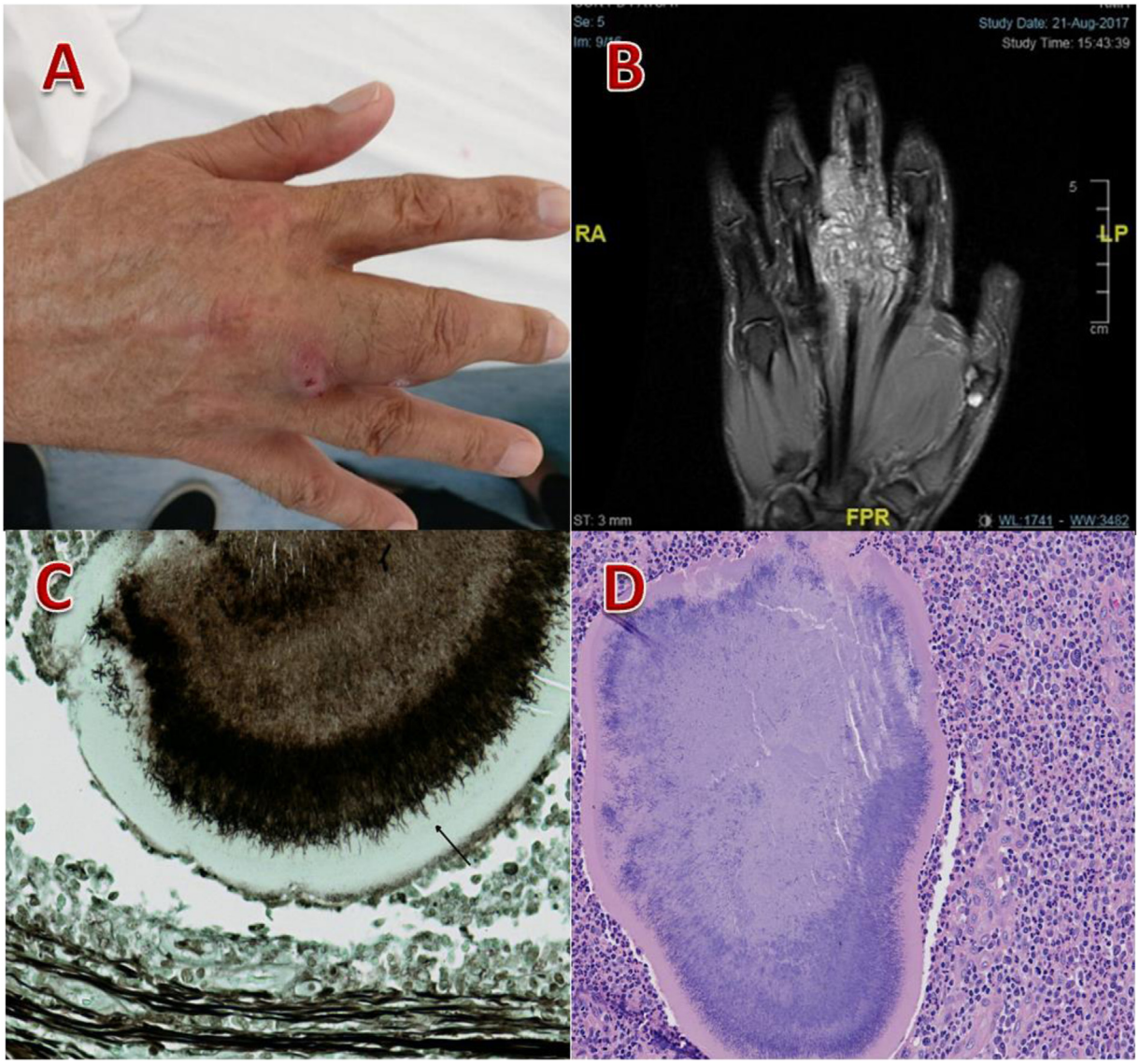

Fig. 2. (A) ℞hand photo showing soft tissue swelling of the middle finger and a sinus. (B) MRI of the ℞hand showing multilobulated enhancing soft tissue mass at the base of the middle finger. (C) & D excisional biopsy revealed dermal infiltration by Gram positive filamentous bacteria with multiple microabscesses formation. GMS special stain (C) and H&E stain (D) highlights the filamentous bacteria.

(Fig. 3). Chest CT showed pulmonary nodules enlargement, which was also noted 2 years prior to this presentation [(Fig. 3B].

The patient received a high dose of intravenous penicillin (6 million units/day) for 6 weeks followed by ceftriaxone for 1 month through a peripherally inserted central catheter. He also received 6 weeks of oral voriconazole for a non-albicans candida tissue infection. Oral amoxicillin was then continued for one year. Furthermore, hyperbaric oxygen (HBO) therapy was also administered, leading to dramatic improvement.

Case 4

A 49-year-old woman presented to the hospital with severe abdominal pain. An intrauterine contraceptive device (IUD) that had been implanted for 8 years had been removed one week prior to presentation (Fig. 4B). There was marked tenderness and guarding of the lower abdomen. Chest radiography revealed gas under the diaphragm (Fig. 4A) and an assessment at the time showed findings consistent with a perforated viscus. Her ESR and CRP level were 91 mm/hour and 396 mg/L, respectively. Abdomen CT showed evidence of pneumoperitoneum with multiple and large loculated collections at the pelvis, and surrounding the sigmoid colon (Fig. 4C).

She underwent emergency left sided hemi-colectomy with a Hartmann end colostomy for a perforated sigmoid colon and fecal peritonitis. A histopathology report confirmed the diagnosis of actinomycosis with prominent muscular and serosal layer involvement in the sigmoid colon (Fig. 4D and E). The tissue was not sent for culture. She received amoxicillin 500 mg every 8 h. Abdomen and pelvis CT performed 9 months later revealed several scattered intra-abdominal lesions with a fluid attenuation lesion near the right side of the urinary bladder dome (3.0×2.0-cm lesion with peripheral enhancement), a lesion near the rectal stump (2.2×1.5 cm), a subcapsular liver lesion (2.5×1.5 cm), and several tiny lesions in the greater momentum. Enlarged lymph nodes were absent, and the patient did not have ascites. Amoxicillin/clavulanic acid (1 g) orally twice daily was continued for 1 year. Follow-up CT in 2018 revealed interval regression of the bowel wall thickening and complete resolution of all previously observed lesions. Finally, Hartman end colostomy reversal was performed, with a good outcome.

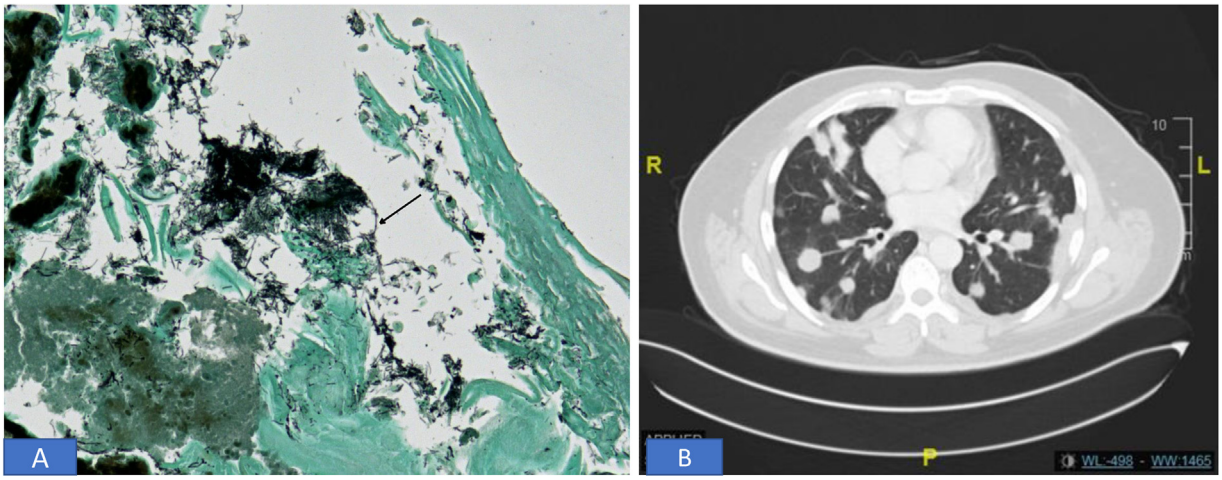

Fig. 3. (A) CT scan of the chest showing pulmonary metastatic nodules. (B) GMS special stain showing clumps of filamentous bacteria within fragments of keratin flakes necrotic mucosal soft tissue and bone of right mandible.

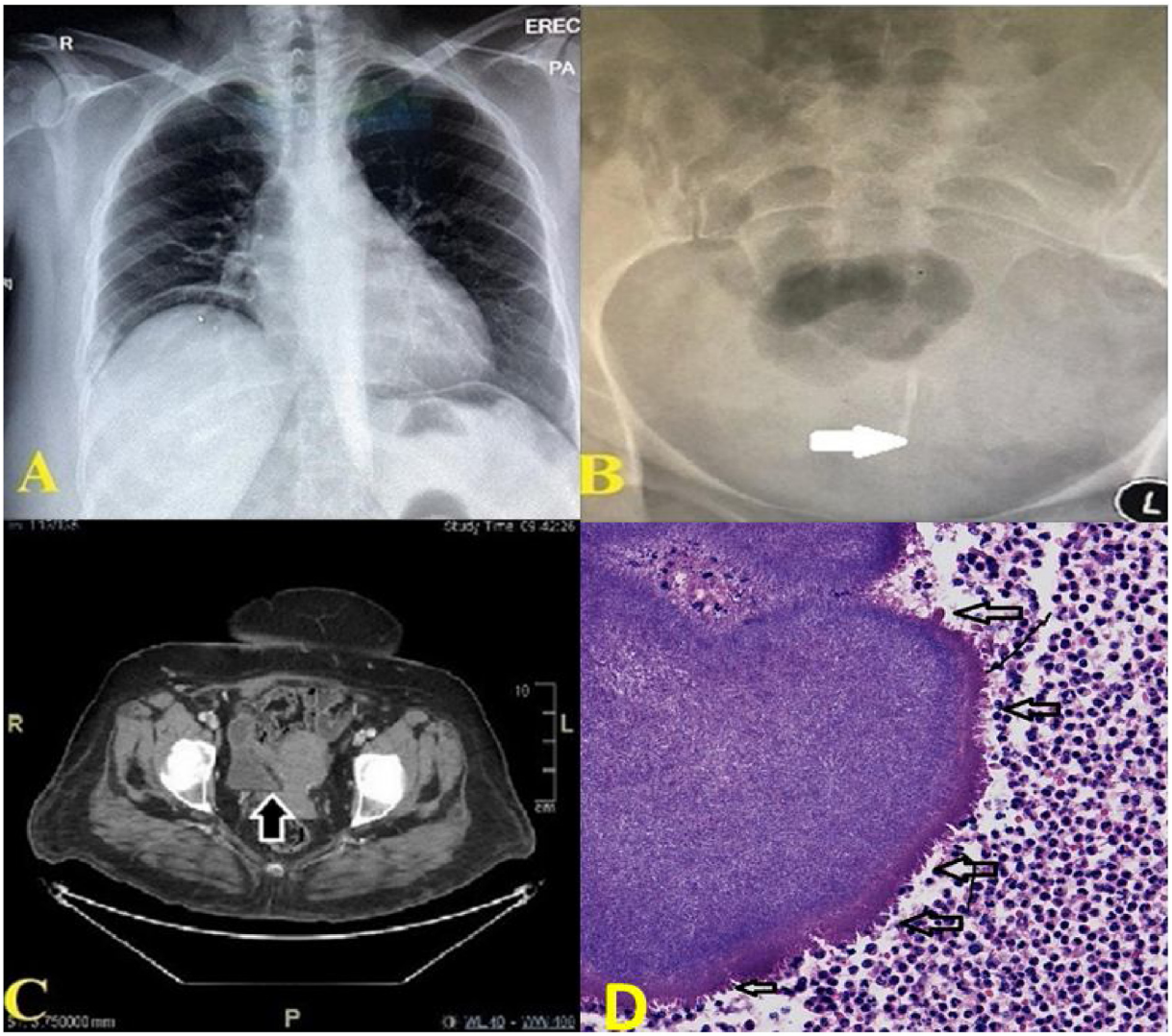

Fig. 4. (A) Chest radiograph showing gas under the diaphragm (B) Plain radiograph of the pelvis showing IUD in site. (C) CT scan of the abdomen and pelvis revealed loculated collections adjacent to rectosigmoid and urinary bladder (D) H&E stain of colonic segment showing sulphur granules as indicated by the black arrows.

Discussion

The cases reported in this series highlight the difficulty in diagnosing actinomycosis. In many cases, the diagnosis was overlooked and was only confirmed after histopathological examination [6].

In this study, three patients presented with a slowly progressing disease and one developed an acute abdomen, secondary to viscus perforation. Two patients had a cervicofacial disease, including hard palate actinomycosis. Orocervicofacial diseasee affects approximately 50% of patients [1]. On the other hand, hard palate involvement in actinomycetes is extremely rare, with only four cases documented in the literature [7]. The fourth patient in our series presented with an abdominopelvic disease, which has been reported in 20% of patients [1]. Presentation with an abdominopelvic disease is not surprising as the bacteria are known commensals of the urogenital tracts. Although the disease is reported to affect immunocompromised patients, most cases are seen in immunocompetent males. Only the third patient in this case series was immunocompromised, following chemoradiation for a submandibular cystic adenocarcinoma.

Our third patient had multiple risk factors, including male gender, an underlying malignancy, immunosuppression. However, we believe that poor dental hygiene was the main predisposing factor. He could not brush his teeth due to limited mouth opening (8 mm), resulting in advanced dental caries that could not be managed by the dentist. The accompanying trismus may have been malignancy-associated; however, the invasion of the facial muscle by actinomycetes has been previously reported [8].

The presentation of our fourth patient with a perforated viscus was challenging. She had an IUD for over 8 years. The association of actinomycosis with IUDs and uterine cervical cerclage was reported as early as the 1920s [9,10]. Although the duration of the IUD use prior to the development of infection was not clearly defined, most patients presented with an IUD in place for >2 years [1]. The colonization rates of IUDs can be up to 11.4%; however, it is not clear which patients progress to infection. In general, IUD removal is recommended every 3–5 years. Annual gynecologic follow-up is also recommended for these patients [11].

Infection can spread through the fallopian tube, causing salpingitis and subsequently, destruction of the ovaries and adjacent organs. Our patient had a left ovarian involvement, and presented with colonic perforation. Actinomycosis manifesting with colonic perforation has been reported in only few case [12]. Other presentations of pelvic actinomycosis include pelvic inflammatory disease, tubo-ovarian abscess and its complications and various presentations that often mimic gynaecological malignancies [11].

There are diagnostic challenges associated with actinomycosis, as the disease presents with non-specific symptoms; however, some key features of the disease include cold abscesses, sinus tracts, and fistulizing diseases. Cold abscesses typically lack the acute inflammatory changes seen in acute pyogenic infection and usually occur in the setting of tuberculosis or fungal infection. Furthermore, actinomycosis can mimic or complicate malignancy [13]. The second patient was referred to our hospital to rule out malignancy of the hand, while the third patient had a malignancy in addition to the infected tumor. In such cases, the presence of regional lymphadenopathy is more likely to indicate malignancy than Actinomyces spp. infections. In rare cases, actinomycosis may also disseminate and mimic a metastatic malignancy [5]. Differentiating between disseminated actinomycosis and metastatic adenoid cystic carcinoma was difficult in our third patient. Subsequent histopathological examinations of lung and renal biopsies revealed findings consistent with metastatic disease.

Diagnosis depends on clinical and histopathological features, along with Gram staining finding from tissue or drained pus. It is difficult to grow the bacteria in media, as they are very sensitive to oxygen, and therefore require immediate transport to an anaerobic environment and prolonged incubation. Failure rates in isolating the organism can reach >50% [1]. In many cases, specimens are not sent for culture as the diagnosis is not decided on preoperatively. Sulfur granules, the hallmark of actinomycosis, are seen in 50% of the cases; however, these are often non-specific, since they can be present in nocardiosis, chromomycosis, and botryomycosis [14]. Of note, actinomycetes can have companion organisms, depending on the location of the lesions. The frequency of concomitant infection varies between 75 and 95%, with *Actinobacillus actinomycetemcomitans* being the most common, followed by Peptostreptococcus, Prevotella, Fusobacterium, and Bacteroides [15]. These concomitant organisms tend to enhance the pathogenicity of Actinomyces spp. by contributing to the anaerobic nature of the tissue, and as a result, further increase the growth potential of Actinomyces spp. Furthermore, concomitant bacteria are associated with a decreased isolation rate [16]. Importantly, the detection of this organism should not deter the clinician from pursuing the diagnosis. New molecular evaluations, including PCR testing, 16srRNA sequencing, and mass spectrometry have been introduced in reference laboratories.

Therapy involves a combination of surgical resection/debridement and prolonged antimicrobial treatment tailored to each patient. In some cases, medical treatment alone may be adequate for curing even advanced infections. There are no randomized controlled studies suggesting the best regimen; however, penicillin is the gold standard. Other beta-lactam antibiotics, including amoxicillin, amoxicillin-clavulanic acid, and ceftriaxone, have been used with good outcomes. In patients allergic to penicillin, doxycycline and clindamycin can be used as alternatives. Conversely, quinolones are usually not effiective in actinomycosis [5]. Traditionally, the diseases are treated for 6–12 months. In patients with adequate surgical resection outcomes, shorter courses of 6–8 weeks could be adequate [17]. Similarly the location of the disease can predict the duration of treatment. Pelvic, thoracic, and orofacial disease have been treated with shorter courses. In all cases, close follow-up with clinical and radiological evaluations is necessary.

Our third patient received HBO therapy. It is not clear how much this contributed to the regression of his disease. Very limited information is available on the use of HBO for treating actinomycosis. However, in cases of refractory actinomycosis, HBO can be added as an adjunctive therapy [18]. It works by stimulating the formation of hydrogen peroxide and free radicals, which are toxic to the anaerobic environment. HBO has been used in a few cases with good outcomes [19].

In conclusion, our case series demonstrates that actinomycosis is a rare but curable disease that requires a high index of suspicion for early diagnosis, as it can mimic many other diseases. The diagnosis is highly dependent on histopathological and microbiological findings. Treatment requires a combination of aggressive surgical and prolonged medical management.

Author contributions

Dr. Elzein, Dr. Almutairy, and Arab looked after the patients, made the diagnoses, and performed the follow-up treatment. Dr. Fadhel Aloteibi reviewed and prepared the histopathology slides. All authors contributed significantly to study conception and design, data acquisition, analysis, and interpretation, in addition to drafting and revising the article critically for intellectual content. All authors have agreed to be accountable for all aspects of the

work related to the accuracy or integrity of any part of the work. All authors gave approval for the final version of the manuscript.

Conflict of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We would like to thank Dr. Hamed Kheir for his valuable help in providing missing data on patient number 4.

References

[1] Wong VK, Turmezei TD. Actinomyces. Britiish Med J 2011, doi:http://dx.doi.org/10.1136/bmj.d6099.
[2] Smego Jr RA, Foglia G. Actinomycosis. Clin Infect Dis 1998;26:1255–61, doi:http://dx.doi.org/10.1086/516337.
[3] Russo TA. Actinomycosis. Clin. Infect. Dis. 2010, doi:http://dx.doi.org/10.1017/CBO9780511722240.122.
[4] Wacharachaisurapol N, Bender JM, Wang L, Bliss D, Ponrartana S, Pannaraj PS. Abdominal Actinomycosis in Children: A Case Report and Literature Review. Pediatr Infect Dis J 2017;36:e76–9, doi:http://dx.doi.org/10.1097/INF.0000000000001416.
[5] Valour F, Sénéchal A, Dupieux C, Karsenty J, Lustig S, Breton P, et al. Actinomycosis: Etiology, clinical features, diagnosis, treatment, and management. Infect Drug Resist 2014, doi:http://dx.doi.org/10.2147/IDR.S39601.
[6] Oostman O, Smego RA. Cervicofacial actinomycosis: Diagnosis and management. Curr Infect Dis Rep 2005;7:170–4, doi:http://dx.doi.org/10.1007/s11908-005-0030-0.
[7] De Andrade ALDL, Novaes MM, Germano AR, Luz KG, De Almeida Freitas R, Galvão HC. Acute primary actinomycosis involving the hard palate of a diabetic patient. J Oral Maxillofac Surg 2014;72:537–41, doi:http://dx.doi.org/10.1016/j.joms.2013.08.006.
[8] Sakai O, Sekiya K, Kaneda T, Uyeda JW, Sasaki Y, Okada H, et al. Actinomycosis in the Mandible: CT and MR Findings. Am J Neuroradiol 2013;3(5):390–4, doi:http://dx.doi.org/10.3174/ajnr.a3673.
[9] Beedham T, Ellice R, Smith H, Usherwood MMD. Female genital actinomycosis. Eur J Obstet Gynecol Reprod Biol 1979, doi:http://dx.doi.org/10.1016/0028-2243(79)90086-8.
[10] Knee DS, Christ MJ, Gries DM, Thompson MW. Actinomyces species and cerclage placement in neonatal sepsis: a case report. J Perinatol 2004;24:389–91, doi:http://dx.doi.org/10.1038/sj.jp.7211097.
[11] García-García A, Ramírez-Durán N, Sandoval-Trujillo H, Romero-Figueroa del MS. Pelvic Actinomycosis. Can J Infect Dis Med Microbiol 2017;2017:1–17, doi:http://dx.doi.org/10.1155/2017/9428650.
[12] Yang SS, Im YC. Severe abdominopelvic actinomycosis with colon perforation and hepatic involvement mimicking advanced sigmoid colon cancer with hepatic metastasis: A case study. BMC Surg 2018;18:51, doi:http://dx.doi.org/10.1186/s12893-018-0386-3.
[13] Acevedo F, Baudrand R, Letelier LM, Gaete P. Actinomycosis: a great pretender. Case reports of unusual presentations and a review of the literature. Int J Infect Dis 2008;2008, doi:http://dx.doi.org/10.1016/j.ijid.2007.10.006.
[14] Boyanova L, Kolarov R, Mateva L, Markovska R, Mitov I. Actinomycosis: A frequently forgotten disease. Future Microbiol 2015;2015, doi:http://dx.doi.org/10.2217/fmb.14.130.
[15] Könönen E, Wade WG. Actinomyces and related organisms in human infections. Clin Microbiol Rev,. 2015, doi:http://dx.doi.org/10.1128/CMR.00100-14.
[16] Bonnefond S, Catroux M, Melenotte C, Karkowski L, Rolland L, Trouillier S, et al. Clinical features of actinomycosis A retrospective, multicenter study of 28 cases of miscellaneous presentations. Med (United States) 2016, doi:http://dx.doi.org/10.1097/MD.0000000000003923.
[17] Wong VK, Turmezei TD, Weston VC. Actinomycosis. BMJ 2011;343:d6099, doi:http://dx.doi.org/10.1136/bmj.d6099.
[18] Manheim SD, Voleti C, Ludwig A, Jacobson JH. Hyperbaric Oxygen in the Treatment of Actinomycosis. vol. 210. American Medical Association 1969, doi:http://dx.doi.org/10.1001/jama.1969.03160290104028.
[19] Shauly Y, Nachum Z, Gdal-On M, Melamed Y, Miller B. Adjunctive hyperbaric oxygen therapy for actinomycotic lacrimal canaliculitis, Graefe's. Arch Clin Exp Ophthalmol 1993, doi:http://dx.doi.org/10.1007/BF00919654.