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Case Report

Dot-in-circle sign in cervical actinomycotic mycetoma: An extremely rare case report ☆

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ABSTRACT

Actinomycosis is an unusual, chronic granulomatous infection caused by *Actinomycetes* spp. The organism also causes mycetoma, a neglected tropical disease in endemic regions. We present a very uncommon case of extensive actinomycosis of the soft tissues in the neck with perivertebral extension that showed the dot-in-circle sign on magnetic resonance imaging. A 29-year-old male patient presented with progressively enlarging hard posterior neck swelling of 4 years duration. Subsequently, magnetic resonance imaging showed the dot-in-circle sign in an avidly enhancing infiltrative lesion with extensive involvement of the neck and perivertebral soft tissue. The pathologic examination was in line with actinomycosis. The patient responded to high doses of combination parenteral and oral antibiotics.

Introduction

Actinomycosis is an uncommon chronic granulomatous bacterial infection caused by *Actinomycetes* spp., which are anaerobic/microaerophilic gram-positive filamentous rods [1]. Regions of the body where the organism has a normal flora favor the infection. By far, it is most common in the cervicofacial region (50%-65%) and follows dental trauma, surgery, or oral infections. Thoracic and abdominopelvic sites are also well recognized [2–7]. *Actinomycetes* spp. are also one of the 2 major agents of mycetoma, a neglected cutaneous and subcutaneous infection of tropical and subtropical regions that occurs among outdoor workers [8–10]. The condition is endemic to Ethiopia [11].

Actinomycosis requires a disruption in the normal mucosal barrier to cause infection. Once it gains access to deep tissues, it leads to the formation of dense fibrotic lesions that are not easily accessible to antimicrobials. In later stages, central suppuration, sinus tract formation to adjacent organs or skin, and osteomyelitis can occur [2,12,13].

Abbreviations: CT, Computed tomography; MRI, Magnetic resonance imaging; HIV, Human immunodeficiency virus; WHO, World health organization; NTD, Neglected tropical disease.

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Human actinomycosis infection usually presents indolently with progressively enlarging hard soft tissue swelling. In endemic regions, mycobacterial or nocardial infections easily confuse the condition, resulting in delayed diagnosis and significant disability in regions with insufficient diagnostic capabilities [14].

A definitive diagnosis requires the isolation of the causative organism. But this is a highly demanding process with a low success rate due to the fastidious nature of the organism and the special culturing criteria required, thus delaying the result by 2 to 3 weeks [5,15]. The cheaper, time-saving, and practical alternative is histopathologic examination, where gram staining identifies the morphology of the bacteria and pathologic features of chronic granuloma [1,15].

Imaging is pivotal in defining the extent of the disease in terms of affected anatomical compartments, neurovascular involvement, and ensuing complications, mainly abscess and sinus tract formation as well as osteomyelitis. Radiography, ultrasound, and cross-sectional imaging contribute variably [2,4,13]. Ultrasound and magnetic resonance imaging (MRI) are especially useful as they show the dot-in-circle sign, a highly sensitive and specific radiological sign recently described for mycetoma caused by *Actinomycetes* spp. and fungi, thus differentiating the infection from its masqueraders and enabling early initiation of confirmatory tests [9,16,17]. Spinal actinomycosis is extremely uncommon but has been reported by multiple authors from all segments of the spinal canal and is usually secondary in form. It can progress to cause spondylodiskitis and spinal cord compression. In spinal cases too, the dot-in-circle sign is extremely helpful and can lead to the correct diagnosis [18–21].

The cornerstone of actinomycosis treatment is prolonged antibiotic therapy, which aims to eradicate the infection and prevent recurrence. The first-line treatment is penicillin [1,7,12]. Surgical treatment is also an adjunct in cases of large infiltrative swellings with an abscess cavity or sinus tract formation [3,13].

Case presentation

A 29-year-old male patient from a tropical part of eastern Ethiopia presented with a posterior neck swelling of 4 years duration, which started off as small nodular lesions that progressively developed into a large swelling (Fig. 1). The patient reported past episodes of discharge from the lesion. Associated limitations of neck movement and heaviness were also present. Two years ago, the patient received a course of IM ceftriaxone at an outside hospital, but the swelling was only reduced for a few days. Otherwise, there was no history of fever, weight loss, or extremity weakness. On physical examination, the patient was not in acute distress. His vital signs included a temperature of 35.3°C, blood pressure of 110/70 mm Hg, a heart rate of 75 beats/min, and mild tachypnea of 22 breaths/min, with an oxygen saturation of 98% on room air. There was an approximately 10 × 11 cm nontender, nondischarging hard posterior neck mass with multiple skin ulcerations. The cervical lymph nodes were not palpable. The rest of the examination, including the oral examination, was unremarkable. Laboratory examination revealed an elevated C-reactive protein level of 23.4 mg/L and mild normocytic normochromic anemia with a hemoglobin level of 12.8 g/dL. The white blood count was within the normal range. Organ function and HIV tests were negative.

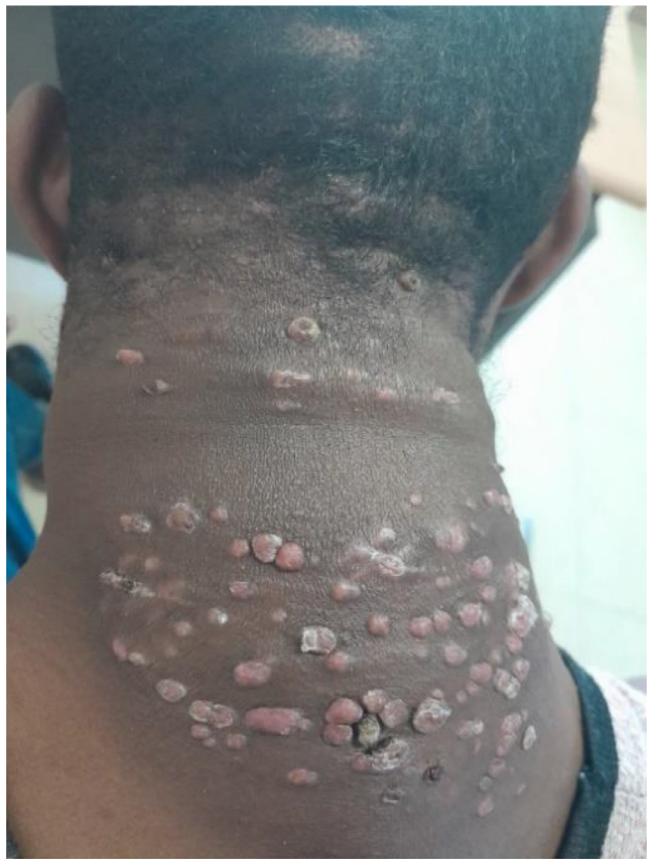

Fig. 1 – Photograph of the lesion.

With an initial clinical impression of a malignant tumor, the patient subsequently underwent pre- and postcontrast cervical computed tomography (CT) and cervical MRI. The cervical CT revealed a large, iso-enhancing, infiltrative soft tissue lesion extending from the suboccipital region to the lower cervical vertebrae level and widely infiltrating the prevertebral muscles. Vertebral cortices were not destroyed (Fig. 2). MRI was superior in showing the heterogeneous nature of the lesion and its vivid contrast uptake. It exhibited different-sized, small, round, and oval T2 hyperintensities distributed throughout, displaying a sharp, dark rim and a central dot of hypointensities representing the dot-in-circle sign (Fig. 4). Multi-level neural foraminal extensions were present with a spared thecal sac. The left vertebral artery was encased. Furthermore, we observed reactive marrow edema of the adjacent posterior elements (Figs. 3-6). We did not detect any signs of an abscess cavity or sinus tracts. These findings were compatible with mycetoma infection.

Subsequently, an incisional biopsy was performed, and pathologic examination confirmed granulomatous inflammation secondary to actinomycosis (Fig. 7).

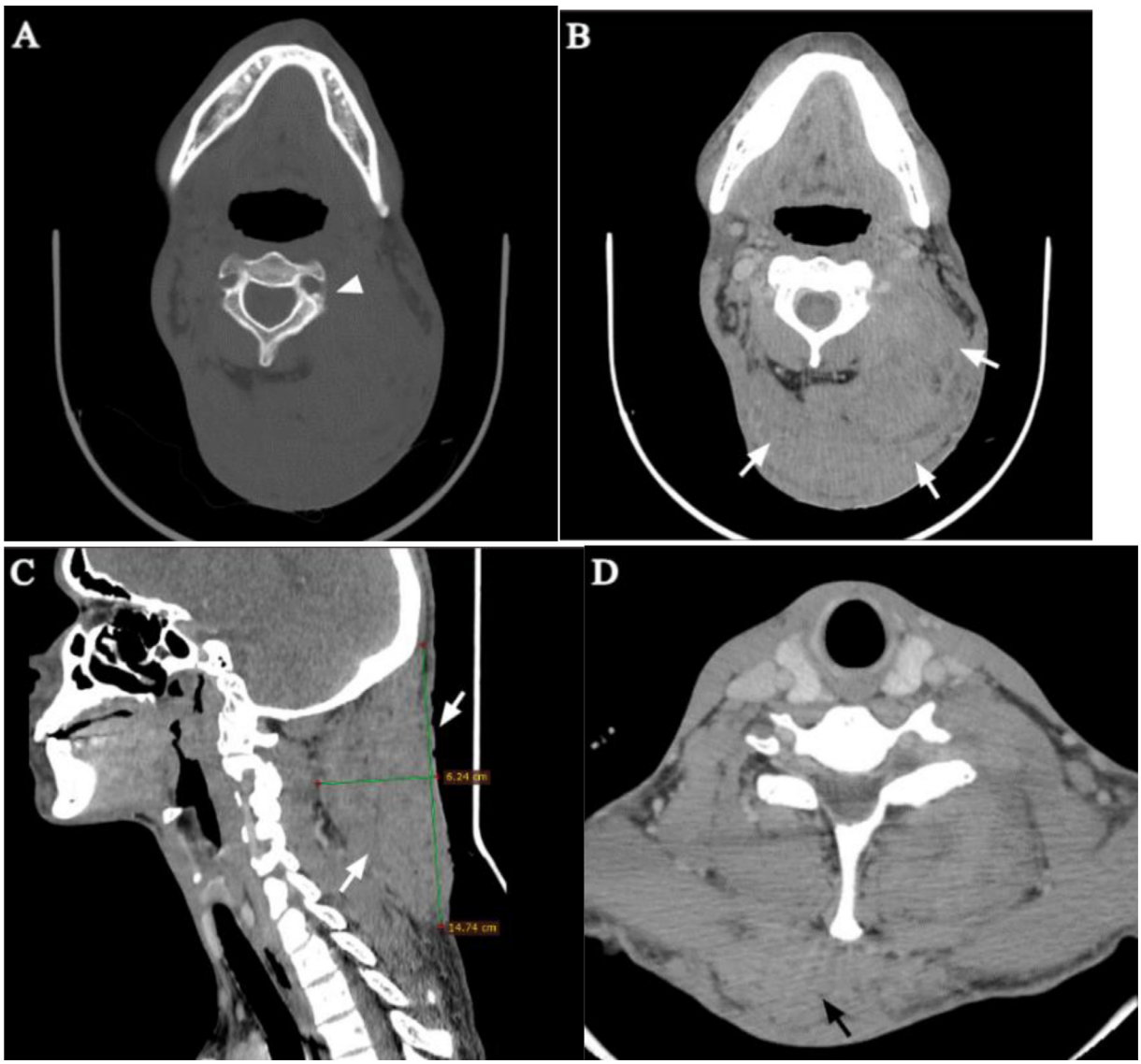

Fig. 2 – Cervical CT with axial pre-contrast (A) and post-contrast (B) views at C2 level, post-contrast left parasagittal view (C), and post-contrast axial view at C7 level (D) - There was a large, 14.7 x 6.3 cm (white arrows in B and C) longitudinally oriented, predominantly left posterior cervical soft tissue swelling that crossed the midline. It spanned from the suboccipital to the cervicothoracic vertebral junction level. The lesion diffusely infiltrated through tissue planes to involve the perivertebral muscles and the left posterior cervical space. More inferiorly, the proximal right trapezium muscle was involved (black arrow in D). Significant surrounding fat stranding as well as skin infiltration were noted. The lesion isoenhanced to adjacent muscles. On precontrast CT, there was non-specific periostitis of the left C2 lamina only (white arrow head in A). Intralesional calcification was not present. No significant cervical lymphadenopathy.

The patient was subsequently started on medical treatment consisting of high-dose intravenous crystalline penicillin G at 6 million IU three times per day and intravenous ceftriaxone 1 gm twice a day for 2 weeks during his admission, with ceftriaxone 2 gm IV to continue on an outpatient basis with a total of 6 weeks of parenteral treatment. Doxycycline 100 mg PO twice a day was also added. Antibiotic treatment is planned for a total of 6 months, but it might be adjusted based on his response. On outpatient follow-up (4 weeks after starting treatment), the lesion decreased in size, and the patient reported better neck motion as well as a decrease in heaviness sensation. Surgical debridement was deferred due to encasement of the left vertebral artery and multilevel neural foraminal extensions.

Discussion

Actinomycosis is an unusual but serious suppurative granulomatous infection that can result in serious morbidity unless treated early [1–3]. The causative organisms belong to

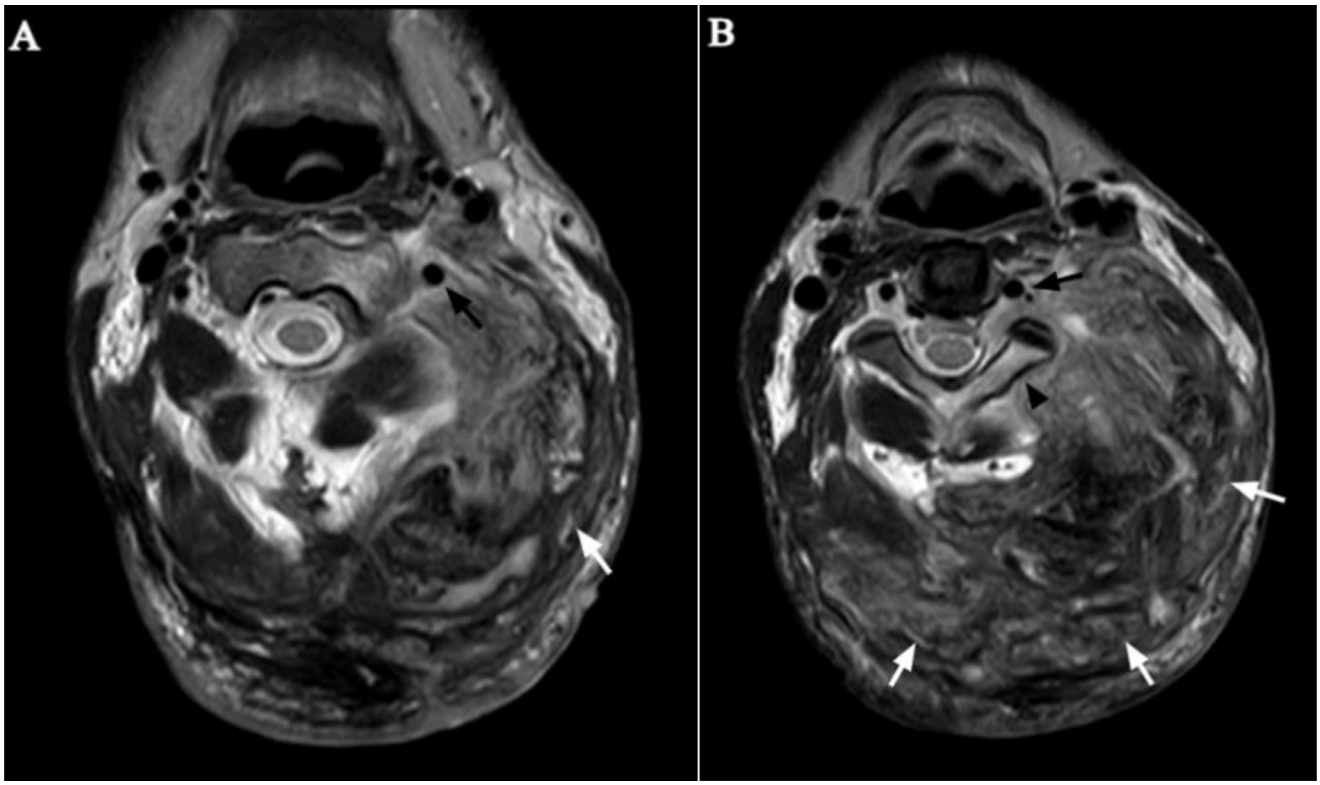

Fig. 3 – Axial T2W images at C2 (A) and C3 (B) levels- The lesion was heterogeneous, with hyperintense T2 regions, and involved the left prevertebral and left and right posterior paravertebral muscles (white arrows in A and B). It extended to multiple intervertebral foramina effacing the left epidural fat but had no significant mass effect on the thecal sac. The adjacent left C3 lamina had a hyperintense marrow signal with an intact cortical outline (black arrowhead on B). The left vertebral artery was completely encased by the lesion but had a normal flow void (black arrows in A and B).

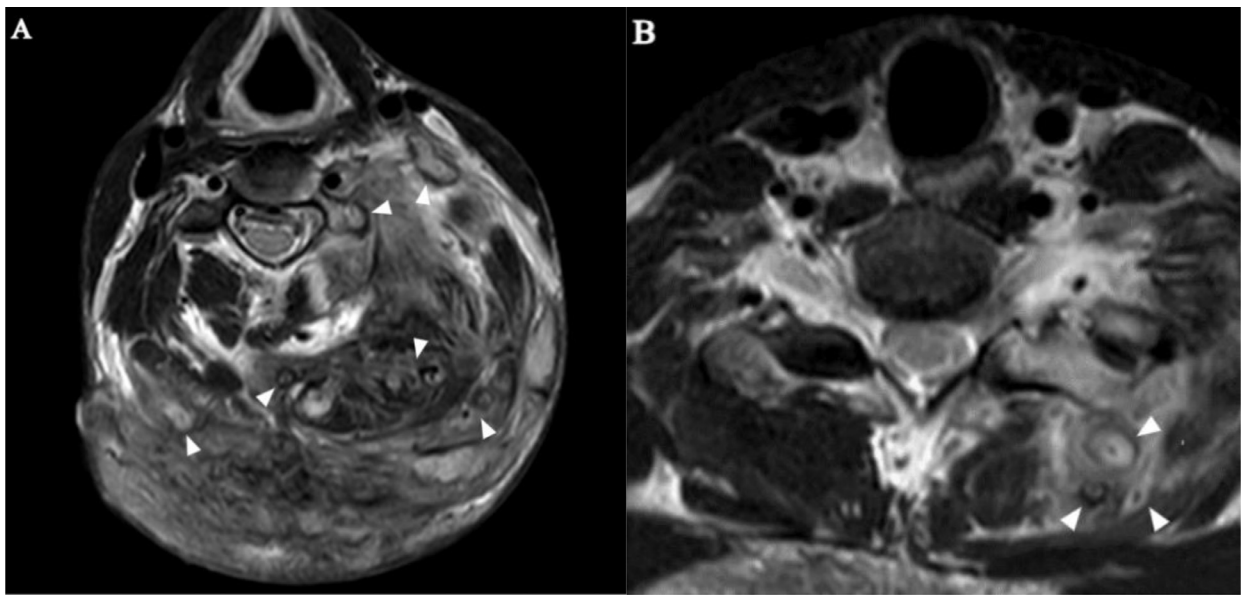

Fig. 4 – Axial T2W images at C4 (A) and C7 (B) levels- Multiple distinct and aggregated (white arrowheads) round and ovoid small T2 hyperintensities with sharp dark rims and hypointense internal foci give the 'dot-in-circle' sign. Similar findings were seen at multiple levels.

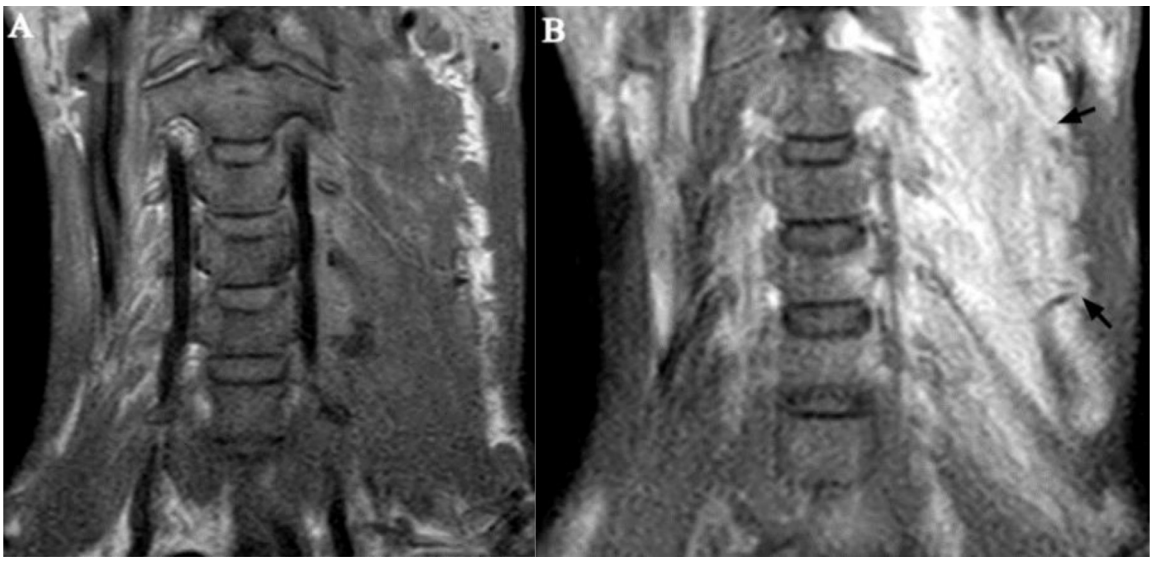

Fig. 5 – Pre (A) and post (B) contrast T1W coronal images- The lesion was predominantly isointense to adjacent muscles and showed avid enhancement (black arrow in B). It protruded into multiple left neural foramina. Intervertebral discs were normal.

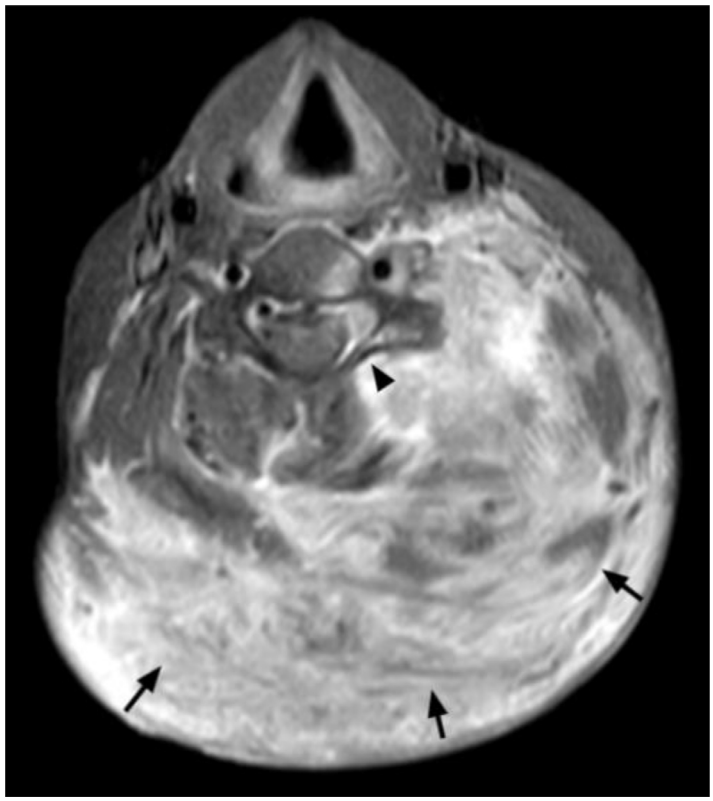

Fig. 6 – Axial postcontrast T1W image at C4 level- The avid enhancement and diffuse extension of the lesion can be better appreciated (black arrows). The adjacent body and lateral neural arch showed enhancement with no cortical change (black arrowhead). No distinct abscess pocket or sinus tract was seen.

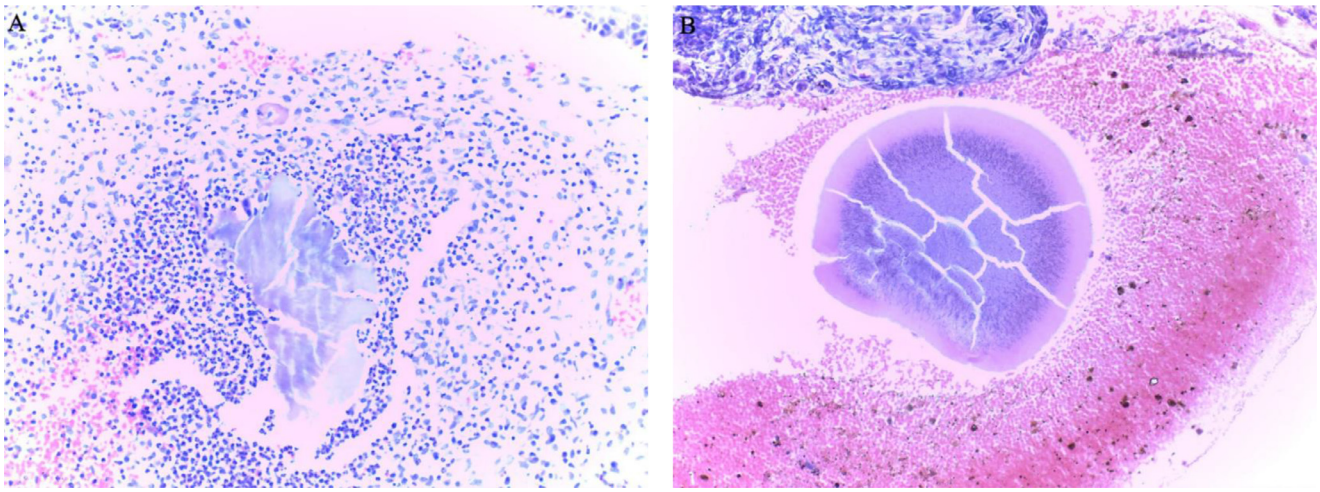

Fig. 7 – H&E stain at 20x magnification demonstrating microabscess with central relatively large basophilic mass resembling Actinomyces (A) and large spherical filamentous organism with peripheral eosinophilic club consistent with Actinomyces (B).

Actinomyces spp., which are anerobic/microaerophilic gram-positive rods with filamentous branches. Actinomyces spp. is a normal flora in the oral and abdominopelvic cavities. However, when phagocytized by host defense cells, they cannot be killed and thus are defined as facultative intracellular parasites similar to Mycoplasma tuberculosis in their disease-causing role [4–6].

Actinomyces spp. are 1 of the 2 etiologic agents for mycetoma, a chronic cutaneous and soft tissue infection. The true fungus (Eumycetoma) is the other causative agent. The World Health Organization (WHO) officially recognized mycetoma as a neglected tropical disease (NTD) in 2016 and included it in the WHO/NTD list [12]. The disease occurs in South America, Africa, the Middle East, and the Indian Subcontinent, among others [8,9]. A retrospective study revealed Ethiopia is an endemic country for mycetoma [11]. Mycetoma usually occurs in 15 to 30-year-old outdoor workers, such as farm workers and laborers [22].

Most cases of actinomycosis occur in immunocompetent patients [6,10], but immunocompromising diseases will also accentuate the infection and include HIV infection, diabetes mellitus, hematologic malignancies, and steroid use [3,8]. Our patient has no evidence of poor immunity.

Once gaining access, the bacteria multiply and have the potential to extensively invade deep tissues (which favorably have low oxygen tension) with no respect for fascial planes. Once established, it forms chronic granulomatous inflammation consisting of yellow sulfur granules made up of solid bacterial filaments and inflammatory tissue. Consequently, suppuration with fibrous wall formation and pus discharging sinus tracts can develop [14]. The fibrous wall has an important treatment implication as it protects the organism from antibiotic access, hence the need for a prolonged course of therapy [8]. The sinus tracts, though, are not present in early stages and might heal spontaneously only to reform in another location [16].

In general, human actinomycosis, including mycetoma infections, share some common clinical features. They tend to have a subacute to chronic duration of illness and commonly form hard, soft tissue swelling. Sinuses and fistulas may become visible at a later stage. An acute presentation of a typical pyogenic abscess also occurs [4,10,12,13,16]. The chronic hard swelling and previous history of discharge in our patient are consistent with the known clinical features. As in our case, a temporary size decrement following antibiotic treatment can also occur in actinomycotic infections [17]. But these symptoms and signs can also occur due to mycobacterial, nocardial, and fungal infections. In addition, the hard and, at times, wood-like consistency of the swelling and its indolent nature mimic a malignancy. As a result of nonspecific findings, the diagnosis of actinomycosis is difficult and often delayed [1,2]. Our patient's diagnosis was not settled for 4 years, even though he had visited health institutions in the past. In the current presentation, too, the initial clinical impression was a soft tissue malignancy.

Microbiologic isolation of actinomycosis is the definitive method of diagnosis, but unfortunately, the process is fraught with many limitations, with a yield of less than 50% [1,4,5]. Actinomycetes spp. grow slowly and require stringent culture and media requirements. Prior antibiotic use and co-infection with other organisms further decrease the result. Furthermore, identification of the exact species requires intricate procedures such as phenotype testing or ribonucleic acid sequencing [5]. Due to the complexity, we did not perform microbiologic analysis in our case.

Histopathology is a very important part of diagnosing actinomycosis. It's worth noting that Nocardia species may exhibit similar morphologic features. Therefore, it is advisable to use special stains such as Grocott methenamine silver and modified acid-fast stains. In addition, the multifocal presence of the organism increases the likelihood of overlooking it in fine needle aspiration and core needle biopsy procedures, po-

tentially leading to misdiagnosis. Consequently, excisional or incisional biopsies are considered the most preferable samples for a reliable diagnosis [1,23].

Radiology plays an important role in the diagnosis of actinomycosis. It can show the involved tissue compartments, their relation to adjacent neurovascular structures, and concurrent osteomyelitis. An infiltrative mass isodense with adjacent muscle and of variable enhancement is visualized on CT. The level of enhancement can be mild (less than adjacent muscle), moderate (iso to adjacent muscle), or avid (more than adjacent muscle but less than vascular enhancement). Dystrophic calcification, although rare, has been described [24]. MRI provides superior soft tissue contrast, aids in sinus tract identification, and enables early detection of osteomyelitis. The lesion appears homogeneous or heterogeneous and is isointense to muscle on the T1W sequence and hyperintense on the T2W sequence. Centrally suppurated regions, fitting the pathogenesis of the infection, can also be detected [4,24]. The bone marrow edema shown in our case is likely reactive rather than true osteomyelitis, given the intact cortex and absence of moth-eaten lytic lesions (better assessed on CT) [12]. The intervertebral discs were also normal, with no signal change on the MRI. Even though intervertebral disc damage occurs late in actinomycosis [18], given the long duration of illness in our patient, it should have been manifest by the time of presentation. Nonetheless, follow-up imaging should confirm this assumption. One interesting aspect of actinomycosis is the absence or paucity of regional lymphadenopathy. The reasons for this are the large size of Actinomycetes spp. and their direct spread pattern, which does not allow for lymphatic spread [7,10]. Thus, an important dissociation arises whereby a sizable, enhancing soft tissue lesion occurs with no or few reactive lymph nodes. Together with the relative lack of adjacent inflammation in malignant lesions, this pattern is helpful to differentiate actinomycosis from malignant lesions [4,6,24].

Mycetoma shows the dot-in-circle sign, which consists of well-defined, rounded T2 hyperintense foci with a dark rim and hypointense central dot. The components of the dot-in-circle sign correlate well with pathologic findings. The central hypointense dot represents grains, the surrounding hyperintense region is the inflammatory granuloma, and the peripheral dark rim is the fibrous matrix. Similar morphologic formation can be detected on sonography, where actinomycotic grains appear as hyper-reflective and closely aggregated fine echoes that gravitate to the bottom of their cavities. The sign is a highly specific one and can aid in noninvasive early imaging diagnosis [12,19,20,25].

Mycetoma commonly affects the foot (70%) [12]. However, infections in less common locations have also occurred. Foot mycetoma is usually fungal, but it has been reported with Actinomycetes spp. too. Al Gannass [26] reported actinomycotic mycetoma in the diabetic foot of a 58-year-old farmer, which showed the typical dot-in-circle sign on an MRI. The patient's diabetes was thought to facilitate the infection. Mycetoma can also occur in an unusual musculoskeletal location. In one report, fungal mycetoma presented as a large, chronic swelling of the right thigh with a typical dot-in-circle sign on an MRI [27].

Spinal involvement with actinomycosis is very rare. Ezaldeen et al [28] reported cervical cord compression from secondary actinomycosis in a 40-year-old Sudanese man who presented with progressive quadriparesis. He had a chronic right shoulder focus that progressed to infiltrate the soft tissue of the right neck and compress the cervical cord. Similarly, sacral spinal compression from extensive actinomycotic abdominal disease has been reported by Cascio et al [29]. Also, a review of thoracic vertebral actinomycosis identified only 14 reported previous cases from 1951 to 2007. A. israelii caused the majority of cases, with 66.7% of them involving the thoracic region [30]. A compressive fungal mycetoma with a positive dot-in-circle sign has also been reported in the lumbar spine [21].

The cervical involvement in our case is likely primary, as there was no clinical or imaging evidence of a nearby or distant focus to suspect direct and hematogenous spread, respectively. To the best of our knowledge, ours is the first case report in the English literature that showed the dot-in-circle sign in cervical actinomycosis.

The cornerstone of actinomycosis treatment is high-dose antimicrobials, and the drug of choice is penicillin. Alternatives such as clindamycin, tetracycline, and erythromycin are used in penicillin-allergic patients. Generally, prolonged treatment (6-12 months) is necessary to eradicate the infection and prevent recurrence [14,26–31]. The exact duration is tailored based on clinical response. Surgery is required for associated osteomyelitis and resection of necrotic tissue, abscesses, and sinus tracts. Surgical debridement also shortens the duration of medical treatment and increases the effectiveness of antibiotic treatment [4,10,14,31].

In conclusion, actinomycosis can cause serious, debilitating infections in atypical locations, either primarily or with secondary spread. We reiterate the significance of the dot-in-circle sign as an important radiological sign that adds specificity to the imaging diagnosis of actinomycosis and has the benefit of contributing to the early treatment initiation of this neglected condition.

Patient consent

Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

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