American Journal of Infectious Diseases and Microbiology, 2018, Vol. 6, No. 3, 66-71
Available online at http://pubs.sciepub.com/ajidm/6/3/1

DOI:10.12691/ajidm-6-3-1

Human Actinomycosis: Report of a Rare Case of Disseminated Actinomycosis Presenting as Varicosities and Deep Vein Thrombosis

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Received October 03, 2018; Revised November 11, 2018; Accepted November 16, 2018

Abstract **Introduction:** Human actinomycosis is characterized by the development of chronic granulomatous lesions of the skin and subcutaneous connective tissues. The condition is also called as mycetoma, and typically presents as granulomatous skin with multiple draining sinuses usually affecting the lower limbs. The pus draining from these lesions show characteristic granules, and the laboratory diagnosis greatly depends on the identification of the causative microorganism from the crushed granules. Actinomycosis is a chronic infection and may cause severe complications when the treatment is not initiated at an appropriate time. In this case report we present a rare instance of disseminated actinomycosis in a patient who presented with varicosities and deep vein thrombosis. **Case presentation:** A-54-year-old male presented with complaints of swelling in the right lower limb, multiple inflammatory swelling like lesions on the thoracic region and chronic lower back pain. The patient started to notice dilated veins on the abdominal wall and around the umbilicus for one month. He was a known case of actinomycosis, who suffered from the complications of mycetoma and had the left leg amputated below the knee. Considering the previous history of the patient, a provisional diagnosis of disseminated actinomycosis was made. Due to the presence of dilated tortuous veins, and the edema varicosities and possible deep vein thrombosis was suspected. Pus was drained from the swelling like lesions, which on microscopy revealed gram-positive filamentous branching bacilli. Culture on Lowenstein-Jensen's (LJ) medium revealed the growth of red colored non-acid-fast gram-positive filamentous branching bacilli which was identified as *Actinomyces* species. **Conclusion:** Human actinomycosis is an underdiagnosed microbial infection. Inadequate treatment could cause disseminated actinomycosis and severe complications as observed in the present case. Bacterial isolation can be hindered by prior antibiotic use and culture on LJ medium may improve the chances of isolation of *Actinomyces*.

Keywords: *human actinomycosis, mycetoma, disseminated actinomycosis, varicosities, deep vein thrombosis*

Cite This Article: Venkataramana Kandi, Vikas Chennamaneni, Suman Kaveti, Ritu Vaish, Padmavali Palange, Sri Sandhya Koka, and Mohan Rao Bhoomigari, "Human Actinomycosis: Report of a Rare Case of Disseminated Actinomycosis Presenting as Varicosities and Deep Vein Thrombosis." *American Journal of Infectious Diseases and Microbiology*, vol. 6, no. 3 (2018): 66-71. doi: 10.12691/ajidm-6-3-1.

1. Introduction

Actinomyces are a group of filamentous, branching, gram positive bacilli. *Actinomyces* constitute the normal flora of human oral cavity, respiratory tract, gastrointestinal tract, and genito-urinary tract [1]. They are a large group of bacteria requiring either aerobic, microaerophilic and anaerobic environment for their growth and survival. Most human infections caused by *Actinomyces* are endogenous in origin, whereas exogenous infections can be caused by *Actinomyces* species (spp.) present in the environment. Infection caused by *Actinomyces* group of bacteria is called as Actinomycosis [2]. Human Actinomycosis presents as a chronic granulomatous, slowly progressing infection affecting the skin and subcutaneous connective tissues, also involving various other organs of the body. The clinical condition is generally called as mycetoma, which can be caused by *Actinomyces* spp. (actinomycotic mycetoma), other bacteria (botryomycosis), and fungi (eumycotic mycetoma).

There are several Actinomyces spp. which have been associated with human infections including *Actinomyces* (*A.*) *israeli* (*A. israeli*), *A. odontolyticus*, *A. meyeri*, *A. viscosus*, *A. naeslundii*, *A. graevenitzii*, *A. gerencseriae*, *A. turicensis*, *A. cardiffensis*, *A. urogenitalis*, *A. neuii*, *A. funkei*, *A. hongkongensis*, and *A. turicensis* [3]. Human actinomycosis usually presents as mycetoma affecting the lower limbs. Cervicofacial actinomycosis, thoracic actinomycosis and pelvic actinomycosis have been frequently reported in literature. Isolated cases of ear, nose, and throat infections, brain abscesses, oral, urinary

tract, bone and joint infections have also been reported [3]. Disseminated actinomycosis has been infrequently reported and is characterized by the spread of the infection to other parts of the body from the site of primary inoculation [4]. This report presents a rare case of disseminated actinomycosis in a patient with a previous history of actinomycosis and presented with varicosities and deep vein thrombosis (DVT).

2. Case Presentation

A 54-year-old male patient presented to the medical outpatient department with complaints of swelling in the right lower limb, multiple inflammatory swelling like lesions on the thoracic region and chronic lower back pain. The patient was otherwise normal 15 days prior, when a low grade, on and off episodes of fever started. The patient started to notice swelling like lesions on the back and dilated veins on the abdominal wall and around the umbilicusfor one month. He was a known case of actinomycosis, who suffered from the complications of mycetoma and had the left leg amputated below the knee. There was no history of hypertension, diabetes mellitus, asthma, goiter, tuberculosis and cardiovascular disease. The patient was a non-smoker, non-alcoholic, and was negative for antibodies against human immunodeficiency virus (HIV) infection. The patient gave a history of constipation for three months.

On physical examination, the patient appeared to be co-operative, and moderately built with normal skin and there was no sign of organomegaly. The clinical examination showed a normal musculoskeletal, genitourinary, cardiovascular, central nervous and respiratory systems. The abdomen was soft, showing dilated tortuous veins all around the umbilicus and the right flank region. Both the right and left lower limbs were swollen up to the thigh region and multiple subcutaneous swellings were observed over the right gluteal, right subcostal, and right paraspinal regions. The right lower limb was non-tender and showed pitting type edema, with no blisters and open pus discharge.

Considering the previous history of the patient, a provisional diagnosis of disseminated actinomycosis was made. Due to the presence of dilated tortuous veins, and the edema it was suspected to be a case of varicosities and possible DVT.Patient was advised doppler study of the right lower limb and a contrast enhanced computed tomography (CECT) of the abdomen.

Doppler study and the two-dimensional CT venography of the right lower limb revealed multiple dilated tortuous subcutaneous veins at the right inguinoscrotal region and extending to the thighs along the great saphenous vein (GSV), which was suggestive of varicosities(Figure 1).

CECT study showed subcutaneous edema below the inguinal region and intramuscular edema at the posterior part of the leg (Figure 2a).Multiple communicating tracks were observed in the right gluteal region (Figure 2b). Multiple subcutaneous hypoechoic collections with internal hyperechoic free debris was noted.

CECT abdomen revealed complete thrombosis of right common iliac vein, near total thrombosis of inferior vana cava and partial thrombosis of left common iliac vein confirming DVT (Figure 3). Evidence of bony erosions with destructive lytic lesions (Figure 4a). Multiple fluid filled abscesses were also seen (Figure 4b).

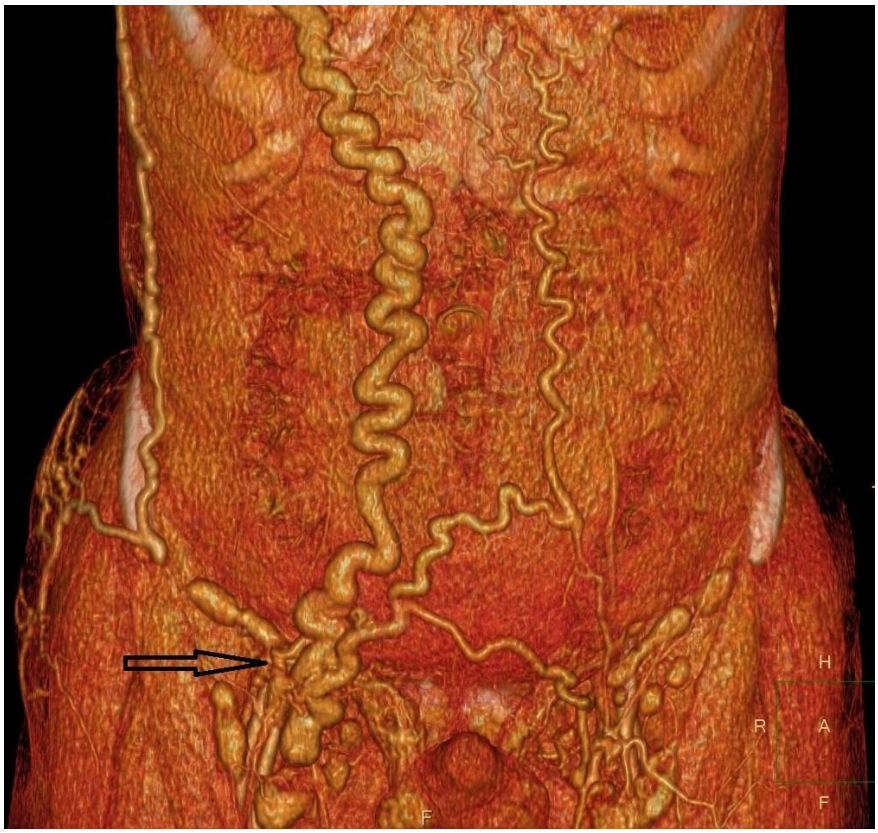

Figure 1. Two-dimensional CT venography scan showing multiple dialated tortuous subcutaneous veins at the right inguinoscrotal region

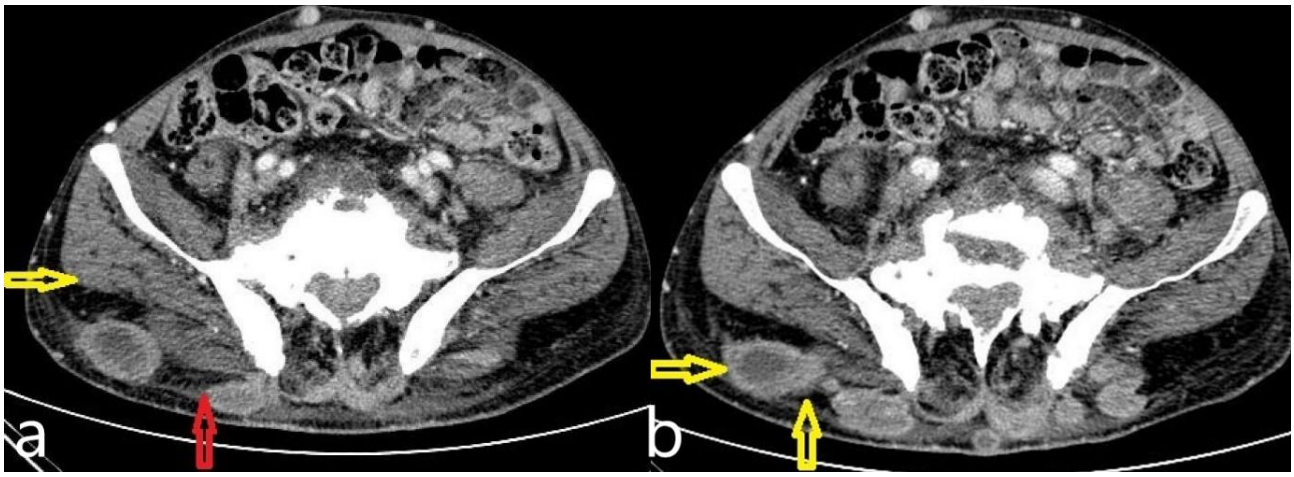

Figure 2. a) Axial CT scan showing subcutaneous edema (red arrow) below the inguinal region and intramuscular edema at the posterior part of the leg (yellow arrow). b) Axial CT scan revealing multiple communicating tracks in the right gluteal region

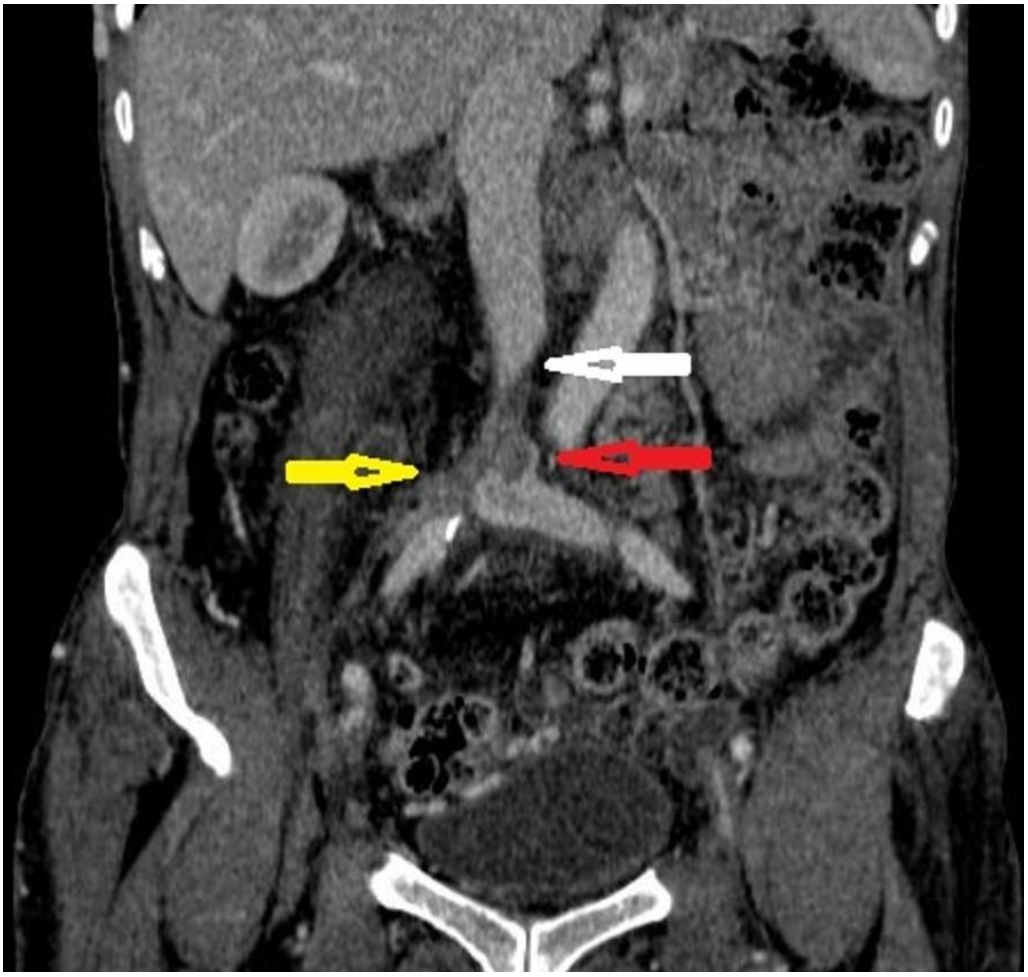

Figure 3. Coronal CT scan showing complete thrombosis of right common iliac vein (yellow arrow), near total thrombosis of inferior vana cava (white arrow) and partial thrombosis of left common iliac vein (red arrow)

Suspecting actinomycosis, pus was drained and collected from the swelling like lesions on the back (thoracic region) of the patient with the help of a syringe for further microbiological analysis. On macroscopic observation (naked eye), the pus was observed to be thick, blood streaked and had specks of granules (Figure 5a). The granules were also crushed and observed by using 10% potassium hydroxide (KOH) mount for the presence of fungal elements. KOH mount was negative for fungal elements but showed the typical sun ray type of appearance revealing the globose structures (probably made from the surrounding tissue) which cover the central microbial region, thereby protecting the bacteria against immunological reactions (Figure 5b). Gram's stain of the pus revealed typical, gram positive, filamentous branching bacilli with beaded appearance (Figure 5c).

Interestingly, the KOH mount of the pus, which was negative for fungal elements revealed actively motile and live bacteria, which were long and filamentous as shown in this Video 1.

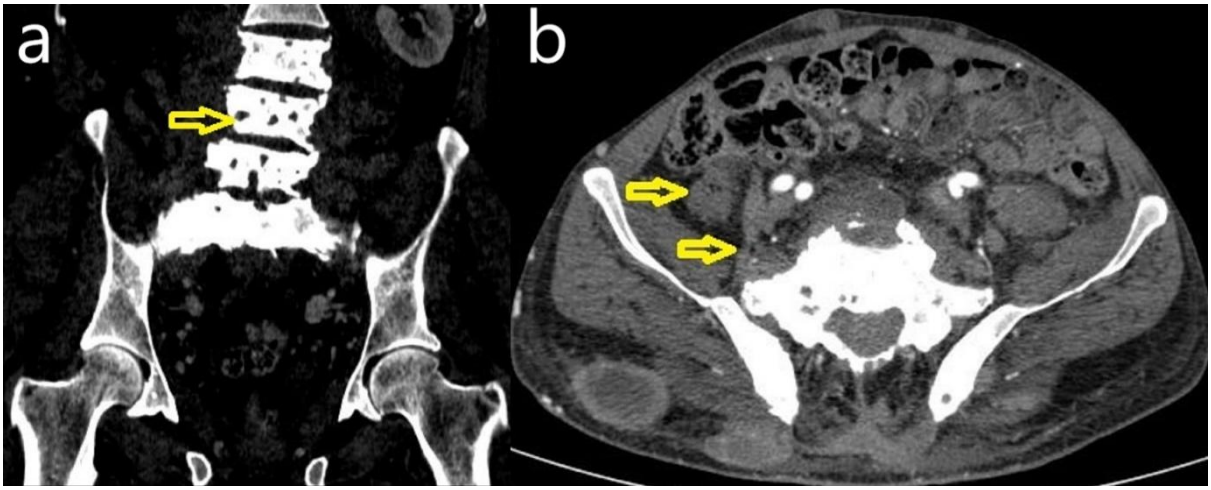

Figure 4. a) Coronal CT scan showing bony erosions with destructive lytic lesions (yellow arrow). b) Axial CT scan showing multiple fluid filled abscesses (yellow arrow)

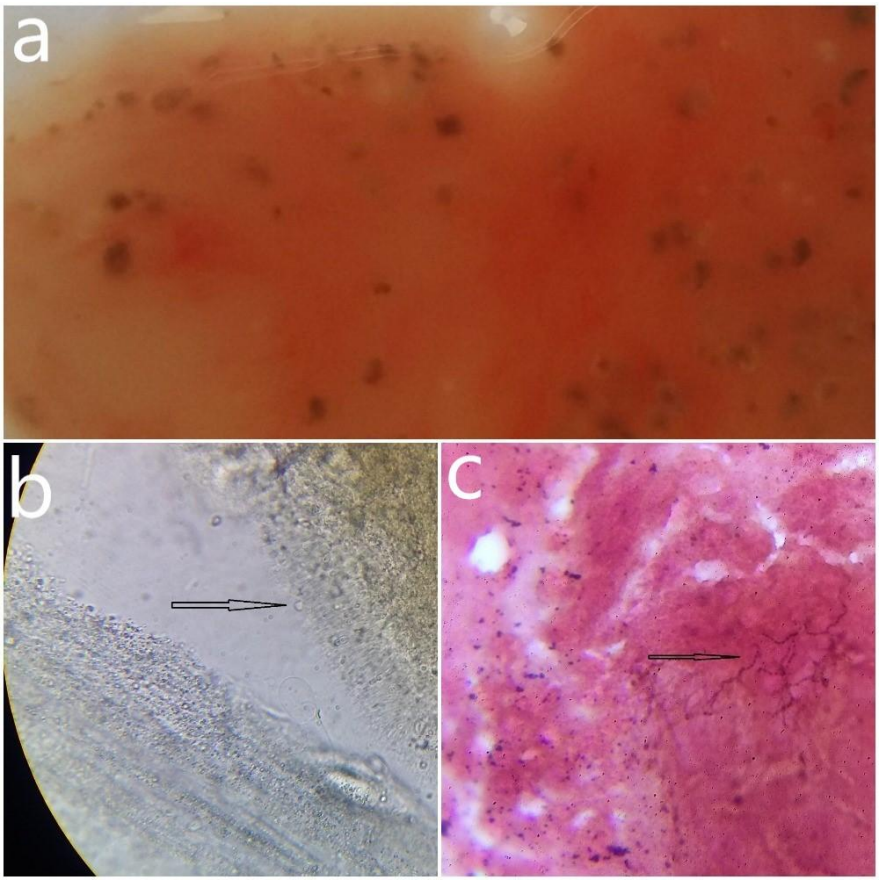

Figure 5. a) Aspirated pus showing granules. b) Crushed granule as observed in KOH mount showing typical sun ray type of appearance. c) Gram's stain of the pus showing typical gram-positive filamentous branching bacilli with beaded appearance

The pus was later inoculated in to a set of two Sabouraud's dextrose agar (SDA), one incubated at 37℃ and the other at room temperature (22℃-30℃) for the isolation of fungus. A set of two blood agars were also inoculated with pus sample, with one incubated under aerobic environment and the other in candle jar. Either cultures revealed no growth even after two weeks of incubation. Modified acid-fast staining of the crushed granule was negative, ruling out Nocardia. Because no growth appeared on routine cultures, the pus specimen was inoculated in to Lowenstein-Jensen's (LJ) medium. A growth of reg pigmented colonies started appearing after one week of incubation (Figure 6a). Gram's stain of the isolated bacterium revealed gram positive filamentous branching bacilli (Figure 6b). The bacteria were non-acid-fast (Figure 6c) and was preliminarily identified as Actinomyces species.

Considering a positive gram's stain picture and the absence of any fungal etiology a diagnosis of actinomycosis was made. Since the patient had a previous history of actinomycosis, and the current status also confirms the presence and dissemination of the bacteria from the site of localization to the thoracic region, a final diagnosis of disseminated actinomycosis with varicosities and deep vein thrombosis was made.

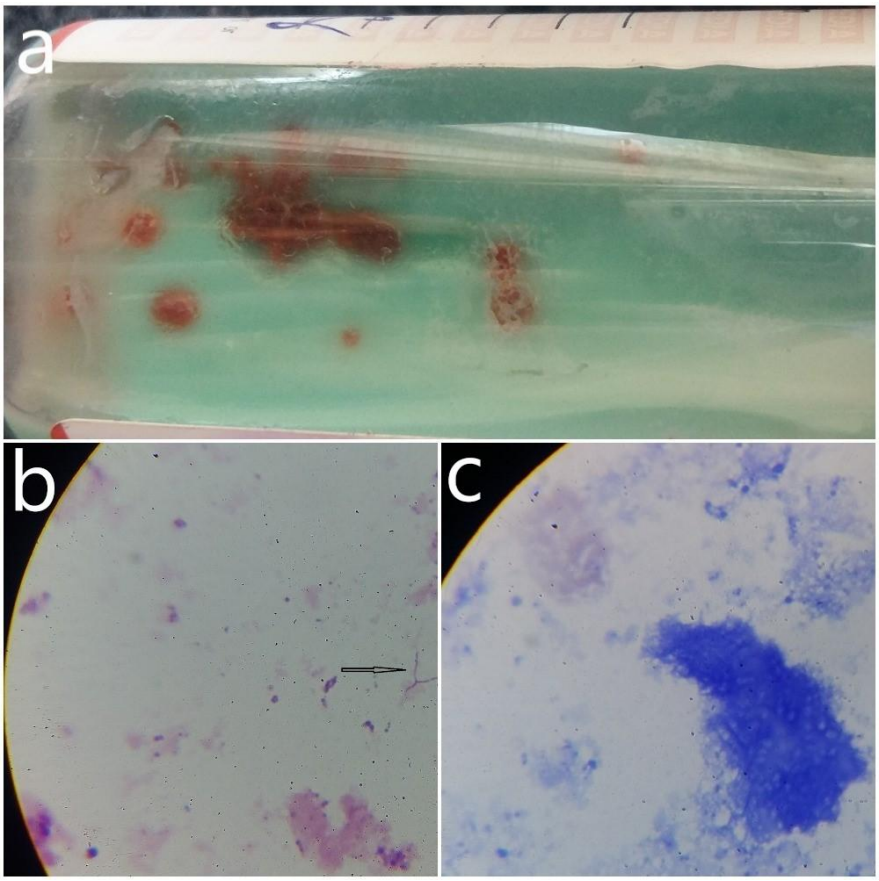

Figure 6. a) Red colored colonies appeared on Lowenstein-Jensen's medium after one week of incubation. b) Gram's stain of the bacterium grown on Lowenstein-Jensen's medium showing branched gram-positive filamentous bacilli. c) Acid-fast staining revealed non-acid-fast bacteria (Video 1: Bacteria as observed directly from the aspirated pus showing long filamentous structure: https://www.youtube.com/watch?v=K4bblPIezzM)

The patient was managed with Clexane injection (Enoxaparin, an anticoagulant) (60 mg once daily), along with a combination of Dapsone (100 mg twice daily) and Tetracycline (500 mg twice daily). Predicting potential complications arising from DVT, the patient was recommended to a vascular surgeon for further treatment and management.

3. Discussion

Actinomyces spp. belong to a divergent group of non-spore forming gram positive bacilli which also include Corynebacteriumdiphtheriae, Mycobacteriumtuberculosis, Listeriamonocytogenes, Erysipelothrixrhusiopathiae, Lactobacillus, Propionibacterium, Nocardia and Rhodococcus species. Among these, Actinomyces spp. have been known to be present as a normal flora of human beings and as frequent causes of endogenous infections [1]. Several other species of Actinomyces are known to be present in the environment (soil) [5]. Of all the non-spore forming gram positive bacilli, most species are facultative anaerobes except Actinomyces (majority are strict anaerobes with some aerotolerant variants), Lactobacillus (aerotolerant anaerobe), Propionibacterium (aerotolerant anaerobe), Nocardia (aerobe), and Rhodococcus (aerobe).

Mycetoma and actinomycosis were first described during 1860's by Vandyke Carter as a special disease of humans. Although a fungus (*Chionyphecarteri*) was attributed to be the cause of the disease, disfiguration of the involved organs (usually foot and hand) due to chronic granulomatous changes of the skin and subcutaneous tissues, edema, draining of pus with granules (different colored and sizes), and numerous fluid filled cavities which are interconnected (sinuses) were a common feature [6]. Mycetoma can be caused by *Actinomyces*spp (Actinomycotic mycetoma), other bacteria (Botryomycosis), and fungi (Eumycotic mycetoma).

Human actinomycosis is a slowly progressing complex disease, which involves various organs of the body and pose a diagnostic challenge [3]. Laboratory diagnosis of mycetoma and actinomycosis assumes greater significance since identification of the etiological agent could provide us with specific direction for the better management of the patients and facilitate improved outcome [7,8]. Clinically actinomyces can present as cervicofacial actinomycosis (lumpy jaw), thoracic actinomycosis, abdomino-pelvic actinomycosis, muskuloskeletal actinomycosis (involve upper and lower limbs), central nervous system actinomycosis and disseminated actinomycosis [3].

Clinical diagnosis of actinomycosis is complex due to its slow and gradual onset and resemblance to nocardiosis, tuberculosis and cancer as suggested by recent reports [9,10,11]. Disseminated actinomycosis is rare and could be associated with severe complications as evidenced from a recent report of central nervous system actinomycosis, invariably proving fatal [4].

A recent report revealed that an initial nasopharyngeal actinomycosis had after a year presented as invasive case of actinomycosis causing brain abscess [12]. This report

signifies the importance of both clinical and laboratory diagnosis of human actinomycosis.

Laboratory diagnosis of cervicofacial actinomycosis by using histopathological staining and grams stain observations in a case of sebaceous cyst was previously reported [13]. Report of a case of primary cutaneous actinomycosis without the evidence of an endogenous infection highlights the significance of potential exogenous sources of infection and the importance of surgical procedures in the management of infected patients [14].

Report of cases of human actinomycosis in patients with hereditary X-linked primary immunodeficiency disorder signifies the importance of genetic predisposition which requires further studies and confirmation [15]. Actinomycotic bacteremia was associated with thrombophlebitis of portal vein as reported recently [16]. This signifies the potential complications arising from disseminated actinomycosis which is not completely understood. A recent report of brain abscess caused as a result of dissemination of infection probably from the lung in an immunocompetent person should be considered as an alarming sign [17].

In the present case, the patient initially suffered from the actinomycosis of the left leg and was managed by the amputation below the knee and antibiotic therapy. Four year later, the same patient started developing similar lesions above the knee on the same limb (left lower limb), on the right lower limb, and also on the thoracic region. This clearly suggests as a case of disseminated actinomycosis.

Occurrence of dilated veins on the abdomen (varicosities), and the presence of DVT, both could be the complications of disseminated actinomycotic infection. Although a previous experimental research could not confirm the role of bacteria as either the cause or consequence of the varicosities, they established that bacterial infection can be considered as a potential risk factor [18]. DVT has been associated with pelvic actinomycosis in a patient with multiple metastatic liver abscesses [19]. In another study, DVT was noted in a case of mixed bacteremia caused by *Actinomyces odontolyticus* [20].

Routine microbiological laboratories rarely process clinical specimens for the isolation of actinomycetes members. Also, due to their stringent growth requirements which include long incubation periods and anaerobic environment, it poses a practical difficulty for their culture. Therefore, direct microscopy appears to be very important for an initial suspicion. Clinical specimens showing characteristic long, filamentous branching gram positive bacilli with characteristic beaded appearance should be appropriately processed to improve the chances of isolation.

Another drawback for the successful isolation of actinomycetes members from clinical specimens could be indiscriminate use of antimicrobial agents prior to the hospital admission as noted in the present case.

4. Conclusion

Human actinomycosis is an underdiagnosed clinical condition which when not recognized at appropriate time could lead to disseminated infection with serious complications and fatal outcome. Direct microscopy i.e. observation of bacteria directly in the clinical specimens using grams stain assumes greater significance in the absence of advanced identification methods. Since cultures could require anaerobic environment and longer incubation times, use of effective anaerobic culture methods like the gas-pak system, dynamicro jar, and McIntosh fildes jar is recommended. Prior antibiotic therapy appears to be the greatest hindrance and the cause for frequent negative cultures. Culture on LJ medium could improve the chances of isolation of *Actinomyces* spp.

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