

# Actinomyces meyeri: A Lung Mass Resembling Lung Cancer

F. Cantile<sup>1</sup>, Vanessa Callegari<sup>1\*</sup>, L. Ferrara<sup>1</sup>, A. Saviola<sup>1</sup>, N. Malavasi<sup>1</sup>, L. Scarabelli<sup>1</sup>, G. Acquaviva<sup>1</sup>, L. Galassi<sup>1</sup>, C. Fiorani<sup>1</sup>, T. Cantile<sup>2,3</sup>, M. Costantini<sup>4</sup>, E. Franceschini<sup>5</sup> and G. Longo<sup>1</sup>

<sup>1</sup>Department of Oncology and Hematology, Modena University Hospital, 41124 Modena, Italy

<sup>2</sup>Department of Neuroscience, Reproductive and Odontomastological Sciences, University of Naples Federico II, 80131 Naples, Italy

<sup>3</sup>Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, 84121 Salerno, Italy

<sup>4</sup>Department of Anatomic Pathology, Modena University Hospital, 41124 Modena, Italy

<sup>5</sup>Department of Infectious Disease, Modena University Hospital, 41124 Modena, Italy

## Abstract

*Actinomyces meyeri* is a rare cause of lung infection. In general, actinomycosis is rare and more frequent in men than in women, exception for pelvic infection. The diagnosis is challenging as actinomycosis can clinically and radiologically mimic other infections and malignancies. Nowadays, thanks to antibiotics availability, the prognosis has improved, so death and deformity occur very rarely. Here is reported the case of a young male presented with a lung mass that was highly suspicious for cancer, so that he was hospitalized in Oncologic Medicine department of Modena University Hospital, Italy. A biopsy of the lesion was performed to obtain a diagnosis. The culture from mass biopsy resulted positive for *Actinomyces meyeri*, so a specific antibiotic therapy was started and prolonged for six weeks, with patient's clinical and radiological remission. His relevant clinical data are reported here, together with radiological and microbiological examinations. Patient's general conditions were good during all the hospitalization period. The aim of this case report is to focus attention on a rare form of infection, with a difficult differential diagnosis with lung cancer. The two diseases have a really different treatment and prognosis. From the anamnesis, it is possible to suspect lung actinomycosis if the patient has an history of alcoholism or bad dental hygiene. The case will be discussed, with references to available literature.

**Keywords:** *Actinomyces meyeri* • Lung cancer • Oral cavity • Abscess • Differential diagnosis

## Introduction

*Actinomyces meyeri* has a variable incidence (about 30% of all Actinomycoses) [1]. Until some years ago, *Actinomyces israelii* was thought to be the most common etiologic agent of Actinomycosis [2]. Recently, Rolfe et al. have found different data, reporting that *Actinomyces meyeri* was more frequent than *Actinomyces israelii*, considering 130 affected patients [1]. In 1970 an incidence of 1 per 300.000 persons was assessed considering all cases of actinomycosis in Cleveland area [3]. It has been reported that this kind of infection is more common between males than females, with a mean age of 42.5 years [4,5].

Until now, 25 species of *Actinomyces* have been isolated from human material [6]. First human cases of Actinomycosis were described in late nineteenth century and *Actinomyces israelii* was isolated as main causative agent [7].

Actinomycosis is an endogenous infection [6]. The involved bacteria survive on mucosa and lesions that interrupt its integrity can make it reach deeper tissues [4]. Here, these bacteria create aggregates that look like masses of branching and filamentous bacilli [5]. They tend to penetrate tissue planes and to create sinus tracts [2]. They are opportunistic, gram-positive, strictly anaerobic, non-acid-resistant bacteria [8].

*Actinomyces* are present in saliva on teeth's surface, where they play a

**\*Address for Correspondence:** Vanessa Callegari, Department of Oncology and Hematology, Modena University Hospital, 41124 Modena, Italy; Tel: +39 059 4222125, E-mail: 224380@studenti.unimore.it

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role in contributing to the formation of dental caries as parasitic organisms [7]. They can reach tissue planes and blood if the mucosal barrier is disrupted by structural diseases, surgery, trauma or other infections [9].

Introduction of dental hygiene and antibiotics probably reduced the frequency of this infection in developed countries [10]. In a review that analysed thirty-two cases of Actinomycosis, more than one third of patients recruited showed gingival or dental infection and/or were alcohol users [2].

Actinomycosis is clinically and radiologically similar to malignancies and other infections, so the differential diagnosis is difficult [5]. Concerning clinical features, productive cough, chest pain, fever and weight loss may be present, but they are not specific for this infection [9]. According to a retrospective study conducted in Korea during the first decade of 21<sup>st</sup> century. The most common symptoms of pulmonary Actinomycosis are cough, hemoptysis and sputum. The same study claimed that most of cases were initially misdiagnosed as lung cancer or another pneumonia [10].

According to literature, the most common site of infection by *Actinomyces meyeri* is lung, but abscess caused by *Actinomyces* can be found also in gastrointestinal tract, skin, soft tissue, breast, bone (osteomyelitis), brain, cervicofacial region [2]. Cases of endocarditis, endophthalmitis, funisitis, pneumonia with empyema and disseminated disease are included too [2]. The most common site of infection of *Actinomyces* in general is the cervicofacial region, that is involved in 50-70% of Actinomycosis reported cases [3]. Actinomycosis has also been related to infected osteoradionecrosis of the jaws [11]. According to Curi et al, the presence of *Actinomyces* was evidenced by histology in 12% of the 50 osteoradionecrosis cases described [12].

A case of mid-facial osteomyelitis in a chronic cocaine abuser, with hard palate, septum, nasal cartilage and soft palate destroyed by drug inhalation, has been reported [13]. Another unusual case regards gastric Actinomycosis as the complication of gastric bypass for morbid obesity [14]. Pulmonary infection is often the source of hematogenous dissemination [15]. In fact, lung infection is present in the majority of patients with disseminated actinomycosis [16,17]. While hematogenous spreading is possible at any time, lymphatic dissemination occurs very rarely [3].

Final diagnosis is generally obtained through bronchoscopic or

percutaneous needle aspiration [9]. The detection is usually microscopic, with gram staining, while cultures need an anaerobic or microaerobic incubation up to 14 days [9]. The histopathologic diagnosis is challenging as tissue sample includes sulfur granules, which may be present also in nocardiosis, coccidioidomycosis and aspergillosis [8]. In the present case the identification of *Actinomyces meyeri* was possible thanks to the addition of microbiological examination. Microbiological culture may not be the solution for a definitive diagnosis, as its failure rate is high due to factors like precedent antibiotic therapy or presence of other organisms [15]. In fact, most actinomycotic infections are polymicrobial, so also other anaerobic or microaerophilic organisms can be found [18,19]. It is thought that concomitant infections cause a reduction in oxygen tension and phagocytes inhibition that increase the *Actinomyces*' pathogenicity [18]. Polymerase chain reaction (PCR) might also be used for diagnosis with reliability [9]. There are PCR-based techniques that use probes specific for rDNA or housekeeping genes and can identify *Actinomyces* species in clinical samples [15,16].

Concerning treatment, historically it was based on high dose of antibiotics such penicillin for 6 to 12 months. Nowadays, the therapy is personalized and can vary on the basis of location, severity of disease and patient clinical and radiological response to treatment [5]. An UK study based on 87 isolates of *Actinomyces* demonstrated their sensibility to  $\beta$  lactams (including amoxicillin and ceftriaxone), doxycycline, clindamycin, erythromycin and clarithromycin [20]. Anyway, antibiogram is required for definitive therapy. The localized disease generally needs only a short course of oral penicillin: from 500 mg to 1 g every 6 hours for two months [2]. For extended disease, according to experts' opinion, intravenous penicillin (18 to 24 million units per day), for two to six weeks, is a better choice and it should precede oral penicillin or amoxicillin (500 mg every 6 hours) [2]. *Actinomyces meyeri* is generally sensible to most of antibiotics and penicillin is chosen as the most cost-effective [18]. Sometimes abscesses have to be drained surgically or percutaneously [2].

## Case Presentation

On 20th January 2022 a 45 years old male presented to emergency department of Modena University Hospital, Italy, with interscapular puncture pain radiated to anterior left thorax. He had a history of appendectomy, bilateral myringoplasty, headache, gastroesophageal reflux, familiarity for colon polyposis. He was an active smoker (three cigarettes/day). He reported an episode of gingivitis two months before, related to bad oral hygiene during a trip. Blood tests only showed leucocytosis (19.200/mm<sup>3</sup>; normal range: 4.000-10.900/mm<sup>3</sup>) with 78.8% neutrophils and C-reactive protein (CRP) was 1.5 mg/dl (normal range: 0-0.7 mg/dl). The other biohumoral parameters were in range. Electrocardiogram was negative, while echocardiogram allowed seeing a little ectasia of the ascendant aorta (42 mm), for which a follow-up was indicated. A thorax X-ray was also performed and an opaque mass of 3.5 cm diameter was pointed out in the middle field of left lung, in mantle region. The patient was so referred to the Medical Oncology department of our institution, in order to go on with diagnostic work-up.

A thorax Computer Tomography (CT) was performed with the purpose of better define the lung mass. The aortic ectasia was confirmed (44 × 44 mm in the ascendant tract), without cardiac surgery indications. A lung mass of 32 × 28 mm was localized in high dorsal segment of the superior lobe of left lung. The mass was adjacent to pleura and scissure. It presented with a peripheric contrast enhancement and hypodense central zone with a modest air quote in the same context. The lesion also had a shaded peripheric alone with a "ground glass" shape (Figure 1). A univocal interpretation of this find was not possible, although it was suspected for neoplastic or infective nature. No lymphadenomegalies or effusions were seen. Blood tests were negative for HIV 1 and HIV 2 and tuberculosis (quantiferon test was negative). The neoplastic markers PSA, CEA, AFP, Ca 19.9 and Beta2microglobulin were in range and so also Immunoglobulins and proteins. The patient was tested positive for HBS Ab, with negative HBS Ag and HBC Ab.

Gargled and sputum were analysed too. A weak positivity for Rhinovirus and Haemophilus influenzae was registered. Anyway, from the beginning an

empiric antibiotic therapy with Ceftriaxone 2 g intravenously every day was administered. During hospitalization the patient maintained good general conditions and the pain progressively decreased. He was treated also with a low dose of steroids, progressively reduced, because he had already started a therapy with Methylprednisolone at home for a lumbosciatic left pain.

The mass' central necrosis zone with the air quote and alone resembled an abscess. On the other hand, the mass was really near the thoracic wall and seemed to infiltrate it, like neoplastic lesions do. So, with the purpose of differential diagnosis, an eco-guided biopsy was achieved. On the bioptic material microbiologic and histologic analyses were performed. The patient was hospitalized for ten days, then, some day after biopsy; he was discharged with an empiric oral antibiotic therapy, moxifloxacin 400 mg/die.

On 2<sup>nd</sup> February cultural examination on biopsy sample identified *Actinomyces meyeri*, sensible to Penicillin, Piperacillin-Tazobactam, Meropenem, Clindamycin and Metronidazole. A targeted antibiotic therapy with Amoxicillin 1 g three times a day was prescribed.

The biopsy final response was negative for neoplastic cells, fungi hyphae or spores. Alcohol and acid resistant bacilli were not identified after Grocott and Ziehl-Neelsen colorations. Instead, histochemical colorations of Grocott and Giemsa allowed to see numerous cocci and rod-shaped bacilli (Figures 2,3 and 4).



Figure 1. Section of the thorax CT that showed the lung mass.

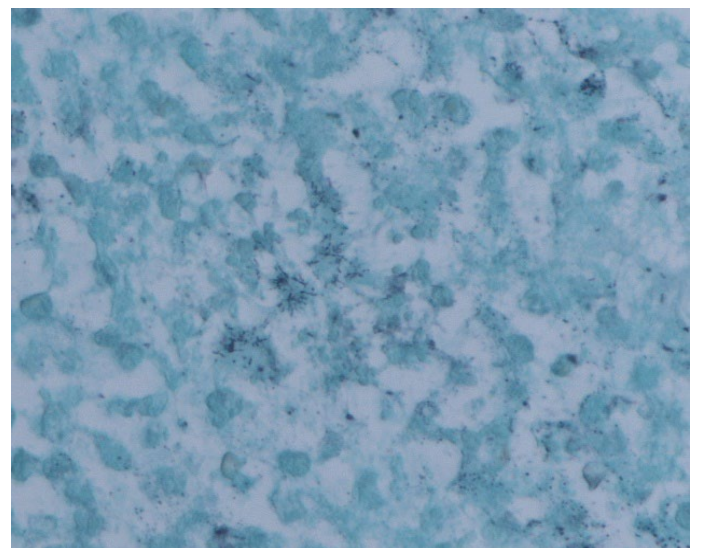
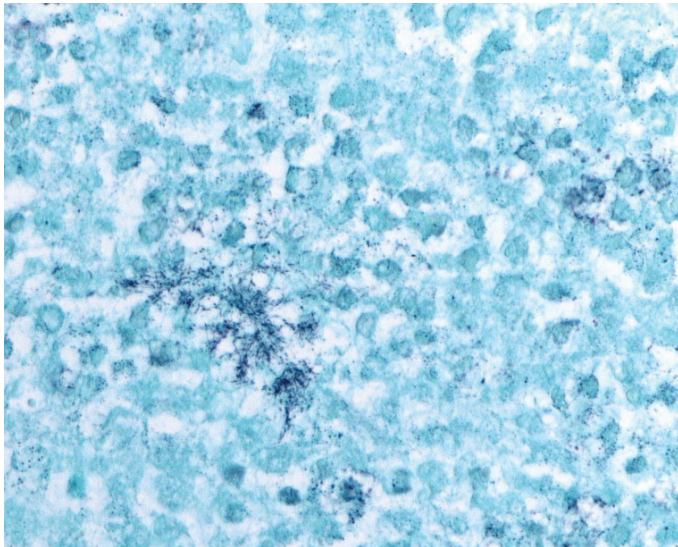
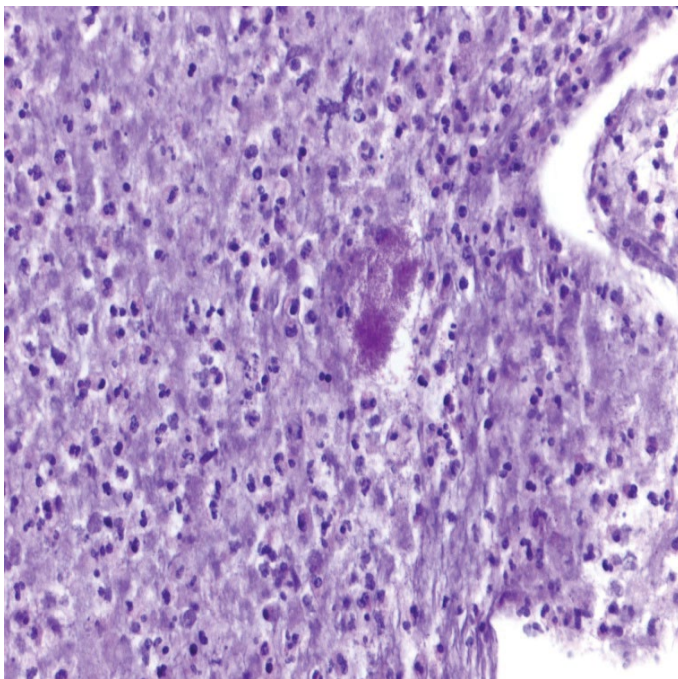


Figure 2. Cocci and rod-shaped bacteria were evidences with Grocott's histochemical coloration, 40X blow-up.



**Figure 3.** Cocci and rod-shaped bacteria were evidences with Grocott's histochemical coloration, 40X blow-up in detail.



**Figure 4.** The presence of a bacterial colony with elongated rod shape, compatible with *Actinomyces*, was evidenced through PAS histochemical coloration.

Considering the presence of three nodules in lungs, their characteristic and the response of biopsy and cultural examination, the most probable diagnosis was abscess from *Actinomyces meyeri*. The Amoxicillin therapy was prolonged for six weeks.

A control CT was achieved after a month, on 2<sup>nd</sup> March. The known mass localized in high dorsal segment of the superior lobe of left lung was markedly reduced: 22 × 17 mm (vs. 32 × 28 mm on previous CT). A blurred "ground glass" alone was still present below this find. The patient was clinically asymptomatic at the moment of CT execution. So, the antibiotic therapy was thought to be effective and it was stopped (Figure 5).

## Discussion

Pneumonia due to *Actinomyces* in our case was probably caused by the pulmonary aspiration of the pathogen from oral cavity. Alcoholism is thought to be a factor of risk [2]. In case of our patient, not significant consumption

of alcohol was declared. Fazili T, et al. reported the case of a patient that had a really bad dental hygiene, partially edentulous. In that case the patchy infiltrate present in left lung evolved generating an empyema and the diagnosis was possible only after open left thoracotomy, followed by decortication and empyema's drainage [2]. So, the site of infection was similar, but the diagnostic and therapeutic procedure was much more invasive if compared to our case.

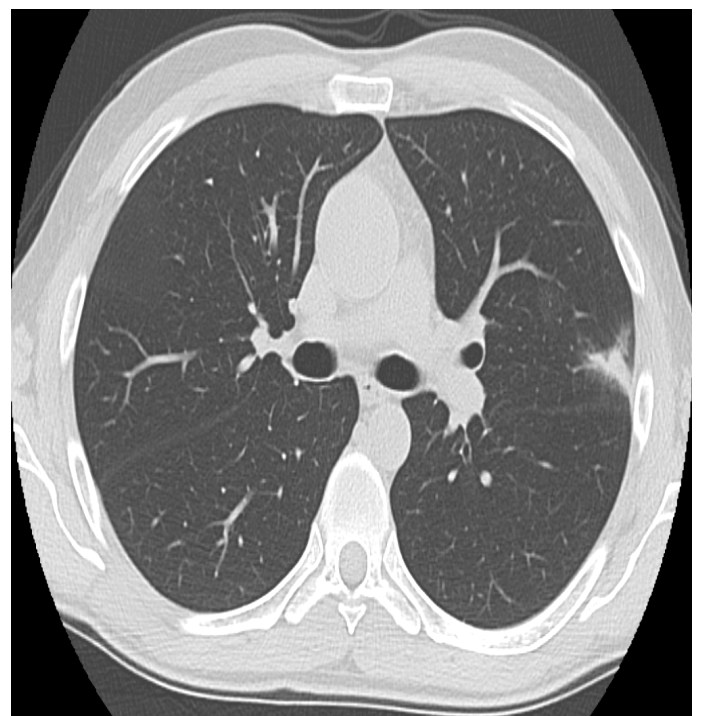
There are different cases of challenging differential diagnosis between pulmonary Actinomycosis and lung cancer in literature. The case described by Cliffe A, et al. was initially interpreted as bronchogenic carcinoma after biopsy of one of the two lung lesions that were present. The aspirate of pleural effusion revealed then the concomitant presence of *Actinomyces meyeri* infection that was treated before bronchogenic carcinoma with 6 months of Amoxicillin [21]. In this case, a pelvic infection was also present, associated with ICD (intrauterine contraceptive device): in fact, the infection of this site is more frequent in women [22]. Like the presented case, differential diagnosis was challenging, but at the end the infection resolution did not need any procedure of surgery or drainage.

Ariel I, et al. reported 5 cases of lung Actinomycosis that resembled bronchogenic carcinoma. All patients described presented with various typical symptoms as cough. In four cases bronchoscopy with biopsy was sufficient for diagnosis, while in one case the biopsy suggested the presence of a tumor and so a lobectomy was performed, with the definitive diagnosis of *Actinomyces* infection [23].

Due to Actinomycosis' mimicking of lung carcinoma, surgery has been performed various times in the past. The detection of an apparently asymptomatic lung mass in a patient that had to undergo an elective herniorrhaphy. He had a history of alcoholism and above all, dental caries, too. In that case, a lobectomy was performed and *Actinomyces meyeri* was isolated by cultural examination [24].

Another patient with a history of poor dental hygiene and gingivitis presented with disseminated Actinomycosis, as illustrated by Liaudet L, et al. In this case, cutaneous and muscular abscesses were secondary to lung infection by *Actinomyces meyeri*. The therapy consisted of oral Amoxicillin for 12 months [25].

Generally, Actinomycosis involves adults, but sometimes *Actinomyces* pneumonia can affect pediatric patients, requiring also chest tube placement



**Figure 5.** Control CT: The mass was significantly reduced.

due to related empyema [26]. *Actinomyces meyeri* infiltrates the lung and then invades the pleural space, generating an empyema, more frequently than other species of *Actinomyces* [27]. The case reported by Hoheisel A, et al. regards a male with a history of alcohol consumption, with a diagnosis of empyema caused by *Actinomyces meyeri*. He needed not only a systemic antibiotic therapy, but also empyema evacuation, pleurectomy and decortication of two lobes [28]. A differential diagnosis with pleural carcinosis was necessary. The patient of our case experienced pain quite soon, probably thanks to the proximity of the lesion to the chest wall. This allowed to obtain a diagnosis before the eventual increase of lesion's excavation and diffusion to the pleura. So, no procedure of decortication was required.

*Actinomyces meyeri* infection generally has a good prognosis, with the proper antibiotic therapy. Despite that, sometimes patient's condition and the type of infection lead to a downward clinical course. Branquinho DF, et al. reported a case of mediastinitis occurred after oesophageal stenting in a patient with oesophageal squamous cell carcinoma and an oesophagomediastinal fistula. The cultures resulted positive for *Actinomyces meyeri*: the patient was an alcoholic; the endoscopic procedure probably carried the germ near fistula that allowed it to reach mediastinum. In this case the intravenous antibiotic therapy with imipenem/cilastatin and metronidazole did not save the patient that died two weeks later [29].

Concerning the diagnosis of pulmonary Actinomycosis, as the suspicion of lung cancer is generally present, lung biopsy is usually unavoidable. Zhu D, et al. described a case initially misdiagnosed as pneumonia caused by *Actinomyces meyeri*: the germ was individuated through metagenomic next generation sequencing on patient's bronchoalveolar lavage fluid. So, the patient was treated with two months of penicillin G intravenously and oral amoxicillin for six weeks: the lung mass initially reduced, but it grew again after a few months. The biopsy collected previously together with bronchoalveolar lavage, during bronchoscopy, showed normal tissue, neither cancer nor sulphur granules or other elements suggestive of Actinomycosis. A new biopsy, CT-guided, was performed in that case, revealing a pulmonary invasive mucinous adenocarcinoma [30]. So, it is important to have a biopsy that confirms microbiological examinations, to exclude contaminations. In our case the biopsy showed clear signs of Actinomycosis infection.

In most of cases of pulmonary Actinomycosis the really challenging part is reaching a definitive diagnosis, as it can simulate other infections and neoplasia. Then, the treatment is generally based on systemic and/or oral antibiotic therapy that sometimes needs to be accompanied by surgical procedures, when the infection went too far. Even if in case of allergy to penicillin, treatment with Ceftriaxone followed by doxycycline resulted effective [31].

## Conclusion

The case presented is similar to other for patient's characteristics and anamnesis: adult male, with a history of gingivitis in a period of bad dental hygiene. Symptoms were not so typical, as he did not have fever, cough or hemoptysis. Furthermore, he was an active smoker, an important risk factor for lung cancer. The radiological imaging did not allow to go too far with differential diagnosis. The fact that the patient was referred to the Oncologic Medicine department was worrying for him and his relatives, even if doctors repeated that there was no cancer diagnosis yet. At the end, the diagnosis was possible with only one biopsy, in spite of other cases discussed: no surgery or drainage was needed. The patient was discharged after a few days of intravenous antibiotic. Like the most of other cases, once discovered the causative agent, the right antibiotic therapy is quite easy and the patient completely recovered. Hopefully in the future molecular diagnostic methods will become more accessible and so the diagnostic procedure will become easier, with less need of surgery and invasive procedure for Actinomycosis diagnosis.

## Conflict of Interest

No conflicts of interest relevant to the content of this case report are declared by the authors.

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