Actinomyces turicensis: a peculiar case of empyema after COVID-19 in a patient with ulcerative colitis

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ABSTRACT

Actinomyces species are recognized as common mucosal bacteria in humans and as a newly discovered source of infection. Since its discovery in 1995, the subspecies *Actinomyces turicensis* has been reported as the causative pathogen of numerous infections. Only two instances of *A. turicensis*-related empyema, however, have been documented in the literature as of late. We report a unique case of polymicrobial empyema caused by *A. turicensis* shortly after a COVID-19 without any clear risk factors for anaerobic aspiration, along with a brief review of the literature. Tetracycline was successfully used for the first time to treat *A. turicensis* empyema, following chest drainage.

Introduction

Actinomycosis is an uncommon chronic infection caused by Actinomyces species, anaerobic gram-positive bacteria commensal of human digestive and genital tract.

Actinomyces turicensis, the novel species first described in 1995, is known to cause heterogeneous infective diseases (*i.e.*, appendicitis, meningitis, endocarditis, bacteremia, *etc.*),[1-4] but the literature has reported only two cases of *A. turicensis* empyema so far. In both cases, the suggested pathogenetic mechanism was the aspiration of oropharyngeal secretions due to individual predisposing risk factors and each patient was successfully treated with ß-lactam agents.[5,6]

To our knowledge, this is the third report in the literature on *A. turicensis* polymicrobial empyema and the first one after COVID-19, in a patient with ulcerative colitis (UC) but without clear risk factors for anaerobic infiltration.

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Case report

A 78-year-old caucasian man presented with a story of fever, dyspnea and cough; symptoms had started in the last 15 days. He had recovered from mild COVID-19 two months before. He quit smoking 10 years before and denied alcohol consumption.

He suffered from coronary artery disease, Monoclonal gammopathy of undetermined significance, atrial fibrillation treated with left atrial appendage occlusion and long-term asymptomatic UC medicated with mesalazine. He was previously certified for cephalosporins allergy.

On physical examination, he was febrile (38°C) and tachypnoic, blood pressure was 102/57 mmHg, heart rate 84/min and oxygen saturation 92%. Chest exam revealed a reduction of vesicular sounds and dull percussion on the lower left lobe. Blood tests showed: C-reactive protein 18 mg/dl (normal value <0.5 mg/dl), hemoglobin 8.5 g/dl, white blood cell count 17520/mmc, creatinine 1,5 mg/dl (normal value <1,2 mg/dl). A nasopharyngeal swab antigen test was negative for SARS-CoV-2.

Chest X-ray and chest computed tomography (CT) scan showed extensive flogistic consolidation of the lower left lobe with concomitant pleural effusion and a minor consolidation of the lingula.

He was treated with empirical levofloxacin, fluid therapy and oxygen, with a gradual clinical improvement in the next few days.

Nevertheless, the fever relapsed a week later along with

an increase in inflammation markers. The lung ultrasound showed left empyema, confirmed at a second chest CT scan (Figures 1 and 2). A chest tube was then applied by a chest surgeon with instant drainage of 1200 ml of purulent and foul-smelling fluid.

Fluids cultures were immediately positive for *Clostridium ramosum* so treatment with levofloxacin was shifted to intravenous metronidazole. Three days later, even *A. turicensis* was isolated.

On the basis of the antibiogram and the known allergy to cephalosporins, metronidazole was discontinued and oral treatment with doxycycline was started, with quick clinical and laboratoristic improvement. A six-month antibiotic home therapy was prescribed.

Six months from discharge, the patient's conditions were good. Doxycicline was well tolerated except for transient oral candidiasis. The latest CT scan showed a complete resolution of the left pleural effusion and the blood test showed normalization of inflammation markers.

Discussion

Actinomycosis is an uncommon chronic infection caused by Actinomyces species; infection usually derives from the breach of the mucous membranes and infiltration of the deeper planes.

Pulmonary actinomycosis accounts for approximately 15% of all cases, and it is supposed to result mainly from aspiration of oropharyngeal or gastrointestinal secretions, although hematogenous dissemination or direct spread from local lesions are possible sources of infection.[2,3,7-9] Noteworthy, Actinomyces are frequently isolated in the context of polymicrobial flora, as it was in the case of our patient, with a wide range of possible coexisting microorganisms.[1,2,4,9]

The disease is more frequent in middle to old-aged males. Poor oral hygiene, alcoholism, chronic lung disease or pulmonary sequelae following tuberculosis are known risk factors.[1,2,7-9]

Among the various Actinomyces species responsible for human disease, A. meyeri, A israelii, A. graevenitzii and A. odontolyticus have a predilection for respiratory sites.[2,10,11]

Pulmonary actinomycosis usually presents with aspecific signs, symptoms (*i.e.*, cough, hemoptysis and sputum production) and CT findings (consolidation, mass and atelectasis); often leading to misdiagnosis (as malignancy, tuberculosis or other infective processes).[1,2,7-9,11,12]

Pleural involvement, such as effusion or empyema, occurs in about 10-50% of cases and usually results from the contiguous spread of a lung lesion.[1-3,8,9,11,12]

Moreover, it is well known that Actinomyces spp. are very difficult to culture and that subspecies identification is quite a challenge, especially in the pleural fluid.[1,9,10]

Thus, obtaining a final diagnosis could be demanding, usually requiring bronchoscopy and lung biopsies for histological examination and bacterial culture.[1,9]

Anaerobes are commonly associated with empyema and their presence in pleural fluid is strongly suggested by malodorous samples.

As concerns specific treatment, Actinomyces spp. showed high susceptibility to ß-lactam agents, which are thus considered as agents of first choice, with and without ß-lactamase inhibitors. A long-term antimicrobial therapy is usually necessary: intravenous administration is recommended for the first 6 weeks, followed by oral treatment between 6 months and 1 year.[2,3,8,9,13,14] On the other hand, high resistance to metronidazole and ciprofloxacin has been reported. in particular *A. turicensis* showed resistance even to clindamycin, tetracyclines and linezolid.[13]

The impact of co-pathogens is not well understood but it has been suggested that antibiotic regimens targeting only Actinomyces are usually curative.[2,3,9]

Medications and duration of treatment need to be tailored to the clinical and radiologic response. Surgical treatment of necrotic lesions or percutaneous drainage of abscesses may be needed.

Our patient, initially diagnosed with community-acquired pneumonia with pleural effusion, was finally found to have an *A. turicensis* polymicrobial empyema. Empyema was first diagnosed at the lung ultrasound (LUS) and then at the chest CT scan (Figure 2), given the better accuracy of LUS in detecting septations.[15]

In our case, pathogenesis was not so clear. Our patient was not an alcohol consumer and he referred routine dental care. Since he was a former smoker, COPD may have played a role. However, it should be noted that he recovered from mild COVID-19 two months before admission. This was an

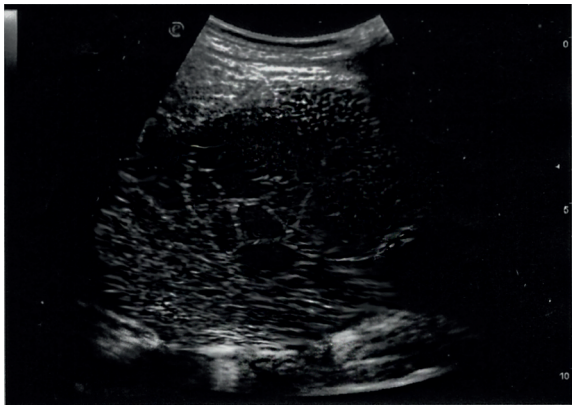

Figure 1. Lung ultrasound showing left empyema.

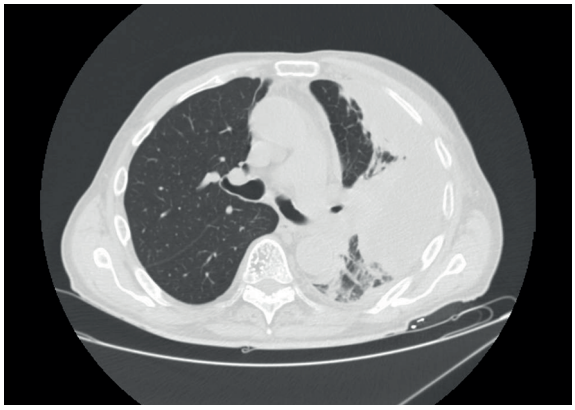

Figure 2. Chest CT scan showing left empyema.

intriguing issue that made the authors deepen in the literature. We found a few studies investigating hospital readmission within 6 months after COVID-19 hospitalization. One of the most frequent causes of hospital readmission was an infection other than COVID-19 (*i.e.*, sepsis or pneumonia), ranging from 3 to 54% of cases.[16-18] Based on previous literature, some of these authors postulated that COVID-19 may produce medium-term immunosuppression leading to superinfection. Likewise, we supposed that recent COVID-19, together with COPD could have played a role in the pathogenesis of *A. turicensis* infection.

Another possible source of infection was the invasion through the gut wall, as our patient was affected by ulcerative colitis, albeit in long remission. Disruption of mucosal integrity in inflammatory bowel diseases can lead to invasion of deeper planes and disseminated infection, especially in Crohn's disease. In literature, we found only two cases of actinomycosis in patients with ulcerative colitis, one following colonoscopy and one under immunosuppressive therapy.[19,20] *C. ramosum* coexistence may suggest the bowel origin of the infection. However, considering the longtime remission of UC, the lack of recent invasive procedures and the concomitant pneumonia, this seemed a less plausible etiopathogenesis.

In the present case, given the allergy to cephalosporins and the failure of the empirical levofloxacin, treatment with doxycycline was started on the basis of an antibiogram. Indeed, a tetracycline is generally considered a suitable alternative for penicillin-allergic patients.[3,8]

Conclusions

To our knowledge, this is the third report of *A. turicensis* polymicrobial empyema in literature. In our peculiar case, recent COVID-19 may have played a role in the pathogenetic mechanism, in accordance with the emerging scenario of post-COVID immunosuppression.

It is still unknown if ulcerative colitis-related mucosal inflammation may have contributed to the disease's etiology in our patient. Moreover, for the first time, a tetracycline was successfully used, after chest drainage, for the treatment of *A. turicensis* empyema. *A. turicensis* is a novel cause of empyema and should be considered especially in patients with aforementioned risk factors in order to avoid unnecessary investigations and surgical interventions.

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