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Comunicación breve

Invasive actinomycosis and lung cancer. Study of three cases

Actinomicosis invasiva y cáncer de pulmón. Estudio de tres casos

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Introduction

Actinomycosis is a rare, possibly underdiagnosed disease caused by Actinomyces spp, a Gram positive facultative anaerobic commensal bacterium commonly found in the oropharyngeal cavity, digestive and genital tract. Invasive actinomycosis can affect the cervicofacial, respiratory, joint, digestive, genito-urinary, cutaneous and central nervous system (CNS) levels forming abscesses and sulphur granules. Dissemination is progressive, simulating a malignant or granulomatous disease process[1].

Its main aetiological agent is *Actinomyces israelii* although other species such as *A. naeslundii A. meyeri, A. odontolyticus, A. gerencseriae or A. viscosus* may also be involved[2].

Mortality ranges from 0 % to 28 % depending on the site of infection, time to diagnosis and initiation of appropriate treatment[3].

Three cases of pulmonary actinomycosis involving a differential diagnosis with a tumour process are presented below.

Clinical cases

Clinical case 1

78-year-old male with a history of dyslipidemia, type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD) and cumulative smoking of 100 packets/year. In June 2021, a lung mass study was started.

A computed tomography (CT) scan (fig. 1A) was requested as a first test. It revealed a mass in the apical-posterior segment of the left upper lobe measuring 6.47 x 5.07 cm, contacting the parietal pleura and a non-specific nodule measuring 1 cm in diameter in the left lung base.

Subsequently, a bronchoscopy was performed in which a biopsy was taken with the result of a moderately differentiated squamous adenocarcinoma; and, apart from that, a bronchoaspirate was sent in which no microorganisms were found.

What is more, biopsies of adenopathies found during the test were taken during Echobronchoscopy and sent for anatomopathological analysis, with negative results for malignancy.

Finally, a videothoracoscopy was performed, in view of the findings of the previous tests. A necrotic mass with infiltration of 4 left costal arches was visualised. Given the characteristics of the mass and the results of the aforementioned tests, a lymphadenectomy of territory 5 was performed. The cytology was negative while the parietal pleural biopsy was positive for malignancy. Pathological staging was therefore established as IVA (pT3N0M1a).

In November 2021 the patient consulted for dyspnoea at rest and fever. On arrival at the Emergency Department, he presented hypotension, tachycardia and tachypnoea with diminished left-based vesicular murmur. Additional tests were ordered and the following findings were highlighted.

Blood tests showed elevated CRP 390 mg/l, procalcitonin 0.94 ng/ml. Arterial blood gas analysis revealed respiratory acidosis. An urgent thoracic CT scan was requested, which revealed two cavitated masses: in the left upper lobe (LUL), the image of the already known tumour, and one of new appearance in the left lower lobe (LLL), voluminous, with a liquid component, without being able to rule out bronchopleural fistula (fig. 1B).

Given the clinical evolution, the patient was admitted to the ICU and mechanical ventilation was started. Drainage of the LLL was performed with a debit of 320 cc of purulent exudate. Penicillin-sensitive *Streptococcus anginosus* and *Actinomyces odontolyticus* were isolated from the exudate culture. Blood cultures were negative. Antibiotic therapy was de-escalated to intravenous amoxicillin-clavulanic acid. One month after hospital admission and initial clinical improvement, palliative chemotherapy was started together with amoxicillin.

Clinical case 2

55-year-old woman with a history of obesity (44 BMI), severe SAHS, primary hypothyroidism, past HBV without prophylactic treatment and active rheumatoid arthritis on treatment with Tocilizumab.

In March 2021 he started with a cough without expectoration and a thoracic CT scan was requested. It showed a mass in the LUL and mediastinal adenopathies next to the aortic arch, compatible with pulmonary neoplasia stage T4N2M0 (fig. 2). In view of the images, it was decided to suspend Tocilizumab and complete the study of the mass.

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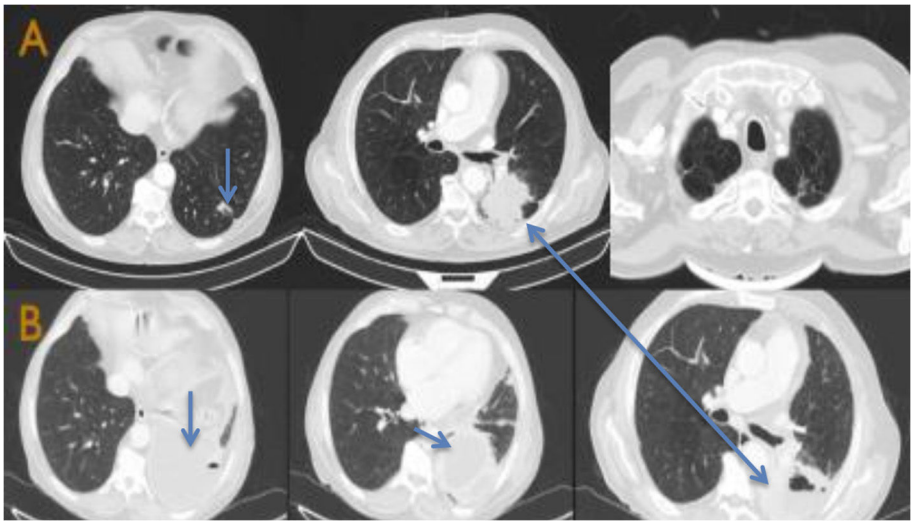

Fig. 1. A CT scan at the start of the lung mass study in case 1. A non-specific nodule of 1 cm in diameter is seen in the left lung base (first image) and a mass in the apicoposterior segment of the left upper lobe measuring 6.47 × 5.07 cm (central image). Fig. 1B CT scan on admission in case 1. Two cavitated masses are seen: one in LUL (already known), and a new one in LLL with a liquid component.

Firstly, Videobronchoscopy was performed, suggesting the presence of acute inflammatory changes in the bronchial tree. Transbronchial brushing and biopsy were negative for malignancy. Bronchoaspirate culture detected methicillin-sensitive *S. aureus*.

Secondly, a PET-CT scan showed a mass in the LUL (73 × 65 mm, SUV 22) and a paramediastinal mass together with a left hilar conglomerate. An ultrasound-guided lung biopsy was performed, the analysis of which was compatible with a peripheral sample of a neoplastic or mesenchymal lesion.

In view of this result, it was decided to perform a second biopsy, which confirmed the presence of an inflammatory component, excluding the solitary fibrous tumour.

The patient consulted in May 2021 for cervical pain with the appearance of a palpable cervical mass with phlogistic signs. *Actinomyces israelii*, *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum* were cultured from the mass biopsy. Surgical debridement of the cervical lesion was performed and intravenous antibiotherapy with Ceftriaxone 2g every 24h was started for 6 weeks, followed by oral amoxicillin.

Clinical case 3

A 47-year-old male smoker of 13 packets/year who was assessed in September 2020 for pleuritic pain and constitutional syndrome. Additional tests were performed.

Chest X-ray suggested probable middle lobe consolidation. It was decided to perform a thoracic CT scan, which revealed a lung mass in the posterior segment of the right lower lobe (6.5 cm) in contact with the mediastinal pleura and diaphragm. Pleural nodules and masses in the right hemithorax (one measuring 7 cm), with infiltration of the thoracic and abdominal wall and contact with the left hepatic lobe. Palpable mass in the anterolateral chest wall. Up to 10 mm high paratracheal adenopathies (fig. 3).

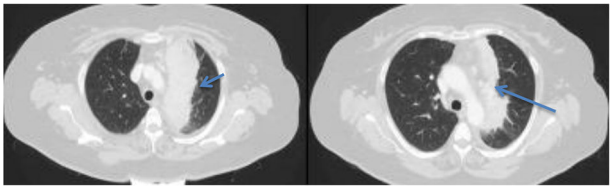

Fig. 2. CT scan at the beginning of the lung mass study in case 2. A mass can be seen in the LUL and mediastinal adenopathies next to the aortic arch.

A bronchoscopy was requested in which a biopsy, brushing and bronchial aspirate culture were performed.

Pending the results, the patient was discharged from hospital. However, a week later, he consulted for dyspnoea on minimal effort, increased cough with brownish expectoration, febrile fever, and enlargement of the tumour in the right hemithorax. The tumour was surgically drained and the exudate was cultured. Laboratory analysis showed a lactate peak of 87 mg/dL, CRP 209 mg/L, procalcitonin 0.79 ng/mL and leukocytes 29600/mm^3.

The patient worsened clinically with tachypnoea and rapid AF together with progression of pleural effusion, and growth of the mass visualised on CT scan.

He was admitted to the ICU requiring orotracheal intubation. The culture of the exudate grew *Actinomyces israelii* and *Fusobacterium nucleatum*, and the mycobacteria study was negative. Given the haemodynamic instability, vasoactive drugs were started, finally leading to multi-organ failure and *exitus* in October 2020.

Discussion

Pulmonary involvement by actinomycosis causes subacute clinical manifestations of cough, dyspnoea, haemoptysis, constitutional syndrome and febrile fever, as reported in the cases described. In the early stages, pulmonary consolidation with lymphadenopathies usually occurs, progressing to cavitation, local invasion and fibrosis. It is therefore known as a mimic of malignancy[1]. Case 3 invaded the chest wall and case 2 the cervical region. In case 1 we cannot determine exactly what corresponds to tumour and infectious invasion, but there is thoracic invasion.

Since it is a commensal microorganism in some tissues, the diagnosis is based primarily on microscopic observation of sulphur granules, when present, in the specimen [tissues, bronchoalveolar lavage (BAL) or body fluids][2]. Their identification in a sterile site confirms the diagnosis. Due to the facultative anaerobic nature of the genus, it requires 10-15 days of culture in appropriate media and atmosphere, with rapid sample remission in the same syringe as the extraction. Therefore, a Gram stain of the sample is usually more sensitive than culture[1]. In all cases multiple lung biopsies were performed without subsequent culture (Table 1). LBA were also not performed. Instead, BAS were cultured: a sample not valid for anaerobic culture. After repeated negative results for malignancy and a

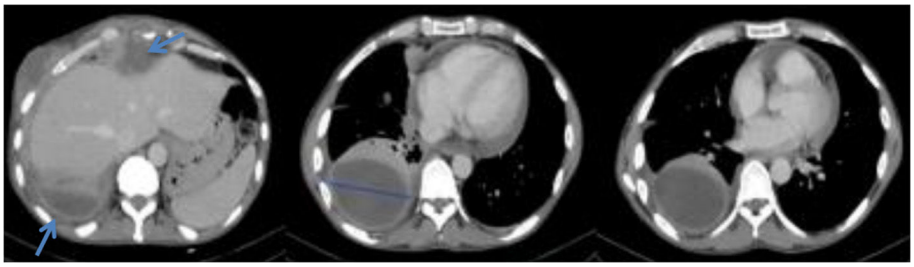

Fig. 3. CT scan at the beginning of the study of the lung mass in case 3. Lung mass in the posterior segment of the LID (6.5 cm) in contact with mediastinal pleura and diaphragm. Pleural nodules and masses in the right hemithorax (one of 7 cm), with infiltration of the thoracic and abdominal wall and contact with the left hepatic lobe. Palpable mass in the anterolateral chest wall (first picture). Up to 10 mm high paratracheal adenopathies.

Table 1
Initial staging and diagnostic process.

CASE	Initial TNM	M	Diagnosis	Biopsies	Lung Biopsy Culture	BAS Culture	Exudate Culture
1	pT3N0M1a	Local	5	4	0	Yes, Acinetobacter baumanii/ haemolyticus	*Streptococcus anginosus*, ***Actinomyces odontolyticus***
2	T4N2M0	No	2	4*	0	Yes *S. aureus*	***Actinomyces israelii,*** *Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum***
3	T4N1M1a	Local	1	1	0	Yes	***Actinomyces israelii,*** *Fusobacterium nucleatum*

Initial TNM: stage of the lung mass under study. T: size of the mass. M: metastases. N: adenopathies. **Diagnosis in months** from detection of lung mass to definitive diagnosis; **Number of biopsies performed** during the diagnostic process, without taking into account transbronchial biopsies; **Lung biopsy culture**; **BAS culture** Bronchoaspirate performed during bronchoscopy; **Exudate culture**: Cases 1, 3: obtained from thoracentesis. Case 2: exudate from cervical mass.
* Of which three biopsies were pulmonary and one cervical.
** Exudate culture obtained by cervical biopsy.

complication compatible with an infectious process, samples were referred to the microbiology department, although case 3 died without initiating treatment.

In the first case, malignancy and actinomycosis appeared sequentially, and a synchronous origin could not be ruled out, since the initial CT scan showed a nodule in the left lung base where the main collection later appeared. VATS showed central necrosis and costal infiltration, common findings in both tumours and actinomycosis. Another hypothesis is that the patient may have been infected during invasive tests.

The coexistence of actinomycosis and lung cancer is rare, although there are cases reported in literature[4–5]. A recent study has shown that activation of T-cells by bacteria may promote tumour proliferation[6].

Conclusion

The semiological features of lung involvement by actinomycosis and neoplasms are similar. Although its prevalence is low, it is one of the differential diagnoses to be performed during the lung mass study.

Cultures are a very economical and profitable test compared to prolonging the diagnostic process and repeating invasive tests.

This would justify the need to include LBA cultures instead of BAS in lung mass study protocols. In patients whose initial transbronchial biopsy has not detected malignancy, lung biopsies should be cultured for at least 10 days, specifying the suspicion.

Ethical considerations

Informed consent was obtained from the patient included in this article, respecting their right to privacy.

Conflict of interest

There is no conflict of interest on behalf of the authors of this article.

Bibliography

1. Valour F, Sénéchal A, Dupieux C, Karsenty J, Lustig S, Ferry T, et al. Actinomycosis: aetiology, clinical features, diagnosis, treatment and management. Infect Drug Resist. 2014;7:183–97. https://doi.org/10.2147/IDR.S39601.
2. Alcalá L, Betriu C, Sánchez JE García, Reig M. Procedures in clinical microbiology. Anaerobic Bacteria. 2004;2:18 [Internet] Emilia Cercenado. [cited 8 March 2022]. Available from: https://www.seimc.org/contenidos/documentoscientificos/procedimientosmicrobiologia/seimc-procedimientomicrobiologia16.pdf.
3. Wong VK, Turmezei TD, Weston VC. Actinomycosis. BMJ. 2011 Oct 11(343), d6099 PMID: 21990282: https://doi.org/10.1136/bmj.d6099.
4. Kell Drozdowicz K, Marquez HA, Burks EJ, Suzuki K. Lung adenocarcinoma and pulmonary actinomycosis: a cautionary tale. Tumori. 2021 Dec;107(6):NP77–80. https://doi.org/10.1177/03008916211010225.
5. Ide S, Sawai T, Kaku N, Nagayoshi Y. Case of pulmonary adenocarcinoma with co-existing pulmonary actinomycosis in one region of the lung. Nihon Kokyuki Gakkai Zasshi. 2009 Sep;47(9):823–7.
6. Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, Tyler J, et al. Commensal microbiota promote lung cancer development via gammadelta T cells. Cell. 2019;176:998–1013. https://doi.org/10.1016/j.cell.2018.12.040.