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CASE REPORT

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# Diagnostic Challenges. Case Report: Deadly Triad of Tuberculosis, Aspergillosis and Squamous Cell Carcinoma of the Lung

## *Desafíos diagnósticos. Reporte de caso: Tríada mortal por tuberculosis, aspergilosis y carcinoma escamoso de pulmón*

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## ABSTRACT

Pulmonary tuberculosis remains a prevalent disease in Latin America and can coexist with other serious respiratory conditions, including lung cancer and opportunistic fungal infections. The overlap of these entities poses a diagnostic and therapeutic challenge, especially in patients with constitutional symptoms and hemoptysis. We present the case of a 62-year-old man with a three-month history of cough, hemoptysis, fever, night sweats, and weight loss. Chest computed tomography scan revealed an irregular mass of 4.2 × 6 cm in the right upper lobe with mediastinal lymphadenopathy. Bronchoscopy revealed friable, bleeding, exophytic endobronchial lesions that hindered visualization of segments I and II. Bronchoalveolar lavage detected Mycobacterium tuberculosis by Xpert MTB/RIF assay with high bacterial load and no rifampicin resistance. Cytological and histological studies confirmed squamous cell carcinoma of the lung. During the course of the illness, pulmonary cavitation was observed with imaging findings suggestive of aspergilloma, confirmed by Aspergillus spp. using galactomannan in bronchoalveolar lavage. Despite the initiated antituberculous and antifungal treatment, the patient experienced tumor progression and died three months after the initial diagnosis. This case illustrates the diagnostic challenges posed by coexisting tuberculosis, lung cancer, and pulmonary aspergillosis, underscoring the need to consider concomitant diagnoses in cases of atypical clinical presentation.

**Key words:** Pulmonary tuberculosis | Lung cancer | Pulmonary aspergillosis | Coinfection | Bronchoscopy | Hemoptysis

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## RESUMEN

La tuberculosis pulmonar continúa siendo una enfermedad prevalente en América Latina y puede coexistir con otras patologías respiratorias graves, incluyendo cáncer de pulmón e infecciones fúngicas oportunistas. La superposición de estas entidades representa un desafío diagnóstico y terapéutico, especialmente en pacientes con síntomas constitucionales y hemoptisis. Presentamos el caso de un varón de 62 años con tres meses de evolución de tos, hemoptisis, fiebre, sudoración nocturna y pérdida de peso. La tomografía computarizada de tórax evidenció una masa irregular de 4,2 × 6 cm en el lóbulo superior derecho con adenopatías mediastinales. La broncoscopía mostró lesiones endobronquiales exofíticas friables y sangrantes que dificultaron la observación de segmento I y II. El lavado broncoalveolar detectó Mycobacterium tuberculosis mediante Xpert MTB/RIF con alta carga bacilar y sin resistencia a rifampicina. Los estudios citológicos e histológicos confirmaron carcinoma escamoso pulmonar. Durante la evolución se observó cavitación pulmonar con imágenes sugestivas de aspergiloma, confirmándose Aspergillus spp. mediante galactomanano en lavado broncoalveolar. A pesar del tratamiento antituberculosis y antifúngico instaurado, el paciente presentó progresión tumoral y falleció tres meses después del diagnóstico inicial. Este caso ilustra la complejidad diagnóstica de la coexistencia de tuberculosis, cáncer pulmonar y aspergilosis pulmonar, así como la importancia de considerar diagnósticos concomitantes ante evolución clínica atípica.


**Palabras clave:** Tuberculosis pulmonar · Cáncer de Pulmón · Aspergilosis pulmonar · Coinfección · Broncoscopia · Hemoptisis

## INTRODUCTION

Tuberculosis (TB) continues to be a major infectious disease in Latin America and worldwide. An estimated 1.7 billion people are infected with *Mycobacterium tuberculosis*.[1] Clinical suspicion of the disease generally includes: cough for 2 to 3 weeks, lymphadenopathy, fever, night sweats, weight loss, and hemoptysis, together with epidemiological history of exposure to the disease. The diagnosis of the disease is definitively established through the isolation of *Mycobacterium tuberculosis*.[2] Among imaging studies, chest X-ray may be performed; however, chest computed tomography (CT) is more sensitive for detecting early parenchymal and lymph node involvement not apparent on radiographs.

Aspergillosis encompasses several forms of disease, including chronic pulmonary aspergillosis (CPA), caused by the proliferation of microorganisms of the *Aspergillus spp*. genus in the lungs of individuals with structural lung disease. Its prevalence varies greatly worldwide; for example, it is estimated at 43 cases per 100,000 people in the Democratic Republic of the Congo and Nigeria.[3] Because CPA often develops late, colonizing residual cavities left by tuberculosis, its burden is greater in regions with a high incidence of TB.[4] The main forms of presentation of CPA are aspergillomas and *Aspergillus spp*. nodules.

Lung cancer continues to be the leading cause of cancer-related death worldwide, according to the World Health Organization (WHO).[5] WHO classification defines pulmonary squamous cell carcinoma by immunohistochemistry studies that currently allow for more precise subtyping through molecular testing, guiding therapeutic decision-making and improving prediction of clinical outcomes.

Diagnosis is fundamentally based on obtaining histological samples through biopsy, since most patients present with advanced stages of the disease and are not candidates for surgical treatment.

Although the coexistence of tuberculosis, lung cancer and pulmonary aspergillosis is rare, it is clinically relevant due to its impact on prognosis and therapeutic decision-making. Clinical overlap among these entities –persistent cough, hemoptysis, fever and weight loss can hinder early diagnosis and delay initiation of appropriate therapy.

We present a case that illustrates the diagnostic and clinical-course challenges associated with the

coexistence of these three entities, which we refer to as a "deadly triad."

## CASE REPORT

62-year-old man, with no biomass exposure, denied any history of smoking and had no prior medical or surgical history, but had an epidemiologic history of exposure to a tuberculosis-endemic area.

He presented with a three-month history of persistent cough, hemoptysis of approximately 10 mL daily, diaphoresis, fever up to 38.6°C, night sweats, and a 12-kg weight loss.

**Initial physical examination** revealed mucocutaneous pallor, blood pressure of 100/80 mmHg, tachycardia of 110 beats per minute, respiratory rate of 22 breaths per minute, and arterial $O_2$ saturation of 78% on room air, at an altitude of 3,600 meters above sea level. Additionally, the patient presented with 1st-degree jugular venous distension. Pulmonary chest examination showed decreased vocal fremitus, crackles, and rhonchi predominantly in the right interscapular region, with relative dullness to percussion. The remainder of the physical examination was unremarkable.

### Complementary examinations

**Laboratory findings:** complete blood count showed hematocrit: 37%; hemoglobin: 12 g/dL; white blood cell count: 11,000 cells/mm³, and 92% neutrophils; elevated PCR; and the remaining blood chemistry values within normal limits, with a negative rapid HIV test.

**Imaging:** the patient underwent an admission chest X-ray, which showed a heterogeneous radiopacity with irregular borders in the apical region of the right lung field (Figure 1). High-resolution contrast-enhanced computed axial tomography revealed a 4.2 × 6 cm irregular mass in the right upper lobe invading the middle lobe, obstructive atelectasis, and lymphadenopathy in stations 4R, 7, 10R, and 11, as well as a pleural effusion of approximately 150 mL (Figure 2).

Diagnostic and therapeutic **flexible bronchoscopy** was performed for control of pulmonary bleeding upon hospital admission. The procedure findings highlighted the following: Right upper lobe with irregular mucosa, friable exophytic papillary formations that bled on contact, and elevated bronchial mucosa hindering visualization of segments I and II; in the middle lobe, extrinsic compression observed at the 3 o'clock position (Figure 3).

An 80 cc cold saline lavage was performed for bleeding control, followed by biopsy and cytology sampling with bronchoalveolar lavage (**BAL**). Finally, tranexamic acid was instilled for bleeding control.

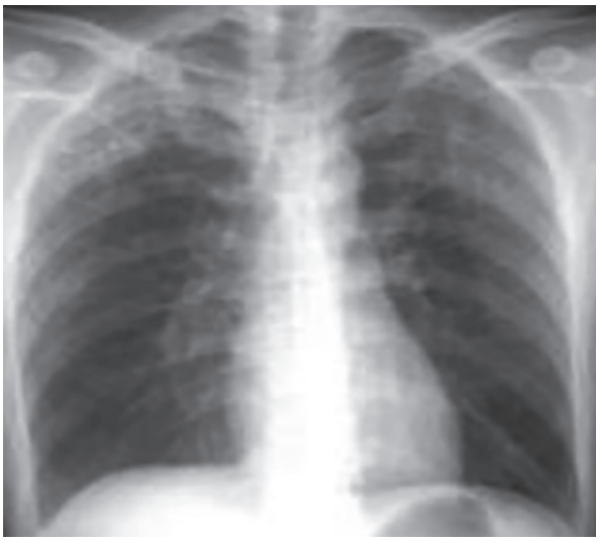

**Figure 1.** Posteroanterior chest radiograph showing heterogeneous radiopaque image in the apical and lateral region of the right lung field.

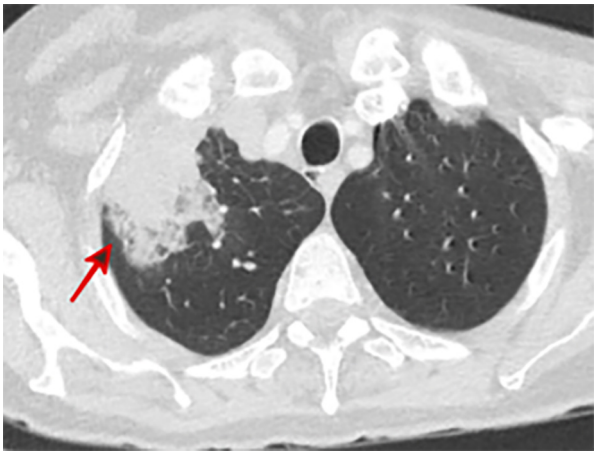

**Figure 2.** Contrast-enhanced computed axial tomography image, lung window, showing irregular mass with poorly defined borders in the right upper lobe.

BAL was positive for Mycobacterium tuberculosis by Xpert MTB/RIF, with high bacillary load and no rifampicin resistance detected. BAL culture was positive for *Streptococcus pneumoniae* sensitive to cephalosporins, and the cytological and histological report was compatible with squamous cell carcinoma of the lung. Immunohistochemistry demonstrated expression of p40, p63, and CK6, confirming non-keratinizing squamous cell carcinoma.

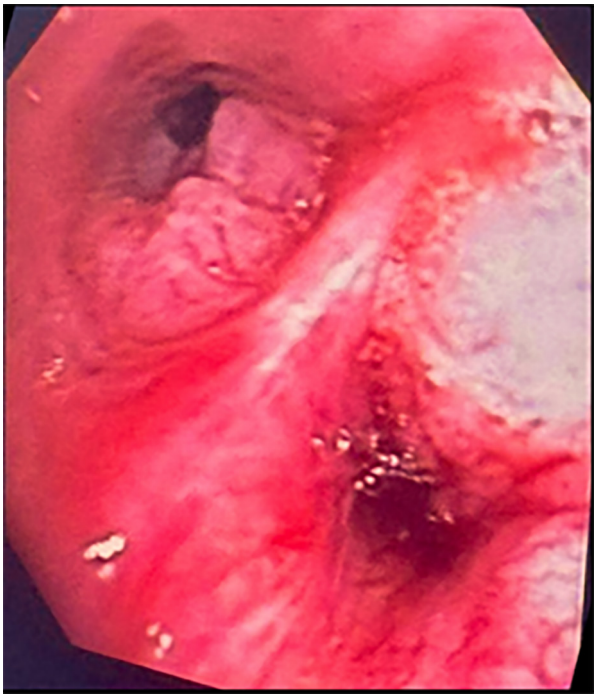

**Figure 3.** Video fibrobronchoscopy image showing right upper lobe and segments I and III with friable, exophytic papillary lesions with bleeding, obstruction of segment II, and irregular bronchial mucosa.

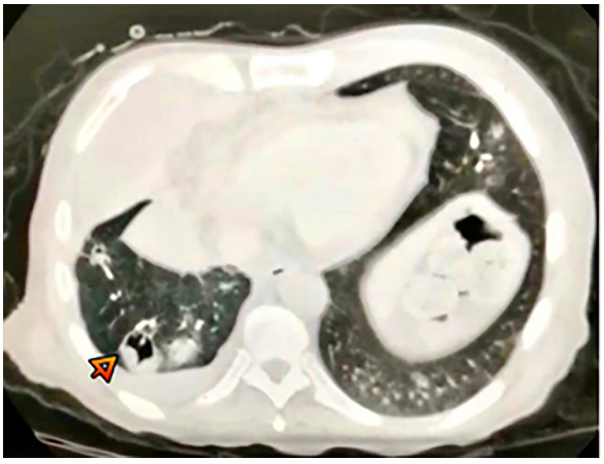

**Figure 4.** Computed axial tomography image, lung window, at the right lower lobe level, showing cavitary lesions with the air crescent sign (arrow) and an Aspergillus nodule. Mild right pleural effusion also observed.

Antituberculous treatment was initiated with the standard regimen of isoniazid, rifampicin, ethambutol, and pyrazinamide, together with third-generation cephalosporin for 7 days due to the isolation of *Streptococcus pneumoniae*. Oncology evaluation determined advanced stage IV disease. As the patient was not a candidate for surgical treatment, palliative systemic therapy was suggested, with chemotherapy sessions to be initiated after resolution of the infectious processes.

At three months, the patient presented clinical deterioration, with progressive grade III dyspnea and hemoptysis of 18 cc within 24 hours. A follow-up tomography scan was performed, revealing tumor growth, with an 8.4 × 9.6 cm mass in the right upper lobe invading toward the inferior vena cava, as well as cavitary nodular formations in the right lower lobe suggestive of aspergilloma, with the air crescent sign (meniscus sign). (Figure 4)

A new bronchoscopy was performed due to suspected pulmonary aspergillosis and for partial control of bleeding. BAL analysis for galactomannan confirmed the presence of *Aspergillus spp*. Systemic antifungal treatment with voriconazole was initiated, and maintenance tuberculosis treatment (isoniazid and rifampicin) was continued at doses per kilogram of weight, with poor tolerance. Despite the therapeutic measures initiated, the patient experienced an unfavorable clinical course with tumor progression, and died three months after being diagnosed with tuberculosis, chronic pulmonary aspergillosis, and squamous cell carcinoma of the lung.

## DISCUSSION

Post-primary tuberculosis among adults is common in our setting, particularly when there is prolonged exposure in an endemic area, such as this case. Symptoms and physical findings vary and may include: persistent cough for more than two weeks, fever, diaphoresis, hemoptysis, and weight loss. However, these findings are also associated with lung cancer, thus it is important to rule out one disease or the other. A CT scan of the chest is useful in patients with suspected TB and for detecting lung cancer, as it can reveal small lesions not visible on chest radiographs. It is particularly useful for detecting hilar or mediastinal lymphadenopathy, and the CT may also show consolidation, cavities, pleural effusions, and/or fibrotic lesions that cause distortion of the pulmonary parenchyma.[6] The association between TB and lung cancer has become increasingly evident. The National Cancer Institute of China found that pulmonary tuberculosis was related to an increased lung cancer risk –after active smoking and socioeconomic status– with an odds ratio of 2.1 (95% CI: 1.4-3.1).[7] Similarly, another meta-analysis study found that tuberculosis was associated with a

1.78-fold increase of lung cancer risk among non-smokers, with a relative risk of 1.6 (95% CI: 1.2-2.1).[8]

The diagnosis of squamous cell carcinoma of the lung is based on the identification of keratin production by tumor cells and/or the presence of desmosomes. Immunohistochemistry is compatible with this subtype when there is expression of markers such as p40, p63, and CK5/6. The variants include the keratinizing, non-keratinizing, and basaloid subtypes.[9] In this case, immunohistochemistry showed expression of p40, p63, and CK5/6, confirming the diagnosis of non-keratinizing squamous cell carcinoma.

Tumors are established by morphology as keratinizing (with keratinization); non-keratinizing (without keratinization), or basaloid (when this pattern comprises more than 50% of the tumor). In non-keratinizing carcinomas, immunohistochemistry is essential to differentiate between squamous cell carcinoma, solid adenocarcinoma, and large cell carcinoma. In this context, diffuse reactivity with squamous markers is recommended, with p40 as the most specific marker, as p63 may also be expressed in adenocarcinomas.

Squamous cell carcinoma of the lung classically presents with a central location and develops through a sequence of metaplasia, dysplasia, and carcinoma in situ; however, at present it may also occur as a peripheral lesion.[10] Both central and peripheral forms may show extensive necrosis with cavitation. A small subgroup of well-differentiated central tumors presents as exophytic papillary endobronchial lesions, which usually manifest with persistent cough, recurrent hemoptysis, or repeated respiratory infections secondary to airway obstruction. This latter form of presentation corresponds to this case, demonstrating from the onset of symptoms the association between tuberculosis and squamous cell carcinoma of the lung.

Chronic pulmonary aspergillosis is usually preceded by some form of structural lung disease, often with residual cavities, bullae, or scarring. Specific risk factors include pulmonary tuberculosis, which is the most important risk factor globally.[11] Madden Aeet et al found a combined prevalence of chronic pulmonary aspergillosis (CPA) of 13% after treatment for pulmonary tuberculosis.[12] The two forms of presentation of CPA include aspergilloma, which appears as a well-formed round mass within a preexisting cavity, commonly referred to as a "fungus ball" or "mycetoma." An aspergilloma may sometimes present with air pockets or calcification inside it and has the characteristic crescent shape known as the "air crescent sign," an image demonstrated in the clinical case; the other form of presentation is *Aspergillus* nodules, which form when fungi replicate locally in the pulmonary parenchyma, unlike aspergillomas, which develop within preexisting cavities.[13]

Finally, in this case, the high mortality rate associated with lung cancer must be considered, particularly when concomitant tuberculosis and chronic pulmonary aspergillosis coinfections are present, as these worsen the prognosis and may preclude systemic oncologic treatment.

## CONCLUSION

The coexistence of pulmonary tuberculosis, squamous cell carcinoma of the lung, and pulmonary aspergillosis is uncommon but clinically relevant, posing a significant diagnostic challenge because of overlapping clinical manifestations and radiological findings. This concurrence may lead to diagnostic delays, negatively affecting patient outcomes and prognosis.

This case highlights the need to maintain a high index of suspicion and to perform a comprehensive diagnostic evaluation in patients with hemoptysis and complex pulmonary lesions, especially in settings with a high prevalence of tuberculosis. It also underscores the importance of considering concomitant diagnoses in the presence of atypical clinical evolution, while promptly incorporating microbiological, radiological, and histopathological diagnostic tools.

A timely multidisciplinary approach is essential to optimize therapeutic decision-making, improve clinical outcomes, and reduce the morbidity and mortality associated with these complex pathological interactions.

### Conflict of interest

Authors have no conflicts of interest to declare.

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