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## Case Report

# Adjuvant surgical treatment of non-tuberculous mycobacterial lung disease in chronic thromboembolic pulmonary hypertension: A first case report

F.R. Bertuccio<sup>a,b,\*</sup>, N. Baio<sup>a,b</sup>, S. Montini<sup>b</sup>, V. Ferroni<sup>a,b</sup>, V. Chino<sup>a,b</sup>, L. Pisanu<sup>a,b</sup>, M. Russo<sup>b</sup>, I. Giana<sup>b</sup>, A. Cascina<sup>a,b</sup>, V. Conio<sup>a,b</sup>, C. Primiceri<sup>c</sup>, G.M. Stella<sup>a,b</sup>, A.G. Corsico<sup>a,b</sup>

<sup>a</sup> Cardiothoracic and Vascular Department, Unit of Respiratory Disease, IRCCS Policlinico San Matteo, Viale Golgi 19, 27100 Pavia, Italy

<sup>b</sup> Department of Internal Medicine and Pharmacology, University of Pavia, Pavia 27100, Italy

<sup>c</sup> Department of Thoracic Surgery, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

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## ABSTRACT

Pulmonary hypertension (PH) is not considered a known risk factor for non-tuberculous mycobacterial lung disease (NTM-LD), despite that many studies state that incidence is almost equal to other chronic lung diseases. Current standard of care for NTM-LD consists in multidrug antibiotic regimen for several months. However, it results in negative culture conversion in a minority of cases. Therefore, when feasible an adjuvant surgical approach is indicated. In this case report we highlight the importance of multidisciplinary team discussion in providing the best therapeutic strategy in presence of significant comorbidities like chronic thromboembolic pulmonary hypertension.

## 1. Introduction

Pulmonary hypertension (PH) has not been recognised as a risk factor for Non tuberculous Mycobacterial lung disease (NTM-LD) yet despite some studies highlighted that the incidence of NTM-LD in patients with chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension (CTEPH and IPAH) is similar to the incidence in patients with other chronic pulmonary diseases that are considered to be risk groups [1].

Consequently, NTM-LD should be suspected in patients with CTEPH presenting with productive cough, constitutional symptoms, and pulmonary infiltrates.

Most cases of new lung infiltrates (especially cavities) in CTEPH patients could be frequently associated with chronic lung parenchyma ischemia, although in some cases they are associated with chronic granulomatous diseases, reinforcing the need for active investigation of infectious agents in this setting.

Nontuberculous mycobacteria (NTM), comprising more than two hundred mycobacteria other than *Mycobacterium leprae* and the *Mycobacterium TB* (TB) complex, are ubiquitous environmental microorganisms commonly isolated from soil, dust, and water. NTM can cause symptomatic infections in humans, and the most common manifestation is pulmonary disease [2]. The incidence and prevalence of

nontuberculous mycobacterial pulmonary disease are increasing worldwide and are becoming a significant health-care burden [3,4].

The mainstay of NTM-LD treatment is long-term antibiotic therapy [2]. Generally, multidrug regimens based on macrolides are administered for at least 12 months after culture conversion; reported success, measured by the rate of mycobacterial culture negative conversion, is as low as 34 % to 65 %, depending on the causative species. Furthermore, the recurrence and reinfection rates after successful treatment are frequent, ranging 17 % to 48 % [5,6].

Therefore, surgical resection has been used as an adjunctive therapy in NTM-LD [7], similar to its role in patients with multidrug-resistant TB [8], to enhance treatment success and reduce the recurrence rate by removing the bulk of the mycobacterial burden. To date, several studies have reported generally favourable outcomes of adjunctive surgery for NTM-LD [9–17].

For this reason, international treatment guidelines recommend surgical resection of the diseased lung as an adjuvant to medical therapy in selected patients: those for whom medical management has failed, which has been defined as the re-emergence or persistence of positive culture results typically after > 12 months of antibiotic treatment; cavitary disease; drug-resistant isolates; complications such as haemoptysis or severe bronchiectasis [2,7,18].

Although surgical resection has been regarded as an effective

\* Corresponding author at: Viale Camillo Golgi 19, 27100 Pavia, Italy.

E-mail address: [francesco.bertuccio01@gmail.com](mailto:francesco.bertuccio01@gmail.com) (F.R. Bertuccio).

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adjunctive therapy for NTM-LD, most studies reporting outcomes have been conducted in a single institution with a small number of patients, and therefore were vulnerable to potential biases.

To our knowledge this is an original case report providing important concepts in complications of chronic thromboembolic pulmonary disease and showing the considerable relevance of multidisciplinary team discussion in choosing therapeutic strategy in frail patients. Highlighting these concepts could be helpful in real-life clinical activity.

## 2. Case presentation

A 37-year-old woman was sent to our outpatient Respiratory Disease Department for chest CT scans' appearance of subpleural thin-walled cavitory lesion in the right upper lobe (Fig. 1) without evidence of perfusion defects. The patient was under cardiac-surgery surveillance for previous pulmonary endarterectomy intervention sustained 2018 in chronic thromboembolic pulmonary hypertension.

She is a homozygous C677T mutation in the MTHFR gene and a previous smoker. She reported no allergy and was on therapy with warfarin for chronic thromboembolic pulmonary hypertension. She has no known risk factors for NTM-LD. She has normal level of alpha-1-antitrypsin and no immunoglobulin deficiency.

Mean PAP (pulmonary artery pressure) measured by right heart catheterization before surgical treatment was 60 mmHg; while after the intervention was normal with absence of indirect signs of pulmonary hypertension too.

For 3 months she complaint progressive dyspnea on exertion in absence of any other symptoms (cough, haemoptysis, fever, night sweats and weight loss).

After that radiological finding it was indicated to perform HIV, HBV, and HCV serology, which were all negative; quantiferon test was negative too; immunoglobulin dosage was normal together with lymphocyte phenotype flow cytometry. Autoimmune serology panel was not significant. She never performed a sputum culture since she never had productive cough.

After multidisciplinary team discussions (composed by thoracic surgeons, radiologists, and pulmonologists) it was decided to perform a percutaneous CT-scan guided lung fine needle aspiration biopsy to exclude malignant etiology.

Histological analysis did not evidence any malignant cellular component but showed necrotic debris and focal calcific materials. Microbiological exam revealed isolation of *Mycobacterium xenopi*; the strain's antibiogram showed sensitivity to amikacin, clarithromycin, linezolid, rifabutin, moxifloxacin, tmp/smx and resistance to rifampicin, doxycycline.

Considering the pathogen identification and cavitory disease on CT scan antimycobacterial treatment with oral azithromycin, rifabutin, ethambutol together with nebulised amikacin was started.

Two chest CT scan were performed after 3 and 6 months from treatment start (Fig. 2), however they both showed no change in cavity.

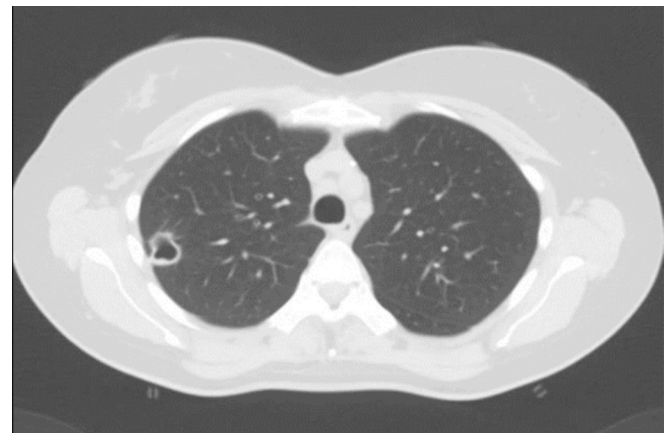


Fig. 2. Chest CT scan performed after several months of multidrug antibiotic therapy showing no reduction in size and extension of the right upper lobe cavitory lesion.

Moreover, persistence of positive culture on sputum analysis was evidenced.

Subsequently another multidisciplinary team discussion was performed; the team agreed on adjuvant surgical approach considering the persistence of pathogen isolation on sputum and the persistence of cavitory disease. Therefore, an upper lobe wedge resection was performed under Video-assisted thoracoscopic surgery (VATS), without complications (Fig. 3). The histological analysis revealed pulmonary parenchyma with central necrosis with calcifications and peripheral chronic lymphoplasmacellular infiltrates associated with multi-nucleated giant cellular granulomatous reaction.

The patient was discharged home and in the subsequent months, sputum culture were repeatedly negative after intervention. Nowadays patient's symptoms have vanished, and she is proceeding with respiratory disease outpatient follow-up.

## 3. Discussion

The appearance of new infiltrations with cavitation in CTEPH patients may arouse a suspicion of the recurrence of pulmonary embolism. The absence of new vascular lesions in chest angio-CT scan, should lead to diagnostics targeted at the respiratory system infection. Among the factors that could influence an increased risk of NTM-LD in patients with PH are structural lesions that could be the basis for colonisation with non-tuberculous mycobacteria, such as scars, foci of fibrosis (as sequela of CTEPH), or postinfarction cavities [1]. In literature, there are reports concerning the negative impact of infection on the prognosis of pH patients since they could be a cause of exacerbations of right heart insufficiency.

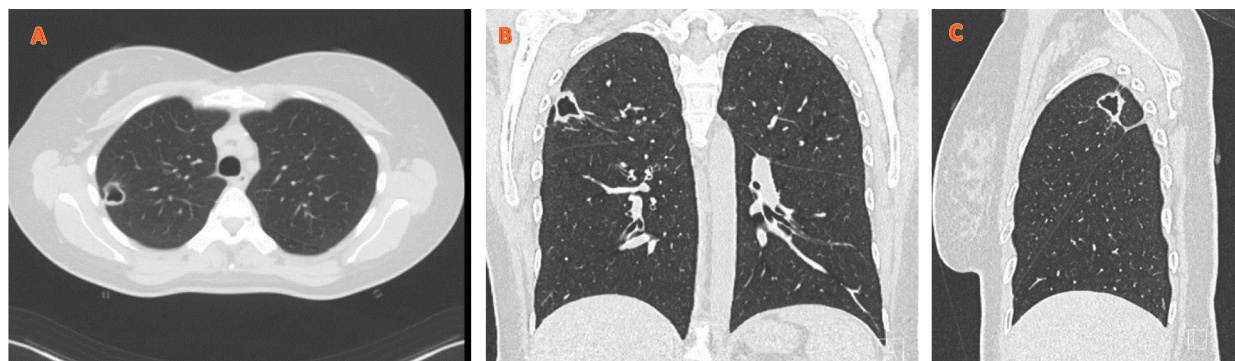
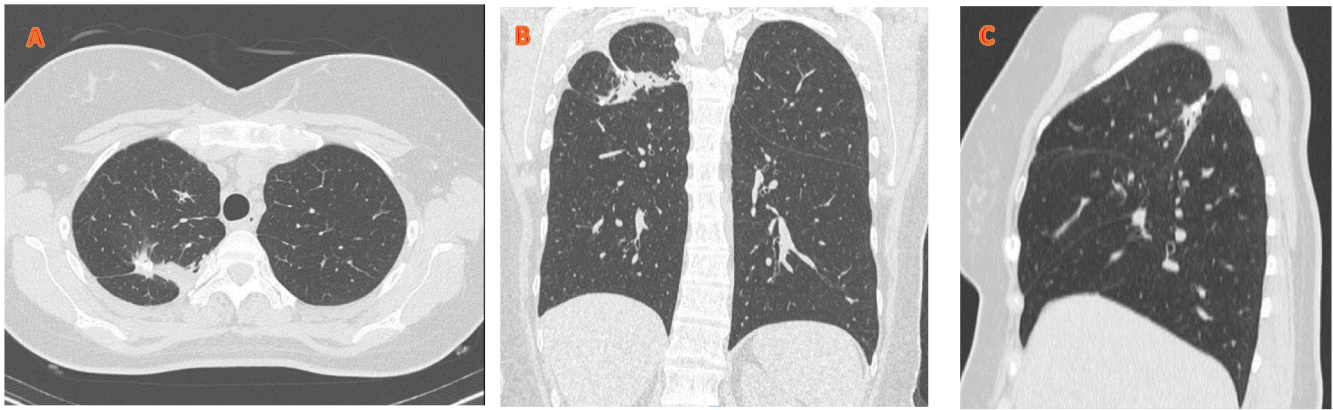


Fig. 1. Chest CT scan evidencing right upper lobe cavitory lesion. A: axial plane; B: coronal plane; C: sagittal plane.



**Fig. 3.** Chest CT scan performed after wedge resection of right upper lobe with residual surgical clips. A: axial plane, B: coronal plane; C: sagittal plane.

In the case report discussed above, lung parenchyma structural lesions derived from previous blood flow hypoperfusion due to CTEPH could be the base for infection with non-tuberculous mycobacteria.

Concerning with therapeutic approach, the unsatisfactory results of antibiotic therapy and the high recurrence or reinfection rates, suggest that surgical treatment could be a convincing therapeutic option for selected patients with NTM-LD. Culture negative conversion, which is defined by the finding of at least three consecutive negative mycobacterial culture results from respiratory samples collected at least 4 weeks apart [19], has been an important primary outcome in clinical trials for NTM-LD. However, it is well established that the rate of culture negative conversion achieved through antibiotic treatment is low and frequently interrupted by the re-emergence of mycobacteria. In this respect, it is reported a postoperative culture negative conversion rate of 93 % and recurrence rate of 9 % after a median follow-up of 34 months [15]; these data have important clinical implications for patients with NTM-PD who are refractory to antibiotic treatment alone. Serious postoperative complications are rarely reported after adjunctive surgery for NTM-PD. Bronchopleural fistula is reported to occur only 2 % of all surgical patients, comprising 12 % of postoperative complications. In addition, in-hospital mortality after surgery was significantly low. Although it is necessary to weigh the risks and benefits of surgical strategies based on the extent of the disease, postoperative lung function, and the general condition of each patient, adjunctive surgery is well tolerated if conducted in adequately selected patients by experienced surgeons. However, it should also be considered that surgical resection leads to significant postoperative pain and prolonged recovery time, which patients may not experience if they received only medical therapy.

Many questions remain unanswered and require further research:

- Controversy remains regarding the timing of surgical resection and optimal duration of antibiotic treatment before and after surgery.
- Despite current surgical indication by international guidelines the decision to undergo surgical treatment was left to the physicians' judgment in many studies, which may have contributed to the heterogeneity of research results.
- Finally, changes in quality of life in relationship to lung function after surgery remain unknown. Future studies on the optimal extent of surgery that allows maximum disease control without compromising quality of life may be helpful.

#### 4. Conclusion

- To our knowledge this is the first case report highlighting the role of adjuvant surgical treatment in NTM-LD in patient affected by CTEPH.
- Although antibiotic therapy is the mainstay of treatment for patients with NTM-LD, our case report demonstrate that surgical resection is

a safe and effective adjunctive option; moreover, it yields favourable microbiological outcomes.

- More specific recommendations for the use of surgical therapy in NTM-LD are lacking; a prospective multicentre study could provide more data since many issues remain to be clarified: establishing the criteria for patient selection, finding out the optimal timing for surgery, and determining the optimal duration of postoperative antibiotic treatment.
- NTM-LD should be suspected in patients with CTEPH presenting with new pulmonary infiltrate with cavitation. Special attention should be paid to new lesions without accompanying thrombus in the artery supplying the area.

#### Consent

The patient provided written consent to be included in this manuscript.

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#### CRediT authorship contribution statement

**F.R. Bertuccio:** Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization. **N. Baio:** Data curation. **S. Montini:** Data curation. **V. Ferroni:** Data curation. **V. Chino:** Data curation. **L. Pisanu:** Data curation. **M. Russo:** Data curation. **I. Giana:** Data curation. **A. Cascina:** Writing – review & editing. **V. Conio:** Writing – review & editing. **C. Primiceri:** Writing – review & editing. **G.M. Stella:** Supervision. **A.G. Corsico:** Supervision.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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