Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Seminara MM, Visca D, Repossi AC, Spanevello A. ***Mycobacterium chimaera*: a case report from Italy.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2933

Mycobacterium chimaera: a case report from Italy

Martina Maria Seminara,[1,2] Dina Visca,[1,2]
Alice Claudia Repossi[3], Antonio Spanevello[1,2]

[1]Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese, Como; [2]Respiratory Rehabilitation Unit, Istituti Clinici Scientifici Maugeri, IRCCS, Pavia; [3]Regional Tuberculosis Reference Center, Villa Marelli Institute, Niguarda Hospital, Milan, Italy

Correspondence: Martina Maria Seminara, MD, Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese, Como, Italy.
E-mail: mmseminara@studenti.uninsubria.it

Contributions: MMS, DV, conceptualization, methodology, data curation, writing-original draft preparation; MMS, DV, ACR, investigation; DV, ACR, AS, writing-review and editing; DV, AS, supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: the authors have no conflicts of interest to declare.

E**thics approval and consent to participate**: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient included in this study.

Patient consent for publication: the patient gave her written consent to use her personal data for the publication of this case report and any accompanying images.

Funding: this research received no external funding.

Availability of data and materials: all data underlying the findings are fully available.

Abstract

Mycobacterium chimaera is an environmental non-tuberculous mycobacterium belonging to *Mycobacterium avium* complex (MAC). It has been widely known to be associated with disseminated infection after cardiac surgery, related to heater-cooler units used during these procedures. Although *M. chimaera* seems to be a less virulent species compared to *M. avium* and *M. intracellulare* among MAC, several cases of *M. Chimaera* lung infections have been reported in settings of chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, malignancy, or immunosuppression. Here, we present an Italian case report in association with newly diagnosed COPD.

Key words: non-tuberculous Mycobacterium, *Mycobacterium chimaera*, coronary bypass, heater-cooler units, pulmonary rehabilitation.

Introduction

Mycobacterium chimaera is an environmental non-tuberculous mycobacterium belonging to MAC, first isolated and identified in 2004 [1]. It is a ubiquitous mycobacterium, mainly present in water, soil, and dust. *Mycobacterium chimaera*'s infections were reported worldwide and linked to an outbreak associated with heater-cooler devices utilized during cardio-surgery procedures in 2013 [2]. The first case of *M. chimaera* infection in Italy, as part of this global outbreak, was described in December 2016 in a woman with a history of cardiac surgery who developed disseminated infection and vertebral osteomyelitis [3]. Although M. *chimaera* seems to be a less virulent species compared to *M.avium* and *M. intracellulare* among MAC, it can also affect people with underlying pulmonary affections [4], such as the ones presenting a history of COPD [5]. In fact, the association between NTM-PD and COPD can worsen the evolution of COPD and increase the mortality. Furthermore, the use of inhaled corticosteroids is considered a risk factor for the development of NTM-PD [6].

Case Report

An 84-year-old woman presented to the Respiratory Rehabilitation Unit Clinic in IRCCS Maugeri on March 6th, 2023, complaining of worsening dyspnoea at rest, productive cough, weight loss and lack of appetite over the previous six months. As regards her past medical history, she never smoked and had no work exposure to inhalants. She also reported multiple annual bronchitic exacerbations requiring antibiotic therapy. It is worth mentioning that chronic respiratory failure developed in 2020 when long-term oxygen therapy (LTOT) was

started. Regarding other non-respiratory comorbidities, she suffered from not hemodynamically significant bilateral carotid atheroma, arterial hypertension, deficiency anaemia, anxious-depressive syndrome and an allergy to iodine.

At the presentation, she denied a previous history of cardio-thoracic surgery, recent travels, and contact with birds or wild animals. Blood pressure was 120/80 mmHg, heart rate was 90 beats per minute, respiration rate was 18 breaths per minute, her oxygen saturation was 92% in O_2 1 L/min and temperature was 36 °C, weight was 50 kg, BMI 19.5 kg/m^2. Arterial blood test on supplemental oxygen (1 L/min) documented partially compensated chronic hypercapnic respiratory failure.

Blood tests were all in range according to the patient's age, except for iron deficiency anaemia and vitamin D lack, which were promptly supplemented. QuantiFERON test and HIV test were negative. No other immunosuppressive conditions were found. Lung function tests were performed, and she was diagnosed with COPD: forced expiratory volume in 1 second (FEV-1) was 0.47 L (27% of predicted), forced vital capacity (FVC) 0.60 L (26%), FEV-1/FVC ratio was 46.8%, residual volume (RV) 3.62 L (163%) and total lung capacity (TLC) was 97%. It was first diagnosed with COPD GOLD 4 category, class E. Her mMRC was 3, while CAT was 20. According to functional tests (global spirometry), multidimensional questionnaires (modified Medical Research Council dyspnea scale and COPD Assessment Test) and GOLD 2023 guidelines [7], the patient was started on triple closed inhalator therapy.

She also performed six-minute walking test while supplemented firstly with 1 L/min, then with 2 L/min, reaching a borderline oxygen saturation of 89%. A chest x-ray showed a left-sided apical opacity, confirmed by high-resolution computed tomography (HRCT), which highlighted a 3 cm of diameter pulmonary cavitation in the left lung apex. Additionally, patchy reticulonodular opacities, emphysema and multiple bronchiectasis spread all over the lungs were found (Figures 1 and 2). The images led to the diagnosis of cavitary pneumonia, so blood cultures and sputum cultures were performed. Sputum samples were negative for acid-fast bacilli at the microscopic examination, and PCR testing for *Mycobacterium tuberculosis* was also negative. Bacterial and fungal culture tests were negative. Samples were cultured on solid and liquid media for almost five weeks, and mycobacteria were identified in > 2 separate sputum samples. Species identification was performed, and finally, *M. chimaera* was isolated. All samples were susceptible to macrolides and aminoglycosides. Blood cultures were negative. According to the ATS/ERS/ESCMID/IDSA Clinical Practice Guidelines published in 2020 [8], the patient was diagnosed with NTM pulmonary disease (NTM-PD).

Beyond that, although a diagnosis was made, the patient needed further follow-up to ensure a global resolution of her acute condition. Nocturnal non-invasive mechanical ventilation

(NIMV) was started, and oxygen titration at rest and on exertion was optimized with a prompt improvement in respiratory failure. Respiratory physiotherapy techniques tailored to the patient's needs were implemented, with a progressive benefit on mucus-ciliary clearance throughout cyclical sessions with high-flow nasal cannula oxygen therapy (HFNC) and Expiratory Flow Accelerator techniques. The patient was also taught how to perform inhalation techniques properly and manage the NIMV and HFNC devices to get more confidence and autonomy. As for the pulmonary rehabilitation (PR) program, strength training was performed through bodyweight exercises, while the physical reconditioning to effort was performed with interval training by using a stationary cycle ergometer and reaching a daily load of 15 Watts for 30 minutes with a constant load mode. She was discharged with mMRC 2 and CAT 2. Because of weight loss history and borderline BMI, the patient was also followed by a dietary counsellor. Additionally, a psychological support program was implemented, with both group and individual counselling sessions.

She was finally directed to the Regional TB Reference Centre, Villa Marelli Institute, Niguarda Hospital, Milan. In May 2023, she was started on a multidrug regimen with a combination of rifampicin, ethambutol and azithromycin. During the follow-up, a progressive reduction of respiratory symptoms and radiological improvement were noted. Progressive cavitation reduction, weight gain and respiratory improvements were obtained in the first four months of treatment, as shown in Figure 3 and Table 1.

Discussion

Mycobacterium chimaera is part of the *Mycobacterium avium* complex, as the two more common species, *M. avium* and *M. intracellulare*, and several other closely related mycobacteria. Initially, *M. chimaera* was misreported as *M. intracellulare* because molecular genetic standard tools in clinical microbiologic laboratories did not differentiate MAC members.

As others NTM, *M.chimaera*'s distribution in human isolates depends on several factors, such as the geochemical characteristic of the environment; its prevalence is less than 2% in bronchiectasis patients, as shown by Suska. et al. in Italy [9]. Literature provides sufficient evidence associating *Mycobacterium chimaera* as the infectious organism in patients undergoing cardiac surgery (specifically, surgeries utilizing heater-cooler units) [10], but there are still few cases described in patients with underlying pulmonary infections. Two case reports by Bills et al. in 2009 [11], and Miskoff et al. in 2018 [5] described a similar case of a patient with a history of COPD and smoking. In addition, a case of cavitary Mycobacterium chimaera with isolation of Candida parapsilosis in sputum was recently presented by Robinson et al. in

2022 [6]. Azzarà et al. reported the first case of NTM-PD due to *M.chimaera* in an oncologic patient receiving immune checkpoint inhibitors [12]. Our patient did not undergo surgery procedures and was not immunocompromised but was first diagnosed with COPD and bronchiectasis. Moreover, the patient was started on inhaled corticosteroids a few days before the diagnosis of NTM-PD, suggesting that it did not contribute as a risk factor [13]. Although transmission of NTM-PD occurs predominantly via water and soil, other less common transmission routes exist such as several hobbies or job-related activities (farming), dusty environments, heater-cooler devices, war contexts, natural disasters or migration. These alternative routes can be handled by using respiratory protective equipment also for domestic or recreational activities, by adopting prophylaxis measurements and by limiting situations of social hardship [14].To the best of our knowledge, this is one of the few cases describing *Mycobacterium chimaera* infection in the Italian scenario. *M. chimaera* infection could be more common and more virulent than expected in chronic respiratory diseases such as COPD, as described also by Tortoli et al. [1]. Interestingly, our case shows a positive effect of combining rehabilitation and pharmacological-specific treatment [8]. In fact, along with pharmacological therapy, the patient was trained to strengthen her respiratory muscles through respiratory physiotherapeutic techniques. In addition, mucus clearance was improved using oscillating positive expiratory pressure devices and high-frequency chest wall oscillation, as recommended by Sharma S. et al. [14], and by O'Neill K. et al. [15]. To reduce breathlessness and fatigue, the patient followed an interval training program interspersing high-intensity exercise with rest periods or lower-intensity exercise. As explained by M. Spruit et al., interval training and continuous training appear to be equally effective in COPD and may be a useful alternative for symptom-limited individuals who cannot tolerate high-intensity continuous training [16].

Indeed, due to the reported association between low BMI and increased mortality in advanced COPD and NTM-PD, the patient was also supported by a dietary counsellor who planned food fortification and vitamin supplementation to gain ideal weight in three months and to promote an anti-inflammatory effect with reduced tissue damage [17].

Beyond that, considering that up to 40% of persons with COPD have depression or anxiety, especially in those using supplemental oxygen [18], and this comorbidity is also described in NTM-PD patients, medical staff should timely identify symptoms and program intervention [15]. Considering all these aspects, during rehabilitation, our patient attended individual and collective psychotherapist counselling to improve psychological symptoms.

Regarding the specific pharmacological treatment, a multidrug regimen composed of rifampicin, ethambutol and azithromycin was started as suggested in guidelines for cavitary

NTM-PD due to MAC [8]. The duration of the therapy is at least 12 months after sputum conversion. Even though indicated in NTM-PD's treatment guideline, in our case, amikacin was not possible to start because of the patient's age and comorbidities.

Nowadays, there are few studies specifically assessing the role of pulmonary rehabilitation in patients with NTM-PD. In the narrative review by Youssefnia A. et al. [19], it is elicited that, since NTM-PD pharmacological treatment has a low percentage of success, in addition to reducing exposures to the NTM and treating it with antibiotics, there are ancillary treatment measures that can help in maximizing treatment outcomes such as airway clearance, physical and pulmonary rehabilitation, nutritional support [19]. Other evidence relies on similar studies on diseases resembling NTM-PD, such as bronchiectasis and TB [15,17].

Finally, it has been demonstrated that combined chemotherapy and supervised PR can be provided safely and improve HRQoL and physical function in NTM-PD. Omatsu S. et al. recommend that combined chemotherapy and PR be considered for treating NTM-PD according to the patient's condition [20]. Besides that, further investigations should be done to understand better the best personal and tailored approach for every patient.

Conclusions

We presented the case of an immunocompetent patient with advanced pulmonary *Mycobacterium chimaera* infection with undiagnosed COPD and bronchiectasis. The patient underwent multiple interventions, firstly by stabilizing the COPD, then by building a tailored PR program, by starting a multidrug regimen and by investigating comorbidities such as undernutrition and psychological aspects. The objective improvements in respiratory, radiological, and biometrical parameters observed after a few months suggest that the involvement of a multidisciplinary team may favour patient management.

In summary, Non-tuberculous mycobacteriosis (NTM) is interesting for various reasons:

- Diversity of mycobacteria: NTM encompasses various mycobacterial species with unique characteristics. This diversity is intriguing from a scientific and epidemiological perspective as it requires understanding different species, their growth habits, transmission routes, and clinical manifestations, especially for *Mycobacterium chimaera*.
- Emerging diseases: NTM has been gaining increasing attention due to the rising number of reported cases worldwide, especially among people with chronic lung conditions or immunodeficiencies. This makes NTM an issue of growing relevance in the medical and epidemiological fields.

Research and awareness on this topic are essential for addressing the challenges associated with NTM. For the future, it could be far-sighted to carry out longitudinal studies about NTM-PD tracking infections in COPD by developing management strategies for these patients.

References

1. Tortoli E, Rindi L, Garcia MJ, et al. Proposal to elevate the genetic variant MAC-A included in the Mycobacterium avium complex, to species rank as Mycobacterium chimaera sp. nov. Int J Syst Evol Microbiol 2004;54:1277-85.

2. Wetzstein N, Kohl TA, Diricks M, et al. Clinical characteristics and outcome of Mycobacterium chimaera infections after cardiac surgery: systematic review and meta-analysis of 180 heater-cooler unit-associated cases. Clin Microbiol Infect 2023;29:1008-14.

3. Chiesi S, Piacentini D, Salerno ND, et al. Disseminated Mycobacterium chimaera infection after open heart surgery in an Italian woman: a case report and a review of the literature. Infez Med 2017;3:267-9.

4. Larcher R, Lounnas M, Dumont Y, et al. Mycobacterium chimaera pulmonary disease in cystic fibrosis patients, France, 2010-2017. Emerg Infect Dis 2019;25:611-3.

5. Miskoff JA, Chaudhri M. Mycobacterium Chimaera: a rare presentation. Cureus 2018;10:e2750.

6. Robinson B, Chaudhri M, Miskoff JA. A case of cavitary Mycobacterium chimaera. Cureus 2022;14:e26984.

7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Report 2023.

8. Daley CL, Iaccarino JM, Lange C, et al. Treatment of non-tuberculous mycobacterial pulmonary disease: An official ats/ers/escmid/idsa clinical practice guideline. Clin Infect Dis 2020;71:e1-36.

9. Suska K, Amati F, Sotgiu G, et al. Non-tuberculous mycobacteria infection and pulmonary disease in bronchiectasis. ERJ Open Res 2022;8:00060-2022.

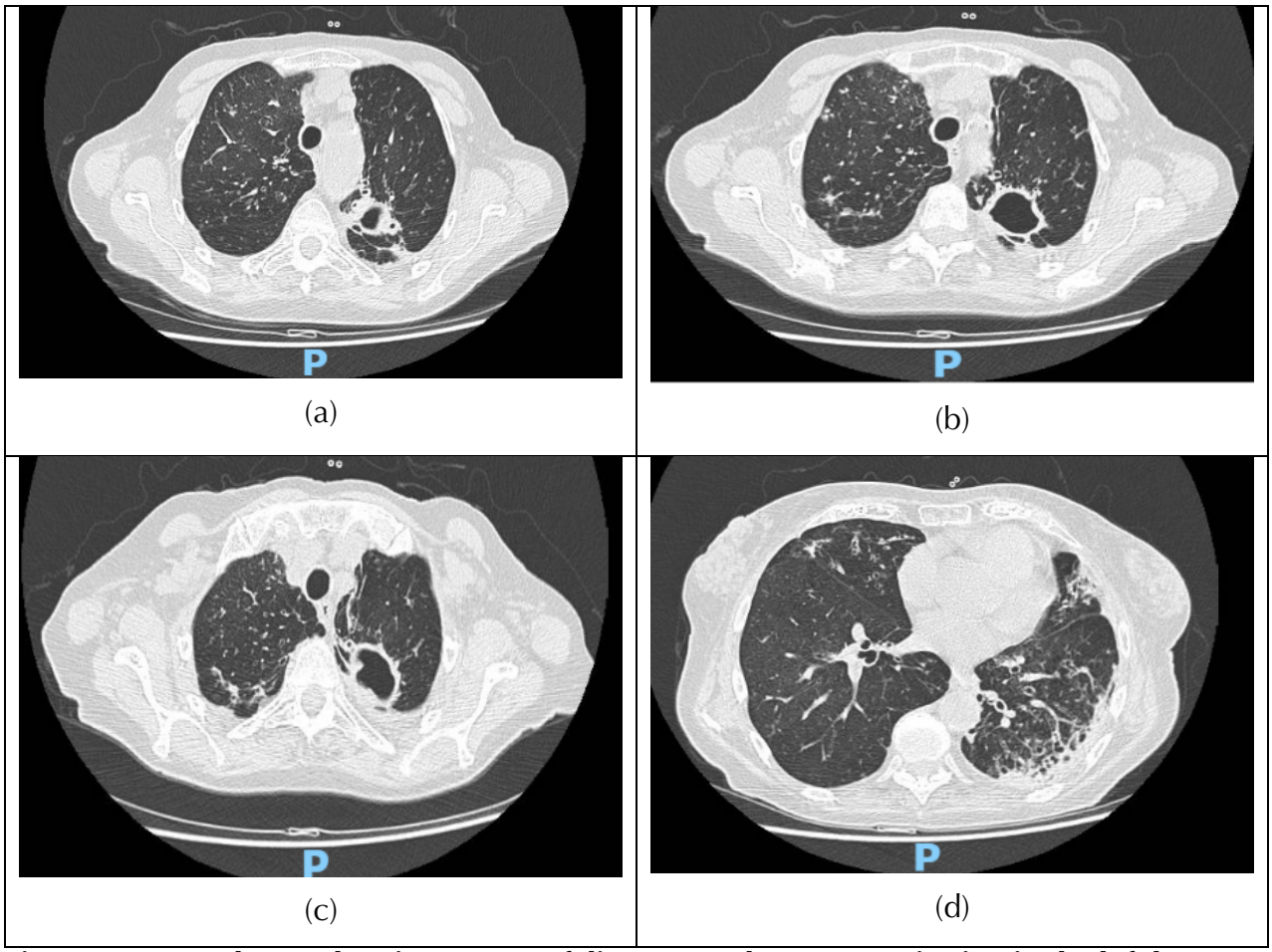
10. Sommerstein R, Rüegg C, Kohler P, et al. Transmission of Mycobacterium chimaera from heater-cooler units during cardiac surgery despite an ultraclean air ventilation system. Emerg Infect Dis 2016;22:1008-13.

11. Bills ND, Hinrichs SH, Aden TA, et al. Molecular identification of Mycobacterium chimaera as a cause of infection in a patient with chronic obstructive pulmonary disease. Diagn Microbiol Infect Dis 2009;63:292-5.

12. Azzarà C, Lombardi A, Gramegna A, et al. Non-tuberculous mycobacteria lung disease due to Mycobacterium chimaera in a 67-year-old man treated with immune checkpoint inhibitors for lung adenocarcinoma: infection due to dysregulated immunity?. BMC Infect Dis 2023;23:573.
13. Loebinger MR, Quint JK, van der Laan R, et al. Risk Factors for Non-tuberculous mycobacterial pulmonary disease: a systematic literature review and meta-analysis. Chest 2023;164:1115-24.
14. Sharma S, Upadhyay V. Epidemiology, diagnosis & treatment of non-tuberculous mycobacterial diseases. Indian J Med Res 2020;152:185-226.
15. O'Neill K, O'Donnell AE, Bradley JM. Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis. Respirology 2019;24:227-37.
16. Spruit MA, Singh SJ, Garvey C, et al. An official American thoracic society/European respiratory society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188:e13-64.
17. Faverio P, De Giacomi F, Bodini BD, et al. Non-tuberculous mycobacterial pulmonary disease: An integrated approach beyond antibiotics. ERJ Open Res 2021;7:00574-2020.
18. Ni S, Chen Y, Hu B, Yuan Z. Anxiety and depression among patients with non-tuberculous mycobacterial disease in Shanghai: a cross-sectional study. Front Psychiatry 2023;14:1132675.
19. Youssefnia A, Pierre A, Hoder JM, et al. Ancillary treatment of patients with lung disease due to non-tuberculous mycobacteria: a narrative review. J Thorac Dis 2022;14:3575-97.
20. Omatsu S, Tabusadani M, Yamane K, et al. Clinical significance and safety of combined treatment with chemotherapy and pulmonary rehabilitation regarding health-related quality of life and physical function in non-tuberculous mycobacterial pulmonary disease. Respir Investig 2022;60:674-83.

Abbreviations	
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
CO2	Carbon dioxide
HFNC	High Flow Nasal Cannula
HRQoL	Health-Related Quality of Life
HRTC	High Resolution Computed Tomography
mMRC	Medical Research Council Questionnaire
NIMV	Nocturnal non-invasive mechanical ventilation
NTM-PD	Non-tuberculous mycobacterial pulmonary disease
PR	Pulmonary rehabilitation

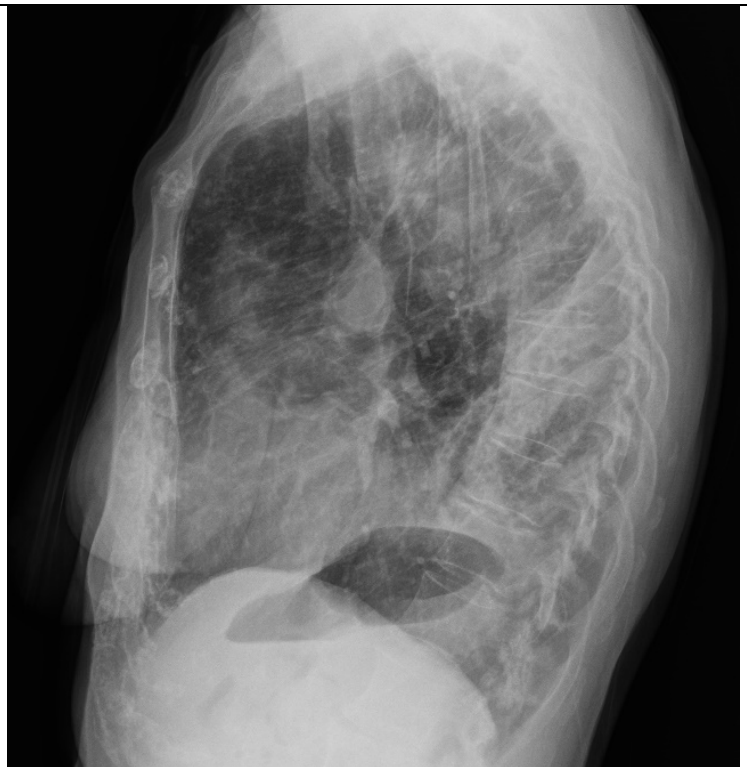
Figure 1. Chest x-ray posterior-anterior view, on initial presentation, illustrating left-sided apical opacity.



(a) (b) (c) (d)

Figure 2. HRTC thorax showing a 3 cm of diameter pulmonary cavitation in the left lung apex surrounded by emphysema and several bronchiectasis as shown by different slices in (a) (b), (c) and (d) moving from the apex to the bottom.

(a)



(b)

Figure 3. (a) Chest x-ray posterior-anterior (PA) and (b) later-lateral (LL) views on follow-up (after four months) presentation, illustrating improvement of left-sided apical opacity.

Table 1. Respiratory, radiological and biometrical parameters at admission and follow-up.

Variables	Admission	Follow-up
CAT	20	2
MRC	3	2
pO_2 (in 1 L/min)	66.6 mmHg	72.2 mmHg
pCO_2 (in 1 L/min)	68.8 mmHg	47.6 mmHg
Weight	50 kg	52 kg
Radiological findings	3 cm left-sided apical cavitation	Reduction of left-sided apical cavitation