UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Mycobacterium kansasii pulmonary disease in a patient with risk factors: Case Report

ÁREA CIENTÍFICA DE PNEUMOLOGIA

Trabalho realizado sob a orientação de:

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MYCOBACTERIUM KANSASII PULMONARY DISEASE IN A PATIENT WITH RISK FACTORS: CASE REPORT

DOENÇA PULMONAR POR MYCOBACTERIUM KANSASII NUM PACIENTE COM FATORES DE RISCO: CASO CLÍNICO

Caso clínico

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ABSTRACT

Mycobacterium kansasii is one of the most relevant non-tuberculous mycobacteria and its incidence has increased all over the world. The risk factors include structural lung disease and prior pulmonary tuberculosis. Asthmatic patients seem to have a higher infection prevalence. The incidence in pulmonary hypertension patients is identical to in other chronic pulmonary diseases considered to be risk groups.

We described the case of a 46 year-old patient with an unusual combination of risk factors and comorbidities that presented at 31st October 2018 with a cavitation on the upper left lobe detected in a routine computed tomography angiography and a positive bacilli detection in sputum smear microscopy. She reported persistent productive cough with mucopurulent sputum, in the past 4 months. Her medical history included pulmonary tuberculosis, bronchial asthma, and pulmonary hypertension type IV. Epidemiological context was irrelevant. Four-drug regimen treatment was initiated and later pyrazinamide was removed when the *Mycobacterium kansasii* was identified by nucleic acid amplification. Bacilloscopy and the cavitation on the X-ray showed complete resolution in October 2019.

In conclusion, the incidence of non-tuberculous bacteria's infection is increasing and it must be considered in all patients with risk factors in our clinical practice.

Keywords: Nontuberculous Mycobacteria, Mycobacterium kansasii, Risk Factors, Asthma, Hypertension, Pulmonary (Medical Subject Headings 2020)

RESUMO

Mycobacterium kansasii é uma das micobactérias não tuberculosas mais relevantes e a sua incidência tem vindo a aumentar em todo o mundo. Doença pulmonar estrutural e tuberculose pulmonar prévia são fatores de risco. Doentes asmáticos apresentam também maior incidência da infeção. Doentes com hipertensão pulmonar apresentam uma incidência semelhante à verificada noutras doenças pulmonares crónicas consideradas fatores de risco.

Descrevemos o caso de uma doente de 46 anos com vários de fatores de risco para a infeção e comorbilidades, que no dia 31 de Outubro de 2018 numa angiografia por tomografia computorizada apresentava uma cavitação no lobo superior esquerdo e uma baciloscopia positiva na expetoração. A doente apresentava tosse produtiva persistente com expetoração mucopurulenta há 4 meses. Os seus antecedentes incluíam tuberculose pulmonar, asma brônquica e hipertensão pulmonar tipo IV. O contexto epidemiológico era irrelevante. O tratamento quadruplo foi iniciado e, mais tarde, a pirazinamida foi removida aquando a identificação de *Mycobacterium kansasii,* por amplificação de ácidos nucleicos. Em Outubro de 2019, a baciloscopia negativou e a cavitação apresentou resolução total.

Concluindo, a incidência da infeção por micobactérias não tuberculosas está a aumentar e deve ser considerada na nossa prática clínica em doentes com fatores de risco.

Palavras-chave: Micobactérias não Tuberculosas, Mycobacterium kansasii, Fatores de risco, Asma, Hipertensão Pulmonar

INTRODUCTION

Mycobacterium kansasii is considered one of the most clinically relevant Nontuberculous Mycobacteria (NTM), a class of atypical bacteria (1).

The incidence of *Mycobacterium kansasii* varied with time and geography (1) but it has been increasing in the non-AIDS population all over the world (2). The aerosol route is responsible for most of the infections rather than person-to-person transmission which does not occur (1).

Among the risk groups for NTM infection are patients with structural lung disease (chronic obstructive pulmonary disease, bronchiectasis, etc), prior pulmonary tuberculosis and immunosuppression (neoplastic diseases, HIV infection, immunosuppressive treatment)(3). Pulmonary vascular diseases (4) and asthma (5) are not considered to be risk factors despite the association with an higher incidence of NTM infections.

The clinical presentation is nonspecific (2). The symptoms are respiratory (persistent productive cough and exaggeration of dyspnoea) (4) and constitutional. In 20% of the cases radiological findings suggest the diagnosis (1) mainly on the chest X-ray. Microbiological confirmation is required for diagnosis (1).

We described a case of a rare diagnosis and an unusual combination of risk factors and comorbidities in a single patient.

CASE REPORT

A 46-year-old caucasian female patient was referred to the *Centro de Diagnóstico Pneumológico* (CDP) in Coimbra at 31st October 2018, presenting a cavitation on the upper left lobe with thickened walls detected in a routine computed tomography angiography. A Ziehl-Neelsen stain showed acid fast staining bacilli in sputum smear.

On 27th October 2018, a routine thoracic computed tomography angiography (Figure 1) for the following of a chronic pulmonary hypertension was done at *Hospital Geral dos Covões*. It described a densification in the upper left lobe, a cavitation with thickened walls (of 3 centimetres of diameter) and consolidations with air bronchogram. There was an ectasia of the pulmonary cone and its branches.

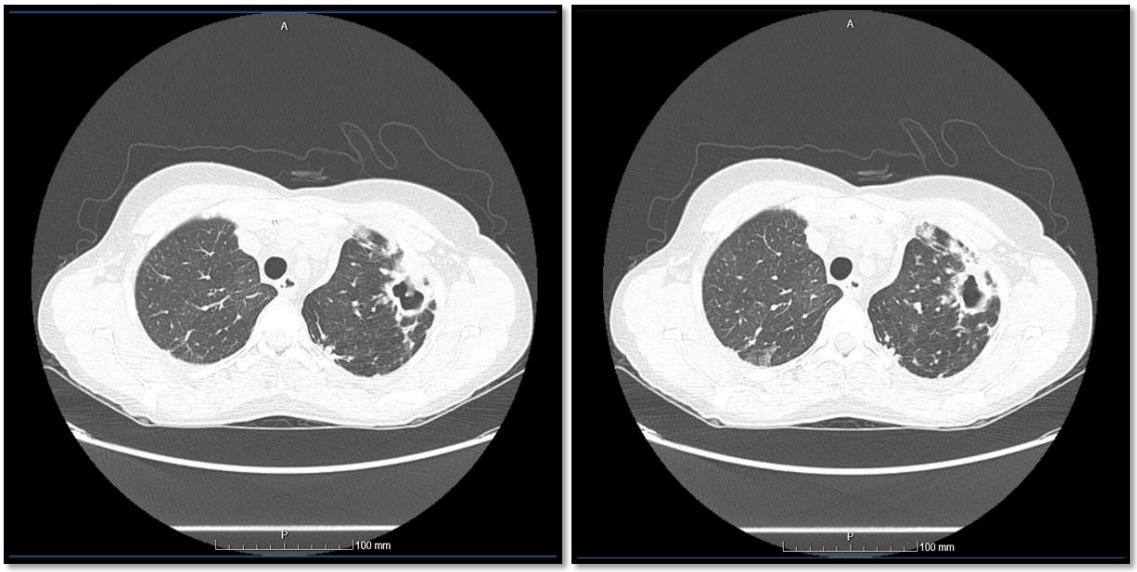

Figure 1- Thoracic computed tomography angiography (27th October 2018) showing a cavitation in the upper left lobe.

She reported persistent productive cough with mucopurulent sputum, during the past 4 months.

The analytic studies on the 29th October 2018, showed no leucocytosis, but lymphopenia (11.1% of total leucocytes, 0.87x10³µ/L) was present. Abnormal values included: mean platelet volume 10.8fL and platelet distribution width 12.1 GSD. Prothrombin time was 33.8 sec and activated partial thromboplastin time 45.0 sec.

Two samples were collected for sputum smear at the 29th and 30th of October. The results of the first sputum smear were negative for acid-fast bacilli by direct observation but the cultures were positive in Lowenstein Jensen (LJ) and liquid media, using Automated Blood

Culture System (BACTEC). A second sputum smear detected acid-fast bacilli by direct observation 1 to 10 *per field* and the cultures remained positive. Polymerase chain reaction (PCR) for the *Mycobacterium* tuberculosis complex was negative in both.

The patient did a bronchofibroscopy at the 31st of October that showed slip shaped bronchial stenosis distal to the level of the left b4b5 spur of cicatricial appearance and mucoceles. Bronchial aspirates results matched the first sputum smear.

On the 31st October 2018, the patient was referred to CDP. At admission, the patient had good general condition. Her Body Mass Index (BMI) was 21.7 kg/m^2.

Her medical history included pulmonary tuberculosis, bronchial asthma, rhinosinusitis, hypothyroidism, pulmonary hypertension type 4 (since 2012) and cardiac failure (New York Heart Association class III).

Pulmonary tuberculosis was suspected at 14 years old because of a typical clinical presentation. Acid-fast bacilli detection were positive. Chest X-ray showed unspecific alterations in the upper left lobe. Treatment was successful.

Surgical history included a cardiac catheterization in 2012 because of progressive dyspnoea for minor activities and fatigue. It showed a mean pulmonary arterial pressure (mPAP) of 67mmHg at rest, mean right atrium pressure of 7mmHg and pulmonary vascular resistance of 23 dynes-sec-cm^{-5}. Computed tomography angiography showed stenosis in the pulmonary arteries and poor distal perfusion in all pulmonary lobes. Pulmonary endarterectomy was done in 2013 in Paris.

Allergy history includes esomeprazole and penicillin and inhaled allergens as dust mite, pollen and horse hair presenting symptoms suggestive of allergic bronchial asthma. She denies past transfusions.

Pulmonary function tests on the 22nd June 2016 showed an obstructive ventilatory pattern not reversible with bronchodilators, normal pulmonary volumes and a diminished diffusing capacity for carbon monoxide (DLCO). Maximum inspiratory pressure was decreased. Respiratory alkalosis at rest is present, as shows Table 1.

Table 1 - Pulmonary function tests

22/06/2016	**Ref**	**Pre**	**Pre % Ref**	**Post**	**Post % Ref**	**LLN**
Spirometry						
FVC [L]	3.28	2.91	88.7	2.82	86.0	2.57
FEV 1 [L]	2.82	1.93	68.4	1.90	67.5	2.19
FEV 1 % VC max [%]	80.74	63.15	78.2	65.45	81.1	70.06
FEV 1 % FVC [%]		66.32		67.49		
MEF 75 [L/s]	5.81	2.68	46.2	3.02	52.0	3.60
MEF 50 [L/s]	4.10	1.31	32.0	1.38	33.6	2.30
MEF 25 [L/s]	1.74	0.36	20.7	0.39	22.4	0.61
PEF [L/s]	6.64	5.01	75.4	5.25	79.0	5.17
Pulmonary volumes						
VC max [L]	3.35	3.05	91.1			
TLC-He [L]	5.10	4.40	86.2			
RV-He [L]	1.69	1.35	79.6			
FRC-He [L]	2.74	3.08	112.6			
ERV [L]	1.05	1.74	165.7			
IC [L]	2.30	1.31	57.0			
DLCO [mL/min/mmHg]	25.68	14.87	57.9			
VA [L]	4.95	4.25	85.8			

Arterial Gasometry	**FiO2**	**pH**	**PaCO2**	**PaO2**	**$HCO3^-$**	**BE**	**SaO2**
	0.21	7.51	31.20	90.60	24.30	2.00	97.70

Ref: reference value, Pre: Pre-bronchodilator, Post: Post-bronchodilator, LLN: Lower Limits of Normal, FEV: Forced Expiratory Volume, FEV1: Forced Expiratory Volume in 1 second, MEF: Maximal instantaneous forced Expiratory Flow, PEF: Peak Expiratory Flow, VC: Vital Capacity, TLC-He: Total Lung Capacity by Helium dilution, FRC-He: Functional Residual Capacity by Helium dilution, RV-He: Residual Volume by Helium dilution, FRC-He: Functional Residual Capacity by Helium dilution, ERV: Expiratory Reserve Volume, IC: Inspiratory Capacity, DLCO: Diffusing Lung Capacity for Carbon Monoxide, VA: Alveolar Volume, FiO2: Fraction of inspired oxygen, PaCO2: Partial pressure of

Carbon dioxide, PaO2: Partial pressure of oxygen, $HCO3^-$: bicarbonate, BE: Base Excess, SaO2: Oxygen Saturation;

Her medication included aclidinium/formoterol fumarate dihydrate inhaled 340 µg/dose + 12 µg/dose twice-a-day, and ambrisentane 5mg, furosemide 20mg, spironolactone 25mg, warfarin 5mg, amiodarone 200mg and levothyroxine 100mg, once-a-day. Past medication history included oral contraception and salbutamol 5mg/ml.

Family history was unremarkable.

She had an history of cigarette smoking 2 pack-year and denied alcohol or drug use. Epidemiological context showed no exposures to animals, contaminated water or infected contacts.

At the admission at CDP, standard treatment with 4-drug regimen (pyrazinamide 1500 mg/day, rifampicin 600 mg/day, ethambutol 1200 mg/day and isoniazid 300 mg/day associated with pyridoxine 40 mg/day) was initiated. Full blood count, renal and liver function tests and uric acid dosing at November 5st and showed no alterations except from hyperuricemia (11.8mg/dl, reference value <7mg/dl).

On the 13th of November of 2018, *Mycobacterium kansasii* was identified by nucleic acid amplification test. Treatment was changed to isoniazid (300 mg/day), rifampicin (600 mg/day) and ethambutol (1200 mg/day) associated with pyridoxine (40 mg/day). Susceptibility testing showed no resistances. Chest X-ray is shown in figure 2.

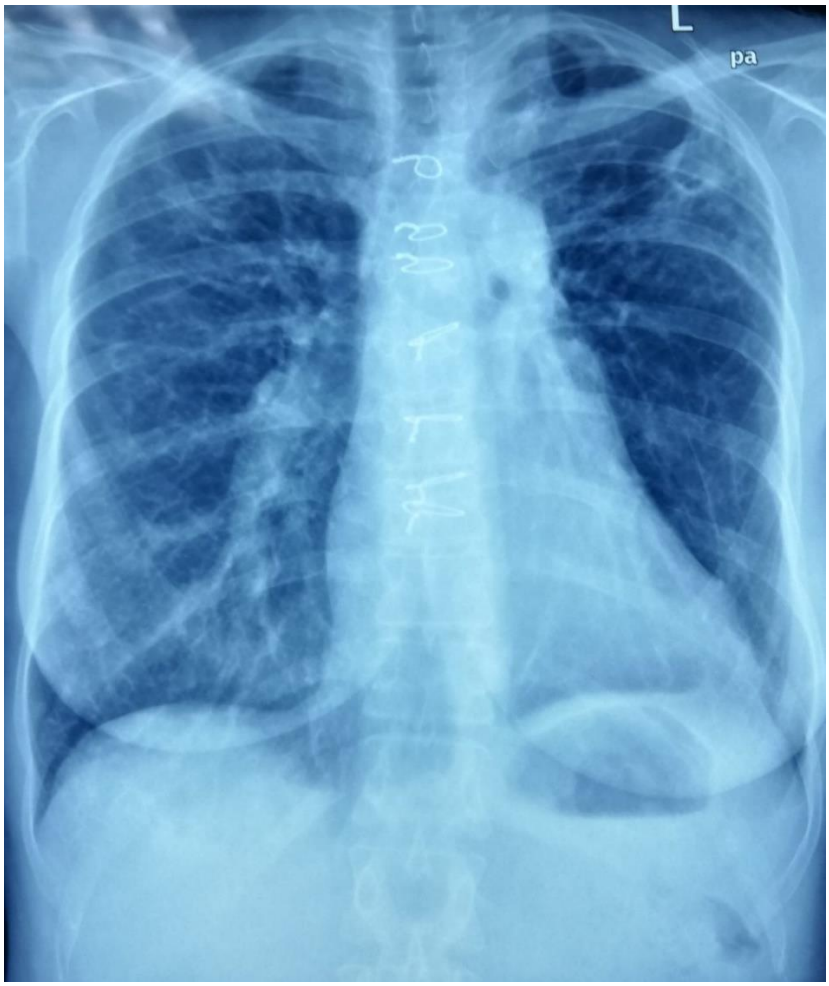

Figure 2 – Chest X-ray (13th of November of 2018) shows prominent bilateral hilar and perihilar bronchovascular markings and residual fibrosis in upper left lobe with a cavitation of 3 centimetres. The cardiothoracic ratio is increased.

Follow up included clinical state assessment, blood tests, chest X-ray and sputum smear every 2 months.

The patient reported myalgias and somnolence in the first month of treatment and an episode of haemoptysis (50 ml of bright red with cloths) that resolved spontaneously. Paraesthesia in both arms were reported and relieved by doubling of pyridoxine's dose.

Bacilloscopy and the cavitation on the X-ray showed complete resolution in October 2019. The patient remains in this follow up and treatment regimen until May of 2020.

DISCUSSION

Mycobacterium kansasii is a nontuberculous bacteria and its pulmonary infection incidence is currently rising (1). The infection occurs mainly in risk groups such as patients with underlying pulmonary comorbidities, such as smoking, chronic obstructive pulmonary disease, bronchiectasis (2-3%) (6), cystic fibrosis (3%) (7) and prior or concurrent Mycobacterium tuberculosis infection (2%) (1,4,8).

Prior tuberculosis is a risk factor found in our patient. Since cavitary NTM pulmonary disease is radiographically and clinically indistinguishable from pulmonary tuberculosis it may lead to misdiagnosis (8). Radiological findings at the time were present in the upper left lobe but no cavity was described.

In a report of 37 patients: 9 (24%) patients were smokers, 11 (30%) were ex-smokers and 14 (38%) were non-smokers (9) supporting the data for considering smoking history a risk factor also present in our case.

Other common comorbidities include alcohol abuse, Human Immunodeficiency Virus (HIV) and malignancies (1). Alcohol abuse or malignancies were not reported in our patient.

Mycobacterium kansasii is the second most common NTM in the Acquired Immunodeficiency Syndrome (AIDS) population (10). The infection is present around an average CD4 count of $<50/mm^3$ (1,10). The majority of patients developed pulmonary disease, with the second most common presentation being disseminated infection (10), more common in severe immunosuppression and it is an AIDS-defining diagnosis (1). Meningitis, cutaneous and oral manifestations were reported (10). It is an important limitation of our case that HIV was not tested.

Asthma and pulmonary hypertension have important pathological features in common, including inflammation, smooth muscle contraction and remodelling (11). None of the two are considered risk factors for *Mycobacterium kansasii* infection. In fact, despite the reference to underlying pulmonary comorbidities as a risk factor, the association with asthma has not been described. A case-control study showed that the estimated prevalence of NTM infections among asthmatic patients was as high as 1.7% (2) in one study and 1.8% (5) in another. It seems that asthmatic patients seem to have a higher prevalence of NTM infections specially if older, with severe airflow limitation and treated with higher doses of inhaled corticosteroids (5). In this case the patient is asthmatic but without present or past inhaled corticoid therapy.

Pulmonary hypertension was not yet recognized as a risk factor but the incidence of NTM disease in patients with pulmonary hypertension (estimated at 3.5%) being identical to in

other chronic pulmonary diseases that are considered to be risk groups (4). This occurs mainly in lower BMI patients and in hypoperfused lung areas: in obstructed pulmonary artery segments (38.5%) and cavities located in the non-perfused segments (12). Presentation consists of productive cough and new pulmonary infiltrate with cavitation, as in our case, and NTM infection should be suspected (4). Our case was diagnosed with chronic thromboembolic pulmonary hypertension (mPAP of 67mmHg) but no low BMI was present. Distal perfusion of all pulmonary lobes was poor, overlapping the location of the cavitation.

The diagnosis is set upon clinical and radiological findings, positive isolations and cultures. Bacilloscopy's sensitivity is low and it fails in 50% of suspicious cases, particularly if small bacillary load. Sputum culture is the standard diagnostic test (sensitivity of 70 to 90% and 100% specific) (13). Cultures should include solid and liquid media because the combination of BACTEC (liquid) and LJ (solid) gives a better positive culture yield (14). In NTM, BACTEC and LJ media detect 88 and 64%, respectively. The contamination rate is significantly higher in BACTEC (5%) than in LJ media (3.3%) (15).

Multiplex polymerase chain reaction system using mycobacterial strains is an auxiliary tool in the differential diagnosis of tuberculosis and NTM and a valuable tool in reducing the time necessary to make clinical diagnoses and begin treatment. In a total of 32.5% of the samples in multiplex PCR exhibit a molecular pattern consistent with NTM, thus disagreeing with the previous diagnosis (16). The negative bacilloscopy in the first sputum smear analysis in our case, may be explained due to its low sensitivity.

Routine susceptibility testing of *Mycobacterium kansasii* isolates is recommended (for rifampicin only) (14) and no resistances were detected.

The positive points were that early empirical treatment was initiated for the most probable pathogen, *Mycobacterium tuberculosis*, and later adapted to the results of nucleic acid amplification as recommended. The main limitation, besides no HIV testing, is the low sensitivity of bacilloscopy (13) that in our case showed to be a confounding factor.

CONCLUSION

In conclusion, the incidence of nontuberculous bacteria, a class of atypical bacteria is rising and it must be considered in all patients with risk factors in our clinical practice. The use of the correct diagnosis methods associated with a clinical awareness will contribute to the early treatment of every patient.

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REFERENCES

1. Johnston JC, Chiang L, Elwood K. Mycobacterium kansasii. Microbiol Spectr. 2017;5(1).

2. Fritscher LG, Marras TK, Bradi AC, Fritscher CC, Balter MS, Chapman KR. Nontuberculous mycobacterial infection as a cause of difficult-to-control asthma: a case-control study. Chest. 2011;139(1):23-7.

3. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society Guideline for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). BMJ Open Respir Res. 2017;4(1):e000242.

4. Wilinska E, Oniszh K, Augustynowicz-Kopec E, Zabost A, Fijalkowska A, Kurzyna M, et al. Non-tuberculous mycobacterial lung disease (NT MLD) in patients with chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension. Pneumonol Alergol Pol. 2014;82(6):495-502.

5. Hojo M, Iikura M, Hirano S, Sugiyama H, Kobayashi N, Kudo K. Increased risk of nontuberculous mycobacterial infection in asthmatic patients using long-term inhaled corticosteroid therapy. Respirology. 2012;17(1):185-90.

6. Wickremasinghe M, Ozerovitch LJ, Davies G, Wodehouse T, Chadwick MV, Abdallah S, et al. Non-tuberculous mycobacteria in patients with bronchiectasis. Thorax. 2005;60(12):1045-51.

7. Olivier KN, Weber DJ, Wallace RJ Jr, Faiz AR, Lee JH, Zhang Y, et al. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med. 2003;167(6):828-34.

8. Yilmaz N, Ucar EY, Saglam L. Mycobacterium Tuberculosis and Nontuberculous Mycobacteria Coinfection of the Lungs. Turk Thorac J. 2017;18(1):23-6.

9. Chong SG, Kent BD, Fitzgerald S, et al. Pulmonary non-tuberculous mycobacteria in a general respiratory population. Ir Med J. 2014;107(7):207-9.

10. Procop GW. HIV and mycobacteria. Semin Diagn Pathol. 2017;34(4):332-9.

11. Said SI, Hamidi SA, Gonzalez Bosc L. Asthma and pulmonary arterial hypertension: do they share a key mechanism of pathogenesis? Eur Respir J. 2010;35(4):730-4.

12. Kuroda F, Tanabe N, Igari H, Sakurai T, Sakao S, Tada Y, et al. Nontuberculous mycobacterium diseases and chronic thromboembolic pulmonary hypertension. Intern Med. 2014;53(20):2273-9.

13. Malacarne J, Heirich AS, Cunha EAT, Kolte IV, Souza-Santos R, Basta PC. Performance of diagnostic tests for pulmonary tuberculosis in indigenous populations in Brazil: the contribution of Rapid Molecular Testing. J Bras Pneumol. 2019;45(2):e20180185.

14. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.

15. Anargyros P, Astill DS, Lim IS. Comparison of improved BACTEC and Lowenstein-Jensen media for culture of mycobacteria from clinical specimens. J Clin Microbiol. 1990;28(6):1288-91.

16. Lima AS, Duarte RS, Montenegro LM, et al. Rapid detection and differentiation of mycobacterial species using a multiplex PCR system. Rev Soc Bras Med Trop. 2013;46(4):447-52.

ATTACHMENTS

Centro de Diagnóstico Pneumológico de Coimbra

DECLARAÇÃO

Para os devidos efeitos se declara que a tese de mestrado da aluna de Medicina **Mariana Santos Pascoal**, realizada com base num caso clínico deste C.D.P., tem a nossa autorização.

Coimbra, 25 de Setembro de 2019

Paulo M. T. Cravo Roxo
MÉDICO PNEUMOLOGISTA
DIRECTOR INTERINO

ARS Centro, I.P.
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GOVERNO DE PORTUGAL
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ARSC ADMINISTRAÇÃO REGIONAL DE SAÚDE DO CENTRO, I.P.

COMISSÃO DE ÉTICA PARA A SAÚDE

PARECER FINAL: FAVORÁVEL	DESPACHO: Homologado 14/11/2019 Conselho Diretivo da A.R.S. do Centro, I.P.

ASSUNTO: Título: "*Mycobacterium kansasii* pulmonar disease in a patient with risk factors: Case Report " **(112/2019).**
Autores: Mariana Santos Pascoal (Trabalho Final do MIM-FMUC), Vitor Manuel Jorge Duque e Paulo Cravo Roxo

Dr. [illegible] Presidente,

Dr. João Rodrigues Vice-Presidente,

Dr. Luís Milhão Cabral Vogal

O objetivo deste trabalho é a divulgação para a comunidade médica de um caso clínico de um doente com infeção pulmonar por *Mycobacterium kansasii* com fatores de risco para a infeção .
Foi enviado o projeto, constituído pela história clínica, os curricula dos autores, a autorização do serviço e o consentimento informado.
Tendo em atenção que se trata de diagnóstico próprio da atividade médica e que há consentimento informado da doente para a publicação do caso, não temos objeções éticas.

Coimbra, 11 de novembro de 2019

O Relator e Presidente da Comissão de Ética da ARS do Centro

Prof. Doutor Carlos Alberto Fontes Ribeiro