Micobatteriosi da Micobatteri Non Tubercolari

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SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

RegioneEmilia-Romagna

Corso di aggiornamento

Tubercolosi: un impegno globale

Nontuberculous mycobacteria (NTM)

- Over 190 species and subspecies (availability of gene sequencing has improved taxonomy of mycobacteria).
- They can affect both pulmonary and extrapulmonary sites.
- Only a small number appear to cause pulmonary disease in humans.
- The pathogenicity varies significantly from organisms like M.gordonae, which rarely cause disease in humans, to M. kansasii, which should usually be considered pathogenic.

Slowly growing	Rapidly growing
Mycobacterium avium complex (twelve separate species; *M. avium, M. intracellulare, M. chimaera)*	*Mycobacterium abscessus*
Mycobacterium kansasii	
Mycobacterium xenopi	

Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous micobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis 2020; 71: 905-13.

Spectrum of Mycobacterial Infections

- Silent colonization: isolation of the organisms from the respiratory tract without evidence of tissue invasion.
  - Pathogen-related factors
    - NTM-specific virulence
    - bacterial load
    - exposure
  - Patient's related factors
    - patient's immune status
    - pre-existing anatomical changes
    - comorbidities
- Pulmonary disease

Faverio et al. Non tuberculous mycobacterial pulmonary disease: an integrated approach beyond antibiotics. ERJ Open Res 2021; 7:00574-2020.

Nontubeculous mycobacteria Pulmonary Disease (NTM-PD)

TABLE 2 Clinical and microbiologic criteria for diagnosis of nontuberculous mycobacterial pulmonary disease[#]

Clinical	Pulmonary or systemic symptoms	***Both clinical and radiologic criteria required***
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules	
And	Appropriate exclusion of other diagnoses	
Microbiologic[¶]	1) Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures	
	or	
	2) Positive culture results from at least one bronchial wash or lavage	
	or	
	3) Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM	

Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007; 175: 367–416

Incidence and prevalence

- Prevalence is 6,5 per 100.000 in European countries.
- Incidence and prevalence are increasing due to:
  - increased surveillance and better access to diagnostic techniques;
  - Increased immune suppression;
  - Rising multimorbidity.
- Five-year mortality 27%.

Risk factors

- Exposure
- Patient’s related factors

Exposure

- NTM are ubiquitous environmental organisms, commonly found in soil and water biofilms.
- NTM infection can be acquired through inhalation of aerosolized droptlets containing NTM, from natural surface or hot water systems
- Activities potentially increasing domestic, occupational or recreational exposure are:
  - Swimming
  - Gardening, mining, agriculture
  - Showering, hot tubes
  - Natural disasters

Faverio et al. Non tuberculous mycobacterial pulmonary disease: an integrated approach beyond antibiotics. ERJ Open Res 2021; 7:00574-2020.

Patient's related factors

- Pre-existing lung diseases;
- Demographic and constitutional factors (Lady Windermere syndrome);
- Defective immunity (primary and acquired immunodeficiency, medications).

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Patient's related factors

- Pre-existing lung diseases;
- Demographic and constitutional factors (Lady Windermere syndrome, GERD, low vit D);
- Defective immunity (primary and acquired immunodeficiency, medications).

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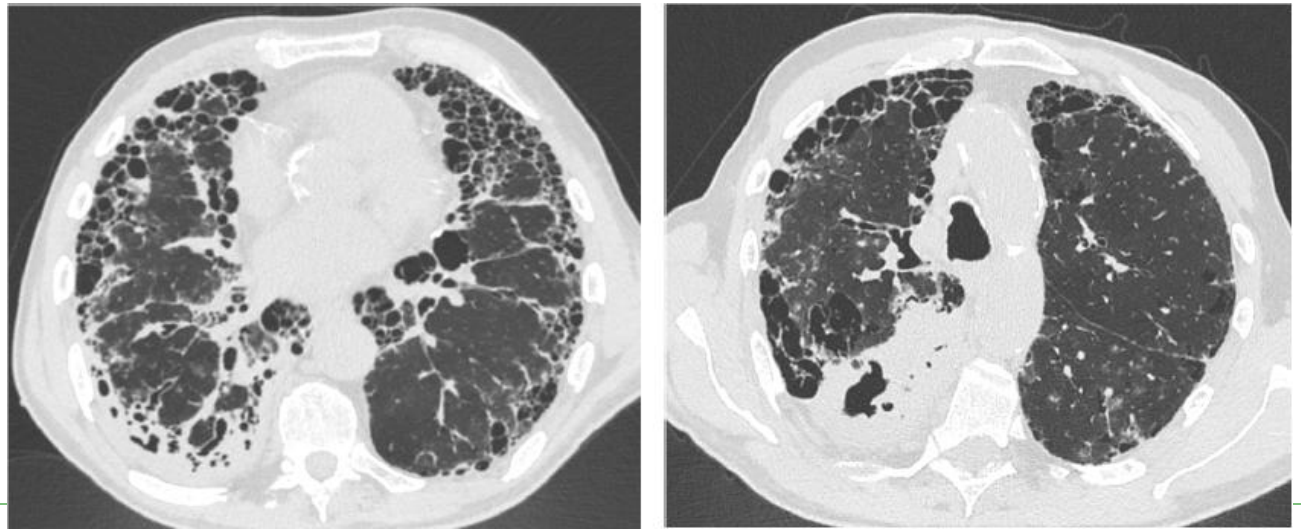
Patient's related factors

- Pre-existing lung diseases;
  - CF
  - Non-CF bronchiectasis
  - Primary ciliary dyskinesia
  - Previous pulmonary tuberculosis
  - Asthma
  - COPD
  - Alpha-1-antitrypsin deficiency
  - Pneumoconiosis (silicosis)
  - Interstitial lung diseases
  - ABPA

Faverio et al. Non tuberculous mycobacterial pulmonary disease: an integrated approach beyond antibiotics. ERJ Open Res 2021; 7:00574-2020.

Interstitial Lung Diseases

- Patients with **ILD** are prone to develop chronic pulmonary infections such as NTM-PD (immunosuppressive drugs and structural and anatomical changes such as honeycombing).
- Radiological and clinical findings of NTM-PD may mimic ILD key features, lung cancer or bacterial pneumonia (lobar or segmental consolidation with or without cavitation).
- Systematic screening for NTM or TB at the time of connective tissue disease diagnosis and meticulous follow-up.



Licata et al. Usual Interstitial Pneumonia Pattern and Mycobacteria Lung Disease: A Case series. Infect. Dis. Rep. 2025, 17, 28.

Patient's related factors

- Pre-existing lung diseases;
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Lady Windermere Syndrome

Specific phenotype "Lady Windermere Syndrome".

- M. avium-PD
- Middle-aged, white, thin, tall, non-immunocompromised women without predisposing pulmonary disease
- Pectus escavatum
- Mitral valve prolapse
- Chronic productive cough
- lingula/middle lobe bronchiectasis

-(Voluntary cough suppression)

-Minor mutations in the cystic fibrosis transmembrane conductance regulator CFTR gene

Reich et al. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The lady Windermere syndrome. Chest 1992: 101: 1605-9.

Patient's related factors

- Pre-existing lung diseases;
- Demographic and constitutional factors (Lady Windermere syndrome);
- Defective immunity (primary and acquired immunodeficiency).

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Defective immunity

- Primary immunodeficiencies: eg. common variable immunodeficiency;
- Acquired immunodeficiencies: HIV, chronic renal failure, diabetes mellitus, inhaled and oral corticosteroids, TNF-alpha antagonists, immunosuppressive treatments for transplantation, chemotherapies.

Clinical data

- Paucisymptomatic
- Chronic symptoms: cough, sputum production, chronic fatigue, weight loss, haemoptysis, fever.

Faverio et al. Non tuberculous mycobacterial pulmonary disease: an integrated approach beyond antibiotics. ERJ Open Res 2021; 7:00574-2020.

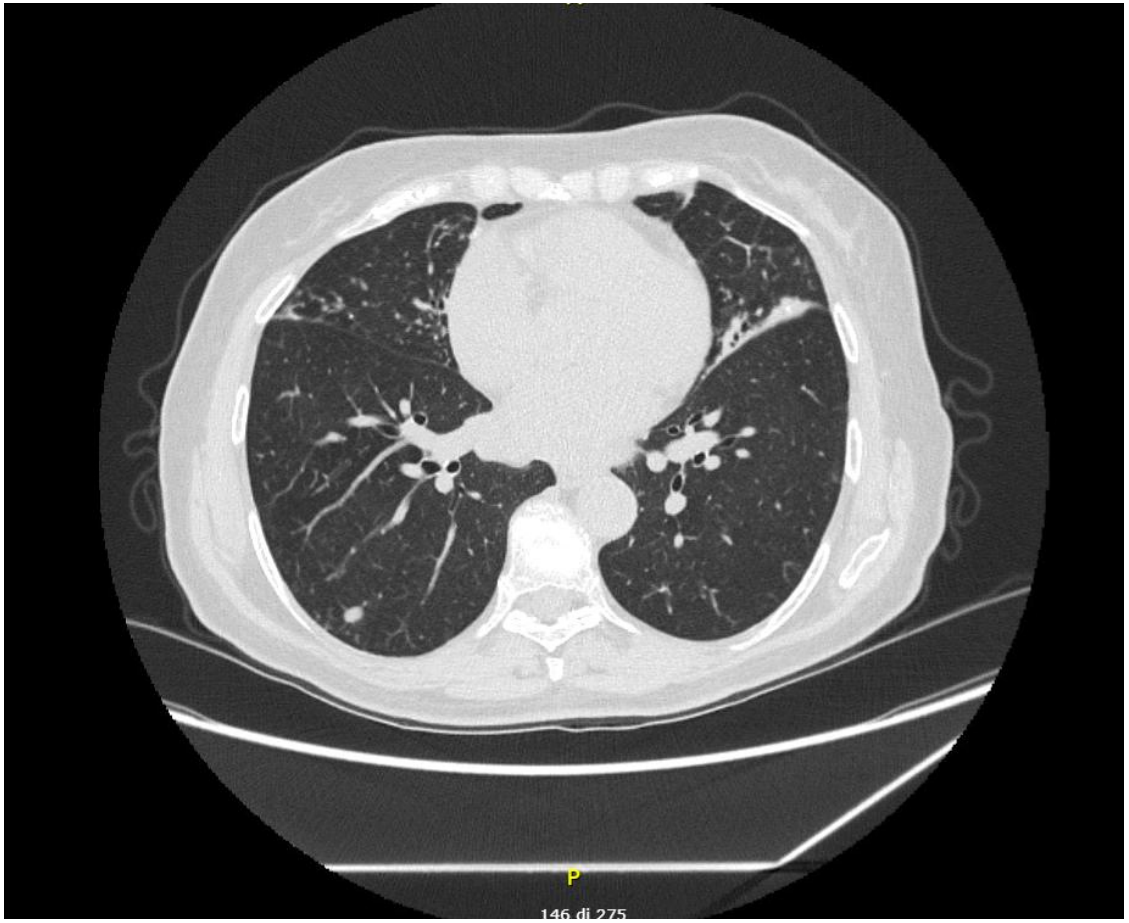
Radiographic data

- Computed tomography (CT) is the method of choice for radiological evaluation of NTM-PD.
- Two different forms:
  - the **nodular-bronchiectatic form:** middle-aged women; nodules, bronchiectasis, branching centrilobular nodules in the middle lobe and lingula (but even in other lobes);
  - the **fibrocavitary form:** men with previous lung disease; heterogeneous nodular and cavitary opacities in the upper lobes, volume loss, pleural thickening.

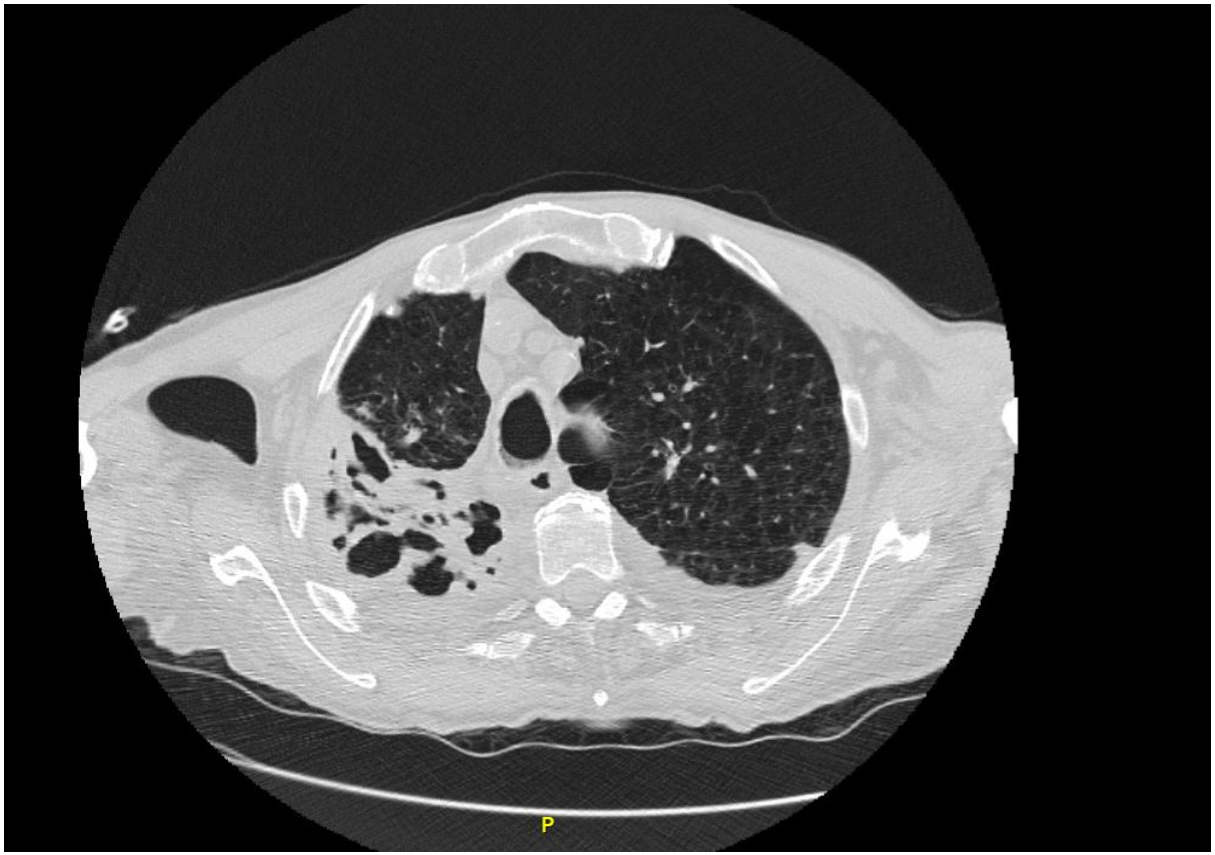
Griffith DE, Aksamit T, Brown-Elliott BA et al (2007) An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367–416.

Dettmer S, Ringshausen FC, Fuge J et al (2021) Computed tomography in adults with bronchiectasis and nontuberculous mycobacterial pulmonary disease: typical imaging findings. J Clin Med 10:2736

nodular-bronchiectatic form



fibrocavitary form



Atypical radiological presentation

NTM-PD can manifest as solitary pulmonary nodule or mass (incidence 3,6%) without typical features of NTM-PD. DD with lung cancer.

- Incidental finding 79%; cough (14%); fever (7%); hemoptysis (0%).
- Normal white blood cell count, normal C-reactive protein.
- Poor contrast enhancement (75%).
- Internal calcification (43%).
- Peripheral location.
- Lobulated border (71%).
- Pleural retraction (28%).
- Strong FDG uptake in PET/CT images

Hong et al Non tuberculous mycobacterial pulmonary disease mimicking lung cancer Medicine (2016) 95: 26(e3978).

Atypical radiological presentation

- Culture of **sputum** or **bronchial washing fluid** can be falsely positive and doesn't exclude the possibility of concomitant lung cancer.
- Culture of **sputum** or **bronchial washing fluid** can be falsely negative (33%) (25-67%)
- **Percutaneous needle aspiration biopsy** (PCNB):
  - mycobacterial istology (chronic granulomatous inflammation with or without necrosis) 55%, acid fast bacilli of NTM species (9%)
  - Positive culture (63%)
- **Surgical biopsy**
  - Myocobacterial istology (chronic granulomatous inflammation with or without necrosis) 100%

- *M. avium, M intracellulare, M. abscessus, M kansasii*

Hong et al. Non tuberculous mycobacterial pulmonary disease mimicking lung cancer. Medicine (2016) 95: 26(e3978).

Microbiological data

- Sputum
- Induced sputum
- Bronchoalveolar lavage
- Transbronchial biopsy/ Percutaneous needle aspiration biopsy
- Surgical biopsy

- Acid fast bacilli clusters
- Cultures

Bronchoalveolar Lavage (BAL)

- It can be directed to specific parts of the lung based on chest CT
- BAL facilitates the diagnosis of NTM-PD since many patients are not able to produce valid respiratory samples for microbiological examination.
- Diagnostic yield of mycobacterial culture was 44% for IS and 95% for BAL (difference more statistically significant in nodular bronchiectatic form)
- Complication of BAL 0-2,3%

[Stanzel. Bronchoalveolar lavage. In Priciples and Practice of Interventional pulmonology; Springer: 2012; 165-176].

Licata et al. Clinical Utility of Induced Sputum and Bronchoalveolar Lavage Cultures in diagnosing Nontuberculous Mycobacterial Pulmonary disease. Pathogens 2024, 13, 1064.

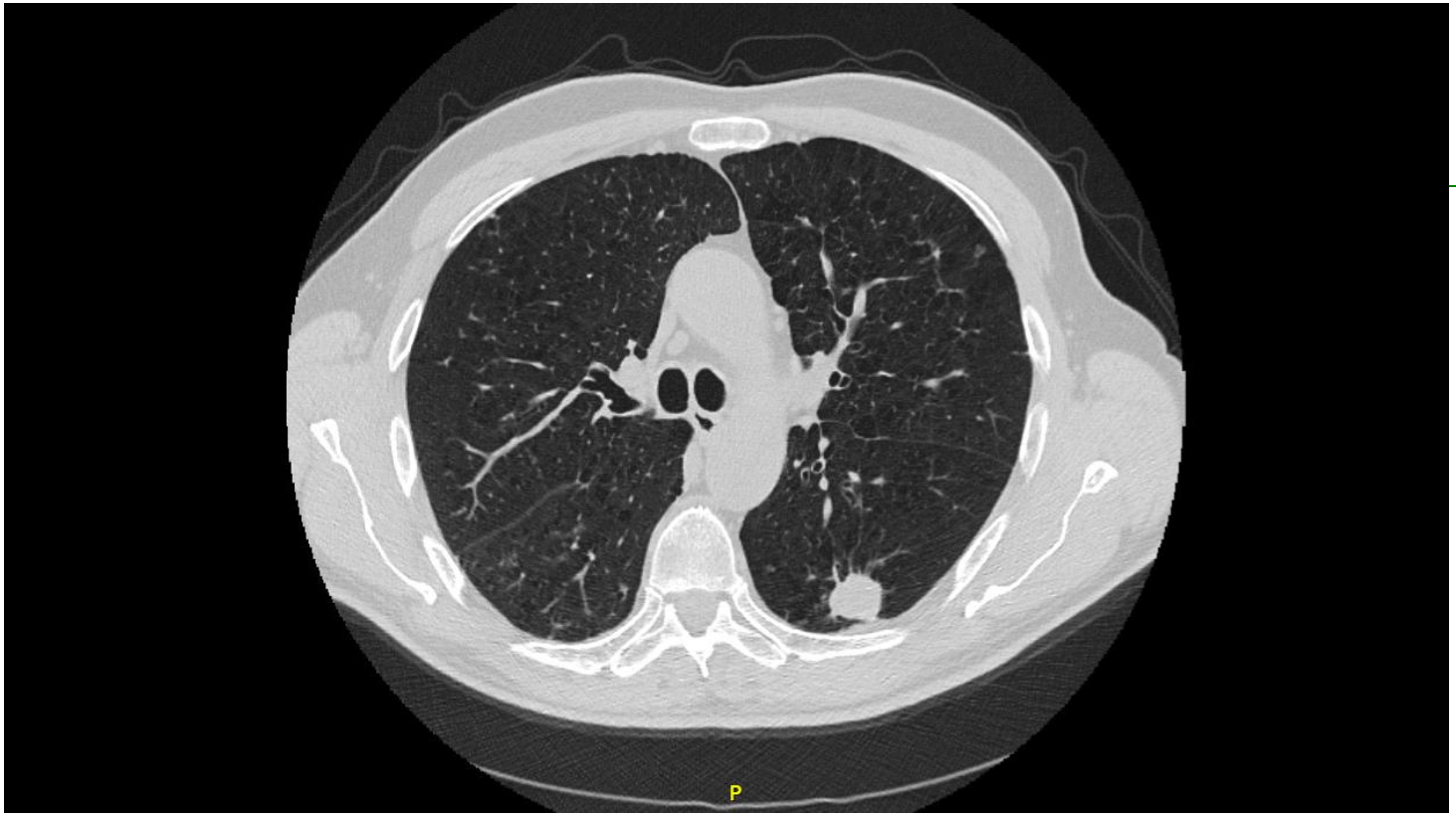
Biopsy

1. **Nodular bronchiectatic form**: bronchiectasis, branching centrilobular nodules in the lingular segment and in the right middle lobe (but even in other lobes)→ bronchiolectasis, bronchiolar and peribronchiolar inflammation with or without granuloma formation, some solid caseous materials within the terminal or respiratory bronchioles.
2. **Cavitary form**→large peribronchial caseating granulomas, extensive peribronchial infiltration of lymphocytes surrounding a dilated bronchus or a bronchiole; the wall of cavitary lesions consisted of caseosus materials, epithelioid cells with multinucleated giant cells, granulation tissue and a fibrous capsule.

Yeon et al. Nontuberculous Mycobacterial Pulmonary Infection in Immunocompetent Patients: Comparison of Thin-Section CT and Histopathologic Findings. Radiology 2004; 231: 880-6.

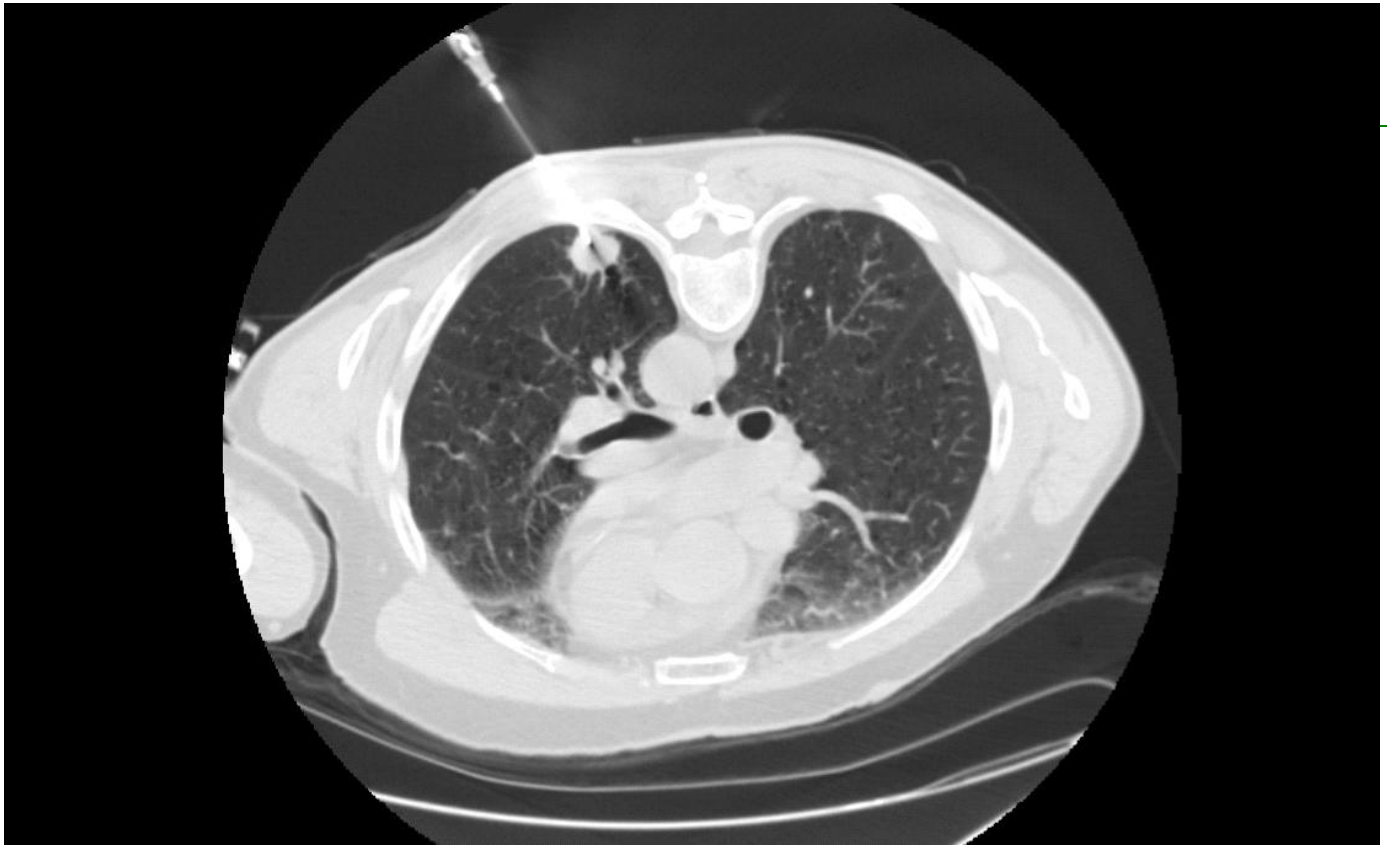
Case 1

- 72 years old man
- Former smoker, 13 years ago, 70 p/y
- Father with lung cancer
- Agent
- Past clinical-radiological diagnosis of Pulmonary Langerhans Cell Histiocytosis (significant improvement after smoking cessation)
- No symptoms
- Lab tests: normal CRP.
- PFTs: FEV1 98%, FVC 103%, IT 72%, DLCO 56%.



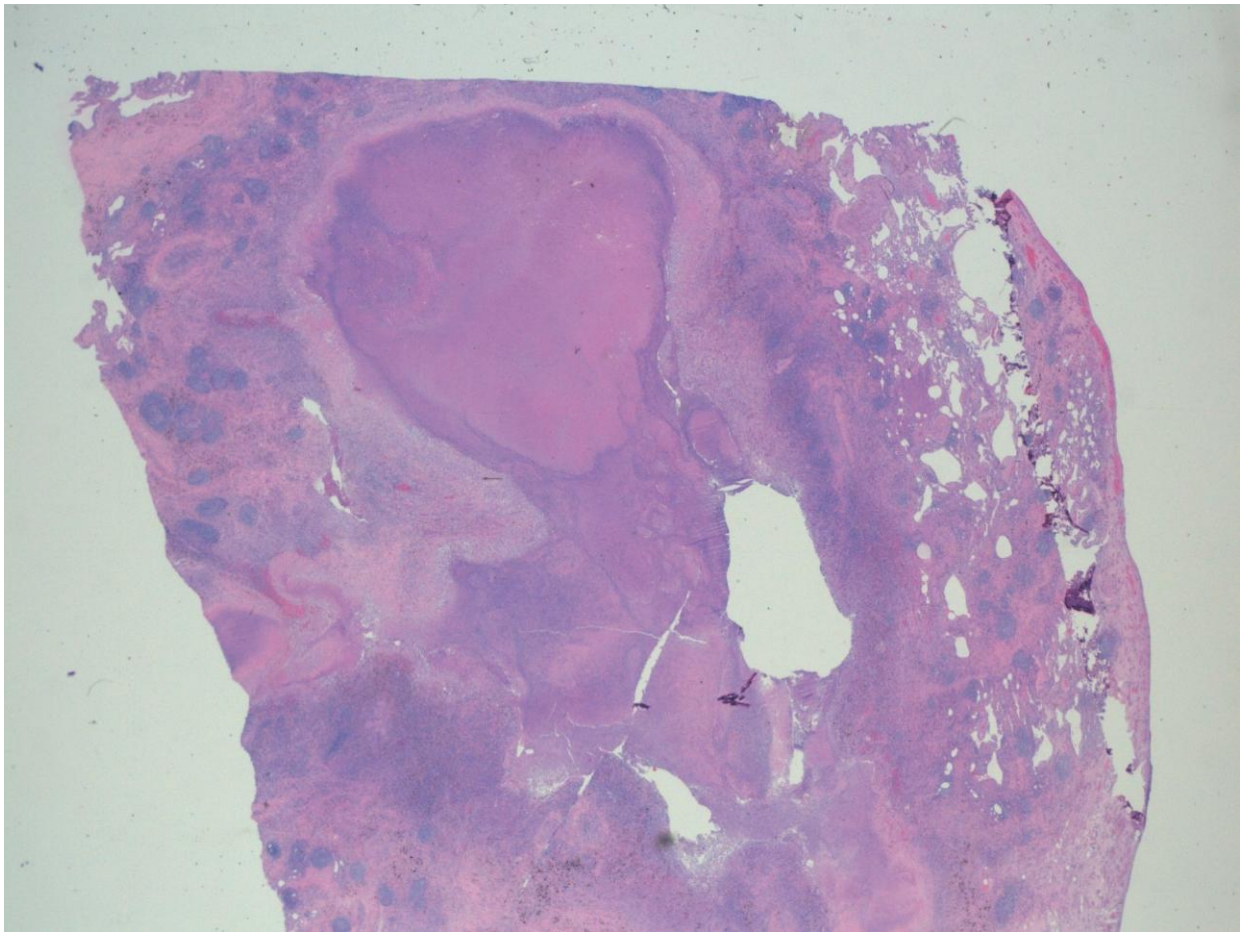
TBB: normal lung.

BL: negative.

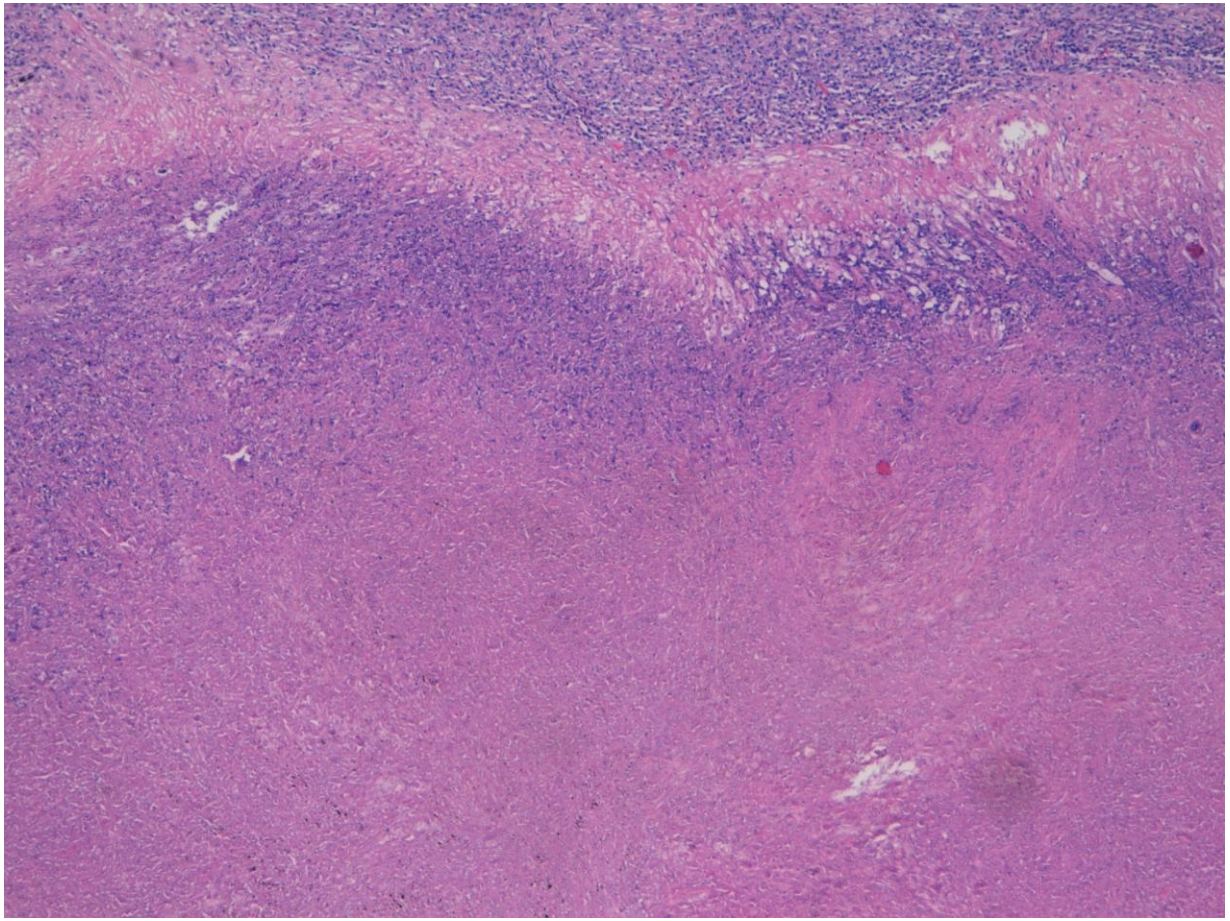


Necrosis.

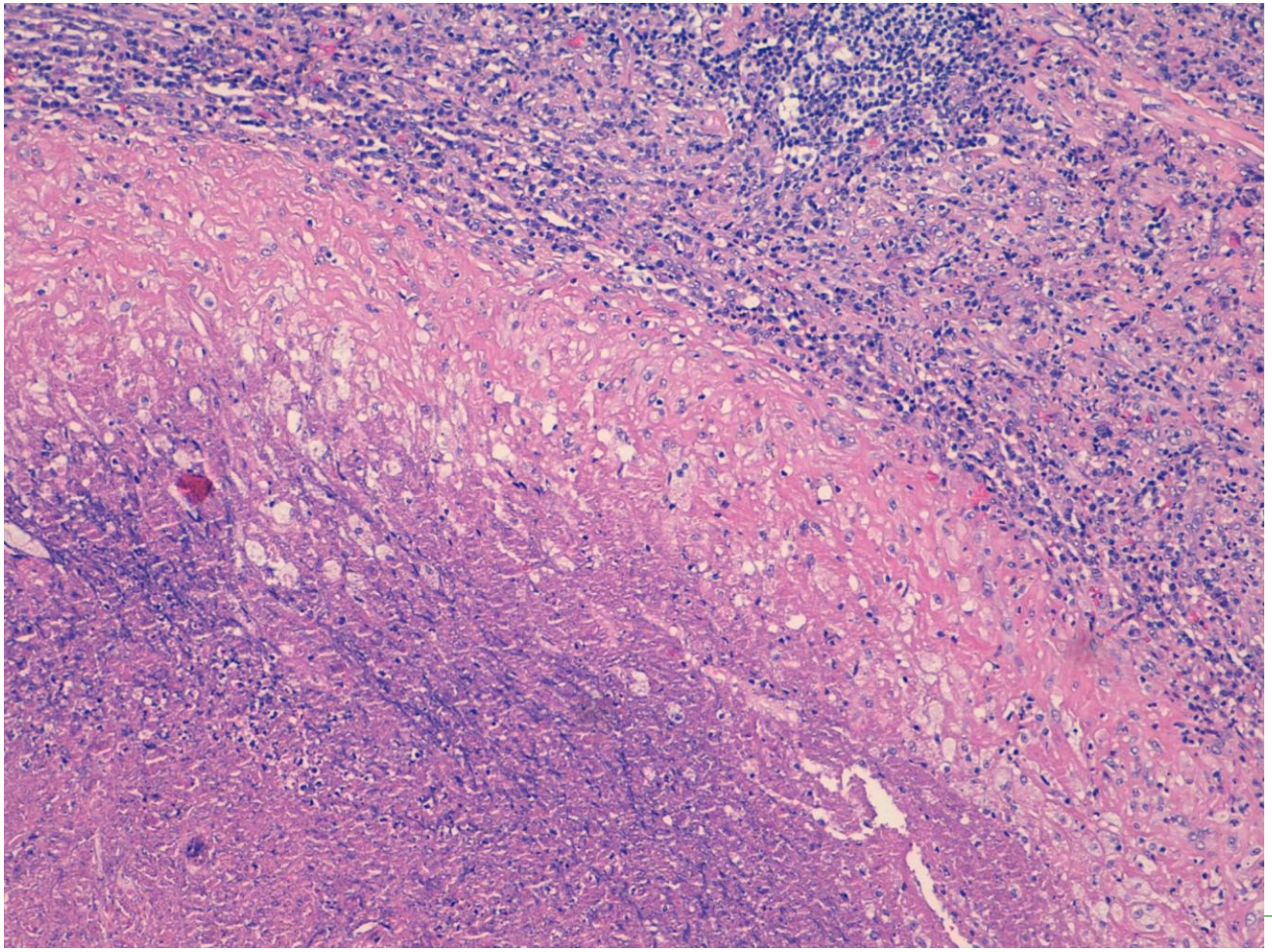
Surgical lung biopsy



Surgical lung biopsy



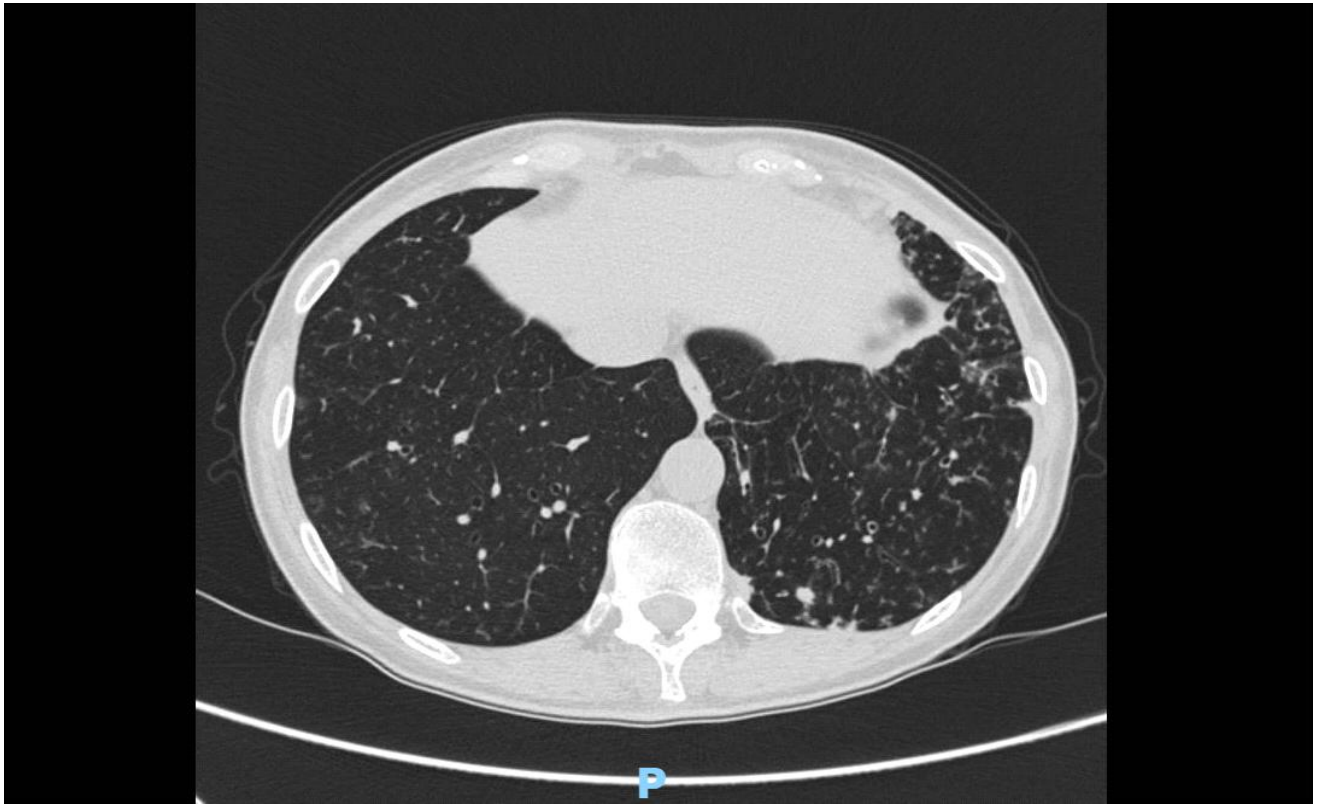
Surgical lung biopsy



Mycobacterium chimaera

Case 2

- 65 years old female
- Physiotherapist
- Never smoker
- Chronic non productive cough
- Lab tests: normal CRP.
- PFTs: normal spirometry, mild reduction of DLCO.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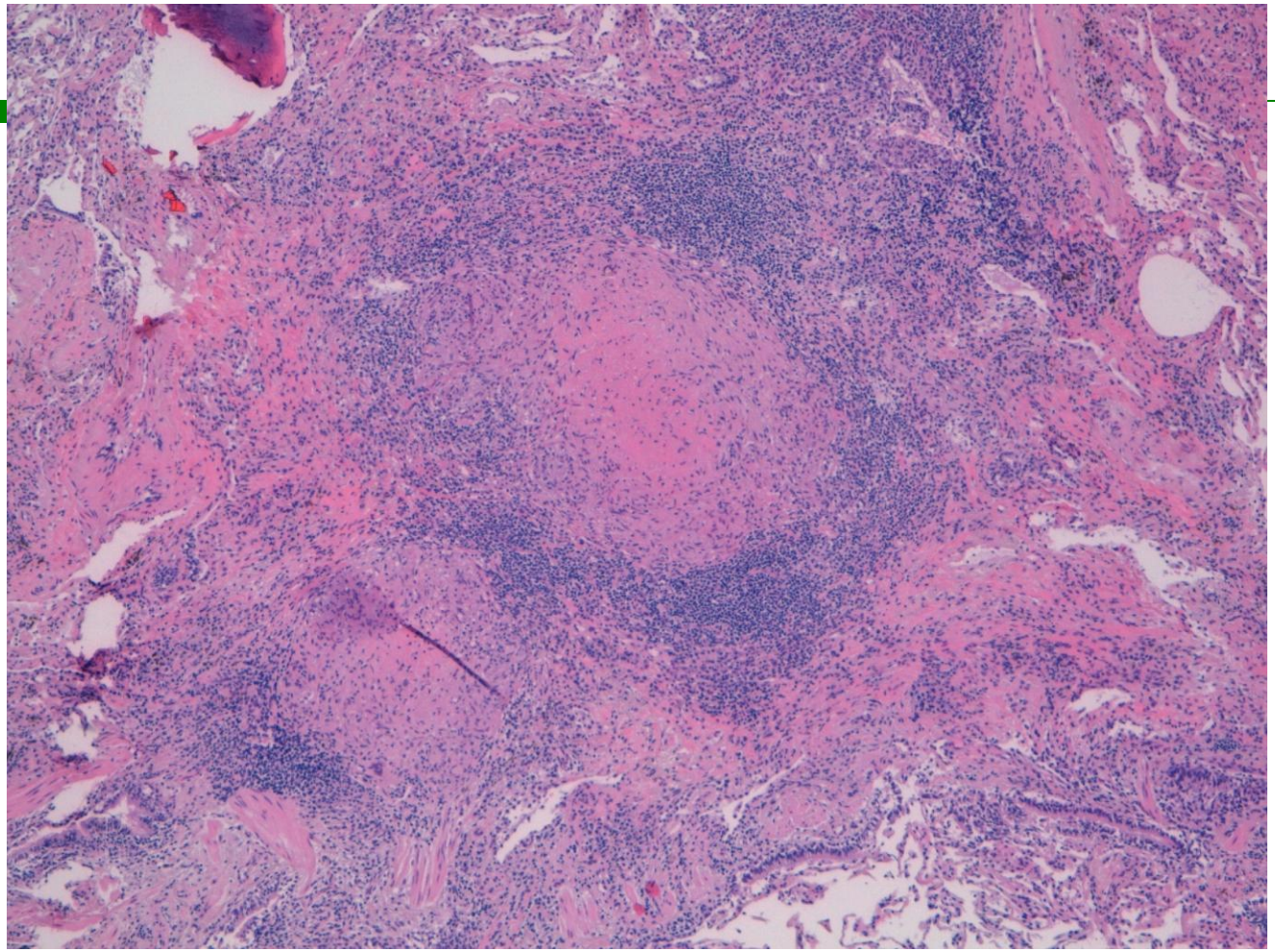

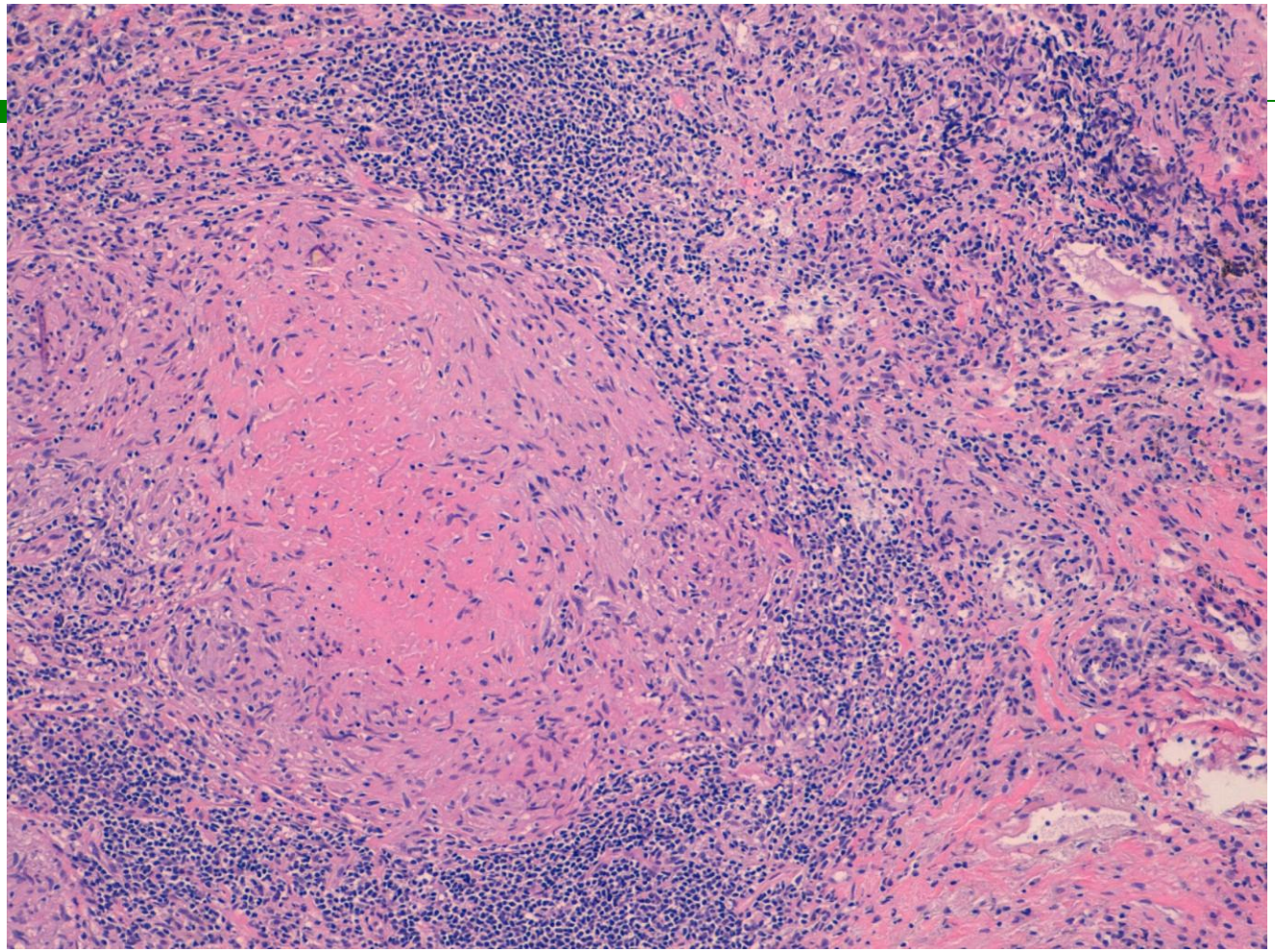

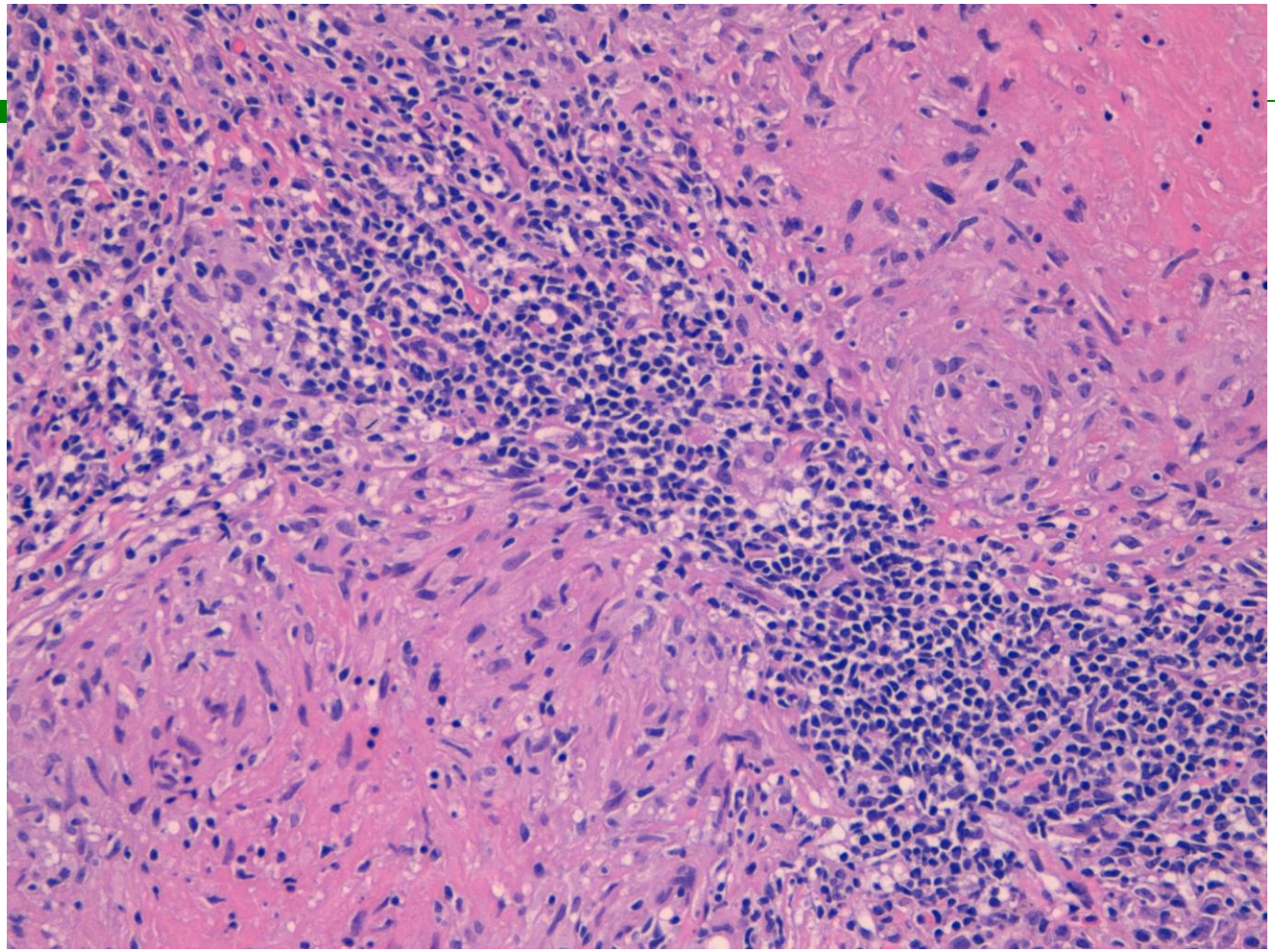

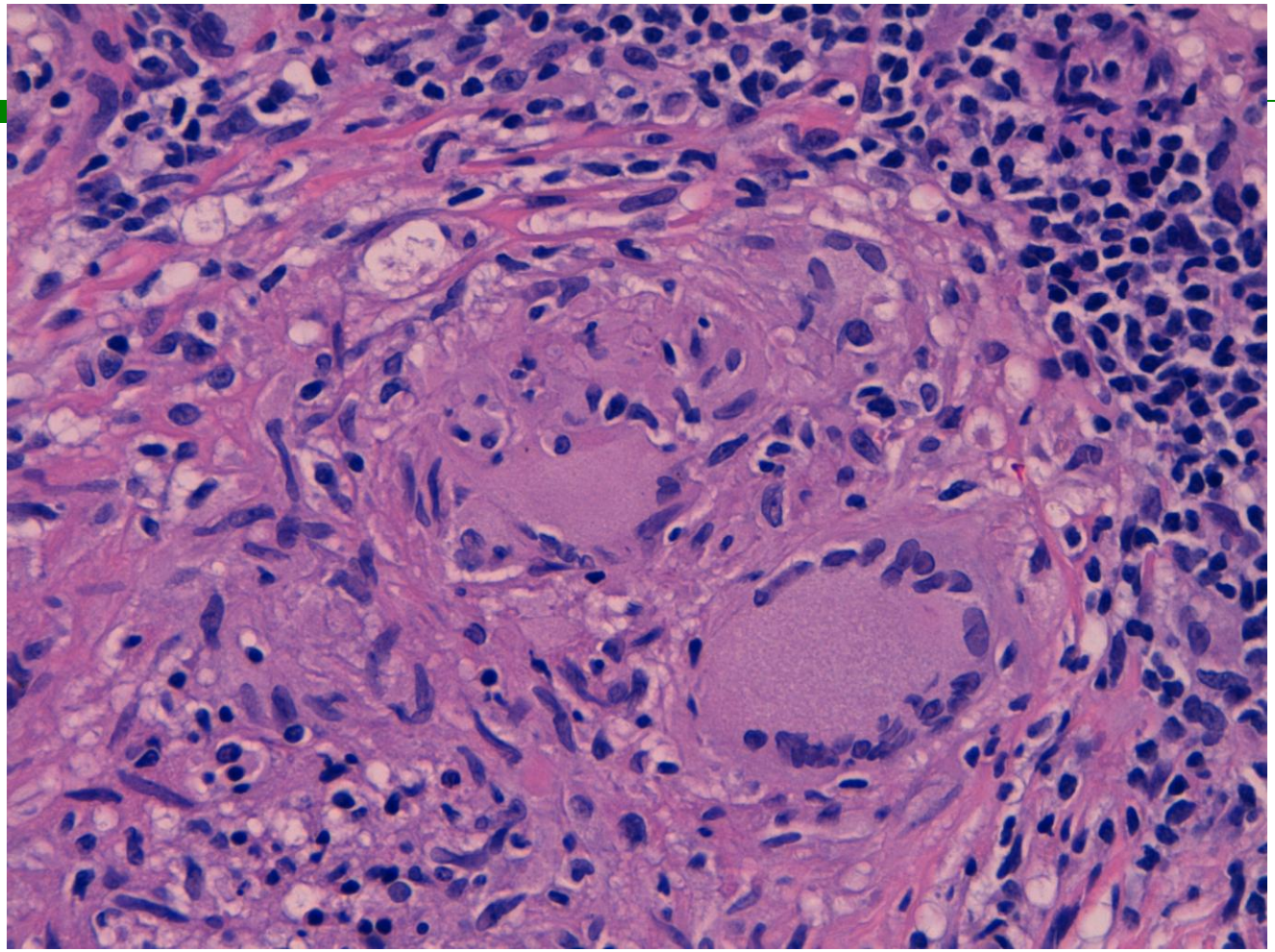

Mycobacterium avium.

Pharmacological Therapy

Treatment of NTM varies depending on factors that predict progressive NTM pulmonary disease:

- Species (M. kansasii)
- Acid-fast bacilli smear positive
- Extent of disease and fibrocavitary disease
- Major symptoms with decrease in quality of life
- Drug susceptibility results
- Underlying comorbidities (underlying immune suppression, low BMI, other therapies)

Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous micobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis 2020; 71: 905-13.

Recommended treatment regimens for Mycobacterium avium complex, M. kansasii, and M. xenopi pulmonary disease

TABLE 4 Recommended treatment regimens for *Mycobacterium avium* complex, *M. kansasii*, and *M. xenopi* pulmonary disease

Organism	Number of drugs	Preferred drug regimen[#]	Dosing frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin [clarithromycin] Rifampicin [rifabutin] Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin [clarithromycin] Rifampicin [rifabutin] Ethambutol Amikacin IV [streptomycin][¶]	Daily [3 times weekly may be used with aminoglycosides]
Refractory[*]	≥4	Azithromycin [clarithromycin] Rifampicin [rifabutin] Ethambutol Amikacin liposome inhalation suspension or amikacin IV [streptomycin][¶]	Daily [3 times weekly may be used with aminoglycosides]
M. kansasii			
	3	Azithromycin [clarithromycin] Rifampicin [rifabutin] Ethambutol	Daily
	3	Azithromycin [clarithromycin] Rifampicin [rifabutin] Ethambutol	3 times weekly
	3	Isoniazid Rifampicin [rifabutin] Ethambutol	Daily
M. xenopi			
	≥3	Azithromycin [clarithromycin] and/or moxifloxacin Rifampicin [rifabutin] Ethambutol Amikacin[¶]	Daily [3 times weekly may be used with aminoglycosides]

Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous micobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis 2020; 71: 905-13.

Treatment Monitoring

- **EFFICACY**
  - **Microbiological outcomes**
  - **Radiological outcomes**
  - **Clinical outcomes**
- **SAFETY**

Haworth et al. British Thoracic Society Guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 72, ii1-ii64 (2017).

Treatment Monitoring

Microbiological outcomes: sputum every 4-12 weeks during treatment and for 12 months after completing treatment. In individuals who are unable to expectorate sputum, a CT-scan followed by a CT directed bronchial wash after 6 and 12 months of treatment.

- **CULTURE CONVERSION**: three consecutive negative mycobacterial sputum cultures collected over a minimum of three months. In patients unable to expectorate sputum, a single negative mycobacterial culture of a CT directed bronchial wash is indicative of culture conversion.
- **RECURRENCE**: two positive mycobacterial cultures following culture conversion. If available, genotyping may help distinguish **RELAPSE** from **REINFECTION**.
- **REFRACTORY DISEASE**: failure to culture convert after 12 months of non-tuberculous mycobacterial treatment.

Haworth et al. British Thoracic Society Guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 72, ii1-ii64 (2017).

Treatment Monitoring

- **Radiological outcomes**: a CT-scan after 6 months and at the end of treatment.
  - Cavities, consolidations and bronchiolitis are useful to asses treatment response, whereas bronchiectasis and nodules may remain stable despite successful treatment.

    Dettmer at al. European radiology (2025) 35:798-805.

- **Clinical outcomes**: symptoms, BMI, spirometry, 6MWT, CRP.

Haworth et al. British Thoracic Society Guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 72, ii1-ii64 (2017).

Treatment Monitoring

SAFETY:

- Laboratory tests;
- audiometry;
- visual acuity and colour vision;
- ECG
- Terapeutic Drug Monitoring.

Haworth et al. British Thoracic Society Guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 72, ii1-ii64 (2017).

Non-Pharmacological Interventions

- Avoiding exposure
- Nutritional evaluation and intervention (supplementation of vitamin D deficiencies and specific nutritional assessment) + rehabilitative intervention (sarcopenia)
- Pulmonary rehabilitation, exercise training and respiratory physiotherapy (Airway clearance techniques ACTs)
- Management of comorbidities

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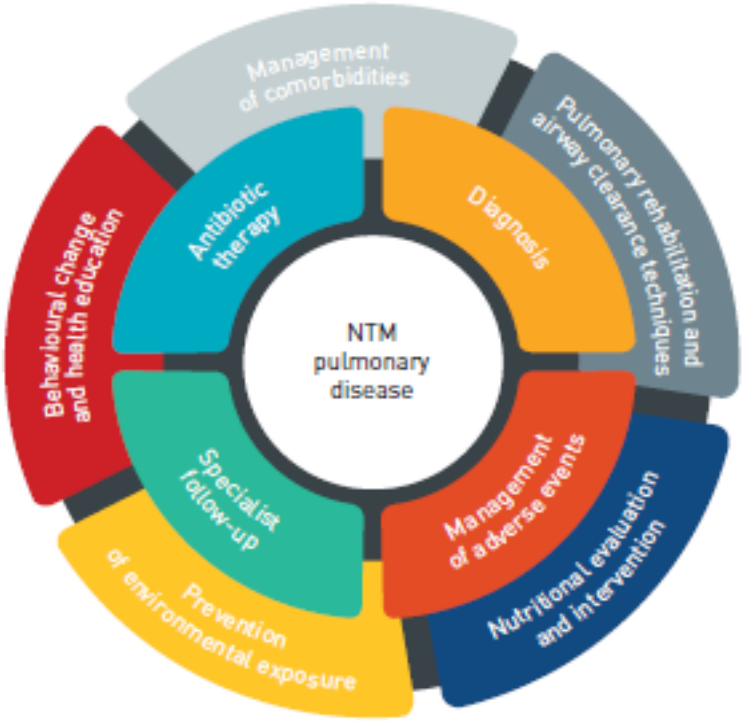
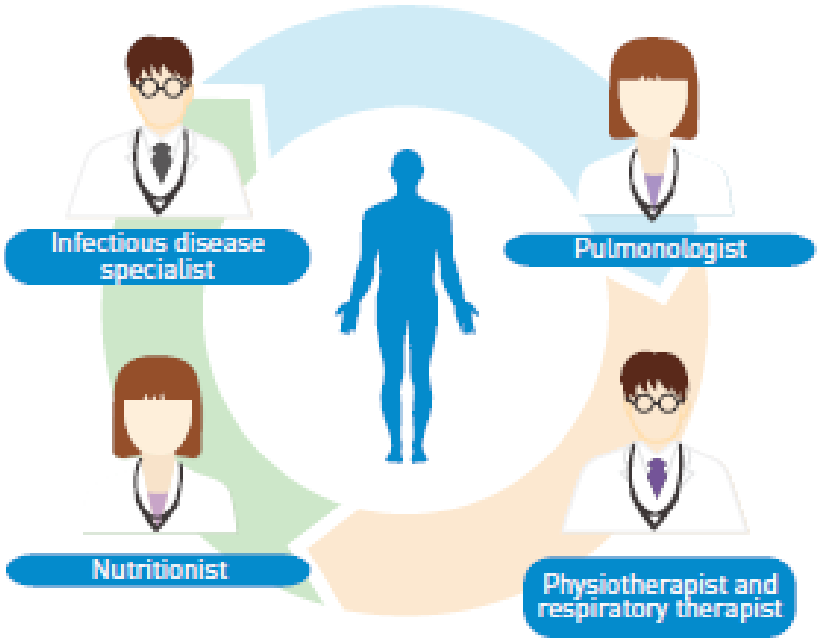
Multidisciplinary discussion





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Thank you