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# Incidental diagnosis of pulmonary mycobacteriosis among patients scheduled for lung cancer surgery: results from a series of 3224 consecutive operations

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## Abstract

**Background:** The relation between pulmonary mycobacteriosis and lung cancer has been scrutinized for many years but the current evidence is inconsistent as some studies found an association between the two, whereas others have reported an insignificant relation.

**Materials and methods:** 3224 consecutive patients undergoing elective thoracic surgery at the Department of Thoracic Surgery of a comprehensive cancer center over a four-year period were considered. Patients diagnosed with pulmonary mycobacteriosis with microbiological confirmation on their surgical specimen were further analyzed.

**Results:** 30 patients were diagnosed with pulmonary mycobacteriosis: six of them had a history of cancer. 18 patients received wedge resection, four patients received anatomic segmentectomy, two were submitted to lobectomy, one underwent pneumonectomy and five patients received other types of lesser procedures.

Pulmonary mycobacteriosis and synchronous lung cancer were observed in four patients.

**Conclusions:** Although rare, the incidental diagnoses of pulmonary mycobacteriosis among patients scheduled for lung cancer resection is not negligible. Pulmonologists, anesthesiologists and thoracic surgeons should be aware of this possibility before planning pulmonary resections of histologically undiagnosed lung nodules.

Keywords: Infectious disease, Surgery

## 1. Introduction

Lung cancer accounts for more than 1.8 million newly diagnosed cancer cases (13% of the total diagnosed cancer cases) and 1.6 million cancer-related deaths (19.4% of the total) worldwide every year [1]. It is one of the most frequently diagnosed cancers and is the leading global cause of cancer-related death [2].

Tuberculosis (TB) is a mycobacteriosis caused by *M. tuberculosis* and represents a global public health problem, remaining one of the major causes of death among infectious diseases. About one third of the human population is estimated to harbor TB in its latent form [3]. Pulmonary TB represents about 85% of clinical TB cases and as a chronic inflammation process may lead to carcinogenesis of the lung [4].

Currently, more than 125 non-tuberculous mycobacteria (NTM) species have been cataloged. They may cause both asymptomatic infection and symptomatic illness in humans, whose most common clinical manifestation is lung disease, although lymphatic, skin, soft tissue and disseminated disease have also been reported [5].

The probable relation between pulmonary mycobacteriosis and subsequent lung cancer development has been scrutinized for many years. However, the current evidence is inconsistent as some studies found an association between the two, whereas others have reported an insignificant relation [6].

## 2. Materials and methods

This is an observational retrospective study. Data were collected prospectively and entered into our institutional general thoracic database at the point of care and reviewed and double-checked retrospectively. Our sample included three thousand two hundred and twenty-four consecutive patients undergoing elective thoracic surgery for therapeutic or diagnostic purposes at the Department of Thoracic Surgery of a referral comprehensive cancer center over a four-year period (September 2006–March 2010). Among them, patients diagnosed with pulmonary mycobacteriosis with microbiological confirmation on their surgical specimen were further

analyzed. Written informed consent to undergo the procedure and the use of clinical and imaging data for scientific or educational purposes, or both, were obtained from all patients before surgery.

Age, gender, smoking habits, risk factors for pulmonary tuberculosis and non-tuberculous mycobacteriosis, type, side and extent of surgical resection, oncologic history, microbiologic diagnosis and relative antibiograms, bacterioscopic findings, pathological findings, preoperative bronchoscopic results, computed tomography (CT) and positive emission tomography (PET) findings, postoperative course, 30-day or in-hospital morbidity and mortality rates and long-term follow-up data were collected.

Postoperative death was defined as 30-day mortality or longer if mortality occurred during hospitalization. Complications were classified according to the Thoracic Morbidity and Mortality classification system [7] as minor (grades I and II) and major (grade IIIa, grade IIIb; grade IVa, grade IVb; grade V).

### 3. Results

Among the 3224 operated patients, 30 were diagnosed with pulmonary mycobacteriosis, accounting for 0.9% of the whole study population. They comprised 18 males (60.0%) and 12 females (40.0%); mean age was  $61 \pm 13$  years; eight patients (26.7%) were non-smokers, 12 (40.0%) were smokers and ten (33.3%) were former smokers; six patients (20.0%) presented risk factors related to tuberculous or non-tuberculous mycobacteriosis: one was human immunodeficiency virus (HIV)-positive, three had autoimmune diseases treated by immunomodulation, while two had chronic obstructive pulmonary disease (COPD).

Six patients (20.0%) had a history of cancer (3 renal cell carcinomas, 1 Hodgkin lymphoma, 1 breast carcinoma and 1 breast carcinoma and endometrial cancer). Preoperative bronchoscopy was performed in 19 patients and was positive for mycobacteriosis in one case and for squamous carcinoma in one case. Preoperative PET scan was performed in all patients but one and was negative on the target pulmonary lesion in five cases (17.2%) and positive in the remaining 24 cases (82.8%). Mean standardized uptake value was  $4.85 \pm 5.2$ ; the SUV values on the target lesions where cancer was also present were 4.2, 5.4, 10.4 and 24.9. Hilar or mediastinal lymph nodes were suspicious in six patients (20.7%). Preoperative CT scan disclosed solid target lesions in 27 patients (90.0%), cavitated lesions in three (10.0%) and suspicious lymphadenomegalies in four (13.3%). Mean major diameter of the lesion was 26 mm (range: 8–61 mm); 5 nodules were located in the left upper lobe (16.7%); 5 in the left lower lobe (16.7%); 2 in the middle lobe (6.7%); 3 in the right lower lobe (10.0%); 13 in the right upper lobe (43.2%); in two patients there were multiple nodules in different lobes (6.7%).

Eighteen patients (60.0%) received non-anatomic pulmonary resection (wedge resection), four patients (13.3%) received anatomic segmentectomy, two (6.7%) were submitted to lobectomy, one (3.3%) underwent pneumonectomy and five patients (16.7%) received other types of lesser procedures (on the pleura or lymphnodes).

*Mycobacterium tuberculosis* was diagnosed by microbiological examination in 13 cases (43.3%), *Mycobacterium xenopi* in 13 cases (43.3%), *Mycobacterium africanum* in two cases (6.8%), *Mycobacterium gordonae* in one case (3.3%) and *Mycobacterium intracellulare* in one case (3.3%).

Antibiograms showed the following sensitivity (single or combined): ethambutol in 14 cases, rifabutin in five cases, rifampicin in 25 cases, streptomycin in 13 cases, isoniazid in 13 cases, pyrazinamide in 12 cases. No case of multidrug-resistant mycobacterium was observed. Postoperative bacterioscopic evaluation was positive in 14 cases (46.7%).

Sputum culture was then routinely performed three times for each patient with suspected mycobacteriosis: it was positive at least once in six patients (20.0%): *Mycobacterium xenopi* was diagnosed in 2 cases; *Mycobacterium africanum* in 1 case; *Mycobacterium tuberculosis* in 3 cases.

In four patients we observed pulmonary mycobacteriosis and synchronous lung cancer: squamous carcinoma in two cases, neuroendocrine tumorlets in one case and poorly differentiated non-small cell cancer in one case. No oncologic patient received adjuvant treatments, three because of early stage disease and one because he died after surgery.

Eight patients (26.7%) presented postoperative complications: three had minor complications and five (16.7%) had major complications: among them four presented respiratory failure requiring non-invasive ventilation and one pleural empyema not requiring redo surgical exploration. The patient who developed respiratory failure after right pneumonectomy for poorly differentiated carcinoma died on postoperative day 41 from single lung acute respiratory distress syndrome (ARDS) (postoperative mortality: 3.3%). Mean length of hospital stay was  $5 \pm 1.7$  days.

All patients with a diagnosis of mycobacterium tuberculosis infection received complete therapy except one because of liver toxicity. All patients with a diagnosis of non-tuberculous mycobacteriosis were successfully treated. No case of recurrence has been notified since.

After a mean follow-up of  $103 \pm 44.1$  months, among patients with a diagnosis of synchronous lung cancer one was alive without any evident disease after 145 months, one was alive with recurrent disease after 16 months, one patient died after 116 months from other causes without any evident disease and one died 41 days after

the procedure, as reported above, from complications related to the surgical procedure [Tables 1 and 2].

#### 4. Discussion

Although the European region accounts only for 5% of world TB cases, tuberculosis has re-emerged as a public health concern in high-income countries in the last few

**Table 1.** Clinico-pathological features of the study population (categorical variables).

		N (%)
Sex	Female	18 (60.0)
	Male	12 (40.0)
Smoking status	Smoker	12 (40.0)
	Former smoker	10 (33.3)
	Non-smoker	8 (26.7)
Risk factors for TB and NTM (N = 6)	HIV	1
	Autoimmune diseases	3
	COPD	2
History of cancer (N = 6)	Renal cell carcinoma	3
	Hodgkin lymphoma	1
	Breast carcinoma	1
	Breast carcinoma + endometrial cancer	1
Pre-operative PET scan (N = 29)	Negative	5 (17.2)
	Positive	24 (82.8)
Pre-operative CT scan	Solid	27 (90.0)
	Cavitated	3 (10.0)
	Suspicious lymphadenomegalies	4 (13.3)
Surgical procedure	Wedge resection	18 (60.0)
	Anatomic segmentectomy	4 (13.3)
	Lobectomy	2 (6.7)
	Pneumonectomy	1 (3.3)
	Other	5 (16.7)
Mycobacteria	M. Tuberculosis	13 (43.3)
	M. Xenopi	13 (43.3)
	M. Africanum	2 (6.8)
	M. Gordonae	1 (3.3)
	M. Intracellulare	1 (3.3)
Postoperative complications	Overall	8 (26.6)
	Major	3 (10.0)
	Minor	5 (16.6)

**Table 2.** Clinico-pathological features of the study population (continuous variables).

	N	Mean $\pm$ SD <sup>§</sup>	min,max
Age at Surgery, years	30	61 $\pm$ 13	26,77
Mean standardized uptake value, SUV	29	4.85 $\pm$ 5.2	0.6,24.9
Length of stay, days	30	5 $\pm$ 1.7	3,41

<sup>§</sup>SD: Standard Deviation.

decades [8]. As CT and PET findings of TB and NTM are very similar to those observed in lung cancer patients, differential diagnosis can be difficult, particularly when lung cancer and pulmonary mycobacteriosis coexist in the same mass or in different anatomical structures (lung, lymph node or pleura) in the same patient. Moreover, lung cancer and pulmonary mycobacteriosis often share the same symptoms such as fever, cough, expectoration, hemoptysis, weight loss and anorexia [9, 10].

Although the incidence of TB in Italy has remained constant at under 10 cases/100,000 inhabitants - the threshold considered to define a country as low prevalence - the incidence rate is 3.8 cases per 100,000 for people born in Italy and 50–60 cases per 100,000 for those born abroad [11]. Hence it can be argued that even in European high-income countries the frequency of pulmonary mycobacteriosis is not anecdotal, and given the high incidence of lung cancer in industrialized countries, the coexistence of both diseases may represent a diagnostic and therapeutic challenge.

Mycobacteriosis – in particular tuberculosis – and lung cancer share similar risk factors, like smoking. The reduced clearance of airway secretions and impaired activity of alveolar macrophages observed in smoker patients contribute to *M. tuberculosis* escaping from the host's first line of defence [12]. On the other hand, the causal relation between smoking and lung cancer has been historically well proven. Although eight patients in our series were never smokers, the vast majority were active or former smokers and only among these patients was the coexistence of lung cancer and mycobacteriosis diagnosed.

Our CT findings disclosed solid lesions in 90.0% of patients, thus confirming that pulmonary mycobacteriosis is almost identical to lung cancer. Similarly, SUV values of mycobacteriosis were the same as those of neoplastic lesions. Although in our experience patients presenting with concomitant diseases (mycobacteriosis and lung cancer) presented higher SUV values, no clear cut-off was identified to discriminate between neoplastic and infective lesions.

In our series diagnostic bronchoscopy was performed in 19 out of 30 patients with tuberculous infection detected preoperatively only in one case: this aspect merits several methodological and clinical considerations. Firstly, all patients were referred

to a specialist thoracic oncology service because of a clinical diagnosis of lung cancer. Therefore flexible bronchoscopy was planned whenever the lesion was attainable by endoscopic approach, whereas very peripheral lesions were submitted to transthoracic CT-guided pulmonary biopsy for histologic characterization. In some cases of small highly suspicious lesions, the preoperative diagnostic approach was skipped and surgery performed for diagnostic purposes. The study was conducted in a low TB prevalence country, in particular on patients born in Italy whose TB incidence rate is 3.8 per 100,000, thus making our final findings almost unexpected. During the study period acid fast bacilli (AFB) culture using bronchial washing fluid (BAL) was not routinely performed, although non tuberculous mycobacteriosis could be effectively diagnosed by bronchoscopy [13]. On the basis of these results, an acid-fast bacilli smear and mycobacterial culture is now always performed on samples of bronchial secretions in case of potential TB lesions. This will identify patients as smear-positive pulmonary TB and smear-negative pulmonary TB, according to World Health Organization criteria [14]. Due to the same reasons, we did not routinely performed serologic investigation for mycobacteriosis, being this a limit of the present study.

In conclusion, although rare, the incidental diagnoses of pulmonary mycobacteriosis among patients scheduled for lung cancer resection is not negligible. Considering the increasing trend of these infections in industrialized countries, pulmonologists, anesthesiologists and thoracic surgeons should be always aware of this possibility before planning pulmonary resections of non-histologically characterized lung nodules.

## Declarations

### Author contribution statement

Francesco Petrella, Monica Casiraghi, Elena Prisciandaro, Lorenzo Gherzi, Lorenzo Spaggiari: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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### Competing interest statement

The authors declare no conflict of interest.

## Additional information

No additional information is available for this paper.

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