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Does Every Necrotizing Granulomatous Inflammation Identified by NSCLC Resection Material Require Treatment?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Lung cancer and tuberculosis (TB) are two major public health problems. They can coexist or appear sequentially. In patients with TB, lung cancer risk is increased. However, vice versa is not crystal clear. In this study, we aimed to determine the development of TB in patients with resectable non-small cell lung cancer (NSCLC) in a 2-year postoperative follow-up period.





Material/Methods: We conducted a retrospective cohort study at three university hospitals. Patients who had NSCLC surgery between 2009 and 2013 were included and patient records were reviewed for the presence of necrotizing granulomatous inflammation (NGI) in resected specimens. Demographic properties, tumor type, stage, location, type of surgery, tuberculosis history, and thorax CT findings were recorded. We searched for the development of tuberculosis within a 2-year period after surgery.

Results: A total of 1027 patient cases were reviewed, of which 48 patients had NGI. The median age was 63 years. The most common type of cancer was squamous carcinoma; and lobectomy was the preferred operation (70.8%). Cancer involvement most commonly included the right lung (61.8%) and upper lobes (47.9%). Only 11 patients had anti-TB treatment postoperatively, which was based on radiological findings. Prior tuberculosis or anti-TB history, type, stage or localization of cancer, and adjuvant/neoadjuvant therapy were not found to be related to TB treatment. None of the study population had TB during the two-year follow-up period. Treatment decisions appeared mostly related to physician experience. There was no difference in the risk of developing TB between patients with or without treatment. This finding may change the management of our patients.

Conclusions: Every NGI discovered in NSCLC resected material does not always require anti-TB treatment.

MeSH Keywords: **Antitubercular Agents • Carcinoma, Non-Small-Cell Lung • Tuberculosis, Pulmonary**

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Background

Lung cancer is one of the most frightening types of cancer and the leading cause of cancer death worldwide [1]. Annually, 1.3 million people die due to lung cancer. Previous studies have reported that a history of pulmonary tuberculosis (TB) is a risk factor for lung cancer [2]. In addition, TB is a major public health problem. Globally, in 2014, there was an estimated 9.6 million cases and 1.5 million deaths from TB [3]. TB prevalence in Turkey in 2014 was 22 per 100,000 population [3].

Non-small cell lung cancer (NSCLC) patients may have granulomatous inflammation identifiable in resection materials. This kind of inflammation may occur in lymph nodes, or in lung parenchyma adjacent or distant to the tumor [4]. As we know from the literature, granulomatous inflammation at seminoma of the testis [5], renal cell carcinoma [6, 7], nasopharyngeal carcinoma [8], and lung cancer [9, 10] may occur due to immunological mechanisms. As in other cancers, the sarcoid reaction is often considered a form of “defense” or “reaction” of the host to tumor antigens [10]. The prevalence of granulomatous reactions in the lung is reported to be 2.2–3.4% [9,10].

Pathologists may identify necrotizing granulomatous inflammation (NGI) on examination of resected material [11]. This inflammation may be identified in lymph nodes or lung parenchyma resected materials. There are only a few available tests for TB that are suitable for paraffin-embedded tissue, including real-time PCR for *Mycobacterium tuberculosis* [11]. The identification of necrosis in granulomas is important because granulomas with necrosis tend to have infectious causes [12]. For NSCLC patients living in countries with a moderate-to-high TB prevalence, with addition of parenchyma sequelae or calcification can complicate management. Does the NSCLC patient with NGI also have tuberculosis? The management of these patient conditions is not well established. In Turkey, physicians make treatment decision about starting anti-TB treatment or follow-up care depending on his/her own experiences. However, the decision is a double-sided knife: either starting an unnecessary treatment or withholding a necessary treatment. Although the simultaneous occurrence of lung cancer and pulmonary TB has been reported in some case reports [13,14], there are no studies investigating the risk of pulmonary TB development based on NGI presence in NSCLC patients with negative acid fast stain (AFS) specimens.

The primary objective of our study was to determine whether there is a risk of TB development within two-years after surgery in NSCLC patients with NGI.

Table 1. Inclusion and exclusion criteria.

Inclusion	Exclusion
Diagnosis of non-small cell lung cancer	<18 years
Presence of Necrotizing granulomatous inflammation at specimen	Nonnecrotizing granulomatous inflammation at specimen
Cancer should be technically and medically operable	Metastatic disease
	Presence of secondary malignancy or active infections
	Death within 3 months

Material and Methods

We conducted a retrospective cohort study using retrospective data of patients with a diagnosis of resectable NSCLC at three tertiary care hospitals in Istanbul between 2009 and 2013. Patients who were diagnosed with NGI identified in surgical specimens were included in the study. Patients with a diagnosis of secondary malignancy, metastatic disease, or under 18 years of age were excluded (Table 1). NGI was defined as an area of inflammation in which tissue had died. Demographic data included age, gender, tumor type, location and stage, operation type, NGI location, ratio of necrosis at tumors, tissue AFS, history of smoking, tuberculosis, and anti-TB treatment in the postoperative period, presence of adjuvant or neoadjuvant therapy, death (presence/absence, time to death and possible causes), radiological findings including sequel of lesions, calcification at parenchyma or mediastinum, cavity, infiltration, bronchiectasis, apical fibrosis or pleural thickening and development of TB within two years after surgery. NGI presence was diagnosed by two experienced pulmonary pathologists. Radiological abnormalities were reported by two experienced pulmonary radiologists. Data were acquired from hospital records and confirmed by the patient or a first-degree relative. TB and anti-TB treatment history were also confirmed by patient records of the Department of Fight against Tuberculosis, Public Health Institution of Turkey. The primary outcomes of the study were the development of tuberculosis and the initiation of anti-TB treatment within two years after cancer surgery. Although the study design included up to six years of follow-up, patient records were only consistently available for a two-year follow-up study period.

Statistical analysis

Data were analyzed using SPSS 16.0 (IBM, SPSS Armonk, N.Y., USA). We carried out a descriptive analysis of the variables.

Table 2. Sociodemographic and disease characteristics of the study population.

Sociodemographic and disease characteristics	Results	
Gender*		
Male	35	(72.9%)
Female	13	(27.1%)
Age, years**	63	(40–76)
Smoking***	37.7±22	
History of tuberculosis*		
Not present	38	(85.4%)
Present	7	(14.6%)
Type of cancer*		
Squamous carcinoma	24	(50%)
Adenocarcinoma	19	(39.6%)
Others	5	(10.4%)
Location of Cancer*		
Upper lobe	23	(47.9%)
Middle lobe	5	(10.4%)
Lower lobe	20	(41.7%)
Cancer stage*		
Stage 1	23	(47.9%)
Stage 2	17	(35.4%)
Stage 3	8	(16.7%)
Type of surgery*		
Sub-lobar resection	34	(70.8%)
Lobectomy	11	(22.9%)
Pneumonectomy	3	(6.3%)

* Values expressed as n (%); ** Values expressed as median (range); *** Values expressed as pack years mean±standard deviation.

Continuous variables were expressed as means and standard deviation (SD) or medians and quartiles.

Local ethical committee approval was provided for the study and informed consents were signed by all study patients.

Results

1027 patients had surgery for resectable NSCLC between 2009 and 2013. In 51 patients, NGI was detected at either lymph nodes (mediastinal/bronchial) or lung parenchyma. Three patients were excluded from the study because of death due to pneumonia in an early period after surgery (<1 month).

Table 3. Radiological findings.

Thorax CT findings	n (%)	Postoperative Anti-TB treatment
Normal	23 (47.9%)	None
Abnormal	25 (52.1%)*	
Lymph node calcification	12 (25%)	6
Apical fibrosis	8 (16.7%)	2
Parenchyma calcification	7 (14.6%)	3
Pleural thickening	7 (14.6%)	2
Cavity	5 (10.4%)	5
Others (bronchiectasis, infiltration)	2 (4.2%)	0

* Some patients had more than one abnormality at CT at the same time. Values expressed as n (%). CT – computerized tomography.

However, none of these patients had positive AFS or sputum TB cultures. Forty-eight patients (35 male, 13 female) were included to the study and followed for at least two years. The prevalence of NGI was 4.6%. The median age was 63 years (range 40 to 76 years). Demographic properties are presented in Table 2. Three patients were nonsmokers. Half of the patients had squamous carcinoma (24/48) and 19 had adenocarcinoma. Cancer involvement of the right lung was more common than the left lung (61,8% vs. 31,2%). Upper lobes were the most common site for cancer (47.9%) and lower lobes were the second most common site (41.7%). While lobectomy was the most common choice of surgery (70.8%), only three patients required pneumonectomy (6.3%). Twenty-eight patients had no lymph node metastasis (N₀) and in 13 patients the common lymph node station was involved (9/20). Only six patients had N2 (4R-L and 7) metastasis. Adjuvant therapy was given to 15 patients. Necrotizing granulomatous inflammation of the lymph nodes and parenchyma were present in 35 and 17 patients, respectively (four patients had NGI at both lymph node and parenchyma). One patient had a lobectomy for a second lung cancer in a different lobe after three years and the follow-up tissue specimen contain NGI. Tissue AFS of the resection specimen was performed for only half of the patients (25/48) and none of the specimens showed any presence of mycobacteria. Seven of our patients (14.6%) had tuberculosis history, however, only four could recall having anti-TB treatment previously. Regardless of their anti-TB treatment history (received or not), four of these seven patients had anti-TB treatment postoperatively. Computerized tomography showed abnormal parenchymal or mediastinal abnormalities at 25 cases (Table 3). Despite presence of radiological abnormalities, only 11 patients received anti-TB treatment.

The standard anti-TB treatment in Turkey is a four drug regimen (isoniazid, rifampicin, ethambutol, pyrazinamide) and all patients who received anti-TB treatment, received the standard regimen for six months. All five patients with a presence of cavity formation had anti-TB treatment ($p < 0.001$). Also, parenchymal calcification and pleural thickening presence were correlated with anti-TB treatment ($p < 0.05$). Anti-TB treatment at the postoperative period was not associated with tumor type, location, cancer stage, prior tuberculosis history, adjuvant or neoadjuvant chemotherapy, or NGI location. With or without treatment, none of our study population had pulmonary TB during the follow-up period. Thirteen patients expired during the five-year postoperative time interval with a median of 2 ± 1.5 years; disease progression ($n=5$), pneumonia ($n=5$), and three patients died due to other conditions (cerebrovascular disease, myocardial infarction).

Discussion

The most important finding of the study is that no patient in the study population had pulmonary TB during the two-year follow-up period. Although, we report on incidence of TB development within two years after surgery, some patients had six years of follow up without pulmonary TB.

The second important finding was that initiation of anti-TB treatment was related to radiological sequel presence more than to tumor type, location, cancer stage, invasion of lymph nodes, or tissue AFS. In our study, every patient who had cavity lesions had also received anti-TB treatment ($p < 0.01$). Parenchymal calcification and pleural thickening were also associated with anti-TB treatment ($p < 0.05$), which may show that physicians tend to accept patients with radiological sequels as having TB. However, patients who had sequel of lesions but did not receive anti-TB treatment (except cavity lesions) did not have evidence of pulmonary TB during the study period. Also, Kamboj and Sepkowitz [15] reported that patients who are born in countries with low TB incidence and an underlying solid tumor had the same TB risk as persons without cancer.

There are some published case reports stating the coexistence of TB and lung cancer [16,17]. However, these reports mostly observed lung cancer in patients with a history of TB. A population-based study reported the risk of cancer was increased in patients with TB diagnosis [18]. Also, Shiels et al. [19] reported that lung cancer risk was highest within two years after TB diagnosis, but there was no information about the risk of TB after cancer development. In our study, we searched for this risk and observed that none of the patients had TB during a two-year follow-up period. The causality is not yet clear, whether TB causes cancer by inflammation-induced carcinogenesis [20] or

cancer causes immunosuppression and activation of the dormant foci of sequel of TB.

Adjuvant/neoadjuvant therapy is one of the most complicating issues for cancer patients with sequels [21]. Immunosuppression caused by chemotherapy agents makes patients vulnerable to infectious agents, not only Mycobacterium tuberculosis but also to bacteria that may cause only mild symptoms or sub-clinical infections in patients with normal immunity. Although there are new chemotherapeutic agents (targeted therapies), infection risk is still a controversy complication. However, in our study we did not find an association with adjuvant/neoadjuvant treatment and postoperative anti-TB treatment, which may be due to the small numbers of patients requiring these treatment modalities.

Studies have reported that squamous cell carcinoma associated with granuloma formation [22] and adenocarcinoma [16]. However, we did not find any statistical significant association for type of cancer (squamous, 24 cases/adenocarcinoma, 19 cases).

Granuloma formation within or around the tumor is commonly related to T cells or cytokines derived immunological reaction to tumor antigens [23,24]. This mechanism may cause sarcoid like reactions in lymph nodes, which drains the tumor to the lymphatic system [24]. However, in our study we excluded patients with non-necrotizing granulomas and looked only at patients with NGI. NGI is a more specific reaction to infectious agents and granulomatosis with polyangiitis. Ulbright and Katzenstein [25] examined 86 consecutive necrotizing granulomas and found that 61 were infectious (AFS or fungi), 22 remained unexplained after clinical, radiological, and microbiological correlations, three were granulomatosis with polyangiitis and two were hyalinizing granuloma. In our study, although we had records of tissue AFS for half of the study population, none of these patients had positive AFS stains.

There were several limitations to our study. First and most important was the limited number of cases. However, the existence of NGI in lung cancer specimens is rare. It was 4.6% in our study, 2.1% [26] and (5.1%) [27] in other studies, which limits the number of available study cases. Second, our study was a retrospective cohort study continued as a retrospective study, mainly due to the rarity of NGI cases. Third, the lack of tissue polymerase chain reaction for Mycobacterium tuberculosis in paraffin embedded tissues was mainly due to technical inexpertise. Fourth, we had a two-year follow-up period. We picked the first two years because this time period was the most fragile period for patients due to the burden of surgery and adjuvant therapy. Fifth, none of our study patients had TB, which might be due to the initiation of anti-TB treatment empirically in some cases which might have prevented its development. Sixth, our study lacked PPD or Quantiferon

test results because this data was not available from patient records. However, neither PPD nor Quantiferon tests have been shown to prove that a patient actually has TB. Last, these results are only applicable for early stage lung cancers (\leq Stage 3a)

The implication of the study is that NGI detected in surgical resection does not require anti-TB treatment unless there is a strong clinical suspicion of active disease.

Conclusions

None of the patients with NGI formation in our study had TB within a 2-year follow-up period, although some patients had previously received anti-TB treatment without any microbiological evidence of disease. To define the real risk of

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TB development in all lung cancer patients, we need a multi-center, prospective, long-term follow-up study.

Statement

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Conflict of interest

None of the author declares any conflict of interest.

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