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Original Artricle

Investigation of Granulomatous Inflammations in Terms of Tuberculosis Diagnosis: A 5-Year Multi-center Laboratory Study

Derya Öztomurcuk[1], Özlem Terzi[2], Canan Demirci[3], Zeki Kılıçaslan[4]

[1]Samsun Tuberculosis Dispensary of Health Directorate, Samsun, Turkey
[2]Department of Public Health, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[3]Departman of Pathology, Gazi Hospital, Samsun, Turkey
[4]Department Of Chest Diseases, Faculty of Çapa Medicine, İstanbul University, İstanbul, Turkey

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Abstract

OBJECTIVE: Granulomatous inflammation showing "caseification necrosis" is considered pathognomonic for tuberculosis. This study aimed to evaluate patients with granulomatous inflammation and some characteristics to diagnose tuberculosis.

MATERIAL AND METHODS: This is a cross-sectional descriptive study. The study includes all pathology laboratories in Samsun between the years 2012 and 2017. Pathology reports that contained the term *granulomatous* were selected between all patient reports of these laboratories. The patient reports were examined by comparing the dispensary records and the presence of a diagnosis of tuberculosis.

RESULTS: In the 703 pathology reports, it was found that 38% were only granulomatous and 33% were caseous granulomatosis lesions. When the prevalence of tuberculosis according to the presence of microscopic necrosis was observed in granulomatous tissue samples, 85% tuberculosis was found in patients with necrotic granulomatous tissue and 14% tuberculosis was found with non-necrotic lesions. The presence of tuberculosis in necrotic granulomatous tissues was statistically significantly higher ($P < .00001$).

CONCLUSION: As a result, when examining a pathology report for the presence of tuberculosis, the existence of a granulomatous reaction should be considered first. Getting stuck on the definition of caseification necrosis will cause the case to be skipped. An indication of necrosis in the pathologic evaluation will guide the diagnosis of tuberculosis.

KEYWORDS: Caseification, extrapulmonary tuberculosis, granulomatous, pathology report
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INTRODUCTION

Approximately one-quarter of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Although most patients can be treated with early diagnosis and correct treatment, tuberculosis (TB) is still among one of the top 10 causes of death worldwide. According to data of the World Health Organization, there were an estimated 10 million new TB cases worldwide and 1.2 million TB deaths in 2020.[1]

For 60%-65% of cases, TB is seen with pulmonary involvement, and mycobacterial culture positivity is the gold standard for diagnosis. The extrapulmonary (EP) form is mostly seen in lymph nodes and the pleura. In a 2017 TB surveillance report prepared by the WHO, the incidence of extrapulmonary tuberculosis (EPTB) was reported as 22.5% for Europe, 46.4% in the United Kingdom, 43.1% in the Netherlands, and 35.4% in Turkey.[2] The definitive diagnosis is more difficult than the pulmonary disease, and the diagnosis is made through pathological biopsy material with positive mycobacterial culture or positive staining or with the presence of a granulomatous reaction in the histopathologic examination. Granulomatous inflammation is defined as a special type of chronic inflammation dominated by mononuclear phagocyte system cells. It is consideredas an immune mechanism that develops against infections or some non-neoplastic conditions.[3,4] The most common causes are infective agents such as mycobacteria, fungi, parasites, and non-infective etiologies such as sarcoidosis, foreign bodies, and Crohn's disease. Granulomatous inflammation showing "caseification necrosis" is considered pathognomonic for TB.[4,5]

Caseous necrosis is in fact a macroscopic description and has no equivalent in examination. For this reason, getting stuck in the definition of caseous necrosis may cause a case failure.

The aim of this study was to evaluate patients with granulomatous inflammation through the presence of necrosis, the lymph node taken, and some demographic characteristics to diagnose TB.

Corresponding author: Derya Öztomurcuk, e-mail: deryavsd@hotmail.com

MATERIAL AND METHODS

Data Collection

The study includes all pathology laboratories in Samsun (university, private, and public hospital laboratories [9 units]), between the years 2012 and 2017. Reports that contained the term *granulomatous* (e.g., necrotizing, caseous, non-caseous, large-celled) were selected between all patient reports of these laboratories. It is found that the reports belonged to various tissue samples such as lymph node (LN) aspiration material, lung parenchyma taken during surgery, wedge resections, lung parenchyma, breast, pleura, prostate, bladder, and skin (Table 1). A total of 707 reports were determined to comply with the study criteria. A second grouping was made based on the presence of necrosis at the microscopic level. Granulomas exhibiting Langhans giant cells and including central necrosis appearing like eosinophilic amorphous debris were accepted as "caseous" granulomas. Other granulomas with coagulative central necrosis which include neutrophils and nuclear debris were accepted as "necrotizing" granulomas. According to the new grouping, the reports of caseous granulomatosis and necrotizing granulomatosis were accepted as "necrotizing granulomatous" and those of granulomatous, non-necrotizing, and non-caseous were considered as "non-necrotizing" granulomatosis.

Evaluation of Tuberculosis

The patient reports were examined by comparing the dispensary records and the presence of a diagnosis of TB. Patients who were not seen in the dispensary records were invited to the dispensary closest to them. After informing the patients who came to the dispensary and receiving their approval, the dispensary physician performed the necessary medical examination for TB (chest graph, tuberculin skin test (by Mantoux method), acid-fast bacilli smear microscopy, mycobacterial culture). Patients who were suspicious of TB were referred to the Chest Diseases Hospital, and all patients were investigated and confirmed as having or not having TB.

Statistical Analysis

The Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA) was used for the statistical analysis of the study data. When the data were evaluated, continuous variables were expressed as mean ± standard deviation or median (range), and frequencies were written as numbers and percentages (%). The chi-square test was used for the comparison of the frequency of data. The level of statistical significance was accepted as $P < .05$.

RESULTS

In the pathology report, 4 out of 707 individuals with "granulomatous" expression could not be contacted and the study was completed with 703 patients. The median age of the 703 patients was 48 ± 16 (2-89) years, and 68% of the patients were female. The female patients [median: 47 (2-89) years] were younger than the male patients [median: 51 (2-79) years], but the difference was not statistically significant ($P = .053$). Most of the patients (74%) were residing in Samsun.

Analysis According to the Type of Granulomatous Reaction

It was found that 38.7% of the investigated reports were only granulomatous, 33% were caseous granulomatosis, 18% were non-caseous granulomatosis, 5.8% were necrotizing granulomatosis, and 4% were non-necrotizing granulomatosis. Of the 703 patients, 42% were diagnosed as having TB as a result of the study. The most frequently diagnosed TB cases were caseous granulomatosis (91%) and necrotizing granulomatosis (53.7%) (Table 2).

When the data were regrouped according to the presence of microscopic necrosis, 39% (n = 274) were necrotizing and 61% (n = 429) were non-necrotizing granulomatosis. When the prevalence of TB according to the presence of microscopic necrosis was observed in granulomatous tissue samples, 85% TB was found in patients with necrotic granulomatous tissue and 14% TB was found with non-necrotic lesions. In the statistical comparison, the presence of TB in necrotic granulomatous tissues was statistically significantly higher ($\chi^2 = 342.3$, $P < .00001$). It was determined that 40 non-TB patients with necrotizing granulomatous reaction were diagnosed with sarcoidosis (14/40), cancer (12), foreign body (4), infection (4), Crohn's disease (2), etc. (Table 3).

Classification and Analysis According to the Tissue Taken

It was determined that most of the 703 pathology investigated reports were extrathoracic LN (23%), intrathoracic LN (16%), lung (14%), and breast (13.8%). In the study, the incidence of TB in pulmonary tissue samples was 48% (48/100), whereas, in extrapulmonary samples, the frequency of TB was 41% (248/603). There was no statistically significant difference in the frequency of TB in pulmonary and extrapulmonary granulomatous samples ($P = .22$). When the tissue samples of 296 patients with TB were evaluated according to the localization of TB, 16% (48/296) of the patients had pulmonary TB and 83.8% (248/296) of them had extrapulmonary TB. The incidence of EPTB was highest in extrathoracic LN (46.8%), followed by pleural (16.8%) and intrathoracic

MAIN POINTS

- Tuberculosis (TB) is still among the top 10 causes of death worldwide.
- For 35%-40% of cases, TB is seen with extrapulmonary (EP) involvement and the definitive diagnosis is more difficult than the pulmonary disease.
- TB diagnosis is made through pathological biopsy material with positive mycobacterial culture or positive staining or with the presence of a granulomatous reaction in the histopathologic examination.
- The differential diagnosis of extrapulmonary tuberculosis should also be done with other histo-pathologically similar granulomatous diseases.
- Granulomatous inflammation showing "caseification necrosis" is considered pathognomonic for TB.
- Caseous necrosis is in fact a macroscopic description and has no equivalent in the examination. For this reason, getting stuck in the definition of at caseous necrosis may cause a case failure.

Table 1. The Interventional Methods Used to Obtain the Specimens

Extrathoracic LN	166 fine needle aspiration biopsy 3 excisional biopsy
Intrathoracic LN	121 excisional biopsy
Breast	97 excisional biopsy
Lung	51 thoracoscopic biopsy 35 excisional biopsy 6 wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS) 4 wedge resection 4 transbronchial biopsy
Pleural	3 pleural fluid 45 pleural biopsy
Skin	51 surgical excision
Gastrointestinal System-peritoneum	10 endoscopic biopsy 20 surgical resection
Genitourinary system	5 cystoscopic 40 surgical resection
Soft tissue	8 excisional biopsy
Bone-joint	8 excisional biopsy 1 fine-needle aspiration biopsy 2 arthroscopic biopsy
Others	13 excisional biopsy

LN (12.8%), respectively. Table 4 presents the distribution of patients' diagnosis of TB according to granulomatous tissue samples types:

The most frequently detected TB in the extrathoracic LN was cervical (52% = 61/117), axillary (29% = 34/117), and supraclavicular (6% = 7/117) (Figure1), whereas it was mediastinal in the intrathoracic LN (87.5% = 28/32).

Age and Sex Evaluation

When the age of the patients was evaluated by dividing the decades, the incidence of TB ranged from 16.2% to 19.6% between the 4th and 7th decades, whereas it was 10% or less in the other decades. In terms of sex, the prevalence of TB in women with granulomatous reaction was 42.9%, and the frequency of TB in men was 40.5%; there was no statistically significant difference between the sexes ($\chi^2 = 0.26$, $P = .61$).

DISCUSSION

In our study, it was determined that 42.1% (n = 296) of the 703 patients who had granulomatous inflammation in pathology reports were diagnosed as having TB. As our study was laboratory-based, only granulomatous diagnosed reports were considered and the diagnosis of TB was not based on accurate bacteriologic results for each patient, we are of the opinion that the results do not reflect the public.

Although definitive diagnosis for EPTB is established by the presence of acid-fast bacilli (AFB) and isolation in culture, there are problems in diagnosis from time to time. It has been reported in published studies that the AFB-positive rate in patients diagnosed as having EPTB varies between 12% and 78% depending on the presence or absence of necrosis, and the culture was found positive between 10% and 58%.[6-9] For this reason, in addition to definitive diagnostic methods in EPTB cases, pathologic evaluation still remains important for physicians.

In the literature, it is reported that caseous granulomatous reaction is a predominant finding that supports TB in particular.[10-12] In this study, almost all patients with caseous lesions were diagnosed as having TB. However, if the histologic specimens to be evaluated are too small, pathognomonic features such as caseous necrosis cannot be determined.[13] In the absence of caseification, the final diagnosis for TB depends on granulomatous inflammation. In our study, it was determined that 18% of patients whose reports had no details, and were only indicated as granulomatous inflammation, were diagnosed as having TB.

It is reported that a granulomatous reaction with no necrosis is more likely to be observed in non-infectious conditions such as sarcoidosis.[11] However, the differential diagnosis of EPTB should also be done with other histopathological similar granulomatous diseases (e.g., carcinoma, lymphoma or sarcoma, viral or bacterial adenitis, fungal disease, toxoplasmosis, cat scratch fever, and collagen vascular diseases).[10,14] Inadequate descriptions of pathology reports are an important issue leading to delays in diagnosis and initiation of treatment. We believe that avoiding the use of the term *granulomatous* as far as possible in the pathologic evaluation and clearly indicating if there is necrosis in the tissue section may increase the frequency of early diagnosis.

Table 2. Distribution of Pathology Results According to Tuberculosis

		TB Status, n (%)**			
Pathology Results	**Total, n (%)***	**TB Diagnosis**	**Not TB Diagnosis**	X^2	***P***
Granulomatosis	272 (38.7)	49 (18.0)	223 (82.0)	369.1	<.0001
Non-caseous granulomatosis	128 (18.2)	11 (8.6)	117 (91.4)		
Non-necrotizing granulomatosis	29 (4.1)	2 (6.9)	27 (93.1)		
Necrotizing granulomatosis	41 (5.8)	22 (53.7)	19 (46.3)		
Caseous granulomatosis	233 (33.1)	212 (91.0)	21 (9.0)		
Total	703 (100.0)	296 (42.1)	407 (57.9)		

*Column percentage; **Row percentage.

Table 3. Distribution of Patient Results According to Presence of Necrosis

	TB Diagnosis (n = 296)	Not TB Diagnosis (n = 407)	Total (n = 703)	X^2	*P*
Necrotic, n (%)	234 (85.4)	40 (14.6)	274 (100.0)	342.2	.0001
Non-necrotic, n (%)	62 (14.5)	367 (85.5)	429 (100.0)		

In some studies, it is also seen that the term *necrotizing* is used instead of *caseating* for granulomas in the lung.[15,16] Caseating refers to a gross, cheesy appearance. However, in granulomas, remnants of lung parenchyma or inflammatory cells may be found. El-Zammar and Katzenstein[17] stated that they have suggested using the term "necrotizing" instead of caseating to express the microscopic change.[17] In spite of this condition, it should be kept in mind that cell necrosis does not exist, and patients with non-caseous and non-necrotizing inflammation may also have TB. In the literature, it is stated that TB diagnosis is unnoticed in patients with non-caseous granulomatous inflammation and false-negative results can be obtained in immunocompromised patients.[17] In this study, TB was detected in patients with non-caseous or non-necrotizing lesions, even with a low grade (8.6% and 6.9%, respectively).

The most common form of EPTB is TB lymphadenitis.[6,9,14] In a study conducted in the United States (US), 30%-50% of patients with EPTB were reported to have TB lymphadenitis and mostly hold cervical LN.[18] Other studies showed that TB LN were cervical 25-47%, axillary 20%, and supraclavicular 12-10%.[19,20] In our study, LN were classified as extrathoracic and intrathoracic. The most common cervical involvement was observed in extrathoracic LN, in accordance with the literature, and the second most frequent involvement was axillary. In intrathoracic LN, the most common involvement was mediastinal, which is in agreement with the literature.[21]

Table 4. The Distribution of Patients According to Granulomatous Tissue Samples and Diagnosis of TB

	Total, n (%)*	TB, n (%)**	Not TB, n (%)**	X^2	*P*
Extrathoracic LN	169 (28.0)	115 (68.0)	54 (32.0)	1.6	.22
Intrathoracic LN	121 (20.1)	32 (26.5)	89 (73.5)		
Breast	97 (16.1)	6 (6.2)	91 (93.8)		
Lung	100 (14.2)	48 (48)	52 (52)		
Pleural	48 (8.0)	42 (87.5)	6 (12.5)		
Skin	51 (8.5)	8 (15.7)	43 (84.3)		
GIS—Peritoneum	40 (6.6)	19 (47.5)	21 (52.5)		
GUS	45 (7.5)	7 (15.5)	38 (84.5)		
Bone-joint	11 (1.8)	9 (82)	2 (18)		
Soft tissue	8 (1.3)	1 (12.5)	7 (87.5)		
Others	13 (2.2)	9 (39)	4 (61)		
Total**	703 (100.0)	296 (42.1)	405 (57.9)		

*Column percentage; **Row percentage.
LN, lymph nodes; GIS, gastrointestinal system; GUS, genitourinary system; Others: meninx, thyroid, auricular.

For TB lymphadenitis, the bacteriologic confirmation of the diagnosis is difficult because of the small number of bacilli and the difficulty of sampling from treated tissue. In previous studies, the culture positivity in patients with TB lymphadenitis was reported to be between 10% and 60%.[9,22] An important deficiency of our study is that we do not have any data on biopsy samples with spread and culture and TB baseline search studies and positivity rates.

One of the common forms of EPTB is pleural TB, and its prevalence is increasing in developing countries.[23] The diagnosis of pleural TB is very difficult because TB-related pleural effusion contains relatively few organisms, and invasive procedures and pathologic evaluations such as pleural biopsy are often needed in the diagnosis.[24] Hospital-based studies have reported very different frequencies. For example, in the study of Chakrabarti and Davies,[25] it was reported that pleural involvement was observed as between 4% and 38%. In another study conducted in our country, it was found to be 34%, and this result was higher than our study.[26]

Unlike the EPTB distributions in our study, in a study in which cases of EPTB in the US, lymphatic TB was 40%, pleural TB was 20%, bone/joint TB was 117%, genitourinary TB was 7%, and peritoneal TB was 5%.[6] In different sources, it is described that 25% of patients with EPTB have involvement in the musculoskeletal system,[27] 11%-16% have GIS involvement,[13,28] and 0.1% have skin involvement.[29]

In our study, TB was more frequent in the 4th and 7th decades than in the other decades. This situation was evaluated to be in accordance with the literature.[7,30] No significant difference was found between the sexes in terms of TB. In many studies, TB was more common in the male sex.[31,32] In addition to this, some studies on TB lymphadenitis suggest that female sex is more dominant.[33,34] The worldwide distribution of TB in

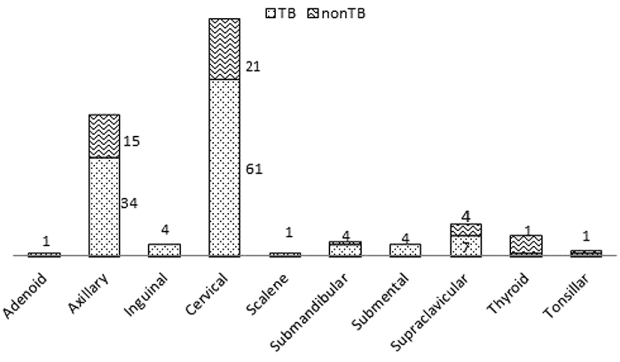

Figure 1. The distribution of extrathoracic lymph nodes according of TB. TB, tuberculosis.

2020 was reported as 56% of TB patients are male, 32% are female, and 12% are children.[1] According to the current TB report in our country, 57.7% of TB patients are male, 42.3% are female, while the distribution of patients by age is 4.6% at 0-14 years, 15.4% at 15-24 years, and 80% at ≥ 25 years.[35]

Given the worldwide prevalence, physicians and pathologists must recognize many clinical variants of TB and know its diversity in different tissues. Thus, many missed or delayed diagnoses of TB will be prevented.[14,36] As a result, when examining a pathology report for the presence of TB, the existence of a granulomatous reaction should be considered first. Getting stuck on the definition of caseification necrosis will cause the case to be skipped. An indication of necrosis in the pathologic evaluation will guide the diagnosis of TB.

Study Limitation

This study had some limitations. First, study data were obtained from only one province's pathology laboratories. This limits the generalizability of the results. Second, no confirmation was made for patients whose dispensary records indicated they had tuberculosis, and these diagnoses were assumed to be correct.

Ethics Committee Approval: This study was approved by Ethics committee of Ondokuz Mayıs University, (Approval No: OMU KAEK:2018/96).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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