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Tuberculosis Presenting as Suspected Malignancy: A Retrospective Analysis of Granulomatous Biopsy Cases

Özlem Düvenci Birben[1*], Esma Sevil Akkurt[1], Çigdem Ozdilekcan[1], Gülşen İskender[2], Mustafa Ertek[2], Nazan Bozdogan[3], Ayşen Atasoy[1], Derya Yenibertiz[1]

[1]Department of Chest Diseases, University of Health Sciences, Ankara Oncology Training and Research Hospital Ankara, Türkiye
[2]Department of Infectious Diseases, University of Health Sciences, Ankara Oncology Training and Research Hospital, Ankara, Türkiye
[3]Department of Pathology, University of Health Sciences, Ankara Oncology Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Tuberculosis, particularly its extrapulmonary forms, may mimic malignancy, causing diagnostic uncertainty and treatment delays. This study evaluated clinical, radiological, histopathological, and microbiological features of patients initially assessed for suspected malignancy but subsequently diagnosed with tuberculosis.

This retrospective study included patients who underwent biopsy for suspected malignancy between 2019 and 2022, showed granulomatous inflammation histopathologically, and had confirmed tuberculosis. Demographic, clinical, radiological, biopsy, histopathological, and microbiological data were recorded, and comparisons were made by history of malignancy, TB-PCR status, and granuloma type. Tuberculosis was diagnosed based on histopathological, microbiological, and/or compatible clinical findings.

Among 104 patients, the median age was 54 years (IQR, 41–65), and 77 (74.0%) were female. The most common complaint was palpable swelling (29.8%), while 38 (36.5%) were asymptomatic. Tru-cut (42.3%) and excisional (25.0%) biopsies were most frequent, and the breast (19.2%) and cervical and axillary lymph nodes (8.7% each) were the most common sites. Histopathology showed granulomatous inflammation in 49 (47.1%), caseating in 45 (43.3%), and non-caseating in 10 (9.6%). TB-PCR was positive in 23/44 (52.3%), tissue culture in 12/48 (25.0%), body fluid AFB smear in 3/22 (13.6%), and sputum AFB smear in 2/35 (5.7%). Patients with prior malignancy were significantly older ($p<0.001$), with no differences in microbiological or histopathological findings.

Extrapulmonary tuberculosis may closely mimic malignancy, particularly in breast and lymph node lesions. Histopathology remains the diagnostic cornerstone, while microbiological tests show limited sensitivity. Tuberculosis should be considered in the differential diagnosis of granulomatous lesions detected during malignancy work-up.

Keywords: Tuberculosis, Extrapulmonary Tuberculosis, Granulomatous Inflammation

Introduction

Despite significant advances in diagnosis and treatment, tuberculosis (TB) continues to represent a substantial global health burden. The World Health Organization estimates that more than 10 million new tuberculosis cases are reported each year worldwide. (1). In endemic regions, TB presents with a wide clinical spectrum and contributes substantially to morbidity, not only through pulmonary involvement but also through extrapulmonary disease. Extrapulmonary TB accounts for nearly 15–20% of all cases and most commonly involves the cervical lymph nodes, pleura, skeletal system, breast, peritoneum, and genitourinary tract (2,3).

Among these forms, breast and extrathoracic lymph node tuberculosis represent particular diagnostic challenges, as their clinical and radiological manifestations frequently resemble malignancy, potentially leading to delayed or inappropriate management (4). Although relatively uncommon, breast TB may present with features highly suggestive of cancer, including a palpable mass, fistula formation, skin changes, and axillary lymphadenopathy (5).

Histopathologically, the presence of caseating granulomas is considered characteristic of TB; however, similar granulomatous patterns may also

***Corresponding Author:** Özlem Düvenci Birben, MD Department of Chest Diseases, SBÜ Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ankara, Türkiye
E-mail: drozlemd.birben@gmail.com, Mobil Phone: +905434326161, phone: 0312 336 09 09, fax: 0312 334 03 52
ORCID ID: Özlem Düvenci Birben: 0009-0002-3631-6819, **Esma Sevil Akkurt:** 0000-0002-5416-3783, **Çigdem Ozdilekcan:** 0000-0001-5335-0571, **Gülşen İskender:** 0000-0001-7619-1366, **Mustafa Ertek:** 0000-0002-9397-8432, **Nazan Bozdogan:** 0000-0001-8484-5040, **Ayşen Atasoy:** 0009-0009-7968-3281, **Derya Yenibertiz:** 0000-0002-1783-4015
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be observed in sarcoidosis, fungal infections, and certain malignancies (6). This overlap underscores the importance of meticulous clinical and pathological evaluation in patients undergoing biopsy with a preliminary diagnosis of malignancy. Failure to consider TB in the differential diagnosis may result in unnecessary anxiety, additional invasive procedures, or delayed initiation of appropriate therapy.

In this retrospective study, we evaluated patients who underwent biopsy with a preliminary diagnosis of malignancy between 2019 and 2022 and were subsequently found to have granulomatous inflammation on histopathological examination, with a confirmed diagnosis of tuberculosis. The aim was to analyze the clinical, radiological, and laboratory findings, as well as the characteristics of biopsy specimens, in order to better define the diagnostic features of pulmonary and extrapulmonary TB in cases initially suspected of malignancy.

Materials and Methods

Study Design and Patient Selection: In this retrospective analysis, patients who were referred to the Department of Chest Diseases at an Oncology Branch Hospital between 2019 and 2022 and underwent excisional biopsy, incisional biopsy, tru-cut biopsy, or fine-needle aspiration biopsy (FNAB) were included. Among these patients, only cases with histopathologically confirmed granulomatous inflammation and a definitive diagnosis of tuberculosis were included.

Demographic characteristics of the included patients (age, sex, place of residence, occupation, and year of admission), clinical features (initial presenting complaints, preliminary clinical diagnoses, history of known malignancy prior to admission, if present the type, stage, extent of malignancy, and history of chemotherapy or radiotherapy), biopsy-related data (anatomical site of biopsy and biopsy method), and radiological findings (chest radiography, thoracic computed tomography, magnetic resonance imaging, and ultrasonography) were recorded in detail.

Patients diagnosed with extrapulmonary tuberculosis were additionally evaluated for a prior history of tuberculosis, history of contact (exposure), and radiographic evidence of active or sequelae tuberculosis on chest radiography.

Definition of Tuberculosis Diagnosis: A definitive diagnosis of tuberculosis was made when at least one of the following criteria was present: detection of acid-fast bacilli in sputum, body fluids, or biopsy material; confirmation by tuberculosis polymerase chain reaction testing; histopathological identification of caseating granulomatous inflammation in biopsy specimens; positive tissue culture; and/or clinical diagnosis consistent with tuberculosis.

Ethics Approval and Informed Consent: The study was approved by the Institutional Ethics Committee of the relevant hospital (Approval No: 2022-05/90; Date: 25/08/2022) and was conducted in accordance with the principles of the Declaration of Helsinki. Because the study had a retrospective design and used anonymized patient data, the Ethics Committee waived the requirement for written informed consent. Patient confidentiality was strictly maintained, and all data were analyzed in anonymized form.

Statistical Analysis: All statistical analyses were performed using R statistical software (version 4.5.2). Descriptive statistics were expressed as number (n), percentage (%), mean ± standard deviation (SD), or median (interquartile range [IQR]), as appropriate. The normality of continuous variables was assessed using the Shapiro–Wilk test and Q–Q plots. Comparisons between two independent groups were performed using the independent samples t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. A two-sided p value <0.05 was considered statistically significant. To identify factors independently associated with caseating granulomatous inflammation, a multivariable logistic regression analysis was performed. Age, sex, history of malignancy, and previous tuberculosis were entered into the model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results

A total of 104 patients were included in the study. Of these, 77 (74.0%) were female and 27 (26.0%) were male, with a median age of 54 years (IQR, 41–65 years). Occupational information was available for 74 patients, of whom 24 (32.4%) were housewives, 30 (40.5%) were employed, and 20 (27.0%) were retired.

The most common presenting complaint was a palpable swelling, reported in 31 patients (29.8%), followed by breast pain and fever (7 patients each, 6.7%), and cough (6 patients, 5.8%). Thirty-eight

Table 1: Baseline Demographic, Clinical, Radiological, Histopathological, and Microbiological Characteristics of The Study Population

Characteristic	N = 104
Sex	
Female	77 (74%)
Male	27 (26%)
Age	54 (41–65)
Occupation	
Housewife	24 (32%)
Employed	30 (41%)
Retired	20 (27%)
Presenting complaint	
Fever	7 (6.7%)
Leg pain	1 (1.0%)
Headache	1 (1.0%)
Low back pain	1 (1.0%)
Dyspepsia	1 (1.0%)
Joint pain	1 (1.0%)
Palpable swelling	31 (30%)
Night sweats	1 (1.0%)
Ocular symptoms	1 (1.0%)
Hemoptysis	1 (1.0%)
Non-healing wound	1 (1.0%)
Abdominal pain	5 (4.8%)
Breast pain	7 (6.7%)
Dyspnea	1 (1.0%)
Cough	6 (5.8%)
None	38 (37%)
Clinical preliminary diagnosis	
Actinic keratosis	1 (1.1%)
Acute bronchitis	1 (1.1%)
Acute lymphadenitis	1 (1.1%)
Amyloidosis	1 (1.1%)
Appendicitis	1 (1.1%)
Abscess	4 (4.3%)
Benign prostatic hyperplasia	1 (1.1%)
COVID-19	4 (4.3%)
Dyspepsia	1 (1.1%)
Embolism	2 (2.1%)
Encephalitis	1 (1.1%)
Galactocele	1 (1.1%)
Inflammatory bowel disease	1 (1.1%)
Abdominal mass	1 (1.1%)
Cholelithiasis	2 (2.1%)
Lymphadenitis	15 (16%)
Lymphoma	5 (5.3%)
Malignancy	21 (22%)

Characteristic	N = 104
Mastitis	9 (9.6%)
Unspecified breast mass	1 (1.1%)
Meningitis	1 (1.1%)
Metastasis	1 (1.1%)
Sarcoidosis	1 (1.1%)
Sequela	1 (1.1%)
Synovial sarcoma	1 (1.1%)
Other thyroid disorders	1 (1.1%)
Tuberculosis	2 (2.1%)
None	12 (13%)
History of malignancy	
No	78 (75%)
Yes	26 (25%)
Primary malignancy site	
Lung	1 (3.8%)
Brain and lung	1 (3.8%)
Endometrium	1 (3.8%)
Endocervix	1 (3.8%)
Hematological malignancy	5 (19%)
Lymph node	1 (3.8%)
Breast	7 (27%)
Stomach	4 (15%)
Omentum	1 (3.8%)
Oropharynx	1 (3.8%)
Rectum	1 (3.8%)
Cervix	1 (3.8%)
Ureter	1 (3.8%)
Active cancer treatment	
No	14 (67%)
Yes	7 (33%)
Smoking status	
Never smoker	9 (75%)
Former smoker	1 (8.3%)
Current smoker	2 (17%)
History of tuberculosis	
No	97 (93%)
Yes	7 (6.7%)
History of anti-tuberculosis treatment	
No	98 (94%)
Yes	6 (5.8%)
History of tuberculosis contact	
No	97 (93%)
Yes	7 (6.7%)
Chest radiography	
Normal	31 (46%)
Sequela	1 (1.5%)
Infiltration	36 (53%)

Characteristic	N = 104
Tumor markers	
Normal	6 (55%)
Elevated	5 (45%)
Biopsy technique	
Fine-needle biopsy	18 (18%)
Excisional biopsy	26 (26%)
Incisional biopsy	10 (10%)
Tru-cut biopsy	44 (44%)
Biopsy/Curettage	2 (2.0%)
Biopsy site	
Abdomen	1 (1.0%)
Lung	8 (7.7%)
Axillary lymph node	9 (8.7%)
Lower extremity	1 (1.0%)
Appendix	2 (1.9%)
Head, face, and neck	1 (1.0%)
Brain	1 (1.0%)
Unknown	4 (3.8%)
Bronchus	1 (1.0%)
Nose	1 (1.0%)
Eye	1 (1.0%)
Ileum	1 (1.0%)
Infraclavicular lymph node	1 (1.0%)
Inguinal lymph node	2 (1.9%)
Intrathoracic lymph node	4 (3.8%)
Bone marrow	2 (1.9%)
Arm	1 (1.0%)
Colon	1 (1.0%)
Lymph node	5 (4.8%)
Mediastinum	1 (1.0%)
Breast	20 (19%)
Mesenteric lymph node	1 (1.0%)
Stomach	1 (1.0%)
Omentum	1 (1.0%)
Shoulder soft tissue	2 (1.9%)
Parotid gland	1 (1.0%)
Peripheral lymph node	1 (1.0%)
Peritoneum	3 (2.9%)
Popliteal fossa	1 (1.0%)
Prostate	1 (1.0%)
Psoas muscle	1 (1.0%)
Gallbladder	2 (1.9%)
Cervical lymph node	9 (8.7%)
Submandibular lymph node	2 (1.9%)
Supraclavicular lymph node	3 (2.9%)
Thyroid	1 (1.0%)
Thigh	1 (1.0%)

Characteristic	N = 104
Vertebra	4 (3.8%)
Facial skin	1 (1.0%)
Department performing biopsy	
Neurosurgery	3 (2.9%)
Unknown	6 (5.8%)
Surgical oncology	7 (6.7%)
Internal medicine	3 (2.9%)
Dermatology	3 (2.9%)
Infectious diseases	6 (5.8%)
Gastroenterology	1 (1.0%)
General surgery	30 (29%)
Interventional radiology	6 (5.8%)
Thoracic surgery	5 (4.8%)
Chest diseases	6 (5.8%)
Ophthalmology	1 (1.0%)
Hematology	2 (1.9%)
Gynecologic oncology	1 (1.0%)
Otorhinolaryngology	13 (13%)
Breast and endocrine surgery	2 (1.9%)
Medical oncology clinic	1 (1.0%)
Orthopedics	3 (2.9%)
Medical oncology	4 (3.8%)
Urology	1 (1.0%)
Histopathological findings	
Granulomatous inflammation	49 (47%)
Caseating granulomatous inflammation	45 (43%)
Non-caseating granulomatous inflammation	10 (9.6%)
TB-PCR	
Negative	21 (48%)
Positive	23 (52%)
Tissue culture	
Negative	36 (75%)
Positive	12 (25%)
Sputum AFB smear	
Negative	33 (94%)
Positive	2 (5.7%)
Body fluid AFB smear	
Negative	19 (86%)
Positive	3 (14%)
QuantiFERON	
Negative	6 (38%)
Positive	5 (31%)
Indeterminate	5 (31%)
Anti-tuberculosis treatment	
No	1 (1.0%)
Yes	103 (99%)
Mortality	

Characteristic	N = 104
No	13 (100%)
Yes	0 (0%)
Response to anti-tuberculosis treatment	
No	1 (13%)
Yes	7 (88%)
COVID-19 pandemic period	
No	42 (40%)
Yes	62 (60%)

Data are presented as n (%) or median (Q1–Q3).
TB-PCR: Tuberculosis polymerase chain reaction; AFB: Acid-fast bacilli; COVID-19: Coronavirus disease 2019

patients (36.5%) were asymptomatic at presentation. Among the 91 patients with available clinical pre-diagnoses, the most frequent preliminary diagnoses were malignancy (21, 23.1%), lymphadenitis (15, 16.5%), and mastitis (9, 9.9%).

A previous history of malignancy was present in 26 patients (25.0%), most commonly involving the breast (7/26, 26.9%), hematological malignancies (5/26, 19.2%), and stomach (4/26, 15.4%). Active cancer treatment was documented in 7 of 21 patients (33.3%) with available treatment information. Previous tuberculosis, prior anti-tuberculosis treatment, and a history of tuberculosis contact were identified in 7 (6.7%), 6 (5.8%), and 7 (6.7%) patients, respectively.

Chest radiography findings were available for 68 patients. Normal radiographs were observed in 31 patients (45.6%), infiltrative abnormalities in 36 (52.9%), and sequela lesions in one patient (1.5%). In a representative case, thoracic computed tomography revealed enlarged subcarinal mediastinal lymph nodes initially suspected of malignancy, which were subsequently diagnosed as tuberculous granulomatous lymphadenitis on biopsy (Figure 1). Tru-cut biopsy (44 patients, 42.3%) and excisional biopsy (26 patients, 25.0%) were the most frequently used sampling methods. The breast (20 patients, 19.2%), axillary lymph nodes (9 patients, 8.7%), and cervical lymph nodes (9 patients, 8.7%) were the most common biopsy sites. Most specimens were obtained by the departments of General Surgery (30 patients, 28.8%) and Otorhinolaryngology (13 patients, 12.5%).

Histopathological examination demonstrated granulomatous inflammation in 49 patients (47.1%), caseating granulomatous inflammation in 45 (43.3%), and non-caseating granulomatous inflammation in 10 (9.6%). A representative specimen showed a necrotizing granuloma with central caseous necrosis bordered by an inflammatory infiltrate, consistent with tuberculous involvement (Figure 2). Among the patients who underwent microbiological testing, TB-PCR was positive in 23 of 44 patients (52.3%), tissue culture yielded growth in 12 of 48 (25.0%), sputum acid-fast bacilli (AFB) smear was positive in 2 of 35 (5.7%), and body fluid AFB smear was positive in 3 of 22 patients (13.6%). QuantiFERON testing was performed in 16 patients and yielded positive, negative, and indeterminate results in 5 (31.3%), 6 (37.5%), and 5 (31.3%) patients, respectively. Anti-tuberculosis treatment was administered to 103 of 104 patients (99.0%). Among the 13 patients with available mortality data, no deaths were recorded. Treatment response data were available for eight patients, of whom seven (87.5%) demonstrated a favorable response. Sixty-two patients (59.6%) were evaluated during the COVID-19 pandemic period. The demographic and clinical characteristics of the study population are presented in Table 1.

Patients with and without a history of malignancy were compared (Table 2). Patients with a previous history of malignancy were significantly older than those without malignancy (median age, 65 [IQR, 55–74] vs. 49 [IQR, 39–61] years; $p<0.001$). No statistically significant differences were observed between the groups regarding sex, previous tuberculosis, tuberculosis contact history, chest radiographic findings, histopathological pattern, microbiological test results, or pandemic period (all $p> 0.05$).

Male sex was significantly more frequent among PCR-positive patients than PCR-negative patients (39.1% vs. 9.5%; $p = 0.023$). In addition, PCR-positive patients were more frequently evaluated during the COVID-19 pandemic period (87.0% vs. 57.1%; $p = 0.027$). No significant differences were found between PCR-positive and PCR-negative

Table 2: Comparison of Patient Characteristics According To History of Malignancy

Characteristic	No (N = 78)	Yes (N = 26)	p-value
Sex			0.519
Female	59 (76%)	18 (69%)	
Male	19 (24%)	8 (31%)	
Age (years)	49 (39–61)	65 (55–74)	<0.001
Smoking status			0.470
Never smoker	5 (100%)	4 (57%)	
Former smoker	0 (0%)	1 (14%)	
Current smoker	0 (0%)	2 (29%)	
History of tuberculosis			0.064
No	75 (96%)	22 (85%)	
Yes	3 (3.8%)	4 (15%)	
History of anti-tuberculosis treatment			0.163
No	75 (96%)	23 (88%)	
Yes	3 (3.8%)	3 (12%)	
History of tuberculosis contact			0.363
No	74 (95%)	23 (88%)	
Yes	4 (5.1%)	3 (12%)	
Chest radiography			0.058
Normal	25 (53%)	6 (29%)	
Sequela	0 (0%)	1 (4.8%)	
Infiltration	22 (47%)	14 (67%)	
Tumor markers			0.182
Normal	0 (0%)	6 (67%)	
Elevated	2 (100%)	3 (33%)	
Histopathological findings			0.947
Granulomatous inflammation	37 (47%)	12 (46%)	
Caseating granulomatous inflammation	33 (42%)	12 (46%)	
Non-caseating granulomatous inflammation	8 (10%)	2 (7.7%)	
TB-PCR			0.601
Negative	15 (45%)	6 (55%)	
Positive	18 (55%)	5 (45%)	
Tissue culture			>0.999
Negative	28 (74%)	8 (80%)	
Positive	10 (26%)	2 (20%)	
Sputum AFB smear			0.092
Negative	24 (100%)	9 (82%)	
Positive	0 (0%)	2 (18%)	
Body fluid AFB smear			0.470
Negative	16 (89%)	3 (75%)	
Positive	2 (11%)	1 (25%)	
QuantiFERON			0.732
Negative	4 (31%)	2 (67%)	
Positive	4 (31%)	1 (33%)	
Indeterminate	5 (38%)	0 (0%)	

Characteristic	No (N = 78)	Yes (N = 26)	p-value
Anti-tuberculosis treatment			0.250
No	0 (0%)	1 (3.8%)	
Yes	78 (100%)	25 (96%)	
Mortality			>0.999
No	9 (100%)	4 (100%)	
Yes	0 (0%)	0 (0%)	
Response to anti-tuberculosis treatment			0.250
No	0 (0%)	1 (50%)	
Yes	6 (100%)	1 (50%)	
COVID-19 pandemic period			0.489
No	30 (38%)	12 (46%)	
Yes	48 (62%)	14 (54%)	
Granuloma type			0.947
Caseating	33 (42%)	12 (46%)	
Granulomatous	37 (47%)	12 (46%)	
Non-caseating	8 (10%)	2 (7.7%)	

Data are presented as n (%) or median (Q1–Q3). P-values were calculated using Pearson's chi-square test, Fisher's exact test, or the Wilcoxon rank-sum test, as appropriate.
TB-PCR: Tuberculosis polymerase chain reaction; AFB: Acid-fast bacilli; COVID-19: Coronavirus disease 2019

patients regarding age, malignancy history, previous tuberculosis, histopathological findings, microbiological culture results, or other clinical variables (all p> 0.05). Comparisons according to TB-PCR status are presented in Table 3.

Patients were further categorized according to histopathological findings as caseating granulomatous inflammation (n = 45) and non-caseating/granulomatous inflammation (n = 59) (Table 4). No statistically significant differences were observed between the groups with respect to demographic characteristics, malignancy history, tuberculosis-related variables, chest radiographic findings, biopsy site, microbiological test results, treatment variables, or pandemic period (all p> 0.05).

Finally, multivariable logistic regression analysis was performed to identify independent factors associated with caseating granulomatous inflammation. Age, sex, history of malignancy, and previous tuberculosis were included in the model. None of these variables was independently associated with the presence of caseating granulomatous inflammation (all p > 0.05) (Table 5).

Discussion

The clinical, radiological, and microbiological characteristics of histopathologically confirmed tuberculosis cases were examined in the present study. The findings demonstrate that extrapulmonary lesions, in particular, may mimic malignancy and potentially lead to delays in diagnosis. In patients with a previous history of malignancy, this similarity may further complicate diagnostic evaluation and may increase the need for invasive diagnostic procedures. These findings highlight the importance of including tuberculosis in the differential diagnosis of patients presenting with granulomatous inflammation. Notably, patients with a history of malignancy were significantly older than those without malignancy, whereas no significant differences were observed regarding histopathological patterns, microbiological findings, or radiological features. These findings suggest that although a previous malignancy may increase clinical suspicion, it does not appear to alter the clinicopathological presentation of tuberculosis in this cohort. The demographic characteristics observed in the present study are generally in line with previously reported findings in the literature. Previous studies have suggested that female sex is associated with an increased risk of extrapulmonary tuberculosis (EPTB) (7). Similarly, in our series, the proportion of female patients was markedly higher than that of males. This finding may be related to hormonal, immunological, or social factors. With respect to age distribution, several studies have highlighted that EPTB is more frequently observed in middle-aged individuals, while the risk increases in older populations due to age-related immune decline

Table 3: Comparison of Patient Characteristics According to TB-PCR Results

Characteristic	Negative (N = 21)	Positive (N = 23)	p-value
Sex			0.023
Female	19 (90%)	14 (61%)	
Male	2 (9.5%)	9 (39%)	
Age (years)	53 ± 16	49 ± 15	0.353
History of malignancy			0.601
No	15 (71%)	18 (78%)	
Yes	6 (29%)	5 (22%)	
Smoking status			>0.999
Never smoker	3 (75%)	2 (67%)	
Former smoker	0 (0%)	0 (0%)	
Current smoker	1 (25%)	1 (33%)	
History of tuberculosis			>0.999
No	20 (95%)	21 (91%)	
Yes	1 (4.8%)	2 (8.7%)	
History of anti-tuberculosis treatment			>0.999
No	20 (95%)	21 (91%)	
Yes	1 (4.8%)	2 (8.7%)	
History of tuberculosis contact			0.609
No	20 (95%)	20 (87%)	
Yes	1 (4.8%)	3 (13%)	
Chest radiography			>0.999
Normal	8 (53%)	8 (44%)	
Sequela	0 (0%)	1 (5.6%)	
Infiltration	7 (47%)	9 (50%)	
Tumor markers			0.400
Normal	2 (100%)	1 (33%)	
Elevated	0 (0%)	2 (67%)	
Histopathological findings			0.742
Granulomatous inflammation	10 (48%)	9 (39%)	
Caseating granulomatous inflammation	10 (48%)	11 (48%)	
Non-caseating granulomatous inflammation	1 (4.8%)	3 (13%)	
Tissue culture			>0.999
Negative	13 (72%)	15 (75%)	
Positive	5 (28%)	5 (25%)	
Sputum AFB smear			>0.999
Negative	15 (94%)	12 (100%)	
Positive	1 (6.3%)	0 (0%)	
Body fluid AFB smear			0.521
Negative	7 (100%)	11 (85%)	
Positive	0 (0%)	2 (15%)	
QuantiFERON			>0.999
Negative	3 (50%)	1 (50%)	
Positive	1 (17%)	1 (50%)	
Indeterminate	2 (33%)	0 (0%)	

Characteristic	Negative (N = 21)	Positive (N = 23)	p-value
Anti-tuberculosis treatment			0.477
No	1 (4.8%)	0 (0%)	
Yes	20 (95%)	23 (100%)	
Mortality			>0.999
No	1 (100%)	8 (100%)	
Yes	0 (0%)	0 (0%)	
Response to anti-tuberculosis treatment			0.200
No	1 (100%)	0 (0%)	
Yes	0 (0%)	4 (100%)	
COVID-19 pandemic period			0.027
No	9 (43%)	3 (13%)	
Yes	12 (57%)	20 (87%)	
Granuloma type			0.742
Caseating	10 (48%)	11 (48%)	
Granulomatous	10 (48%)	9 (39%)	
Non-caseating	1 (4.8%)	3 (13%)	

Data are presented as n (%) or mean ± standard deviation (SD). P-values were calculated using Pearson's chi-square test, Welch's two-sample t-test, or Fisher's exact test, as appropriate.
TB-PCR: Tuberculosis polymerase chain reaction; AFB: Acid-fast bacilli; COVID-19: Coronavirus disease 2019

(3,8). Data reported from Türkiye have shown comparable results, indicating that EPTB is more commonly detected in women and that age represents an important determinant (9). In this context, early consideration of EPTB in the differential diagnosis, particularly in older female patients, may contribute to a more rapid diagnostic process and reduction in morbidity.

Chest radiography was available for 68 patients, of whom 45.6% had normal findings, 52.9% demonstrated infiltrative abnormalities, and 1.5% had sequela lesions. These findings are consistent with the literature. In one study, approximately 86% of patients diagnosed with EPTB had normal chest radiographs, whereas more advanced pathological findings could be detected with thoracic computed tomography (10). Furthermore, guidelines from the World Health Organization (WHO) and the European Respiratory Society (ERS) emphasize that although chest radiography has high sensitivity, its specificity is limited and the method is subject to interobserver variability (11,12). Therefore, chest radiography should be regarded as a complementary diagnostic tool. In the presence of clinical suspicion, advanced imaging modalities and histopathological evaluation remain indispensable for accurate diagnosis. The diagnostic approach in extrapulmonary tuberculosis is often more complex and time-consuming compared with pulmonary TB. Due to the relatively low sensitivity of microbiological methods, histopathological examination frequently constitutes the cornerstone of diagnosis in many cases (3). Although caseating granulomatous inflammation is considered highly suggestive of tuberculosis, our comparative analyses demonstrated no significant clinical, radiological, or microbiological differences between patients with caseating and non-caseating/granulomatous inflammation. Furthermore, multivariable logistic regression analysis did not identify age, sex, history of malignancy, or previous tuberculosis as independent predictors of caseating granuloma formation. Therefore, biopsy procedures play an essential role in establishing the diagnosis. Consistent with previous reports, tru-cut biopsy and excisional biopsy were the most frequently utilized diagnostic methods in our cohort (13,14).

In recent years, molecular tests have increasingly been incorporated into the diagnostic work-up of extrapulmonary TB. Polymerase chain reaction–based assays, such as Xpert MTB/RIF, demonstrate high specificity; however, their sensitivity in extrapulmonary samples is heterogeneous and varies depending on specimen type (15). Accordingly, a positive polymerase chain reaction result provides supportive evidence for the diagnosis, whereas a negative result does not rule out tuberculosis. In the present study, TB-PCR positivity was detected in 52.3% of the tested patients, which is comparable to the

Table 4: Comparison of Patient Characteristics According To Granuloma Type

Characteristic	Caseating (N = 45)	Non-caseating (N = 59)	p-value
Sex			0.134
Female	30 (67%)	47 (80%)	
Male	15 (33%)	12 (20%)	
Age (years)	53 (41–65)	55 (41–65)	0.531
History of malignancy			0.732
No	33 (73%)	45 (76%)	
Yes	12 (27%)	14 (24%)	
Smoking status			0.470
Never smoker	4 (80%)	5 (71%)	
Former smoker	1 (20%)	0 (0%)	
Current smoker	0 (0%)	2 (29%)	
History of tuberculosis			0.696
No	43 (96%)	54 (92%)	
Yes	2 (4.4%)	5 (8.5%)	
History of anti-tuberculosis treatment			0.696
No	43 (96%)	55 (93%)	
Yes	2 (4.4%)	4 (6.8%)	
History of tuberculosis contact			>0.999
No	42 (93%)	55 (93%)	
Yes	3 (6.7%)	4 (6.8%)	
Chest radiography			0.898
Normal	14 (44%)	17 (47%)	
Sequela	0 (0%)	1 (2.8%)	
Infiltration	18 (56%)	18 (50%)	
Tumor markers			>0.999
Normal	3 (50%)	3 (60%)	
Elevated	3 (50%)	2 (40%)	
Biopsy site			0.694
Lung/Bronchus/Mediastinum/Intrathoracic lymph node	6 (15%)	8 (17%)	
Axillary lymph node	2 (5.0%)	7 (15%)	
Head and neck	3 (7.5%)	3 (6.3%)	
Other lymph nodes	4 (10%)	6 (13%)	
Intra-abdominal	8 (20%)	6 (13%)	
Bone/Vertebra/Soft tissue	3 (7.5%)	3 (6.3%)	
Breast	8 (20%)	12 (25%)	
Cervical lymph node	6 (15%)	3 (6.3%)	
TB-PCR			0.989
Negative	10 (48%)	11 (48%)	
Positive	11 (52%)	12 (52%)	
Tissue culture			0.738
Negative	16 (73%)	20 (77%)	
Positive	6 (27%)	6 (23%)	
Sputum AFB smear			0.229
Negative	15 (88%)	18 (100%)	
Positive	2 (12%)	0 (0%)	
Body fluid AFB smear			>0.999
Negative	10 (83%)	9 (90%)	
Positive	2 (17%)	1 (10%)	
QuantiFERON			0.179
Negative	3 (50%)	3 (30%)	
Positive	0 (0%)	5 (50%)	

Characteristic	Caseating (N = 45)	Non-caseating (N = 59)	p-value
Indeterminate	3 (50%)	2 (20%)	
Anti-tuberculosis treatment			0.433
No	1 (2.2%)	0 (0%)	
Yes	44 (98%)	59 (100%)	
Mortality			>0.999
No	7 (100%)	6 (100%)	
Yes	0 (0%)	0 (0%)	
Response to anti-tuberculosis treatment			>0.999
No	1 (20%)	0 (0%)	
Yes	4 (80%)	3 (100%)	
COVID-19 pandemic period			0.944
No	18 (40%)	24 (41%)	

Data are presented as n (%) or median (Q1–Q3). P-values were calculated using Pearson's chi-square test, Fisher's exact test, or the Wilcoxon rank-sum test, as appropriate.
TB-PCR: Tuberculosis polymerase chain reaction; AFB: Acid-fast bacilli; COVID-19: Coronavirus disease 2019

Table 5: Multivariable Logistic Regression Analysis For Factors Associated With Caseating Granulomatous Inflammation

Characteristic	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Age (years)	0.98	0.95–1.01	0.211
Sex			0.075
Female	Reference	—	
Male	2.32	0.92–6.07	
History of malignancy			0.327
No	Reference	—	
Yes	1.69	0.59–4.91	
History of tuberculosis			0.154
No	Reference	—	
Yes	0.28	0.03–1.58	

Abbreviations: CI, confidence interval; OR, odds ratio

variable sensitivities reported in previous studies of extrapulmonary tuberculosis. Interestingly, PCR positivity was significantly more frequent among male patients and among those evaluated during the COVID-19 pandemic period. However, no significant associations were observed with previous malignancy, histopathological pattern, or other microbiological findings. This finding should be interpreted with caution, as the higher PCR positivity observed during the COVID-19 pandemic may reflect changes in referral patterns, patient selection, or diagnostic practices rather than a true biological association.

Extrapulmonary tuberculosis frequently mimics malignancy, lymphoma, or other inflammatory conditions in clinical practice. Particularly in cases involving breast tissue and peripheral lymph nodes, TB is often overlooked in the initial differential diagnosis, and patients are referred for advanced diagnostic procedures with a preliminary suspicion of malignancy (3). In our study, malignancy was the most commonly reported preliminary clinical diagnosis, which aligns with findings in the literature. In rare forms such as breast tuberculosis, clinical features including mass formation, pain, axillary lymphadenopathy, and fistula are frequently reported and may strongly resemble malignant disease (4,16).

Lymph node tuberculosis, especially when localized in the cervical region, may be confused with lymphoma, leading to diagnostic delays and unnecessary invasive interventions (17). It has been reported that failure to consider TB among the leading preliminary diagnoses may delay diagnosis by an average of 2–6 months (18). Accordingly, tuberculosis should be included in the differential diagnosis of granulomatous diseases. Due to overlapping clinical and

radiological features, definitive distinction is often possible only through histopathological evaluation.

Several limitations of this study should be acknowledged. First, because of the retrospective design, complete access to some clinical data was not always available. In addition, etiological confirmation by culture, polymerase chain reaction, or acid-fast bacilli staining could not be achieved in all cases with histopathologically identified granulomatous inflammation, which may have resulted in potential classification bias. The single-center nature of the study also limits the generalizability of the findings. Nevertheless, the systematic evaluation of a relatively large patient cohort constitutes a major strength of the study.

Although microbiological tests represent the gold standard for diagnosing tuberculosis, their sensitivity remains limited, particularly in extrapulmonary disease. Insufficient sample volume, low bacillary load, and technical constraints contribute to this limitation. Consequently, in many cases without microbiological confirmation, histopathological examination becomes the decisive diagnostic modality. Although caseating granulomatous inflammation is traditionally regarded as highly suggestive of tuberculosis, our findings indicate that histopathological diagnosis should always be interpreted together with clinical and microbiological data. In our study, microbiological positivity remained modest despite comprehensive microbiological evaluation, whereas histopathological findings constituted the principal basis for diagnosis. These findings further support the indispensable role of tissue diagnosis in patients with suspected extrapulmonary tuberculosis presenting as possible malignancy.

In conclusion, tuberculosis should always be considered in the differential diagnosis of granulomatous lesions identified during the evaluation of suspected malignancy. This is particularly important in patients with breast and lymph node lesions, where extrapulmonary tuberculosis may closely mimic malignant disease. Because microbiological confirmation is frequently limited in extrapulmonary tuberculosis, histopathological examination remains a cornerstone of diagnosis. A comprehensive approach integrating clinical, radiological, microbiological, and histopathological findings is essential to achieve an accurate diagnosis, avoid unnecessary invasive procedures, and ensure timely initiation of appropriate treatment.

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