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Original Research Article

Clinical, Radiological and Microbiological Characteristics of Smear-Negative Pulmonary Tuberculosis: A Prospective Observational Study

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Abstract

Background: Smear-negative pulmonary tuberculosis is difficult to diagnose because of its low bacillary burden and variable clinical and radiological presentation. Additional molecular, culture and respiratory sampling methods may improve microbiological confirmation.

Materials and Methods: This hospital-based prospective observational study included 150 adults with clinical or radiological features suggestive of pulmonary tuberculosis and at least two sputum smears negative for acid-fast bacilli. Patient enrolment was conducted from January to June 2025 at RVRS Medical College, Bhilwara, and Rajasthan. Clinical characteristics and imaging findings were recorded. Spontaneous sputum was examined using CBNAAT and mycobacterial culture.

Results: The mean age was 42.6±15.2 years, and 60.7% were male. Cough (82.7%), fever (70.0%), weight loss (66.0%) and loss of appetite (62.7%) were the predominant symptoms. Consolidation or infiltration (48.0%) was the most common chest radiographic finding. Among 90 patients undergoing chest computed tomography, centrilobular nodules (64.4%) and tree-in-bud opacities (46.7%) were common. Spontaneous sputum CBNAAT and culture confirmed pulmonary tuberculosis in 58 patients (38.7%). Induced sputum confirmed three additional cases and bronchoalveolar lavage confirmed two, increasing overall microbiological confirmation to 63 patients (42.0%). The remaining 87 patients (58.0%) fulfilled the criteria for clinically diagnosed pulmonary tuberculosis after eight weeks of follow-up.

Conclusion: Smear-negative pulmonary tuberculosis had a variable clinical and imaging profile. Sequential use of CBNAAT, culture, induced sputum and bronchoalveolar lavage improved microbiological confirmation. Diagnosis in microbiologically unconfirmed patients required integrated clinical, radiological and follow-up assessment.

Keywords: Bronchoalveolar lavage; CBNAAT; Mycobacterial culture; Pulmonary tuberculosis; Smear-negative tuberculosis.

Introduction

Tuberculosis (TB) continues to contribute substantially to illness and death from infectious diseases, although effective methods for its prevention and treatment are available. An estimated 10 million people developed TB in 2018, and more than 1.5 million deaths were attributed to the disease. Pulmonary tuberculosis (PTB) accounts for approximately 85% of TB cases in India and represents the main source of transmission. [1] Timely identification of pulmonary disease is therefore important for initiating treatment and limiting further spread. Sputum microscopy for acid-fast bacilli (AFB) is commonly used for the initial evaluation of patients with suspected PTB because it is inexpensive, rapid and widely available. However, it detects only 50–70% of culture-confirmed cases, with lower sensitivity in patients who have a small number of bacilli. [2,3]. Mycobacterial culture provides greater sensitivity and specificity and is regarded as the microbiological reference standard. Its clinical utility is limited by the time required for growth, approximately six weeks in liquid culture and eight weeks on solid media. [4,5] Rapid molecular methods were developed to reduce the diagnostic delay associated with conventional culture. Xpert

MTB/RIF, also referred to as the cartridge-based nucleic acid amplification test (CBNAAT), simultaneously detects Mycobacterium tuberculosis and rifampicin resistance. The World Health Organization recommends its use as an initial investigation for TB and rifampicin-resistant TB. [6] Nevertheless, the performance of CBNAAT is influenced by bacillary load, and its sensitivity is lower in smear-negative and paucibacillary disease.

Pulmonary tuberculosis may be diagnosed on the basis of clinical, microbiological and radiological evidence. Establishing the diagnosis is more difficult when sputum smears are negative because additional microbiological investigations may also fail to detect the organism. More than 40% of patients with PTB may not have bacteriological confirmation and may be treated on the basis of compatible symptoms and imaging findings. Access to rapid molecular testing also remains unequal, and only about one-third of newly diagnosed patients receive GeneXpert as the initial diagnostic test in some settings. This limitation has particular relevance among people living with HIV, in whom PTB is often paucibacillary and requires prompt diagnosis. [7]

Clinical assessment and thoracic imaging remain important when sputum smear microscopy and GeneXpert are negative. [8,9] Chest radiography and computed tomography may show consolidation, nodules, cavitation, centrilobular opacities, a tree-in-bud pattern, lymphadenopathy or pleural abnormalities. Reliance on these features without adequate microbiological evaluation may consequently result in delayed treatment, incorrect diagnosis or unnecessary exposure to antitubercular drugs. [10-13] Diagnostic delay in smear-negative PTB has been associated with poor outcomes, and higher mortality than that observed in smear-positive disease has been reported in some populations. Delayed recognition and treatment initiation may partly account for this difference. [14,15] Although CBNAAT has improved the detection of smear-negative disease in research settings, nearly 43% of PTB cases may remain undiagnosed under routine field conditions. [16]

An approach that integrates clinical assessment, chest imaging, CBNAAT and mycobacterial culture may improve the identification of smear-negative PTB. Induced sputum and bronchoalveolar lavage may provide additional respiratory specimens when spontaneous sputum investigations are negative or inadequate. However, local evidence regarding the clinical presentation and microbiological profile of smear-negative PTB remains limited. The present study was therefore undertaken to assess the clinical and microbiological characteristics of patients with smear-negative pulmonary tuberculosis.

Materials and Methods

This hospital-based prospective observational study was conducted in the Department of Medicine in collaboration with the Department of Microbiology at RVRS Medical College, Bhilwara, and Rajasthan. Patient enrolment was conducted from January to June 2025, and enrolled patients were followed for a minimum of eight weeks after treatment initiation.

Adult patients attending the outpatient department or admitted to the hospital with clinical or radiological features suggestive of pulmonary tuberculosis were screened for eligibility. Patients aged 18 years or above who had symptoms suggestive of pulmonary tuberculosis, chest radiography or computed tomography findings compatible with pulmonary tuberculosis, and at least two sputum specimens negative for acid-fast bacilli on smear microscopy were included. Patients with smear-positive pulmonary tuberculosis, isolated extrapulmonary tuberculosis, an already established alternative diagnosis, previous antitubercular treatment exceeding seven days, inability to undergo the required investigations, or refusal to provide written informed consent were excluded.

The final sample size was 150 patients. Eligible patients were recruited consecutively until the required sample size was achieved. After obtaining written informed consent, demographic and clinical information was recorded using a predesigned study proforma. Information regarding contact with a patient with tuberculosis, previous tuberculosis, prior antitubercular treatment, and relevant comorbidities was also collected. Confidentiality was maintained by assigning a unique identification number to each participant. All investigations and treatment decisions were made according to the prevailing guidelines of the National Tuberculosis Elimination Programme.

Chest radiography was performed in all patients. Radiological findings were recorded as consolidation or infiltration, cavitation, nodular opacities, fibrotic changes, bronchiectatic changes, miliary opacities, pleural effusion, hilar or mediastinal lymphadenopathy and collapse or atelectasis. Computed tomography of the chest was performed when clinically indicated.

At least two sputum specimens, including an early-morning specimen wherever feasible, were collected from each patient. The quality and volume of the specimens were assessed before microbiological processing. Sputum smear microscopy was performed using Ziehl–Neelsen staining. Patients with negative results in both sputum specimens were classified as having smear-negative presumptive pulmonary tuberculosis. At

least one sputum specimen was subsequently tested by CBNAAT/Xpert MTB/RIF for the detection of Mycobacterium tuberculosis complex and rifampicin resistance. Mycobacterial culture was performed according to the available laboratory facilities. Patients whose spontaneous sputum CBNAAT and mycobacterial culture were negative but who continued to have clinical or radiological features suggestive of pulmonary tuberculosis were assessed for sputum induction. Bronchoscopy was performed only when clinically indicated and after obtaining specific consent. Bronchoalveolar lavage specimens were examined by AFB smear microscopy, CBNAAT and mycobacterial culture.

Operational definitions

Smear-negative presumptive pulmonary tuberculosis: A patient with clinical or radiological features suggestive of pulmonary tuberculosis and at least two sputum specimens negative for acid-fast bacilli on smear microscopy.

Microbiologically confirmed pulmonary tuberculosis: Detection of M. tuberculosis in sputum, induced sputum or bronchoalveolar lavage by CBNAAT/Xpert MTB/RIF or mycobacterial culture.

Clinically diagnosed pulmonary tuberculosis: A patient with smear-negative presumptive pulmonary tuberculosis was classified as having clinically diagnosed pulmonary tuberculosis when microbiological investigations were negative, clinical and radiological findings remained compatible with tuberculosis, no more likely alternative diagnosis was identified, and clinical and/or radiological improvement was documented after a minimum of eight weeks of antitubercular treatment.

Patients without microbiological confirmation were followed for a minimum of eight weeks after initiation of antitubercular treatment. Clinical response was assessed by improvement in presenting symptoms, including cough, fever, appetite and weight-related complaints. Radiological response was assessed by improvement in previously documented chest radiographic or CT abnormalities, where repeat imaging was clinically indicated.

Patients who did not improve were reassessed for treatment adherence, drug resistance and alternative diagnoses.

Statistical Analysis: The collected data were entered into Microsoft Excel and analysed using SPSS. Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as mean with standard deviation. The chi-square test was used to compare categorical variables. A p-value below 0.05 was considered statistically significant.

Results

[Table-1] In our study, the mean age of the patients was 42.6 ± 15.2 years. Maximum proportion belonged to the 31–40-year age group. Males constituted 60.7% of the study population, with a male-to-female ratio of 1.54:1.

In our study, smoking was the most commonly reported behavioural risk factor in 60(40.0%), followed by use of smokeless tobacco in 43(28.7%) patients, while 29 patients (19.3%) had a history of alcohol consumption. A history of contact with a patient with tuberculosis was present in 30(20.0%) patients, and 24(16.0%) patients had previously been treated for tuberculosis. Diabetes mellitus was the most common comorbidity in 31(20.7%) patients, followed by hypertension in 22(14.7%) and COPD or another chronic respiratory disease in 17 (11.3%). Chronic kidney disease was reported in six patients (4.0%), while five patients (3.3%) were HIV-positive. Overall, 78 patients (52.0%) had no identified comorbidity.

In our study, Cough was the most common presenting symptom in 124(82.7%) patients. Fever was present in 105(70.0%) patients, while 99(66.0%) patients reported weight loss and 94 (62.7%) had loss of appetite. Expectoration was present in 83(55.3%) patients, Night sweats were reported by 62(41.3%) patients, and breathlessness was present in 55 (36.7%). Chest pain was reported by 41 patients (27.3%). Haemoptysis was the least frequently reported symptom in 18(12.0%) patients.

[Table -2] Most patients had symptoms for 2–6 weeks (34.0%), followed by 6–12 weeks (30.7%) and more than 12 weeks (23.3%). Only 12.0% presented within two weeks of symptom onset.

Chest radiographic findings: Consolidation or infiltration was the most common chest radiographic finding in 72(48.0%) patients. Nodular opacities were present in 45(30.0%) patients, while fibrotic changes were identified in 35 (23.3%). Cavitary lesions were observed in 30(20.0%) patients. Bronchiectatic changes were observed in 24(16.0%) patients, and hilar or mediastinal lymphadenopathy was present in 21 (14.0%). Pleural effusion was detected in 18(12.0%) patients, while collapse or atelectasis was noted in 10 (6.7%). Miliary opacities were the least common finding and were observed in six patients (4.0%). No definite radiographic abnormality was identified in 12 patients (8.0%).

Computed tomography findings: Chest computed tomography was performed in 90 patients who had persistent clinical suspicion, inconclusive chest

radiographic findings or required further characterisation of pulmonary lesions. Centrilobular nodules were the most common CT finding in 58(64.4%) patients. A tree-in-bud appearance was present in 42 patients (46.7%), while consolidation was detected in 39 (43.3%). Cavitary lesions were identified on CT in 26(28.9%) patients. Bronchiectasis was present in 24(26.7%) patients, while fibrotic changes were observed in 18 (20.0%). Mediastinal or hilar lymphadenopathy was detected in 15 patients (16.7%), and pleural involvement was present in 11 (12.2%). Collapse or atelectasis was the least common CT finding and was observed in eight patients (8.9%).

In current study, among the 150 patients with smear-negative presumptive pulmonary tuberculosis, 37 (24.7%) were positive for Mycobacterium tuberculosis by both CBNAAT and culture. Eight patients (5.3%) were CBNAAT-positive but culture-negative, while 13 (8.7%) were CBNAAT-negative but culture-positive, leaving 92(61.3%) patients without confirmation. Of these, 40 underwent sputum induction, and three additional patients were confirmed. After this stage, 89 patients remained microbiologically unconfirmed. Fibreoptic bronchoscopy with bronchoalveolar lavage was performed in 35 selected patients with persistent clinical or radiological suspicion and confirmed two additional cases. Overall, 63 patients (42.0%) were microbiologically confirmed. The remaining 87 patients (58.0%) were evaluated clinically and followed after initiation of antitubercular treatment.

[Table- 4] A previous history of tuberculosis was present in 11.1% of microbiologically confirmed patients and 19.5% of clinically diagnosed patients. The association between previous tuberculosis and microbiological confirmation was not statistically significant (χ^2=1.93, p=0.165).

Table 1: Age and sex wise distribution of patients (n=150)

Characteristic	Number	Percentage
Age group (years)		
18–30	38	25.3
31–40	43	28.7
41–50	30	20
51–60	24	16
>60	15	10
Sex		
Male	91	60.7
Female	59	39.3

Table 2: Duration of symptoms before presentation (n=150)

Duration of symptoms	Number	Percentage
≤2 weeks	18	12
>2–6 weeks	51	34
>6–12 weeks	46	30.7
>12 weeks	35	23.3
Total	**150**	**100**

Table 3: Sequential microbiological confirmation according to specimen type

Diagnostic stage	Patients eligible	Patients tested	Positive by both tests	CBNAAT only positive	Culture only positive	Newly confirmed	Cumulative confirmed
Spontaneous sputum	150	150	37	8	13	58	58
Induced sputum	92	40	1	1	1	3	61
Bronchoalveolar lavage	89	35	1	0	1	2	63

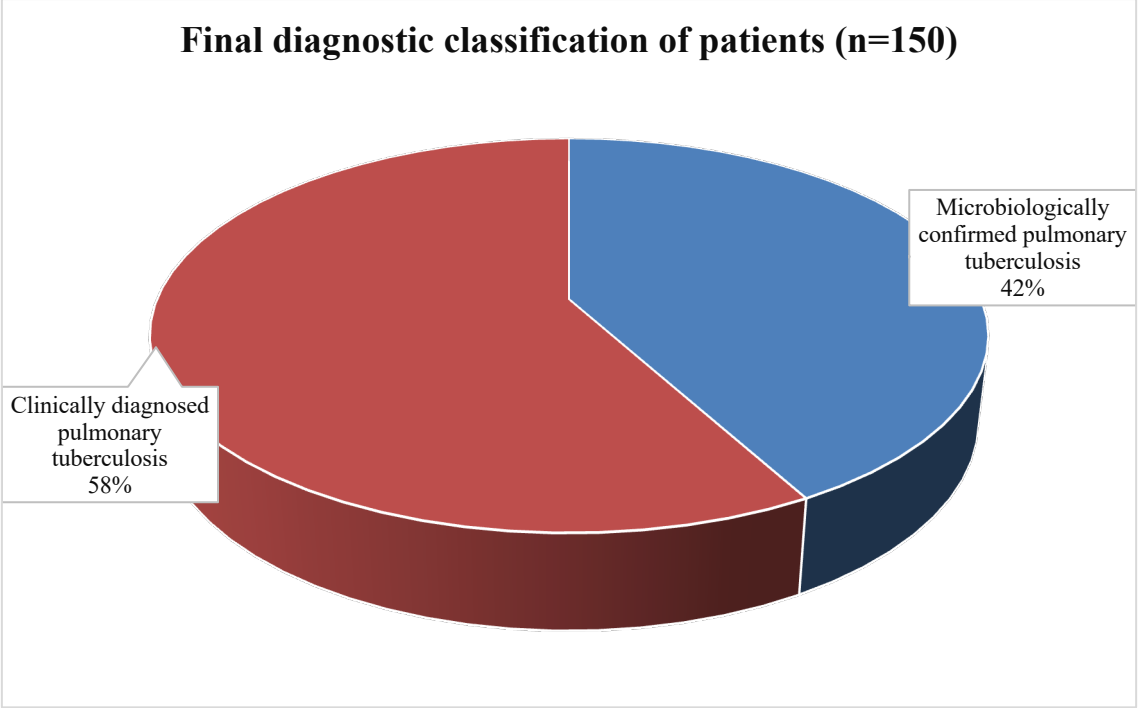

Figure 1: Final diagnostic classification of patients (n=150)

Table 4: Association between previous tuberculosis and microbiological confirmation (n=150)

Previous history of tuberculosis	Microbiologically confirmed, n (%)	Clinically diagnosed, n (%)	Total
Present	7 (11.1)	17 (19.5)	24
Absent	56 (88.9)	70 (80.5)	126
Total	**63 (100.0)**	**87 (100.0)**	**150**

Discussion

The present prospective observational study evaluated the clinical, radiological and microbiological characteristics of 150 adults with smear-negative presumptive pulmonary tuberculosis. Microbiological confirmation was obtained in 63 patients (42.0%), while the remaining 87 patients (58.0%) were diagnosed clinically.

Age distribution: In our study, the mean age of the patients in the present study was 42.6 ± 15.2 years. The largest proportion belonged to the 31–40-year age group.

This indicates that smear-negative pulmonary tuberculosis commonly affected young and middle-aged adults. The predominance of this age group may reflect greater occupational exposure, social contact and mobility.

Nguyen et al [17] reported a median age of 42 years among patients with culture-negative pulmonary tuberculosis. Kadian et al18 found that 48.7% of their smear-negative patients were aged 31–60 years, while Johar et al [19] reported that 59.3% belonged to the 20–40-year age group. Campos et al [20] observed a mean age of 46.6 ± 17.1 years among 129 patients with smear-negative pulmonary tuberculosis.

Risk factors, exposure history and comorbidities: In current study, Smoking was the most common behavioural risk factor reported by 40.0% of patients. Smokeless tobacco use was present in 28.7%, while 19.3% had a history of alcohol consumption. Tobacco smoke can impair mucociliary clearance and local pulmonary immune responses, which may increase susceptibility to pulmonary infection.

The frequency of smoking was close to the 38.7% reported by Johar et al [19] but lower than the 51.3% reported by Kadian et al [18] Campos et al [20] reported 36.4% current smokers and 14.7% former smokers among smear-negative patients.

A history of contact with a patient with tuberculosis was present in 20.0% of patients, while 16.0% had a previous history of tuberculosis. Previous tuberculosis may complicate diagnosis because residual fibrosis, bronchiectasis and nodular opacities can resemble active disease.

Diabetes mellitus was the most common comorbidity in the present study and was present in 20.7% of patients. This was closely comparable to the 22.0% reported by Johar et al [19] Diabetes

may increase susceptibility to tuberculosis through impaired cellular immunity and reduced macrophage function. Hypertension was present in 14.7%, while COPD or another chronic respiratory disease was present in 11.3%. The coexistence of chronic respiratory disease may complicate clinical and radiological assessment because cough, breathlessness, fibrosis and bronchiectatic changes may not be specific to tuberculosis.

Clinical Characteristics: Cough was the most common presenting symptom and was reported by 82.7% of patients. Fever was present in 70.0%, weight loss in 66.0%, loss of appetite in 62.7%, and expectoration in 55.3%. These findings suggest that patients with smear-negative pulmonary tuberculosis may continue to have classical respiratory and constitutional symptoms despite the absence of bacilli on smear microscopy.

Kadian et al [18] reported cough in 70.5%, fever in 58.3%, appetite or weight loss in 55.8%, breathlessness in 27.6%, and chest pain in 24.4% and haemoptysis in 18.0%. The present study showed higher frequencies of cough, fever, weight loss and breathlessness but a lower frequency of haemoptysis. Johar et al [19] reported cough in 96.0%, which was higher than the 82.7% observed in the present study.

Campos et al [20] reported cough in 55.0%, fever in 45.7%, weight loss in 53.5%, and dyspnoea in 27.1% and haemoptysis in 3.1% among smear-negative patients. Nguyen et al [17] similarly found that culture-negative patients had fewer symptoms than culture-positive patients. Cough was present in 68% of culture-negative patients compared with 89% of culture-positive patients, while weight loss was present in 39% and 51%, respectively.

Haemoptysis was the least frequent symptom in the present study and occurred in 12.0% of patients. The relatively low frequency may be explained by the lower occurrence of extensive cavitary disease in smear-negative pulmonary tuberculosis. Campos et al [20] also found haemoptysis to be less frequent in smear-negative than smear-positive disease.

Chest radiographic findings: Consolidation or infiltration was the most common chest radiographic finding and was observed in 48.0% of patients. Nodular opacities were present in 30.0%, fibrotic changes in 23.3%, and cavitary lesions in 20.0%. Alemayehu et al [21] reported cavitation in 18.3% of smear-negative patients compared with 39.4% of smear-positive patients. The lower occurrence of cavitation in smear-negative disease may reflect an earlier or paucibacillary stage of pulmonary tuberculosis. Cavities communicate with the bronchial tree and are generally associated with a higher bacillary load.

Nguyen et al [17] reported cavitation on chest radiography in only 7% of culture-negative patients compared with 28% of culture-positive patients. Campos et al [20] reported a radiographic pattern typical of tuberculosis in 58.1% of smear-negative patients compared with 72.5% of smear-positive patients.

No definite abnormality was detected on chest radiography in 8.0% of patients. This finding indicates that a normal or inconclusive chest radiograph does not completely exclude pulmonary tuberculosis.

Computed Tomography Findings: Chest CT was performed in 90 patients. Centrilobular nodules were the most common CT finding and were observed in 64.4%, followed by tree-in-bud appearance in 46.7%, consolidation in 43.3%, and cavitation in 28.9% and bronchiectasis in 26.7%. It suggests endobronchial spread, which may be detectable on CT even when chest radiography is inconclusive.

Lee et al [22] reported centrilobular nodules in 85.8% and tree-in-bud appearance in 40.6% of Xpert-negative smear-negative patients. Consolidation and cavitation were reported in 21.7% and 23.6%, respectively, among Xpert-negative patients. In the present study, consolidation was more frequent at 43.3%, while the frequency of cavitation was slightly higher at 28.9%.

Nguyen et al [17] reported cavitation on CT in 26% of culture-negative patients compared with 59% of culture-positive patients. Together, these findings suggest that cavitation may be present in smear-negative disease but is generally less common than in patients with a higher bacillary burden.

Mediastinal or hilar lymphadenopathy and pleural involvement were observed in 16.7% and 12.2% of patients, respectively. These findings broaden the imaging spectrum of smear-negative pulmonary tuberculosis and reinforce the need to interpret CT patterns in conjunction with clinical and microbiological information.

Initial and sequential microbiological confirmation: Among 150 patients with smear-negative presumptive pulmonary tuberculosis, spontaneous sputum testing detected M. tuberculosis by both CBNAAT and culture in 37 (24.7%), by CBNAAT alone in eight (5.3%), and by culture alone in 13 (8.7%). Overall, CBNAAT was positive in 45 patients (30.0%) and culture in 50 (33.3%). When both methods were considered together, spontaneous sputum provided microbiological confirmation in 58 patients (38.7%).

Culture positivity was reported in 42% of 173 smear-negative patients by Alemayehu et al [21] while Lee et al [22] reported a sputum Xpert MTB/RIF sensitivity of 41.1%. Differences from the present findings may reflect variations in specimen quality, bacillary load, patient selection and diagnostic definitions. The detection of culture-positive but CBNAAT-negative cases in the present study further indicates that molecular testing and culture are complementary rather than interchangeable. [23]

Among patients who remained unconfirmed after spontaneous sputum testing, induced sputum identified three additional cases and bronchoalveolar lavage identified two. Sequential evaluation therefore increased the number of microbiologically confirmed patients from 58 (38.7%) to 63 (42.0%).

Kadian et al [18] reported CBNAAT positivity in 43 of 80 patients (53.8%) who successfully underwent sputum induction, and their sequential use of induced sputum and BAL achieved 97.7% sensitivity against a composite reference standard. Johar et al [19] reported BAL AFB and CBNAAT positivity of 52.7% and 54.7%, respectively. Differences in selection for bronchoscopy and the extent of radiological disease may also have contributed.

Overall, 63 patients (42.0%) were microbiologically confirmed and 87 (58.0%) were clinically diagnosed after microbiological investigations remained negative. The latter group required diagnosis based on compatible clinical and radiological findings, exclusion of an alternative condition and documented response to antitubercular treatment. The overall confirmation rate was comparable to the 42% culture positivity reported by Alemayehu et al. [21]

Conclusion

Smear-negative pulmonary tuberculosis showed a variable clinical and radiological presentation, with cough, fever, weight loss and loss of appetite being the predominant symptoms. Although conventional sputum smear microscopy was negative in all patients, microbiological confirmation was achieved in 42.0% through the sequential application of CBNAAT, mycobacterial culture, induced sputum and bronchoalveolar lavage. The identification of culture-positive but CBNAAT-negative cases demonstrated that a negative molecular test did not exclude pulmonary tuberculosis. Chest CT provided additional diagnostic information, particularly through the detection of centrilobular nodules and tree-in-bud opacities in patients with persistent clinical suspicion. These findings indicate that the diagnosis of smear-negative pulmonary tuberculosis should be based on an integrated assessment of clinical presentation, radiological findings and complementary microbiological investigations.

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