Albanian Journal of Trauma and Emergency Surgery (2025) 9/1:1606 - 1610
DOI: https://doi.org/10.32391/ajtes.v9i1.446

LATEST ARTICLES

Can Tuberculosis Present as a Neutrophilic Pleural Effusion?

Zoi Tsilogianni[1], Vasileios Leivaditis[2], Athanasios Papatriantafyllou[2], Benjamin Ehle[3], Emmanouil Dimopoulos[4], Michail Galanis[5], Anastasia Papaporfyriou[6], Efstratios Koletsis[7], Francesk Mulita[8*], Elias Liolis[9], Agron Dogjani[10], Nina Miteva[11], Andreas Antzoulas[8], Dimitrios Litsas[12], Manfred Dahm[2], Konstantinos Grapatsas[13],

Received: 13 October 2024 / *Accepted:* 8 November 2024 / *Published online:* 20 January 2025
This article is published with open access at ***https://journal.astes.org.al***

Abstract

Introduction: Tuberculous pleuritis accounts for approximately 10% of tuberculosis cases and represents a significant proportion of extrapulmonary tuberculosis manifestations. This review aims to consolidate current evidence concerning the prevalence, natural course, diagnostic challenges, and treatment responses associated with neutrophilic tuberculous pleural effusions (TPE).

Materials and Methods: A comprehensive search of the PubMed database was conducted using specific search terms related to the topic. A total of 67 articles were initially retrieved, with a meticulous screening process ultimately resulting in the inclusion of 8 relevant articles.

Results: Tuberculous pleural effusion is traditionally characterized as a lymphocytic exudate. However, some studies have reported the prevalence of neutrophilic TPE to be around 10% or even higher. The differential diagnosis of a neutrophilic pleural effusion can be challenging, as tuberculosis (TB) should not be readily ruled out. Neutrophilic tuberculous pleural fluid exhibits distinct characteristics, including lower pH, elevated lactate dehydrogenase (LDH) levels, increased adenosine deaminase (ADA) levels, and a higher likelihood of positive results in TB-PCR and mycobacterium tuberculosis cultures when compared to the lymphocytic variety. It has been observed that a cutoff value of 5.62 for the ADA/serum CRP ratio provides increased sensitivity and specificity in indicating TPE.

Conclusion: The diagnosis of TB relies on a combination of pleural fluid predominantly characterized by lymphocytes and elevated ADA levels. However, this classical presentation is not universal; at times, neutrophilic TPE predominates, complicating the differential diagnosis. Physicians must be aware of this exception to avoid misdiagnosis.

Keywords: Tuberculosis, neutrophilic pleural effusion, pleural effusion

Original article, no submission or publication in advance or in parallel

* ***Corresponding author:***
Francesk Mulita MD, PhD
✉ *rajmondatare@gmail.com*

1 Second Respiratory Medicine Department, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, GREECE
2 Department of Cardiothoracic and Vascular Surgery, WestpfalzKlinikum, Kasiserslautern, GERMANY.
3 Department of Thoracic Surgery, Asklepios Lung Clinic Munich-Gauting, Gauting, GERMANY.
4 Department of General and Visceral Surgery, Marienhospital Stuttgart, Stuttgart, GERMANY.
5 Department of Thoracic Surgery, Inselspital, Bern University Hospital, University of Bern, Bern, SWITZERLAND
6 Department of Pulmonology, Internal Medicine II, Vienna University Hospital, 1090 Vienna, AUSTRIA.
7 Department of Cardiothoracic Surgery, University Hospital of Patras, Patras, GREECE.
8 Department of General Surgery, University Hospital of Patras, Patras, GREECE.
9 Department of Oncology, University Hospital of Patras, Patras, GREECE.
10 University Hospital of Trauma, Tirana, ALBANIA
11 Democritus University of Thrace Didymóteicho, GREECE
12 Department of General Surgery, General Hospital of Lamia, Lamia, GREECE.
13 Department of Thoracic Surgery and Thoracic Endoscopy, Ruhrlandklinik, West German Lung Center, University Hospital Essen, University Duisburg-Essen Essen, GERMANY.

Introduction

Tuberculous pleuritis, representing approximately 10% of tuberculosis cases, is a significant extrapulmonary manifestation of the disease [1]. In areas with a high prevalence of tuberculosis, it is considered one of the leading causes of pleural effusion [2]. Timely diagnosis and treatment of tuberculous pleural effusion (TPE) are critical, as these patients are at an increased risk of developing active tuberculosis in the future [3].

The composition of tuberculous effusion can vary from being predominantly lymphocytic to containing a significant neutrophilic component, dependent on the level of inflammation. However, the applicability and effectiveness of diagnostic criteria, such as adenosine deaminase (ADA) levels and the lymphocyte/neutrophil (L/N) ratio, have not been comprehensively evaluated across various disease conditions [4]. Additionally, recent analysis has shown that the diagnostic parameters for tuberculous effusion are influenced by the patient's inflammatory status as the condition progresses [4]. In the context of tuberculosis diagnosis, it is important to acknowledge the decreased accuracy of tuberculous effusion criteria in cases with high levels of inflammation.

For diagnosing tuberculous pleural effusion, ADA testing in pleural fluid appears to offer the best diagnostic performance, as it is an economical and rapid method [1]. An ADA level of 40 U/l is commonly recognized as the diagnostic threshold for tuberculosis. Elevated levels are associated with an increased likelihood of a positive diagnosis [1]. However, in some instances, elevated ADA levels can be observed in patients with empyema, malignancies, certain infections, and connective tissue diseases, posing challenges for differential diagnosis [5].

Diagnostic thoracocentesis typically reveals an exudative pleural fluid in which mononuclear cells predominate. A lymphocyte-to-neutrophil ratio in pleural fluid greater than 0.75, combined with ADA levels exceeding 70U/l, can safely indicate a tuberculosis diagnosis. When the same ratio exists alongside ADA levels between 40 and 70 U/L, consideration should be given to needle biopsy or thoracoscopy [3]. Repeatedly low ADA levels (below 35 U/l) can exclude tuberculosis safely, even if clinical suspicion is high. However, in cases of increased lymphocytes in pleural fluid, a biopsy may also be considered [3].

Nonetheless, the conventional presentation of TPE is not always observed. Occasionally, TPE may manifest as a neutrophil-predominant exudate, particularly during the early stages of the disease [6, 7]. The purpose of this review is to consolidate existing evidence concerning the prevalence, natural progression, diagnostic challenges, and treatment response associated with neutrophilic TPE.

Material and Methods

We conducted a comprehensive search of the PubMed database using specific search terms related to the topic: "tuberculous pleural fluid neutrophilic," "neutrophilic TPE," "tuberculosis pleural effusion neutrophilic," "TB pleural effusion/fluid neutrophilic", and "polymorphonuclear tuberculosis pleural effusion/fluid/TPE."

This search yielded 67 articles, of which 29 were excluded for duplication. The remaining 38 articles were carefully screened, and 17 were excluded for being entirely irrelevant to the subject. Additionally, 8 articles, while related to the topic, did not contribute substantially to our specific inquiry. Ultimately, 8 articles were selected for inclusion in this review.

Results

Tuberculous pleural effusion is a common presentation of tuberculosis, especially in endemic regions. It is often considered a prime differential diagnosis for pleural effusions. Traditionally, tuberculous pleural fluid is characterized as a lymphocytic exudate. However, some studies have reported the prevalence of neutrophilic TPE to be around 10% or even higher [8, 9]. Notably, polymorphonuclear tuberculous pleural effusion is associated with increased mortality and an elevated risk of transmission, characterized by a higher mycobacterial burden in sputum culture [10, 11].

The initial host response to tubercle bacilli is initiated by polymorphonuclear leucocytes, which last for 24 hours, followed by macrophages for an additional 72 hours, with lymphocytes eventually predominating [12]. This sequence has been confirmed in patients undergoing repeated thoracocentesis, where each procedure led to an increase in lymphocyte presence [10]. A study aiming to expedite the diagnosis of TPE suggests that when thoracocentesis reveals a polymorphonuclear type one week later, in the case of TPE, thoracentesis reveals a macrophage type [11].

Neutrophilic tuberculous pleural effusion can sometimes be challenging to differentiate from parapneumonic effusions (PPE) with neutrophilic pleural fluid and elevated ADA levels. PPE, particularly when complicated, often exhibits high serum CRP levels and frequently elevated ADA levels. Additionally, the ADA test can yield false-positive results (6). Tuberculous empyema poses another diagnostic puzzle, as neutrophils can predominate even without coexisting bacterial infections, and M. tuberculosis cultures may not consistently yield diagnostic results. Consequently, differentiating it from bacterial empyema can be challenging.

Nevertheless, neutrophilic tuberculous pleural fluid exhibits distinct characteristics, such as lower pH, elevated LDH levels, increased ADA levels, and a higher frequency of positive results in TB-PCR and mycobacterium tuberculosis cultures when compared to the lymphocytic type [8, 10]. It has been observed that, for a cutoff value of 5.62, the ratio of ADA to serum CRP exhibits increased sensitivity and specificity in indicating TPE [13].

Whether neutrophilic or lymphocytic, an ADA level greater than 35 U/L remains the cornerstone for diagnosing tuberculosis. Conversely, a level below 35 U/L in regions with low TB prevalence safely excludes tuberculosis, while levels

above 250 U/L should raise suspicion of other conditions [6]. A high clinical suspicion of tuberculosis is warranted when patients exhibit signs of recent weight loss, initial white blood cell (WBC) counts of ≤11,000/μL, and a poor response to empirical antibiotics after 3 days. Furthermore, a one-week follow-up of pleural fluid is advisable, particularly in cases where macrophages predominate after an initial phase of neutrophilic prevalence [11].

A recent analysis demonstrated that while pleural fluid ADA is a pivotal factor in distinguishing non-purulent tuberculous pleural effusion from parapneumonic pleural effusion (PPE), diagnostic accuracy can be enhanced by combining ADA with pleural fluid lactate dehydrogenase (LDH) for individuals aged 50 years or younger, and by combining ADA with the percentage of neutrophils (pfN%) for individuals older than 50 years [7].

Discussion

Discriminating between neutrophilic loculated TPE and PPE was facilitated by the presence of nodular parenchymal lesions and pleural fluid adenosine deaminase levels, both of which operated as independent distinguishing factors. These findings offer valuable insights for understanding and managing patients with neutrophilic loculated TPE, aiding in their differentiation from individuals with complicated PPE.

The findings from our analysis aim to shed light on the complex nature of TPE and the challenges it poses to diagnosis and differentiation from other pleural conditions. While TPE is traditionally characterized by a predominance of lymphocytes and elevated pleural fluid ADA levels, it has been established that a subset of TPE cases can exhibit a neutrophilic predominance, especially in its early stages [12, 14]. This presentation can complicate the differentiation from PPE and other pleural conditions and it has received limited research attention [14].

The study by Bielsa et al., involving 320 patients with TPE, provides valuable insights into the microbiological aspects of TPE. It revealed that Mycobacterium tuberculosis was detected in the sputum or pleural fluid of 36% of these patients. This emphasizes the significance of microbiological tests in confirming the diagnosis of TPE. Notably, the study identified a higher rate of positive microbiological findings in patients co-infected with the human immunodeficiency virus (HIV) and those with specific pleural fluid characteristics, such as low protein levels (<4g/dL), high neutrophil counts (>60%), and low glucose levels (<40mg/dL). Several factors were identified as predictors of mortality, including HIV co-infection, PF protein levels less than 5g/dL, and advanced age. These factors can serve as valuable indicators for clinicians when evaluating pleural effusions [15].

The observations made by Lee et al. in their study of 344 patients with TPE further illustrate the variability in TPE presentations [16]. Among their subjects, 10% presented with a neutrophilic TPE condition, and 30% of these cases exhibited pleural fluid loculation. This not only highlights the diversity in TPE manifestations but also underscores the need for specific diagnostic criteria to differentiate these cases from other pleural conditions.

Additionally, the study by Lee et al. showed that the levels of classical pleural fluid biomarkers were more pronounced in patients with neutrophilic loculated TPE compared to those with neutrophilic free-flowing TPE [16]. These biomarkers were similar to those observed in patients with complicated PPE. This suggests that specific pleural fluid characteristics can aid in distinguishing between different types of pleural effusions.

Furthermore, high mycobacterial loads were detected in the pleural fluid of patients with neutrophilic TPE, and favorable treatment outcomes were achieved through the administration of antituberculosis drugs alone. This finding reinforces the importance of early diagnosis and appropriate treatment in managing TPE [16].

The identification of independent discriminators for neutrophilic loculated TPE, such as nodular parenchymal lesions and pleural fluid adenosine deaminase levels, further emphasizes the significance of comprehensive clinical and diagnostic evaluation. These findings can assist in distinguishing between neutrophilic loculated TPE and complicated PPE, contributing to more accurate diagnoses and tailored treatment plans.

The results discussed in this review demonstrate the heterogeneity of TPE presentations and the critical role of diagnostic criteria and microbiological testing. Clinicians must be prepared to encounter variations in TPE, including neutrophilic predominance, and should consider a comprehensive set of pleural fluid characteristics to make accurate differential diagnoses. Early identification and appropriate treatment are essential to improve patient outcomes and minimize the risk of transmission in cases of tuberculosis. The findings presented in the results section underscore the complexity of TPE and provide valuable insights into its diagnosis and management.

Conclusion

In conclusion, tuberculous pleural effusion (TPE) represents a substantial portion of extrapulmonary tuberculosis and is often unrecognized, increasing the risk of future active TB. Thoracocentesis and pleural fluid testing remain pivotal for diagnosis, with lymphocytic predominance and elevated ADA levels as the classical presentation. However, the presence of neutrophil predominance in pleural fluid occasionally complicates the diagnosis, necessitating differentiation from other conditions, such as malignancies and infections.

Nevertheless, in cases of a neutrophilic pleural effusion, the possibility of tuberculosis should never be dismissed. ADA levels continue to play a crucial role, with levels below 35U/l in low-prevalence areas safely excluding TB, while levels above 250U/L should prompt consideration of other conditions. Clinical suspicion of tuberculosis is warranted in the presence of signs such as recent weight loss, initial

white blood cell (WBC) counts of ≤11,000/μL, and an inadequate response to antibiotics. A one-week follow-up of pleural fluid is advisable, particularly when macrophages replace the initial neutrophilic predominance.

Recent analysis demonstrates that while pleural fluid ADA is pivotal in distinguishing non-purulent TPE from PPE, diagnostic accuracy can be enhanced by combining ADA with pleural fluid LDH for individuals aged 50 years or younger, and with the percentage of neutrophils for individuals older than 50 years.

Recognizing the potential for neutrophilic predominance in TPE is essential for clinicians, as it can lead to atypical presentations and challenges in differential diagnosis. To ensure accurate and timely diagnosis, clinicians must remain vigilant and consider the full spectrum of pleural fluid characteristics in the context of tuberculosis.

COI Statement: This paper has yet to be submitted in parallel, presented fully or partially at a meeting, podium, or congress, published, or submitted for consideration beforehand.

No relevant or minor financial relationships exist between authors, their relatives, or the next of kin with external companies.

Disclosure: The authors declared no conflict of interest. No funding was received for this article.

Abbreviation

TPE - Tuberculous Pleural Effusion; LDH - Elevated Lactate Dehydrogenase; ADA - Increased Adenosine Deaminase; TB – Tuberculosis; L/N - Lymphocyte/Neutrophil; WBC - White Blood Cell; PPE - Parapneumonic Effusions; CPR - C-Reactive Protein: PCR - Polymerase Chain Reaction; pfN% – Percentage of Neutrophils; HIV - Human Immunodeficiency Virus;

References

1. Porcel J. M. (2009). Tuberculous pleural effusion. Lung, 187(5), 263–270. **https://doi.org/10.1007/s00408-009-9165-3**
2. Valdés, L., Alvarez, D., Valle, J. M., Pose, A., & San José, E. (1996). The etiology of pleural effusions in an area with high incidence of tuberculosis. *Chest*, 109(1), 158–162. **https://doi.org/10.1378/chest.109.1.158**
3. Light R. W. (2010). Update on tuberculous pleural effusion. *Respirology (Carlton, Vic.)*, 15(3), 451–458. **https://doi.org/10.1111/j.1440-1843.2010.01723.x**
4. Jeon, D.S., Kim, SH., Lee, J.H. et al. Conditional diagnostic accuracy according to inflammation status and age for diagnosing tuberculous effusion. *BMC Pulm Med* 23, 400 (2023). **https://doi.org/10.1186/s12890-023-02700-4**
5. Manuel Porcel, J., Vives, M., Esquerda, A., & Ruiz, A. (2006). Usefulness of the British Thoracic Society and the American College of Chest Physicians guidelines in predicting pleural drainage of non-purulent parapneumonic effusions. *Respiratory medicine,* 100(5), 933–937. **https://doi.org/10.1016/j.rmed.2005.06.017**
6. Porcel, J. M., Esquerda, A., & Bielsa, S. (2010). Diagnostic performance of adenosine deaminase activity in pleural fluid: a single-center experience with over 2100 consecutive patients. *European journal of internal medicine,* 21(5), 419–423. **https://doi.org/10.1016/j.ejim.2010.03.011**
7. Jolobe O. M. P. (2019). Atypical manifestations of tuberculous empyema and neutrophil-predominant tuberculous pleural effusions. *QJM: monthly journal of the Association of Physicians,* 112(6), 469–470. **https://doi.org/10.1093/qjmed/hcy189**
8. Lee, J., Lim, J. K., Yoo, S. S., Lee, S. Y., Cha, S. I., Park, J. Y., & Kim, C. H. (2016). Different characteristics of tuberculous pleural effusion according to pleural fluid cellular predominance and loculation. *Journal of thoracic disease*, 8(8), 1935–1942. **https://doi.org/10.21037/jtd.2016.06.54**
9. Epstein, D. M., Kline, L. R., Albelda, S. M., & Miller, W. T. (1987). Tuberculous pleural effusions. *Chest,* 91(1), 106–109. **https://doi.org/10.1378/chest.91.1.106**
10. Bielsa, S., Palma, R., Pardina, M., Esquerda, A., Light, R. W., & Porcel, J. M. (2013). Comparison of polymorphonuclear- and lymphocyte-rich tuberculous pleural effusions. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 17(1), 85–89. **https://doi.org/10.5588/ijtld.12.0236**
11. Lin, M. T., Wang, J. Y., Yu, C. J., Lee, L. N., Yang, P. C., & TAMI Group (2009). Mycobacterium tuberculosis and polymorphonuclear pleural effusion: incidence and clinical pointers. *Respiratory medicine,* 103(6), 820–826. **https://doi.org/10.1016/j.rmed.2008.12.023**
12. Antony, V. B., Repine, J. E., Harada, R. N., Good, J. T., Jr, & Sahn, S. A. (1983). Inflammatory responses in experimental tuberculosis pleurisy. *Acta cytologica,* 27(3), 355–361. PMID: 6346774.
13. Lee, J., Yoo, S. S., Lee, S. Y., Cha, S. I., Park, J. Y., & Kim, C. H. (2017). Pleural fluid adenosine deaminase/serum C-reactive protein ratio for the differentiation of tuberculous and parapneumonic effusions with neutrophilic predominance and high adenosine deaminase levels. *Infection*, 45(1), 59–65. **https://doi.org/10.1007/s15010-016-0928-5**
14. Ren, Z. H., & Xu, L. (2021). Biomarkers of Distinguishing Neutrophil-Predominant Tuberculous Pleural Effusion from Parapneumonic Pleural Effusion. *The American journal of the medical sciences,* 361(4), 469–478. https://doi.org/10.1016/j.amjms.2020.10.015
15. Bielsa, S., Acosta, C., Pardina, M., Civit, C., & Porcel, J. M. (2019). Tuberculous Pleural Effusion: Clinical Characteristics of 320 Patients. Derrame pleural tuberculoso: características clínicas de 320 pacientes. *Archivos de bronconeumologia,* 55(1), 17–22. **https://doi.org/10.1016/j.arbres.2018.04.014**
16. Lee, J., Lim, J. K., Lee, S. Y., Yoo, S. S., Lee, S. Y., Cha, S. I., Park, J. Y., & Kim, C. H. (2016). Neutrophilic Loculated Tuberculous Pleural Effusion: Incidence, Characteristics and Differentiation From Complicated Parapneumonic Effusion. *The American journal of the medical sciences,* 351(2), 153–159. **https://doi.org/10.1016/j.amjms.2015.11.010**