Adenosine Deaminase Negative Pleural Tuberculosis: A Clinical Case

Adenosina Deaminase Negativa na Tuberculose Pleural: Um Caso Clínico

Filipa Pereira[1], Leena Mira[1], Susana Branco[1], Helena Vitorino[2], Sofia Marques Santos[2]*

***Corresponding Author**/Autor Correspondente
Filipa Lemos Pereira [filipaflp7@gmail.com]
Nova Medical School, Campo Mártires da Pátria, 130, 1169-056 Lisboa, Portugal
ORCID iD: https://orcid.org/0000-0002-9859-7065

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Abstract

Tuberculous pleural effusion (TPE) is one of the most common forms of extrapulmonary tuberculosis.

Diagnostic approach of TPE remains the detection of *Mycobacterium* tuberculosis in pleural fluid (PF), or pleural biopsy specimens, by microscopy or culture, or histological demonstration of caseating granulomas in the pleura along with acid-fast bacilli (AFB). Adenosine deaminase (ADA) in PF has been documented to be useful in the diagnosis of TPE, related to its notable negative predictive value.

We present the case of an 81-year-old patient, with clinical signs of fatigue, weight loss and dry cough, whose imaging studies revealed an extensive left pleural effusion. Despite several positive markers for TPE, ADA was negative. Nevertheless, he underwent tuberculostatic therapy with a favorable response.

Due to variability of pleural fluid ADA measurements in PF, namely race of studied population, age, immune status of the patients, among other factors that may affect the ADA levels, this case aims to alert the influence of clinical context in ADA and the necessity of regional studies for determination of specific regional values.

Resumo

O derrame pleural é uma das formas mais comuns de tuberculose extrapulmonar.

A abordagem diagnóstica de derrame pleural por tuberculose passa pela deteção de *Mycobacterium tuberculosis* no líquido pleural (LP) ou espécimes na biópsia pleural, seja por microscopia ou cultura, ou a observação histológica de granulomas caseosos na pleura juntamente com bacilos álcool-ácido resistentes (BAAR). A adenosina deaminase (ADA) no LP tem sido documentada como útil no diagnóstico, pelo seu notável valor preditivo negativo.

Apresentamos o caso de um doente de 81 anos, com sinais de fadiga, emagrecimento e tosse seca, cuja imagiologia revelou extenso derrame pleural esquerdo. Apesar de vários marcadores positivos para tuberculose, a ADA foi negativa. No entanto, o doente realizou tratamento tuberculostático, com resposta favorável.

Devido à variabilidade das dosagens da ADA no líquido pleural, nomeadamente raça da população estudada, idade, estado imunitário dos doentes, entre outros fatores que podem afetar os níveis da ADA, este caso visa alertar para a influência do contexto clínico na ADA e para a necessidade de estudos regionais para determinação de valores regionais específicos.

1. Nova Medical School | Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisboa, Portugal. **2.** Unidade de Medicina Interna | Hospital Lusíadas Lisboa, Lisboa, Portugal

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Introduction

Tuberculosis (TB) is the first leading infectious killer worldwide. Tuberculous pleural effusion (TPE) is the second most common extrapulmonary tuberculosis.[1] Pleural effusion occurs in nearly 5% of all tuberculosis cases.[1] A pleural effusion with a predominant lymphocytic population > 85% is very suggestive of TPE.[1,2]

Acid fast bacilli (AFB) culture of pleural fluid is the gold standard diagnosis of TB.[1,3] Pleural biopsy with closed needle has also been frequently used to diagnose TB, by demonstration of granuloma in pleural tissue.[2,4] Pleural fluid molecular markers have been developed to assist in the diagnosis of TB. Adenosine deaminase (ADA) has been thoroughly studied as a valuable marker, due to its high sensitivity (0.92) and specificity (0.90) for TPE.[3,5] An ADA level less than 40 IU/L has been recommended as the cut-off to exclude TPE, based on this marker notable negative predictive value.[1,3]

Pleural fluid ADA can be a useful tool in the diagnosis of TPE, but its exact threshold and accuracy in clinical decision is not linear.

Case Report

We present a case of a Caucasian, human immunodeficiency virus-negative (types 1 and 2) 81-year-old man with 6 months of progressive fatigue with medium exertion with associated intermittent and non-productive cough, non-selective anorexia, and weight loss (8.9% of body mass loss in one month). The patient has a known history of type 2 diabetes mellitus, dyslipidemia, primary hypertension, mood disorder syndrome, benign prostatic hyperplasia, and obesity. The patient denies smoking habits, recent travels and previous TB infection diagnosis.

A chest radiograph (Fig. 1) and a chest computed tomography (CT) (Fig. 2) showed a large left pleural effusion with complete collapse of the lower lobe and partial collapse of the homolateral upper lobe, causing mediastinal shift to the right, along with pleural thickening in the middle third of the right lung and areas of atelectasis in the adjacent parenchyma of the three lobes. An interferon-gamma release assay (IGRA) was performed, with a positive result. The initial pleural fluid studies showed an exudative effusion by Light's criteria and a cell count with lymphocytic predominancy (2985 white blood cells/µL, with 99.40% mononuclear), pleural lactate dehydrogenase (LDH) was 175 units/L, glucose 127 mg/dL, pH 8.0, total protein 4.4 g/dL and ADA 25 IU/L. Ziehl-Neelsen staining for AFB was positive, with 1-9 AFB in 100 microscopic fields. Pleural effusion culture for bacterial, fungal and AFB were negative. A thoracoscopic pleural biopsy was performed, with inconclusive results.

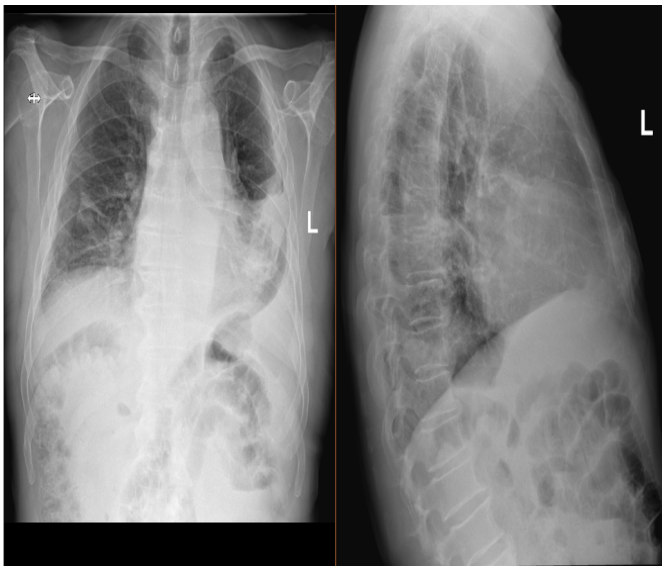

Figure 1. Chest radiograph of the patient showing a left pleural effusion.

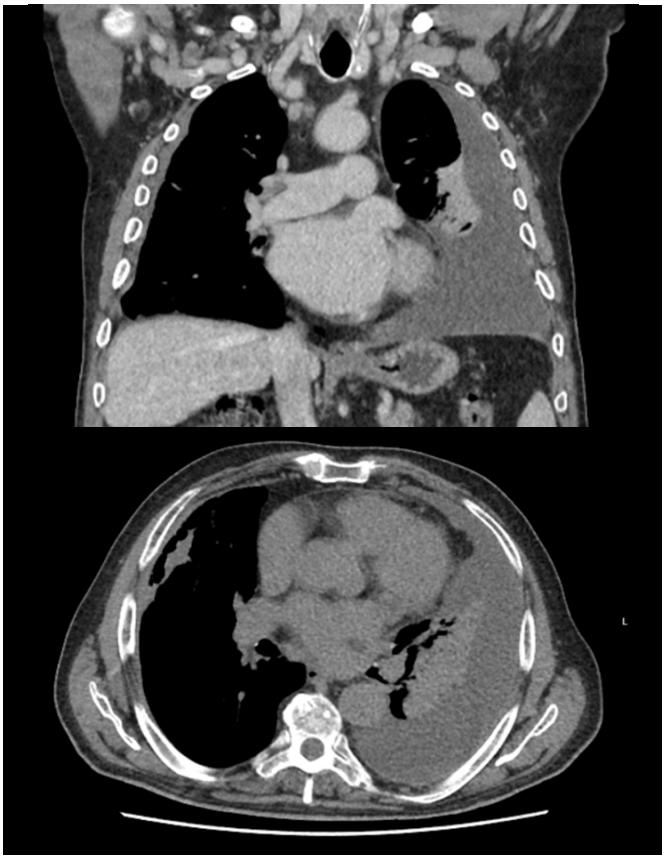

Figure 2. Coronal (left) and axial (right) CT slices of the patient, showing extensive left pleural effusion.

Despite negative culture and low ADA value, a presumptive diagnosis of TPE was made, based on the clinical presentation and positive findings mentioned. A four-drug standard treatment TB regimen (RIPE) was initiated, composed of rifampicin, isoniazid, pyrazinamide, ethambutol, for a period of two months. After a month, the patient was clinically improved, to near baseline health, with a CT (Fig. 3) showing slight reduction of the pleural effusion on the left, compared to the previous study, with multiple atelectatic condensations of bilateral lung parenchyma, superimposed on previous examination.

The intensive phase of TB treatment, the RIPE regimen, was followed by a continuation phase during four months with rifampicin and isoniazid medications (RI regimen) with a clinical resolution of his condition.

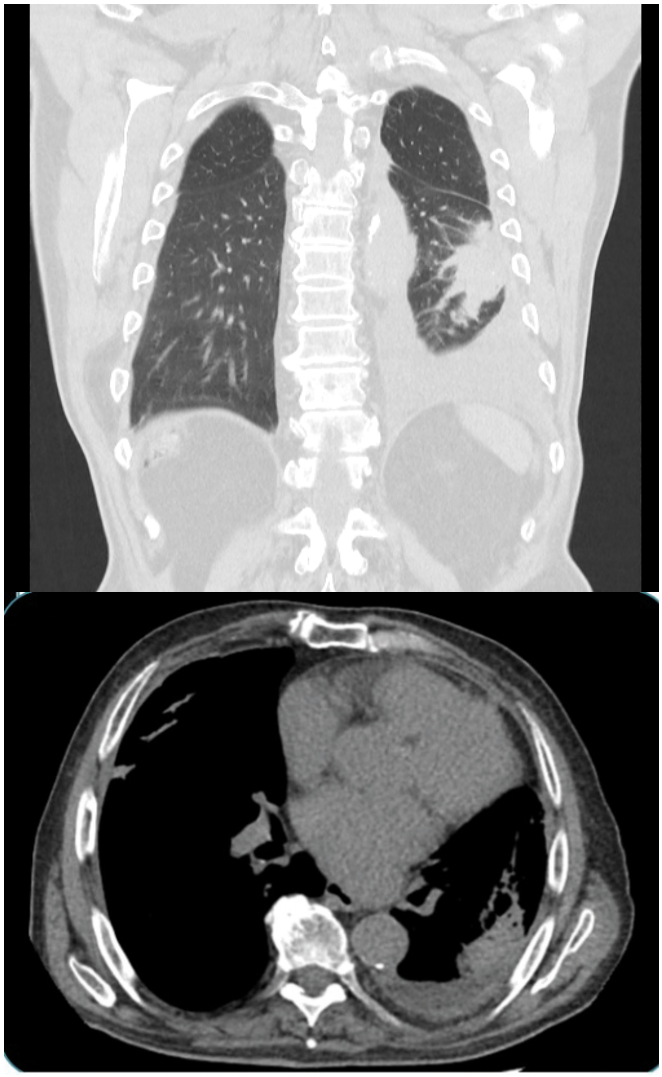

Figure 3. Coronal (left) and axial (right) CT slices of the patient, showing a slight reduction of left pleural effusion, after starting treatment.

Discussion

The diagnosis of TPE is based on the examination of pleural fluid by Zeihl-Neelsen staining, which detects AFB in 10% of cases, and by culture, which gives the definite diagnosis but takes several weeks to return, and is only positive around 30% of the time.[3,6]

This common difficulty in diagnosis was also found in the case presented, where Zeihl-Neelsen staining of pleural fluid was positive for AFB, but pleural effusion culture was negative.

Considering the variability and low sensitivity of mycobacteriological tests, and the delay in the positivity of cultures, several studies have been conducted in the past to find a potential biomarker that facilitate diagnosis, of which ADA stands out, due to its high negative predictive value (98%). A value of less than 40 IU/L has been used worldwide to assist in ruling out TPE.[3,7–11]

Contributing factors to a lower ADA levels have been found. Aging prompts senescence of the immune system, with a decreasing number of naive T cells and macrophages, a reduced T helper function and a weakening activation of T lymphocytes. Since ADA catalyses the conversion of adenosine to inosine and plays an important role in the differentiation of lymphoid cells, age-related changes in the immune system have important consequences for the clinical use of ADA.[3,7,12–14]

Chronic exposure to the chemical components of cigarettes, mainly nicotine, can influence ADA activity, by inhibiting the immune function of T cells.[3,14]

ADA levels are often lower in early stages of infection, due to its relation to lymphocytic proliferation.[3,7,15,16]

The patient presented was of old age, a possible contributor to a lower ADA level. Nevertheless, it has been reported that in the absence of these factors, still ADA level can be low in the context of TB.[3,7]

On the other hand, high levels of ADA in predominantly lymphocytic pleural effusions have been reported in other contexts than TPE, such as parapneumonic effusions, empyema, lymphomas, solid tumours, autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus, and infectious diseases other than TB, like brucellosis, Q fever, histoplasmosis and coccidioidomycosis.[7,9,17]

The epidemiologic context of TB can influence the utility of ADA testing, since its sensibility and specificity may vary with the prevalence of infection.[3]

Regarding Portugal, studies have considered ADA testing a useful mean of diagnosing pleural TB in the Portuguese context. However, the incidence of TB in Portugal decreased to less than 20/100 000 inhabitants since 2015 (the threshold defined

as low incidence).[18] As such, the cut-off value suggested in a publication at the time, which was congruent with the worldwide used value of 40 UI/L, could probably be considerably far from the real ADA value in today's epidemiological context, as it has been recently suggested.[19] A cross sectional study was published in Portugal in 2014, regarding data from 2006-2009, in a context of intermediate TB incidence (25.9/100 000 inhabitants), which reported a pleural fluid ADA cut-off value of 40.5 IU/L. A later cross-sectional retrospective study, from 2016, in a context of low incidence of TB (<20/100 000 inhabitants), suggesting a lower ADA level of cut-off, around 24.9 IU/L.[19]

Attending to this cut-off, the ADA value of the patient presented would be consistent with TPE.

Conclusion

This case demonstrates that ADA should not remain the sole diagnostic test to rule-out TPE when there remains a high suspicion.

The usage of ADA in the diagnosis of TPE depends on the prevalence of the disease. The most recent recommended cut-off level of ADA for the Portuguese population, which shows the best sensitivity (70%) and specificity (87%) seems to be 24.9 UI/L.[7]

No update on the cut-off values of ADA has been published since then. In 2021, incidence of TB in Portugal decreased to 14.2 per 100 000 inhabitants,[18] which further emphasizes the importance of conducting more studies analysing the impact of epidemiologic context in the expression of ADA levels, achieving the best possible cut-off.

Moreover, using lower ADA level to exclude TPE in older patients can reduce the number of false negative results. Other factors, such as immune status and as smoking habits may affect pleural fluid ADA levels. In this context, further research should focus on the predictive accuracy of multiple pleural fluid biomarkers.

Responsabilidades Éticas

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FP, LM e SB: Conceção, recolha de dados, investigação e escrita do artigo.

HV e SMS: Revisão do artigo.

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Contributorship Statement

FP, LM and SB: Conception, data collection, research and article writing.

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