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Contribution of ADA in the diagnosis of serofibrinous pleurisy Review of literature

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Abstract:
Serofibrinous pleurisy is frequent in the daily practice of pulmonologists. It has multiple etiologies, which are mainly dominated in our context, according to numerous studies, by tuberculous pleuritis and malignant pleural effusion. A systematic approach is needed to enable a rapid diagnosis and an appropriate treatment. Recently, many diagnostic tools have been improved, thus contributing to efficient management of this disease. Adenosine deaminase ADA is one of these innovative diagnostic methods. However, its sensitivity and specificity vary from one study to another, affecting its utility. The aim of this article is to review the literature regarding the impact of measuring ADA in pleural effusion on the management of serofibrinous pleurisy.

Introduction:
Tuberculous pleuritis and malignant pleural effusion are the common causes of serofibrinous pleurisy in our context. Many diagnostic tools are improved, without exceeding the important role of the histology, in order to enhance and facilitate the management of this disease.

Discussion:
Adenosine deaminase ADA is produced by all cells, but mainly found in immune system cells such as activated T lymphocytes. this enzyme is involved in purine metabolism as well as in nucleic acid metabolism (1).
ADA is divided in two isoenzymes, namely ADA1 and ADA2. ADA1 is present in most immune cells, including neutrophils, lymphocytes, macrophages, and monocytes. while ADA2 is found in macrophages and monocytes (2). ADA levels are elevated in inflammatory effusions, whether in the pleural, pericardial, or synovial cavities, resulting from bacterial infections, granulomatous diseases, malignancies, or autoimmune conditions (3).
Both are generally elevated in neutrophilic effusions, but this increase lacks specificity and thus offers limited diagnostic value in such contexts. In contrast, ADA levels are typically elevated in lymphocytic effusions related to tuberculosis (4).
World Health Organization describes an estimated 10.6 million people fell ill with tuberculosis worldwide in 2022 (5). According to the latest national statistics 2023 of TB in Morocco, the total number of TB cases is 32 429. Tuberculous pleuritis (TP) is the second form of extrapulmonary TB (27%), the main causes are metastasis and tuberculosis.
The diagnostic challenge of pleural tuberculosis is essentially due to its prevalence in the world, as same as the difficulties in confirming it.
The pleural fluid of TP is usually predominantly lymphocytic. In acute TP we can find an increase in neutrophils. The diagnosis of tuberculous pleural effusions may be difficult because of the low sensitivity of the various diagnostic tools. A lymphocytic exudate which is seen with tuberculous pleuritis, can also occur with other diseases such as malignancy and collagen vascular diseases.
Currently the reference diagnostic method is the microbiological or molecular identification of Mycobacterium tuberculosis in pleural effusion or on a pleural biopsy. The performance of microbiological

tests depends on the quantity of bacilli, which is low in the pleural fluid. For this reason, it is necessary to improve the diagnostic tools and contribute with further studies.

A high ADA levels are found in less than 3% of lymphocytic effusions of non-tuberculous origin (6,7). It has been shown that ADA levels in nontuberculous lymphocytic pleural effusions seldom exceed the cut-off set for tuberculous effusions.

It is known that ADA is considered a reliable biomarker for the diagnosis of TP but the cut-off value for determining a positive ADA result in pleural fluid differs across studies.

In a Moroccan study involving 187 cases, the median pleural adenosine desaminase level was 53 UI/L. The diagnostic performance of the test was characterized by a sensitivity of 89 %, a specificity of 60 %, a positive predictive value (PPV) of 70%, and a negative predictive value (NPV) of 96% (8). On the other hand, a Tunisian study reported a lower median pleural ADA level of 37 UI/L, with a specificity of 81,2% a sensitivity of 66,6 %, PPV of 64,3% NPV of 88,7%. In another study, levels of ADA in pleural fluid > 40 IU/L could indicate pleural tuberculosis with sensitivity (81–100%) and specificity (83–100%) (9). A case-control study in Congo involving 209 patients, showed two ADA useful thresholds in diagnosing serofibrinous pleurisy: ADA values < 36 IU/L effectively rule out the diagnosis, while values > 65 IU/L are suggestive of tuberculous pleurisy (10). Five meta-analyses have uniformly shown that this test possesses high accuracy, with sensitivity and specificity values ranging from 88% to 92%. This fact shed light on the importance of other indirect biological tests (1).

Notwithstanding, some false-positive cases are reported in the literature, attributable to conditions such as empyemas, lymphomas, malignant diseases, and other etiologies, including parapneumonic or collagen vascular diseases (11).

Several methods have been suggested in order to enhance the specificity of the test and reduce the number of false positives. One such method is the specific measurement of ADA2 (predominant isoform in TP). Even though this test has increased sensitivity and specificity to 97.2% and 94.2%, respectively, its contribution to daily clinical practice still modest (12).

second method is combining ADA levels with the lymphocyte-to-neutrophil ratio in pleural fluid. A ratio that exceeds 0.75 associated to an elevated ADA level, increase the specificity of the test to 95% (13).

Combining ADA with other pleural biomarkers, such as interferon-γ or interleukin-27, also measuring ADA levels in pleural fluid and serum, have demonstrated improved specificity (14). these tests are not routinely performed due to their higher cost and limited availability.

Multiple studies have compared the sensitivity and specificity of major diagnostic tools in tuberculosis pleurisy (TP), highlighting those pleural biomarkers exhibit superior sensitivity compared to traditional microbiological tests. ADA level in the effusion with IL 27 were more useful compared to blind pleural biopsy(1).

Conclusion:

Tuberculosis is a worldwide health challenge. Confirmation of TP may be difficult in some cases, which leads to either overtreatment or under-treatment. ADA is an indirect method of diagnosing TP useful for a good management of TP.

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