Reviewer's report

Title: Factors affecting pleural fluid adenosine deaminase level and the implication on the diagnosis of tuberculous pleural effusion: a retrospective cohort study

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Reviewer: Rafal Krenke

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I reviewed the manuscript by Tunn Ren Tay and Augustine Tee “Factors affecting pleural fluid adenosine deaminase level and the implication on the diagnosis of tuberculous pleural effusion: a retrospective cohort study”. This is an interesting paper which adds some new data to the existing literature on the role of ADA in the differentiation between tuberculous and non-tuberculous pleural effusions. I enclose some minor comments and suggestions which in my opinion may help to further improve the paper.

Major compulsory revisions

In my opinion, the rationale for some analyses presented by the authors is doubtful. Consequently, their results can be confusing or even lead to incorrect conclusions. I have the impression that the authors were aware of this when they commented some of their analyses but did not bear it in mind while presenting others. For example, the authors correctly assume that the difference in ADA level seen between the racial groups was likely due to the different proportion of patients with TB in the Chinese, Malay and Indian group. On the other hand, they uncritically analyze the pleural fluid ADA level in two different age groups without reporting the proportion of patients with TPE and parapneumonic pleural effusion in these groups (Table 1). One may expect that the highly significant difference between pleural fluid ADA level in these groups (p<0.001) was due to a higher proportion of patients with tuberculous pleurisy in the younger group and conversely - a high proportion of patients with malignant pleural effusion and chronic heart failure in the older group. Is that right or not? Thus, the significant difference in pleural fluid ADA level between patients younger than 55 and older than 55 years might be considered important only when the proportion of patients with different pleural fluid causes (TB, malignancies, parapneumonic, chronic heart failure) would be the same (not different) in these two groups.

Summarizing this point, my general comment is that the relationship between the age and pleural fluid ADA should be analyzed in separate groups of patients with different pleural fluid causes rather than in patients with pleural effusion as a whole. This allows to avoid the significant confounding factor which is the etiology of pleural effusion. The same refers to the correlation between the age and pleural fluid ADA level.

Minor essential revisions

I think the relationship between age and pleural fluid ADA level is the most interesting and relevant finding. Thus, in my opinion even more broad discussion related to the topic would be justified.

- Although, to my knowledge, there are no studies specifically focused on the relationship between age and pleural fluid ADA level, there are some studies in which only children or young adults were evaluated (e.g. Merino JM et al. Tuberculous pleural effusion in children. Chest 1999; 115: 26-30; Valdes L. et al. Value of adenosine deaminase in the diagnosis of tuberculous pleural effusions in young patients in a region of high prevalence of tuberculosis. Thorax 1995; 50: 600-603). Maybe these studies could be the matter for discussion too? Are the results of these studies consistent with the authors’ finding (high ADA level in young patients with TPE and relatively lower in the older group?)

- The authors discuss the potential mechanism of the age-pleural fluid ADA relationship (the phenomenon of immunosenescence). Although in patients with TPE the negative correlation between age and the pleural fluid ADA level was relatively weak, did the authors consider the TB category: primary (in younger patients) and reactivation (in older patients) as a potential factor affecting pleural fluid ADA?

Minor issues not for publication

The authors state that discrepancies in the diagnostic accuracy of pleural fluid ADA found in different studies “can be due to different methods of ADA analysis”. This is probably true and therefore it is important to report the method of ADA measurement in all original studies. Unfortunately, I did not find this information in the reviewed paper.

There were 35 patients with neutrophilic pleural effusion. Please provide the definition of neutrophilic pleural effusion applied.

Due to the large number of data, Table 2 is difficult to read. Could the authors consider removing some data and make the table more clear?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests