Author’s response to reviews

Title: Diagnostic procedure for idiopathic eosinophilic pleural effusion: A single-center experience

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Dear Anna Melidoni,

Thank you very much for your kindly consideration! We have carefully made a revision in the manuscript. Our point-to-point reply is listed below. We hope the revised manuscript will satisfy the reviewers and meet your journal standards.

Reviewer #1:

IMPORTANCE OF THE QUESTION OR SUBJECT STUDIED
The study of eosinophilic pleural effusion is a very important topic for research. The objectives are clearly stated

ADEQUACY OF APPROACH
The experimental design seems adequate

I would like to clarify why were patients with pleural effusion or pleural pulmonary involvement scanned by chest high-resolution computed tomography (HRCT) excluded?
Response: We are very sorry for this mistake. In fact, 482 patients were scanned using HRCT and had pleural effusion (PE) or pleural pulmonary involvement, but those with PE showing eosinophils of less than 10% were excluded from this study.
We have revised these sentences.

Acceptable from an ethical point of view.

RESULTS
The data are clearly presented
The first paragraph (page 8, lines 20-28) seems more methods than results, hence I think it should be placed in the methods section
Response: We agree with you. These sentences have been placed in the Methods section.

It seems important to know how long these patients were followed.
Response: The median follow-up was 14.4 months (range, 8-16 months).

Tables and figures OK

It seems interesting to know which were the final diagnosis of the EPE patients excluded from the study.
Response: Overall, from the 74 patients with EPE, finally 11 patients with complete clinical data were diagnosed with IEPE, 35 had malignancy, 11 were proved to have pleural parasitic infestation and 17 had true benign disease.

Although it is described in table 1, a brief sentence about the characteristics of chest X ray seems necessary in the main text (how many were bilateral, how many were unilateral-left and how many unilateral-right)
Response: We have added this information in the main text.

DISCUSSION
The discussion is relevant and adequate to the data presented
The authors recognise their limitations
REFERENCES
The references are rather old
I suggest some more recent references

GRAMMAR AND STYLE
The writing clear and easy to follow

I think that English language is satisfactory, however I’m not a native English speaker

ABSTRACT
Adequate and well structured.

Reviewer #2:
Good amount of information. The english is poor and needs major revision.
Response: The quality of language of the manuscript has been highly improved by a professional English editing company. We provide the certificate of language editing.

Reviewer #3:
A detailed characteristics of idiopathic eosinophilic pleural effusion was described in the manuscript. The findings are interesting and useful in clinical practice. However, I have several comments on it.

(1) The results were written poorly. Some information should be integrated into the Methods or Discussion section.
Response: We agree with you. Some sentences have been placed in the Methods or Discussion section.

(2) The methods used in tests for eosinophil, BNP or other tests should be characterized.
Response: We have added these measurements in the Methods section.

(3) Exudates? or transudates? This should be detailed in the Results. In addition, fluid/serum protein ratio, or LDH ratio are preferable for the evaluation.
Response: We agree with you. Transudates and exudates are differentiated by Light’s criteria: effusion/serum protein ratio \( > 0.5 \), effusion/serum LDH ratio \( > 0.6 \). The finding of one of these criteria suggested exudates. We have provided this information in the Results section.

(4) Written informed consent were not included in the study. This is a major fault.
Response: Sorry. We have added this information in the Results section.
(5) As known, IEPEs were all exudates. However, case 7 was misdiagnosed as chronic heart failure. Why?
Response: The fluid typically meets the biochemical characteristics of a transudate, although in 25% of the cases it may fall into the exudative range. (Porcel JM. Pleural effusions from congestive heart failure. Semin Respir Crit Care Med. 2010;31(6):689-97)
This patient had a history of coronary heart disease and we couldn't find any other cause at the beginning, so the diagnosis was considered as CHF.

(6) Page 8, line 34, "Three were 5 male"; Page 25, "Table 3 Pleura effusion examinations", "Protein(g/dl)". These errors should be corrected.
Response: Sorry for these errors. The text for language and grammar has been thoroughly edited.

Reviewer #4:
The authors describe clinical characteristics, laboratory and pathology data of 11 patients with idiopathic eosinophilic pleural effusion (IEPE), and present their response to glucocorticoid treatment after a follow-up ranging from 8 to 16 months. They conclude that diagnosis of IEPE must be made only after careful exclusion of other conditions that may present with pleural eosinophilia.

COMMENTS/QUESTIONS:
1. LANGUAGE. Although most of the key messages can be read easily, a careful edition of syntaxis and quality of language would be needed throughout the manuscript, especially in the Discussion section. For example, on the third page of Discussion (lines 17 to 26) the authors include a phrase quoting that "Archontogeorgis K et al.[13] emphasised that pleuroscopy is mandatory in diagnosing IEPE. In this (Reviewer´s comment: The sentence is confusing in its present form, and "this" should be replaced by "In a previous published") study, pleural samples were collected by using combined ultrasound-guided cutting needle biopsy and standard pleural biopsy, without thoracoscopic assessment. Enough and pleura biopsies were obtained, and the sensitivity and accuracy reached up to 88.6% and 93.8%, respectively [12]". In my opinion, this paragraph is misleading in the text, because the reader might link results that were obtained by the authors themselves in a previous work published in 2016 (reference #12) with the ones published by Archontogerogis and coworkers in 2015 (reference #13). The whole paragraph should be revised and rewritten accordingly.
Response: Thank you for your suggestion. The Discussion section has been reorganized. The quality of language of the manuscript has been highly improved by a professional English editing company. We provide the certificate of language editing.

2. METHODS. In the paragraph related to "Exclusive diagnosis", it is quoted that "The common etiology of EPE including malignant PE (MPE), tubercular PE (TPE), parapneumonic PE (PPE) and pleural parasitic infestation (PPI) were excluded by laboratory tests". In the context of the manuscript, I understand that pleural biopsy was taken in all the 11 patients, and this important point should be included in the Methods section too. Related to this, the first paragraph in sub-section on "Eosinophils and other pleural parameters in pleural fluid" (included in the Results section) states that "Pleural samples were acquired by combined ultrasound-guided cutting needle biopsy and standard pleural biopsy [12]", but I believe that this sentence should be moved from the above-mentioned sub-section of
Results to the Methods section (including the reference #12, that refers to a previous article from the authors).
Response: We totally agree with you. The Methods section has been reorganized.

3. PARASITE-SPECIFIC IgG ANTIBODIES. This important point is referred to in several parts of the manuscript, but I could not find any description of the antibodies that were used in the present study. According to a previous article published recently (Wang et al. BMC Infectious Diseases (2019) 19:576 https://doi.org/10.1186/s12879-019-4179-9), parasitic pleural infestation was diagnosed using IgG antibodies in blood for Paragonimus westermani, Taenia solium, Clonorchis sinensis and Echinococcus granulosus. If those antibodies were actually used in the present study, this critical information should be included in the Methods section, and the results described in the corresponding text and Tables.
Response: Sorry. The article you mentioned is recent publication of my team (BMC Infect Dis. 2019 Jul 4;19(1):576). We have added the information about PARASITE-SPECIFIC IgG ANTIBODIES to the Methods section.

4. PARASITE EGG INVESTIGATION IN STOOL. According to above mentioned article (Wang et al. BMC Infectious Diseases (2019) 19:576 https://doi.org/10.1186/s12879-019-4179-9), this is another critical point for the diagnosis (or exclusion of diagnosis) in some of the parasite pleural infestations. However, in the last sentence of the paragraph corresponding to "Laboratory tests for peripheral blood cell (PBC) and serological examination" the authors mention -surprisingly and with no explanation for a prospective study like the present- that "parasite eggs in stool were not determined".
Response: Sorry for making you confused. The article you mentioned is our recent publication (BMC Infect Dis. 2019 Jul 4;19(1):576). Actually, the test for parasite-specific IgG antibody was negative, and parasite eggs were not found in any stool samples. This sentence has been revised and rewritten.

5. CITATIONS. There is a critical reference in the Discussion section (ref. #21) from the same authors that I could not find in several searches that I performed, including PubMed. Instead, I found the one that I have referred to in several parts of my review (Wang et al. BMC Infectious Diseases (2019) 19:576 https://doi.org/10.1186/s12879-019-4179-9). I wonder if the authors made a serious error when quoting an article referenced in the manuscript as "Jinlin Wang, Weizhan Luo, Panxiao Shen, Yunxiang Zeng, Jianxing He. Clinical characteristics and diagnostic approach to a type of eosinophilic pleural effusion: a retrospective study of 11 pleural parasitic infestations patients. BMC Infectious Diseases 2019; 12879-019-4179-9", and also wonder if this article actually exists in fact.
Response: Sorry. We did make an error when quoting an article. The article you mentioned is our recent publication (BMC Infect Dis. 2019 Jul 4;19(1):576).

6. TABLES. I have a few questions and some concerns related to the three tables included in the manuscript, as follows:
- TABLE 1. Pathology findings in case 4 (pleural biopsy) refers to "Noncaseating granulomas" in a female patient suspected of having a tuberculous pleural effusion. Nothing is commented about this finding (that might be related to sarcoidosis and fungal infection, among others) in the manuscript, but I believe that it might be worth including a comment on this in the Discussion section.
Response: Thank you for your suggestion. We have made comments on case 4 in the Discussion section.
- TABLE 2, Column on "Parasite-specific IgG antibodies": Results on all patients are quoted as "N" (negative). However, since there is no specific information on the antibodies used in the manuscript, I am concerned if ALL the necessary IgG antibodies were actually used IN EACH CASE. If not, the diagnosis of IEPE could not be reliably established.
Response: The necessary IgG antibodies were used EACH PATIENT. We have added the information on the parasite-specific IgG antibodies to the Methods section.

- TABLE 2, Column on "Parasite eggs from stool" (last column in the Table): Again, results are quoted as "N" (negative) in all patients, but -since the authors mentioned that "parasite eggs in stool were not determined" (see my comments on point 4 in this review)- I am seriously concerned about the accuracy of the results shown in the last column of Table 2.
Response: As explained for your comment on point 4, the test for parasite-specific IgG antibody was negative, and parasite eggs were not found in any stool samples.

- TABLE 3. Pathology or pleural biopsy was described on Table 1. I wonder if moving that information to Table 3 would be more adequate. If not, the terms "pleura pathology" should be removed from the title in this Table 3.
Response: Sorry. We agree with you. The terms "pleura pathology" should be removed and the title of Table 3 have been replaced to “Pleural fluid characteristics”.