Peer Review File

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Reviewer #1

General comment: I thank the authors for choosing this relevant and interesting topic to review, since this is an area of pleural disease that puzzles respiratory clinicians. Different aspects are discussed with appropriate references. However, the overall language of the manuscript needs critical revision. In addition, I have the following comments.

Answer:

Thank you too for your constructive comments and suggestions regarding our manuscript. We are also sorry that our writing confused you. The manuscript has been carefully polished by a native English-speaking expert and the assisting language checker "Grammarly" software. We have collected the grammatical issues. If we missed any of the mistakes, please let us know.

Comment 1: The abstract should include some useful data on the subject. At its current state it's not informative enough.

Answer:

Thank you for your valuable suggestions. To make the abstract more informative, we have added the following data and sentences: "Data summarized in this review demonstrated that the incidence of malignancy was lower in EPEs than in non-EPEs (29.7% versus 32.9%). Additionally, MEPE could be a manifestation of a great variety of tumor subtypes, among which lung cancer was the most common cause and accounted for more than 34% of cases. The second common causes were non-Hodgkin lymphoma and metastatic cancers with unknown primary site which were observed in around 5% of cases, respectively. The presence of eosinophils in the pleural effusion may be associated with a positive prognosis of MEPE." (see Page 2, Line 29-36)

Comment 2: This is clearly not a systematic review, and the authors are urged to remove the word 'systematically' in line 55.

Answer:

Thank you for pointing this out. We have removed the word 'systematically' (see Page 3, Line 55-56).

Comment 3: Line 70: the first line of the paragraph should be removed

Answer:

Thank you for your constructive suggestions. We have removed the first line of the paragraph (see Page 4, Line 68).

Comment 4: Line 92: criterion 4 is not separate from criterion 3. They should be combined with 'or' between them

Answer:

Thank you for your constructive suggestions. Criterion 3 and criterion 4 have been combined with 'or'. (see Page 5, Line 87-89)

Comment 5: Lines 93-95: the authors mean to say the pleural fluid cytology has a sensitivity of around 50%. However, the text is confusing, and the explanation given is inaccurate and should be removed.

Answer:

Thank you for your valuable suggestions. We are sorry for our confusing expression and have remove the sentences which gave the inaccurate explanation. (see Page 5, Line 87-89)

Comment 6: Table 1: in the row of the study by Reechaipichitkul et al: the numbers need to be revised (46/50 is calculated as 46%).

Answer:

Thank you for pointing this out. We have checked the data in the Table 1 and revised the number as 92% (45/60) as well as corresponding texts (see Table 1; see Page 2, Line 26/ Page 5, Line 93).

Comment 7: Lines 108-114: the authors discuss the frequency of encountering EPE in idiopathic pleural effusion. It would be useful to include a short discussion about the entity of 'non-specific pleuritis' which is a diagnosis made after obtaining pleural biopsy and not finding a definitive aetiology. Noteworthy that more than 10% of these cases go on to develop malignancy on follow up (see doi: 10.1097/ MCP.0b013e3283470293).

Answer:

Thank you for your constructive suggestions. We have added the following sentences: "Additionally, idiopathic pleural effusions can be defined as non-specific

pleuritis which is a diagnosis made after the pleural biopsy and without a definitive aetiology(12). Of note, more than 10% of these cases could be subsequently found to have malignancy during the follow-up periods(12). " (see Page 6, Line 107-110)

Comment 8: Line 156: it would be useful if the authors could combine the number from different studies cited in table 2 to give relative contribution of different primaries to the overall cases of MEPE. It would also be useful to know the rate of finding an EPE in cases with malignant pleural effusion overall.

Answer:

Thank you for your constructive suggestions! We have re-searched the related articles and regrettably found that to date little work focused on the rate of finding an EPE in cases with malignant pleural effusion (MPE). Most studies were designed based on cases with EPE and evaluated the rate of finding an MPE in cases with EPE (Illustrating this topic in the part **Incidence of MEPE in EPE and Non-EPE)**. To better illustrate the incidence of MEPE in EPE and Non-EPE, we added a table **(see Table 2)** and the following sentence: "this review summarized the latest articles and found that the incidence of malignancy was lower in EPEs than in non-EPEs (29.7% versus 32.9%) **(Table 2)**" (see Page 7-8, Line 150-151)

Even so, we have added data in table 2 to give relative contribution of different primaries to the overall cases of MEPE **(see Table 3)**. We also revised the sentences in the manuscript as following: "In light of literature review, a vast majority of MEPE was associated with solid tumors and only a small group of patients with hematological malignancies developed EPE(7). The etiology of MEPE is clearly shown in **Table 3**. The summary of data demonstrated that lung cancer, especially the non-small-cell lung adenocarcinoma histocyte as well as metastatic cancer to lung (6,7), was the most leading cause of MEPE and accounts for more than 34% MEPE cases (n=23). Non-Hodgkin lymphoma and metastatic carcinomas with unknown primary site were the second most common causes for MEPE accounting for 5% of patients with MEPE. These results corroborated the previous findings illustrating that the percentage of MEPE with unknown primary site of cancer accounted for 5% to 10%(7). Pathological classification mainly included adenocarcinoma, squamous cell carcinoma, dysgerminoma(5,17). Other etiologies (thyroid carcinoma, prostate carcinoma, pancreatic carcinoma, and so forth) were relatively less common. (see Page 8, Line 154-166)"

Comment 9: Lines 197-198: the authors cite some evidence that talc poudrage have

been linked to better survival in malignant effusion. I would like to point the attention of the authors to recent data (PMID 31521977) that suggest that achieving successful pleurodesis was associated with better survival in this patient population.

Answer:

Thank you for pointing this out. We have added the following sentences: "Strategies including chest-tube thoracostomy, needle drainage with thoracentesis, indwelling pleural catheter, or thoracoscopy with pleurodesis may alleviate patient symptoms(34,35). Achieving pleurodesis may impart a survival benefit in patients(35)." (see Page 10, Line 210-213)

Comment 10: Line 201: under this title the authors make unqualified statement about MEPE when they actually mean (and cite references discussing) malignant pleural effusion in general. This section needs revision.

Answer:

Thank you for your constructive suggestions, and we apologize for our negligence. We have revised this part as follows: "As stated above, eosinophils may be established as prognostic markers given their role in cancer progression. They have been shown to be associated with a beneficial prognosis in most cases. For example, high eosinophilic infiltration of the colorectal cancer was associated with a beneficial 5-year overall survival rate(37). A reduced risk of tumor recurrence was present in breast cancer cases with a high peripheral eosinophil count(38). Furthermore, a previous study illustrated a correlation between an increased overall survival as well as disease-free survival and the intensity of tumor-associated tissue eosinophilia(39). Especially, overall survival would increase in intratumoral tumor-associated tissue eosinophilia when compared with other sites(40). In addition, a prospective cohort study found that patients with EPEs had a significantly better survival than those with non-EPEs (a median survival of 16.8 months compared with 7.7 month)(14). To date no evidence has revealed the difference of survival between MEPE and MPE. Evidence showed that survival of MPE may be depended on tumor subtypes, range from 50 days to almost a year(41). We assumed that eosinophils may contribute to a more favourable prognosis for MEPE based on current publications, and further studies in this regard are warranted to verify this assumption.

The association between eosinophil counts and survival was also assessed in carcinoma entities. High levels of eosinophils resulted in an improved survival rate in gastric carcinoma(42) and hepatobiliary cancer(43). Moreover, the possibility of malignancy was inversely related to the pleural eosinophil counts(2). The likelihood

of malignancy was only 7% when a eosinophil count was more than 32%(2). Similarly, Chu et al.(10) found that eosinophil count in pleural effusion was a speculative negative predictor for malignancy in patients with EPE when eosinophils exceeded 15%. The analysis of Krenke et al.(7) revealed that an eosinophil percentage of 40% was the most accurate cut-off level to differentiate between malignant and non-malignant EPE, which supported the study by Kuhn et al.(3) who suggested that eosinophils exceeded 50% in the pleural fluid possessed the strongest negative predictability towards malignancy. Furthermore, a high eosinophil count at baseline was potentially associated with an improved overall survival in participants treated with immune checkpoint inhibitors(44)." (see Page 10-12, Line 216-245)

Reviewer #2

General comment:

This draft is an interesting manuscript that focuses on the malignant eosinophilic pleural effusion (MEPE).

Answer:

Thank you for your constructive comments and suggestions regarding our manuscript.

Comment 1: The authors did a thorough literature review and discussion. The difference between malignant pleural effusion and MPEP should be further discussed in the manuscript in a clinical view.

Answer:

Thank you for your thoughtful suggestions. The difference between malignant pleural effusion (MPE) and malignant eosinophilic pleural effusion (MPEP) may have implications for prognosis. We have further discussed the difference between MPE and MEPE as follows: Increasing work demonstrated that eosinophils were not bystander cells in tumorigenesis due to pleiotropic effects. Eosinophils were able to secrete a range of anti-cancer molecules, including lipid mediators, cytotoxic granules, cytokines， growth factors and chemokines(21). These factors were shown to be cytotoxic in human cancer cell lines both in vivo and vitro. For example, eosinophil cytotoxic granules were shown to serve as a chemoattractant for T cells, neutrophils as well as dendritic cells and possess strong cytotoxic activity against human tumor cell lines(26,27). Tumor-homing eosinophils could also excrete a range of cytokines (such as, TNF-α, IL-4, and IL-5) which were associated with T cells(27) and chemokines which attracted T cells to the carcinoma microenvironment, leading to tumor eradication (28). Besides, eosinophils enhanced dendritic cell maturation

throughout the increased expression of cell surface activation markers(29). Dendritic cells potentially overcame tumor tolerance and were related to good prognosis in carcinoma patients(30). Eosinophils were also able to serve as antigen presenting cells, migrate to local lymph nodes with antigen, and subsequently stimulate the expansion of T lymphocytes(31). Of note, eosinophils had the tumoricidal effects of various cancer cells throughout stable close contacts with target cells, expressing the same receptors and mediators as cytotoxic T lymphocytes(32). (see Page 9-10, Line 187-204).