Peer Review File

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Reviewer A

Comment 1: It is my great pleasure to review your extensively searched, wonderful, very informative review article. My only comment is regarding to pulmonary embolism.

Reply 1: Thank you

Comment 2: As far as I know, most pleural effusion due to pulmonary embolism is neurtrophil dominant. But Erkan L et al (1) reported five patients who developed loculated pleural effusions which were lymphocytic exudates as complications of pulmonary embolism. I think it depends on you to add or not.

Reply 2: We agree that the majority of pleural effusion associated with pulmonary embolism is neutrophil predominant. Given that only a small number of cases showed lymphocyte predominance, we will defer adding this information to our manuscript at this time.

Comment 3: * p8 RIPE--> HRZE

Reply 3: Corrected to HRZE

Comment 4: * Figure 4 Aortic--> aortic, PCIS--> post cardiac injury syndrome

Reply: -

1. Ref: chest 2004 Jul;126(1):298-302

Reviewer B

The authors provide a concise and well-written review of the topic of lymphocytic exudative pleural effusion. The review is informative, and I only have a few comments/suggestions as follows:

Comment 1: The authors seem to speak of post-CABG and post cardiac injury (PCIS) effusions as one and the same entity. While post CABG effusions tend to relate to trauma/injury resulting from surgery. PCIS is probably an immunologic reaction and is exemplified by Dressler syndrome (post myocardial infarction pericarditis or pleuritis). I suggest these two entities are clearly separated.

Reply 1: Thank you for pointing out the difference between post-CABG and PCIS pleural effusions. We agree that early pleural effusion follow cardiac surgery is generally related to injury/trauma resulting from surgery. Late pleural effusion shares similar pathophysiology with PCIS, which is an immune-mediated response to the inflammatory changes in the pericardium. Overall the clinical manifestation of late pleural effusion following cardiac surgery overlaps with that of PCIS, except that fever and chest pain are perhaps less common in late pleural effusion. We will

distinguish this point in our manuscript.
“PCIS is relatively common and seen in almost 30% of patients post cardiac surgery. Late pleural effusion after CABG and PCIS share similar pathophysiology, which is believed to be secondary to an exaggerated immune response to the inflammatory changes of the pleura and myocardial antigens released after myocardial injury. Overall the clinical manifestation of late pleural effusion following cardiac surgery overlaps with that of PCIS, except that fever and chest pain are perhaps less common in late pleural effusion.”

Comment 2: Abstract: I suggest the authors present some detail on the search strategy in the methods.
Reply 2: Additional information has been added to the method section.
“This review is based on a PubMed search of English articles published between 1955 and 2020, using search terms including pleural effusion and lymphocyte predominant to generate a comprehensive literature list.”

Comment 3: Introduction: The authors correctly mention that Light's criteria misclassify exudates in 25% of cases. One famous (and common) example is the concentrated transudate of heart failure under diuretic treatment. It would be useful to mention to the readers the 'fluid to serum protein gradient' which is used to untangle this problem.
Reply 3: We agree that fluid-serum albumin gradient, as well as natriuretic peptides (pro-BNP and/or BNP) are useful to confirm the diagnosis of heart failure associated pleural effusion.
“However, Light’s criteria can misclassify nearly 25% of transudates, particularly in patients with heart failure treated with diuretics. Such misclassification requires additional testing with fluid-serum albumin gradient and natriuretic peptides to confirm the diagnosis.”

Comment 4: Tuberculous pleuritis:
* Can the authors mention briefly the theory about the immunologic/hypersensitivity nature of pleural affection by tuberculous which may explain the difficulty in isolating the organism from the pleural fluid (the paucibacillary nature of involvement).
Reply 4: Thank you for the insightful comments. Given that current literature suggests that the pathogenesis could either be a delayed hypersensitivity reaction or a direct infection to the pleural space, we have added both theories in the manuscript.
“The pathogenesis of TPE was initially thought to be a delayed hypersensitivity reaction to *Mycobacterial* antigens in the pleural space. This theory was further supported by the low yield from solid culture and the presence of lymphocytes in TPF. However, with the improved yield of liquid culture media, *Mycobacterium tuberculosis* can be isolated and TPE is thought to occur as a result of a paucibacillary infection in the pleural space spread from pulmonary lesions [13].”

Comment 5: * Standard TB culture (PMID 12598215) on induced sputum has been

shown to have a yield of >50% in cases with pleural TB even in the abscence of lung affection on chest -ray. Nucleic acid tests (Gene Xpert) on induced sputum in patients with pleural TB had a yield of 25% (DOI 10.1080/23744235.2020.1857431). This should be highlighted by the authors.
Reply 5: Thank you for the additional information on diagnostic yield of induced sputum culture. We have incorporated these numbers into our manuscript.
"Sputum culture has a low diagnostic yield ranging between 0 and 30%. Induced sputum culture has been shown to have a higher yield of 52% even in patients with normal radiograph. Nucleic acid amplification of induced sputum culture in patients with TPE only provides approximately 25% of yield."
Conde MB, Loivos AC, Rezende VM, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. *Am J Respir Crit Care Med*. 2003;167(5):723-725.
Guo S, Han C, He Y, Wang MS. Diagnostic incremental value of sputum in patients with pleural tuberculosis. *Infect Dis (Lond)*. 2021;53(3):184-188.

Comment 6: *Line 121: a word is missing after 'health'.
Reply 6: Word "issue" is added
Changes in the text: Tuberculosis (TB) is a worldwide health issue affecting approximately 10 million individuals each year(8).

Comment 7: * Lin 125: 'active TB' should be replaced by 'open pulmonary TB'.
Reply 7: "Open Pulmonary TB" is used instead of "active TB."
Changes in the text: However, if left untreated, development of open pulmonary TB is seen in 43-65% of patients within the subsequent years

Comment 8: * Line 153: 'diagnostic yield' here is based on a combination on histopathology and microbiology results. This should be clarified.
Reply 8: Yes, it is a combination of histopathology and microbiology results.

Comment 9: Malignant pleural effusion:
* Line 194: the device is either called 'tunnelled' (in US literature) or 'indwelling' (in UK literature) pleural catheter. I would use either but not both.
Reply 9: We will use "indwelling pleural catheter."
Line: Line 194 and 197

Comment 10: * Line 196: the distinction between trapped and entrapped lung is blurry and is no longer considered relevant. The more recent term is 'non-expandable lung'.
Reply 10: Thank you for pointing this out. We agree with this and would like to change the sentence as "In patients with symptomatic MPE and non-expandable lung, indwelling pleural catheters present the only viable option.
L196-197

Comment 11: Chylothorax: it should be mentioned that besides the deleterious effects

on immunity, excessive fat and protein loss can also cause profound malnutrition.
Reply 11: “Prolonged chest tube placement in chylothorax can lead to complications associated with immunosuppression and profound malnutrition due to loss of protein, fat, electrolytes, and immunoglobulins.”

Reviewer C

This is a comprehensive review on Lymphocyte predominant exudative pleural effusions, which I think is helpful for the general reader.

SPECIFIC COMMENTS

Comment 1: TITLE: In spite of the title, It is clear that -besides exudates- some types of transudative pleural effusion have also to be dealt with in this revision, and I would therefore consider deleting the term "exudative" (that could be misleading) from the title of the manuscript.

Reply 1: While we agree that there are many transudative effusions which are lymphocyte predominant, we respectfully disagree with the reviewer in adding all these transudative effusions as well for the reasons as following: 1) Many transudative effusions are lymphocyte predominant but have not been clearly described in literature as it is unlikely to help the clinician as the cause is easily apparent and 2) It would be too extensive a review article if all these entities were outlined and 3) The clinician’s main task is to investigate further into exudative effusions. Information to narrow the differential diagnoses would be of more importance to them which is being highlighted within this review.

Comment 2: APPEARANCE OF MALIGNANT PLEURAL EFFUSION. On the second line of the second paragraph in page 8 (line 161), the authors quote that "malignant pleural effusion (MPE) typically present with a large unilateral pleural effusion." While I generally agree with this statement, I would recommend including the fact that a diffuse pleural thickening with little effusion can be often seen in advanced mesotheliomas.

Reply 2: Thank you for pointing out pleural mesothelioma can produce small, unilateral pleural effusion with diffuse pleural thickening. We agree with that while malignant pleural effusion generally presents as a large unilateral effusion, it can sometimes manifest as small, asymptomatic effusion.

Malignant pleural effusion (MPE) typically presents as a large unilateral effusion, but certain conditions, such as pleural mesothelioma, can present small unilateral effusion without significant symptoms

Line: 161

Comment 3: PLEURAL EFFUSION IN UREMIA. Besides the conditions quoted on this section in the manuscript, I believe that URINOTHORAX should also be included in this review. This is a rare cause of pleural effusion, generally associated to bilateral obstruction of the genitourinary tract or iatrogenic procedures. With

characteristics of a transudate, it is unique in showing a low pleural fluid pH and a high pleural fluid/serum creatinine ratio (>1.0).

Reply 3: Thank you for the additional information on urinothorax, which is a fascinating condition. Our review on current literature suggests that the effusion is transudative with low cell content and no particular pattern in the cell differential. Given that our review focuses mostly on the causes of lymphocyte predominat pleural effusion, we will defer including urinothorax in our manuscript at this time.

1. Garcia-Pachon E, Romero S. Urinothorax: A new approach. *Curr Opin Pulm Med*. 2006;12(4):259-263.
2. Austin A, Jogani SN, Brasher PB, Argula RG, Huggins JT, Chopra A. The urinothorax: A comprehensive review with case series. *Am J Med Sci*. 2017;354(1):44-53

Comment 4: TABLE 1. I basically agree with the types of tumors that are most frequently associated to MPE in men, but would consider mentioning development of mesotheliomas in women in some cases of environmental or home exposure to asbestos.

Reply 4: Thank you again for your valid suggestion. We are however worried that adding that point may be going beyond the focus of this table. Hence, we respectfully disagree and would like to keep the table as it is.