Peer Review File

Article information: https://dx.doi.org/10.21037/med-23-23

Review Comments

Reviewer A

This review of giant mediastinal tumors is easy to read, well documented with an excellent iconography and very concise chapters. It is very helpful for the physicians and pathologists in charge of patients with mediastinal tumors.

We would like to thank the reviewer for the thoughtful review of our manuscript.

Minor comments

Comment 1: the authors should explain why they exclude hematopoietic tumors such as Classical Hodgkin lymphomas, Primary Mediastinal B-cell lymphoma, lymphoblastic lymphoma and others ....than can present as giant tumors . We can understand this choice but it has to be defined early in the review such as non hematopoietic giant tumors

Reply 1: We agree with the reviewer that such neoplasms can present as giant tumors; however; that would expand the already long manuscript even further.

Changes in text 1: We included a few sentences about why we did not include these neoplasms. "We did not include hematolymphoid neoplasms, even though they can present as giant tumors in the mediastinum. However, the large variety of hematolymphoid neoplasms would require a review on its own. Furthermore, for many of these neoplasms biopsies are performed but no resection. If a hematolymphoid neoplasm is in the differential diagnosis of any of the lesions we included, it will be discussed. "

Comment 2-fig 10B: an arrow to show rhabdoid pattern would be helpful

Reply/Changes 2: Arrows have been added. The figure legend was updated.

Comment 3- fig 16D: an arrow to show the weak staining of cytokeratins in tumor cells

Reply/Changes 3: Arrows have been added. The figure legend was updated.

Comment 4: table 3: in the legends: explain SMA, MSA

Reply/Changes 4: Both terms are now explained in a footnote.

Comment 5-page 8 line 99; D2-40 is the antibody therefore it is better to write ; they express podoplanin (D2-40)

Reply/Changes 5: Thank you for pointing that out. This has been updated in the text and figure legend of figure 1.

Comment 6: page 12, 163: is NSE still an helpful marker for neuroblastic tumors? The authors should comment

Reply/Changes 6: We agree, NSE is not very specific. We have added a sentence: "However, while expressed in the tumor cells of neuroblastic tumors, NSE is not a test specific for that entity and indeed is expressed in many other neoplasms and therefore not very useful in the distinction of neuroblastic tumors from its mimickers."

Reviewer B

I am grateful to the handling editor for the opportunity to review the manuscript titled "Histopathological features of giant mediastinal tumors – a literature review" by Brcic and Roden, which is currently under consideration for publication in Mediastinum. I extend my commendations to the authors for their scholarly contribution, which offers an exhaustive literature review on giant mediastinal masses, with an emphasis on their identification and characterization from a pathologist's perspective.

The authors have classified a mediastinal tumour as "giant" if it surpasses 10 cm in its largest dimension. Following this definition, they conducted a literature search on the PubMed database, focusing on articles published in English or German. They also

incorporated their own experiences with such tumours into the review. Their findings reveal that a diverse range of lesions can manifest as a giant tumour in the mediastinum, potentially leading to critical situations due to their proximity to vital structures. The study underscores the importance of precise diagnosis, as the management strategies for these lesions can significantly vary, encompassing local treatments such as surgical resection and radiation therapy, as well as systemic therapies.

The study's conclusions underscore the necessity of a biopsy for most patients to ensure accurate diagnosis. However, the authors wisely caution that due to the potential heterogeneity of lesions, biopsy results must be critically evaluated within the clinical and radiological context to account for potential sampling bias. In certain scenarios, where there is a high pretest probability of a presumptive diagnosis, a biopsy of the giant mediastinal mass may be deemed unnecessary.

In conclusion, the study offers a thorough review of giant mediastinal lesions, emphasizing the critical importance of accurate diagnosis and the careful evaluation of biopsy results within the context of clinical and radiological findings.

The manuscript under review is eloquent and well-structured. The introduction effectively sets the contextual framework, even for readers not deeply familiar with the subject matter. The findings are clearly presented with appropriate tables and figures, and they are discussed within the context of the contemporary literature. Lastly, the conclusions are based on the reported findings and are relevant to clinical practice.

The manuscript stands as a potential significant addition to the existing literature on mediastinal lesions. It presents a comprehensive review of these lesions, uniquely from a pathologist's perspective, a viewpoint that is often underrepresented in the literature. The study's emphasis on “giant tumours” introduces a novel dimension to the existing body of knowledge. Furthermore, the authors delve into the wide array of lesions that can manifest as a giant mass in the mediastinum, enriching the study's depth. The amalgamation of a literature review and practical experience offers a

well-rounded perspective on the subject matter.

In essence, this review holds the potential to shape clinical practice by heightening awareness about the diverse range of lesions that can present as a giant mass in the mediastinum. It highlights the importance of precise diagnosis and the critical evaluation of biopsy results, which could pave the way for more effective diagnostic and treatment strategies for large mediastinal lesions.

We would like to thank the reviewer for the very thorough review of our manuscript.

While the manuscript offers valuable insights, there are areas that could be further refined to enhance the quality and impact of the work. In light of this, I propose the following recommendations:

Comment 1: The authors' choice to define a "giant tumour" as one measuring at least 10 cm in its greatest dimensions appears somewhat arbitrary. It would be beneficial for the authors to elaborate on the rationale behind this definition or explore how alternative definitions might influence the study's findings.

Reply/Changes 1; Thank you for pointing this problem out. It was difficult for us to establish what exactly defines a "giant tumor". Therefore, as we mention in the methods, we arbitrarily defined it as 10 cm in diameter. As this is a review and not a scientific study we felt that further analysis of altering the defining tumor size would add substantial facts to any of the included lesions as essentially all of them can present with a wide range of tumor sizes.

Comment 2: While the study does not purport to be a systematic review, a more explicit delineation of the methodology employed would enhance its clarity. Specifically, outlining the criteria used for selecting articles from PubMed, such as study design or publication year, would allow readers to better comprehend the scope of the literature review and facilitate future replication or expansion of the study.

Reply/Changes 2: We included a few sentences in the methods to better delineate our reasoning for referenced studies and added Table clarifying our approach.

Comment 3: The authors astutely acknowledge the potential for sampling bias in biopsy results. However, the manuscript could be strengthened by offering more detailed strategies to mitigate this bias, such as specific biopsy techniques, recommendations on the number of samples to be taken, or the use of imaging techniques to guide the biopsy process.

Reply/Changes 3: That is a very valuable point. We have included a few sentences to stress this in our manuscript: "To minimize sampling bias, multiple needle cores, potentially sampling via mediastinoscopy, or utilizing image-guidance should be considered. Furthermore, sampling of various areas of the tumor could be helpful to further alleviate sampling bias. Because there is increasing potential for targeted therapy for some of the mediastinal lesions requiring testing on paraffing embedded tissue, biopsy specimens should be distributed into multiple tissue cassettes."

Comment 4: An expanded discussion section that provides a more comprehensive overview of previous research on mediastinal lesions would help situate the current study within the broader field.

Reply/Changes 4: While we agree with the reviewer, unfortunately, our word limit is already maxed out.

Comment 5: In lines 452-454, the authors assert that in a young male patient with a prevascular mediastinal mass, a high AFP or beta-HCG by serology (> 100 IU/L) is virtually diagnostic of a non-seminomatous GCT, negating the need for a biopsy before starting treatment. While this claim is accurate, it would be beneficial to discuss the potential implications of initiating systemic anticancer treatments without a definitive diagnosis.

Reply/Changes 5: Thank you for that suggestion. We added a sentence : "Indeed, with the exception of the above mentioned young male with non-seminomatous germ cell tumor, a biopsy should be performed of any tumor that will not be primarily resected but treated with neoadjuvant or adjuvant therapy."

Comment 6: In lines 454-455, the authors suggest that a diagnosis of thymoma is often highly suspected based on clinical and imaging features, and patients usually undergo resection of the mass without prior biopsy. While this claim is

valid, particularly due to the potential pleural seeding of a thymic tumour, it is primarily applicable to smaller tumours. Bulky tumours, especially those exceeding 10 cm in maximal dimension, may necessitate surgical approaches such as a hemi-clamshell or clamshell incision for resection. Given the invasiveness of these procedures, obtaining a tissue diagnosis may be prudent in these cases. A discussion of such considerations would be beneficial for readers.

Reply/Changes 6: A sentence has been added to clarify this: "However, if there is a suspicion for invasion based on imaging or clinical assessment and the patient will not undergo primary resection of the tumor, a biopsy should be performed before treatment is initiated."

Comment 7: Considering the previous two points, it would be valuable for the authors to underscore the importance of multidisciplinary team meetings in making management decisions. While the primary focus of the paper is not the management of mediastinal tumours, a brief mention of this collaborative approach to management could enrich the manuscript.

Reply/Changes 7: A sentence has been added to underscore this very important point: "A multidisciplinary discussion is important in the workup of any patient with a mediastinal mass."

In conclusion, I would like to reiterate my appreciation to both the editor and the authors for the opportunity to review this intriguing and informative manuscript. I trust that my comments and suggestions could help enhance the comprehensiveness, relevance, and impact of this important work. I look forward to seeing the revised version of the manuscript and wish the authors success in their ongoing research endeavours.