Peer Review File

Article information: https://dx.doi.org/10.21037/med-23-66

Reviewer A

Comment 1: Thanks a lot for submitting your manuscript. The review is well written but given that is a review focusing on imaging of epithelial tumors I would structure the paper as a review without the case series.

Reply 1: Thank you for the comment. Based on discussion with the editorial office, I would like to change the category of my paper and have updated the manuscript's category to Clinical Practice Review and also have updated the title (see Page 1, line 1).

Reviewer B

Comment 2: The author presents a mini review on thymic tumors and their differential diagnosis, illustrated by five case vignettes.
I regard this topic as worth publishing but some shortcomings should be addressed.
A list of abbreviations should be added
I suggest to add a table that includes the imaging features sorted by entities and by imaging tools.

Reply 2: I really appreciate for the comments. Thymic epithelial tumors are such a heterogenous category and have a lot imaging features in common with other tumors as shown in the text and cases, that it is tough to making a table which are not misleading. On the other hand, as you suggested, abbreviation list would help readers to understand the manuscript, I made the list (see Page 2-3).

Comment 3: Endocrine oncologists are familiar with thymic sonography e.g. for detecting ectopic parathyroids. Some reports exist on that issue (DOI: 10.1177/1742271X221124484, DOI: 10.1002/jum.15619, DOI: 10.5152/dir.2019.19344). To the best of my knowledge there are no reports on detected-by-sonography TET. Could you address this? In my opinion there might be a chance of early detection of thymic masses when observed during thyroid sonography.

Reply 3: Thanks for the comments. As pointed, I agree with the concept that ultrasound is a non-invasive and cost-effective imaging modality that can potentially be used to diagnose thymic lesions. I added several sentences and cited the references which the reviewers pointed (see Page 10, line145-152).

Comment 4: You present 5 interesting cases. The thymic ones are all thymoma, maybe you can include a neuroendocrine or carcinoma case? Interestingly these cases show radiologic features that do not really fit to the explanations in the text before. From my

experience this reflects real life conditions quite well. I think you should point it out.

Reply 4: Thank you for giving me a chance to present a new case and so on. I create a new case (case #4, thymic carcinoma (see Page 20-21, line 331-351 and Page 33-34, line 471-478)) as well as added a sentence describing these cases are not typical ones in the abstract (see Page 5, line 62-65). Please also see the reply 9, because these two comments are associated with each other.

Comment 5: In case 1 and 3 you state "no elevated tumor markers". Which markers would you recommend?
Line 190 should read "FDG-PET/CT revealed intense".
Line 191 you describe high-grade thymoma, in line 128 high risk thymoma. Are they synonymous?
Reply 5: I added the tumor markers we had evaluated in case 1 and 3 (see Page 18, line 288-289, and Page 19, line 314-315, respectively). I corrected the typo "PDG" (see Page 18, line 292) and I have unified the terminology regarding high risk/high-grade as the reviewer suggested (see Page 18, line 293).

Comment 6: line 82 should read "tumors are categorized"
Reply 6: Thank you, I corrected as is should be (see Page 10, line 152).

Comment 7: I did not understand the meaning of the sentence on line 91
Reply 7: Thank you, I revised the sentence (see Page 11, line 161).

Comment 8: In section THYMOMA line 123 you state aprevalence of 17-54% of myasthenia gravis in thymoma. Recent publications indicate strong ethnic differences with prevalences between 5.7% and 82.4% (doi: 10.21037/tlcr-23-396). In line 141 you should add that ADC is a MRT based reconstruction. Please review carwefully the text for unexplained abbreviations (e.g. amongst others T1WI or T2WI, line 292)
Reply 8: Thank you for sharing the latest paper. I added a new sentence (see Page 12, line 193). Also, I added the explanation about ADC (see Page 13, line 210-211) as well as created an abbreviation list (see Page 2, line 15).

Comment 9: in section NEUROENDOCRINE TUMOR (170ff) please add information on the impact of somatostatin receptor imaging like DOTATOC PET (doi: 10.3389/fonc.2022.823667, doi: 10.1111/cen.14572). In this section you use the terms NET, NEN and carcinoid without comments. Please explain the differences and add information on thymic neuroendocrine carcinoma.
Reply 9: Thank you. I added sentences describing DOTATOC PET (see Page 16, line 253-263) as well as change the title and phrases following to the WHO classification of tumors 5th edition (see Page 15, line 238, 421-242, Page 16, line 248-249).

Comment 10: in REFERENCES some autors are mentioned by et al, some publications are mentioned with all authors. Please homogenize according to the rules of the editor.

Reply 10: Thank you. The reference list has been modified in accordance with the Submission Rules (see Page 42-49, line 615-746).

Reviewer C

Comment 11: The authors have written a very interesting review describing the imaging features of thymic epithelial neoplasms. The topic is of interest for the readers of the journal. In addition, the use of real-life cases helps putting all the information in the clinical context. I congratulate the authors for writing the review in this way. I have a series of comments that will help improving the quality of the manuscript:

Reply 11: I was really encouraged by the reviewers' comments. I would like to express my sincere appreciation. Below I report my reply and responses to the comments.

Comment 12: 1-In the lines 53 and 54 the authors mention "Thymic epithelial tumors (TETs) encompass thymomas, thymic carcinomas, and thymic neuroendocrine tumors". It is true that TETs encompasses these three types of tumors. However, also other less frequent epithelial tumors can arise in the thymus (e.g., lipofibroadenoma). As such, the authors could rephrase the sentence to mention either that other less frequent TET can also arise from the tumor, or just mention that these three types of TETs are the most frequently found in the thymus.

Reply 12: Thank you for the accurate comment. I rephrased the sentence to "Tumors arising in the thymus are of various histological types, but three types of thymic epithelial tumors (TETs) are the most frequent: Thymic epithelial tumors (TETs) encompass thymomas, thymic carcinomas, and thymic neuroendocrine tumors." (see Page 8, line 112-114)

Comment 13: 2-The authors should mention that there may be high rate of unnecessary thymectomy due to misinterpretation of thymic cysts, thymic hyperplasia, and lymphoma as thymoma on chest CT. A recent study by Ackman et al. [Eur J Radiol. 2015 Mar;84(3):524-533.] showed that differentiating features between thymoma, lymphoma, thymic hyperplasia, and thymic cysts on chest CT which may help triage more patients away from thymectomy toward less invasive and non-invasive means of diagnosis and thereby lower the non-therapeutic thymectomy rate.

Reply 13: Thank you for your valuable comments. It is true that sometimes it looks like a cystic degenerated thymoma but when resected, it turns to be a thymic cyst.
I have added to the manuscript based on your comments and appended the references you shared (see Page 8-9, line 121-126).

Comment 14: 3- The authors should provide a citation supporting this statement "In instances where CT-based differentiation is challenging, T2-weighted images, showing marked high signal intensity and high apparent diffusion coefficient (ADC) values, can suggest cystic lesions, whereas the absence of these features increases the likelihood of a solid lesion."

Reply 14: Thank you for the comments. It is well established in general radiology field,

thus I provide the manuscript with two references supporting the statement throughout a general fields (see Page 9, line 129).

Comment 15: 4-In addition, it would be important that the authors describe longitudinal radiological characteristics of benign cystic lesions of the thymus. Perhaps the authors should describe them as an extra fourth item in the discussion, the same way they did it for Thymoma, thymic carcinoma, and neuroendocrine tumor (NET). The rationale: as cystic lesions can be misinterpreted as malignant lesions, it is important the authors describe the available data in the literature. In fact, specific longitudinal data to differentiate them from the malignant lesions has been published in the current medical literature [Radiology. 2021 Nov;301(2):443-454; Mediastinum. 2023 Mar 20;7:13.].

Reply 15: Thank you for your valuable comment. At the initial drafting stage, I actually deliberated on whether to mention thymic cysts as well, but due to the focus being on thymic epithelial tumors and also considering the constraints of word count, I omitted it. However, I am grateful that the reviewer suggested it, which provided an opportunity to create a section specifically for that purpose. I have also added the references you provided and incorporated them into the supplementary section (see Page 12, line 183-184, see Page 16-18, line 265-284).

Comment 16: 5- When the authors describe the imaging findings of the mediastinal lymphomas they first state that lymphomas have a propensity to progress without directly invading or encasing existing blood vessels. However, later in the same paragraph they state “In addition, as mentioned earlier, the common finding in lymphoma is a penetrating image of blood vessels,”. These sentences require some clarification for the non-radiologists’ readers. What does mean to have a penetrating image of the blood vessels. Does that mean that the vessels are not invaded? It would be best if the authors can rephrase the setences to make it understandable to all the readers.

Reply 16: Thank you for pointing out phrases which is not friendly to non-radiologists’ readers. I added sentences to the manuscript “Malignant lymphomas exhibit less desmoplastic change compared to solid tumors. In cases of lung or thymic epithelia tumors, during the infiltration process, there may be strong compression of blood vessels or direct infiltration leading to occlusion or severe stenosis. However, such imaging changes are less common in lymphomas, serving as a distinguishing feature from solid tumors. Additionally, in lymphomas (especially Hodgkin lymphoma), which develops multicentrically it is not uncommon for vessels to be surrounded. Nevertheless, even in such instances, relatively minimal stenosis is observed, sometimes resembling blood vessels penetrating the tumor interior, which can be considered a characteristic imaging feature of lymphomas” (see Page 10, line 140-147).

Comment 17: 6- The authors should include references for the statements given in these four sentences “Thymomas, for instance, may exhibit positive anti-acetylcholine receptor antibodies, making it desirable to include their measurement as a screening

tool for concurrent myasthenia gravis. Thymomas are also associated with conditions like pure red cell aplasia and hypogammaglobulinemia (Good syndrome), emphasizing the importance of checking complete blood count and globulin. In germ cell tumors, elevated levels of AFP, β-HCG, and LDH are common, while malignant lymphomas often present with elevated LDH and sIL-2R. Additionally, it is crucial not to overlook the possibility of primary lung cancer (or lesions associated with lung cancer), a frequent occurrence in mediastinal masses."

Reply 17: Following your advice, I have attached some documents as references to make it easier for readers to refer to them (see Page 12, line 179, 181).

Comment 18: 7-In figure 1, panels C and D include arrows that appear to be pointing to specific elements. The authors should describe these elements in the figure legend. The authors should also describe all the panels of the figure in the figure legend. Please use descriptors (arrows/arrowheads) to describe specific features of the panels A, B, and E as you did for panels C and D.

Reply 18: Thank you for your valuable comments that will make figure and figure legend easier to understand. Following your advice, I added arrows and legends to the figure and manuscript and revised them (see Page 27-28, line 441-444).

Comment 19: 8-In figure 2 for the images of the contrast enhanced CT studies (abdomen and thorax), it may be important that the authors describe the radiological abnormalities and use descriptors (arrows/arrowheads) to point to these abnormalities in the two panels that were included. This may be important for the non-radiologists' readers that are less familiar with radiological features in the presented images.

Reply 19: Thank you for your valuable comments that will make figure and figure legend easier to understand. Following your advice, I added arrows and legends to the figure and manuscript and revised them (see Page 29, line 453-454).

Comment 20: 9-Can you please describe what was the abnormality during a regular health check-up that was found int the patient of case 3 (male in his fifties). This is not clear in the description given by the authors.

Reply 20: Thank you. I added the information (chest X-ray) to the manuscript (see Page 20, line 321).

Comment 21: 10- In figure 3 for the images of the imaging studies, it may be important that the authors describe the radiological abnormalities and use descriptors (arrows/arrowheads) to point to these abnormalities in the four panels presented. This may be important for the non-radiologists' readers that are less familiar with radiological features in the presented images.

Reply 21: Thank you for your valuable comments that will make figure and figure legend easier to understand. Following your advice, I added arrows and legends to the figure and manuscript and revised them (see Page 31-32, line 464-469).

Comment 22: 11- In figure 4, panel B includes an arrow that appear to be pointing to

a specific element. The authors should describe this element in the figure legend. The authors should also describe all the panels of the figure in the figure legend.
Reply 22: Thank you for your valuable comments that will make figure and figure legend easier to understand. Following your advice, I added arrows and legends to the figure and manuscript and revised them (see Page 36, line 489-491).

Comment 23: 12-In figure 4 please use descriptors (arrows/arrowheads) to describe specific features of the panels A, and C as you did for panel B. This may be important for the non-radiologists' readers that are less familiar with radiological features in the presented images
Reply 23: Thank you for your valuable comments that will make figure and figure legend easier to understand. Following your advice, I added arrows and legends to the figure and manuscript and revised them (see Page 36, line 489-491).

Comment 24: 13-In figure 5 for the images of the imaging studies, it may be important that the authors describe the radiological abnormalities and use descriptors (arrows/arrowheads) to point to these abnormalities in the five panels presented. This may be important for the non-radiologists' readers that are less familiar with radiological features in the presented images
Reply 24: Thank you for your valuable comments that will make figure and figure legend easier to understand. Following your advice, I added arrows and legends to the figure and manuscript and revised them (see Page 37, line 501-505).

Minor comments:
Comment 25: 1- Can you comment on why the JART classification still maintains the traditional concept of the superior mediastinum, or why the ITMIG does not include it? I understand you may not know the answer to it, but it may be important to add a comment on why there's discrepancy between these two classification systems.
Reply 25: Thank you for asking important question. The ITMIG classification selects a 3-compartment model for defining mediastinal compartments primarily due to its advantages over a 4-compartment model. The merit of the 3-compartment model lies in its similarity to established anatomical and clinical models, its less complicated design, and the establishment of compartmental boundaries along true anatomical planes. This model simplifies the classification system and is easier to implement and disseminate. However, one potential demerit is that merging the superior and anterior mediastinal compartments may not adequately separate entities occurring in each location, although this is rarely a clinical issue given the reliability of identifying thyroid goiters on CT scans. The 4-compartment model, on the other hand, has the advantage of similarity to existing models and may be effective in distinguishing specific disease entities. However, it suffers from increased complexity, non-anatomic boundaries, and difficulties in implementation and dissemination. A survey of experts found that 72% preferred the 3-compartment model, citing reasons such as optimal distinction of disease entities, similarity to current practices, anatomical accuracy, and ease of use. As a result, the 3-compartment model was selected as the basis for the CT-

based classification scheme proposed by ITMIG.
I added some sentences stating above to the related place in the manuscript (see Page 6-7, line 85-95).

Comment 26: 2-The sentence in lines 45 and 46 is a bit redundant. It can be deleted or rephrased.
Reply 26: Thank you. Following the advice, I deleted the sentence (see Page 7-8, line 103-15).

Comment 27: 3-The abbreviation for thymic epithelial tumors (TET) should be introduced early in the introduction of the manuscript, and not in the section named "Diagnostic Approach of Thymic Epithelial Tumors".
Reply 27: Thank you for your comment. Throughout the text, we defined TET in the context in which it first appeared, and thereafter unified it with TET (see Page 6, line 69, and so on).

Comment 28: 4- This sentence is incomplete "It has also been reported that the inclusion of pancreatic tissue is associated with the failure [13].", the authors should add more information to describe what's if the pancreatic tissue associated with.
Reply 28: Thank you. Please see Reply #7 (see Page 11, line 168).

Comment 29: 5-This sentence is confusing, and the authors should rewrite it: "Although Castleman disease is considered several different, etiologically unrelated diseases and is divided into unicentric and multicentric, nearly all cases of unicentric Castleman disease are of hyaline-vascular type: hyaline-vascular Castleman disease which has well defined pathological features, and likely represents a neoplasm of stromal origin with bundant associated reactive lymphoid tissue".
Reply 29: Thank you for the comment. I revised them to "Castleman's disease is thought to be a disease that includes several different etiological conditions. It is classified as unicentric or multicentric, and almost all cases of unicentric Castleman disease are of the hyaline vascular type. Hyaline vascular Castleman disease has distinct pathological features and is considered to be a benign clonal neoplasm derived from lymph node stromal cells, possibly follicular dendritic cells." (see Page 23, line 379-383)

Comment 30: 6-The authors should add a title for the "References" in page 23 before listing the references.
Reply 30: I added a title "References" (see Page 40, line 511). Thank you.