

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-778>

Reviewer A

Page 2, line 40: “Lymphangioliomyomatosis is an inheritable disease with a high predilection toward female subjects”. “Inheritable” may not be correct.

Reply & Changes in the text: We changed the word ‘inheritable’ to ‘genetic’

Page 2, line 62: Please check whether “infiltration of the lung parenchyma” is correct or not.

Reply: We changed the sentence as follows:

Changes in the text: “LAM is characterized with metastasis of abnormal smooth muscle-like cells (i.e., LAM cells) to the lung...”

Page 4, line 115: Please delete the memo of Korean language.

Reply & Changes in the text: We are terribly sorry for this error and deleted it.

Page 4, line 132: “(=or?)” is not uncertain memo. There are several similar comments in the manuscript. Please appropriately change them.

Reply & Changes in the text: Sorry again, we erased the redundant phrases.

Page 5, line 145: Meningioma maybe related with female or estrogen. “Meningiomas in LAM are known to be more prevalent than that in the general population.” Please add more words about meningioma.

Reply: We added some description regarding the meningiomas in LAM, of hormonal issues. We also added another literature to the reference list (19. JAMA 2001;286:1879-81).

Changes in the text: While the prevalence of meningioma in general population is around 1:20,000 LAM patients contract more frequently (i.e., around 2% ~3%). Meningioma contains progesterone receptor, and progesterone has a mitogenic effect in LAM patients. For this reason, aside for weak evidence of beneficial effect toward LAM, hormonal therapy is no longer recommended (20); therefore, searching for meningiomas in LAM patients using imaging tools are accordingly less performed.

Page 6, line 189: “American Thoracic Society” should be “American Thoracic Society and Japanese Respiratory Society”. Please change it.

Reply: Thank you for your good comment. We almost forgot the contribution of the two academic societies.

Changes in the text: “The American Thoracic Society and Japanese Respiratory Society claimed...”

Page 6, line 191: Please add one more compatible data (in Japan) about the cut-off level of 800 below, if possible. Hirose et. al. PLoS One. 2019 Feb 28;14(2):e0212776.

Please change the memo “Often” to more appropriate words.

Reply: We thank you for your precious literature recommendation, carefully read it and wrote several sentences on the paragraph.

Changes in the text: One Japanese study verified its utility on diagnosis of LAM, corroborating the recommendations from the two academical societies (26). Of note, cutoff value of serum VEGF-D level at a specific 645 pg/mL showed a sensitivity and specificity of 0.83 and 0.97, respectively, whereas those of the recommended cutoff level (i.e., 800 pg/mL) were 0.72 and 0.100, respectively, expressing a slightly less sensitive result.

Page 6, line 199: Is SLB still a gold standard now? The ref (20) was published in 2016. Please update the sentence.

Reply: We agree that the description is a bit outdated, and searched and added more information with relevant reference. Please refer to the revised manuscript. Thank you very much.

Changes in the text: For tissue procurement, video-assisted thoracoscopic surgery (VATS)-guided surgical lung biopsy was previously the gold standard (21), and less invasive methods including transbronchial lung biopsy (TBLB) or transbronchial lung cryobiopsy (TBLC) are being adopted recently (10)”

Reviewer B

The authors present a review about the use of mTOR in the treatment of lymphangioleiomyomatosis. Aspects were presented from pathophysiology, including clinical and prognostic aspects and treatment. The text was presented clearly and objectively. I have some suggestions:

1) In line 50, in the first paragraph of the conclusion, collateral manifestations are cited. The sentence was confused. I think it needs to be reformulated.

Reply: First of all, thank you for spending your time for review. We tried to clarify the sentence by modifying it as follows.

Changes in the text: “...due to its complex pathogenesis and accompanied by other manifestations.”

2) In lines 69 and 70, in the introduction, the phrase “...intrude the lymphatic system and clog (the) lymphatic flow, causing chylous pleural effusion and ascites.”, was not clear. Avoid abbreviations like the word “the” in parentheses. It can compromise the formality of the text.

Reply: Sorry for the error. We deleted the redundant word. Please refer to our revised manuscript.

Change in the text:” These cells intrude the lymphatic system and clog lymphatic flow, causing...”

3) The expression “so on” appears several times in the text. Avoid unnecessary repetitions.

Reply and Changes in the text: We changed the repetitive “so on” into some other words and phrases (e.g., etc., and so forth). Please refer to the manuscript.

4) In line 115, under pathogenesis, there is a citation in another language. To maintain the

linearity of the text, I suggest that the expressions be written in English. Many readers will not understand the message.

Reply and Changes in the text: We are terribly sorry for this flaw, and erased it.

5) In lines 122-123, the phrase “LAM is a disease that has the strongest sex preference of any non-genitourinary..” was confusing and difficult to understand. Please review.

Reply: Our intention was to emphasize the female-predominance of LAM. We modified the sentence so that the future readers could easily understand.”

Changes in the text:” LAM is a disease that has the strongest female predominance among neoplasms arising from non-urogenital system”.

6) In line 132-133, expressions appear in parentheses that should not appear in this form, compromising the structure of the text - (=or?). The impression is that it is a question for the reader, not an answer.

Reply: We are sorry for the error of and imperfect manuscript. We forgot to erase it. Please check our revised manuscript.

Changes in the text: Clinical manifestations are largely grouped into pulmonary and extrapulmonary symptoms and signs.

7) In line 162, I suggest reinforcing that the HRCT is the exam that provides more data about the disease in relation to the chest X-ray.

Reply: We agree to your opinion and modified the relevant sentence for a better understanding as follows:

Change in the text: “...led to chest radiography, with subsequent high resolution computed tomography (HRCT) that provides additional detailed data about the disease in relation to the X-ray study.”

8) Lines 165-167 show data on the presence of cysts in the general population. But that wasn't clear. I suggest rephrasing the sentence and specifying that it is referring to the general population.

Reply: We supplemented the following phrases for better description. Thank you for pointing out the ambiguous part, and we hope our modification improves the sentence.

➔ Change in the text: “that the prevalence of lung cysts from a general population of Framingham Heart Study cohort was..”.

9) Currently there is some description that the bronchodilator response may indicate disease activity, as described in the prognosis. I believe the authors could cite this in the paragraph about pulmonary function tests, between lines 178-185.

Reply: We added a short sentence regarding the usefulness of PFT response also in the 5. Diagnostic process section.

Change in the text: Rate of FEV1 decline is associated with baseline disease severity (14). The bronchodilator response may indicate disease activity.

10) Review the sentence “Dubbed as MILES Trial, its primary outcome was rate of change of

lung function between control and case groupsFEV1”, in line 246. Adjust for better understanding.

Replyand Change in the text: We are terribly sorry again for this error. We deleted the flaw.

11) Finally, the acronym “ABGA”, on line 259, has no prior citation. Please correct.

Reply: We wrote “arterial blood gas analysis” instead of the acronym ABGA.

Change in the text: .), objective measurements (arterial blood gas analysis, serum VEGF-D levels, etc.),