

Peer Review File

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Reviewer A

This review contains a lot of information about Anti-synthetase Syndrome and some revisions required.

1. Page 6, Table #1 of Diagnostic Criteria. Diagnostic criteria proposed by Connors et al (2010) for Anti-synthetase Syndrome may omit to refer “PM/DM by Peter and Bohan.”

Reply: The aforementioned changes have been made.

2. Page5, line 114-116. The sentence, “Thus, we recommend utilizing Connor’s criteria as a screening test to rule out low risk patients, and using Solomon’s criteria to confirm the diagnosis of anti-synthetase syndrome in patients with anti-synthetase antibody” needs to be improved, because ILD is often recognized as the sole manifestation of anti-synthetase syndrome (line 357), which could lead to underdiagnosis. For example, how to consider the diagnostic problem that there are some cases with one major criterion (ILD) plus one minor criterion which from Table #1.

Reply: We have clarified the wording of the above sentence. The criteria discussed is meant to serve as a stepping stone for evaluating patients with high suspicion for the disease. Symptoms often fall on a spectrum and it is important to evaluate patients for ASD antibodies even if they do not fulfill the complete triad at presentation. We have also included the following text:

“However since patients often present on a spectrum, physicians are more likely to make the diagnosis of anti-synthetase syndrome based on Solomon’s criteria as the

presence of mechanic's hands or ILD are both highly associated with classic presentation of anti-synthetase syndrome. Similarly, a study of 828 patients with diagnosed anti-synthetase syndrome found that while the triad findings were similar amongst the cohort groups, the onset mainly began with a single triad finding in all groups(18). Thus, in patients where there is clinical suspicion of anti-synthetase syndrome present with only one clinical feature, we recommend utilizing Connor's criteria as an initial test to rule out low-risk patients since ILD is often the sole manifestation of anti-synthetase syndrome. Consequently, Solomon's criteria can then serve as a confirmatory test for high-risk patients positive to anti-synthetase antibodies(17).”

3. Page 3, line 65-67. The details in reference 7 may not be able to support the idea.

Reply: Can you please explain this sentence?

4. Page 22, paragraph #2 of the Treatment. Could you give a more detailed recommendation on corticosteroids as they are the 1st Line therapeutic agent. For example: Intravenous or oral initiating dose at 1mg/kg/day? The upper limit dose? Any recommendation for different groups?

Reply: The initial recommended oral dose is 1mg/kg/day. The upper limit dose has also been clarified as 60mg-80mg a day. At present, much of the available research is limited to case series or small scale studies so it is difficult to extrapolate this data in order to provide a recommendation for different groups.

5. Page 22, line 420. It is better to move “We would like to emphasize the importance of antibiotic prophylaxis ...” to paragraph in page 22 because they are about opportunistic infections.

Reply: The aforementioned change has been made.

6. Page 10, table #2. Is it appropriate to describe the clinical feature of Anti-KS* as Antisynthetase syndrome or ILD alone; fever because Antisynthetase syndrome is a constellation of clinical features that includes... (Page 1, line 11-13)

Reply: Thank you for raising this point and allowing us to clarify. This is describing the most typical presentations with this antibody, however the table does not imply that a particular antibody is only associated with those symptoms.

7. Page5, line 102. The reference of Solomon et al has not been listed.

Reply: The aforementioned change has been made.

8. Reference 20 and reference 107 may have input errors.

Reply: The aforementioned change has been made.

9. The page number of reference 51 should be changed into 233-241.

Reply: The aforementioned change has been made.

10. Line 158, the comma between reference 27 and reference 28 should be superscript. The lack of punctuation mark of multiple references also exists in line 180, reference 36,37 and line 357, reference 78-80 and so on.

Reply: The aforementioned change has been made.

11. Adding more contents on the identification of AS-ILD with few extrapulmonary symptoms is suggested, which can be put forward if there are appropriate quantification criteria.

Reply: Thank you for your comment. This review is directed towards the pulmonologists focusing on the pulmonary manifestations of AS syndrome. While we

recognize the importance of understanding the extrapulmonary symptoms, we feel that expanding this review would make it very cumbersome for reader to read.

Reviewer B

The authors made an in-depth description of the Antisynthetase syndrome, including epidemiology, clinical features, image findings, diagnostic strategies, and treatment options (based on their own experience and previous reports, due to the lack of clinical trials). This review considers a rare-low explored disease; despite it is well written and structured, there are some important concerns to correct and include before consider to publish:

1. It could be interesting to add a new section about the pathophysiology of the antisynthetase syndrome, where the genetic susceptibility for the disease and the cells/cytokines that participate in the development and/or progression.

Reply: Thank you for your comment. As the pathophysiology for AS is still largely unknown, we do not believe that it will add to clinical aspect to this review. However should the editors feel this is important, we are willing to include it however we strongly feel it will take away from purpose of review.

2. Lines 100 and 101 are identical to 62-63. Please modify them.

Reply: The aforementioned change has been made.

3. Line 116: “in patients with antisynthetase antibody”, please change for: “in patients positive to antisynthetase antibodies”.

Reply: The aforementioned change has been made.

4. It would be interesting to add a new section about prognosis in antisynthetase syndrome patients. The authors mention some ideas within the text; however, a new section could be easier to read. Here, authors can describe the clinical, laboratory,

infections, comorbidities, and image findings associated with poor prognosis in these patients.

Reply: Due to the lack of large multi-center studies, it is difficult to extrapolate data for determining prognosis percentages. The aim of our review is to understand early and late disease findings in order to allow for a better overall prognosis for these patients. Additionally, from the current literature it appears that anti-Jo-1 antibody is associated with better treatment response, which is stated in the review.

5. Please separate references in line 442.

Reply: The aforementioned change has been made.

6. Please separate references in line 452.

Reply: The aforementioned change has been made.

7. In line 413 authors describe that Methotrexate can be used as a steroid-sparing agent. However, this one is not included in Figure 5 or Table 4. Please correct or explain this.

Reply: The aforementioned change has been made.

8. References 19, 21, 49, 60, 72, 77, 84, 87, 94, and 98 only state “Ibid”. Please provide the correct format references.

Reply: The aforementioned change has been made.

9. Adding the following references provide significant clinical, laboratory, image, and prognosis data from a population that was not included in the manuscript, as well as a multi-center group AENEAS: PMID: 31752231, 31203227, 33330522, 32384594, 26219488, 33602594, 31996780, 33301929, 29255888.

Reply: Thank you for your comment and for the PMIDs provided. Upon further review of these studies, we have added one of them however the remaining either

describe treatment options in non-AS cases, or discuss areas which we already address (such as antibody phenotype relating to disease severity).

10. It would be interesting to add a graphical abstract.

Reply: We do not feel a graphical abstract will add much to our paper as it stands.

Reviewer C

I read with interest the manuscript “Interstitial Lung Disease in Antisynthetase Syndrome: A Clinical Approach” in which the author/s review clinical and radiological features of Antisynthetase Syndrome.

Some points must be addressed before the paper is acceptable for publication.

1. Line 220: Title of paragraph “Radiographic features of AS-ILD”. The term “radiographic” generally refers to chest x-ray while the authors in this paragraph discuss about HRCT findings. Therefore, I suggest changing “radiographic” to “HRCT findings”

Reply: The aforementioned change has been made.

2. Line 224-226: NSIP. According to the Fleischner Society glossary of terms, NSIP is characterized by ground glass opacities generally bilateral, symmetrical and with a prevalently medial and basal distribution. In this background signs of fibrosis can appear. No micronodules or cysts or mosaic perfusion are present in a NSIP pattern.

Reply: The description we have provided for NSIP has been vetted by on board pathologists and is very much in line with the understanding of NSIP required for diagnosis. Our literature search has demonstrated that AS is not just simply NSIP as there are often multiple and overlapping pathologic patterns.

3. I also suggest explaining the difference between cellular NSIP and fibrotic NSIP

Reply: As AS can present with different forms of lung involvement, this review is not on NSIP itself. By going into the differences on a cellular level, we do not feel such a discussion will fit into the purview of this review.

4. Line 257: UIP. The author/s should refer to the ATS/ERS/JRS/ALAT guidelines for defining the UIP pattern.

Reply: Thank you for your comment. We feel that fibrosis is part of the UIP pathology and this sentence is very representative of the disease. Is there any specific sentence which you would like for us to address?

5. Line 258-259: please rephrase, the sentence is not clear.

Reply: Paragraph has been edited.

6. Line 269: multifactorial: maybe the author/s mean “multidisciplinary”?

Reply: The aforementioned change has been made.

7. The author/s did not discuss about the acute presentation of Antisynthetase Syndrome as acute interstitial pneumonia.

Review: Goal of review is to focus on common presentations and not niche presentations, while there are reports, we do not believe it is not a common occurrence in AS.

8. Line 279: I suggest separating “Multidisciplinary discussion” from the radiological paragraph.

Reply: The aforementioned change has been made.

Reviewer D

ABSTRACT

1. It is necessary to characterize the meaning of "DM", "PM", and "IBM"

Reply: The aforementioned change has been made.

2. It should be more succinct and objective

Reply: The aforementioned change has been made.

INTRODUCTION

3. The first sentence is not totally correct. Please review it.

Reply: The aforementioned change has been made.

4. It is important to share Introduction from Materials and Methods, and Results

Reply: The aforementioned change has been made.

5. It could be more succinct and objective- Correct the references from the text: "1213", "2223", "313233", "4647", etc

Reply: The aforementioned change has been made.

6. The authors mentioned at least two "proposed diagnostic criteria for antisynthetase syndrome". However, there are other as Cavagna et al. J Clin Med, 2019, and Behrens Pinto et al., Clin Rheumatol, 2020.

Reply: The aforementioned change has been made.

7. In line 137, "Because these symptoms may occur individually or... ", please include the recent study of Baccaro et al. Reumatismo, 2020.

Reply: Thank you for your comment. We have reviewed the study mentioned and it appears to report information which we have already discussed in our study, however

we have referenced additional studies in regards to anti-Jo-1 patients and disease presentations, which will hopefully suffice.

8. "Diagnostic criteria", "Autoantibodies and AS-ILD", etc... should be more succinct and objective.

Reply: The paragraphs have been edited.

9. Treatment: experience from authors' group:

Please see lines 442-445, 452-459, 464-468. Additional information has been added

CONCLUSIONS

10. It should be more succinct.

Reply: The paragraph has been edited.

REFERENCES

11. It should be reviewed.

Reply: The aforementioned change has been made.