Author’s response to reviews

Title: Autoimmune polyglandular syndrome type 2 and autoimmune hepatitis with thymoma associated myasthenia gravis: case report

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Author’s response to reviews:

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Editor-in-Chief,
BMC Endocrine Disorders

Dear Sir,
We are pleased to enclose an extensively revised manuscript entitled ‘Autoimmune polyglandular syndrome type 2 and autoimmune hepatitis in thymoma-associated myasthenia gravis.’ We would be grateful if the article could be considered for publication in BMC Endocrine Disorders.

We thank you for your comments and suggestions allowing us to improve the quality of the manuscript. We have answered all of the questions raised by reviewers and editors, shown in red lettering. We hope that it is now suitable for publication.

We affirm that the article has not been published in full or in part and it is not under consideration for publication elsewhere.

Thank you for your consideration,

Sincerely yours,

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Reviewer reports:

Can Ebru Bekircan-Kurt (Reviewer 1): It is a case report of multiple autoimmune diseases including autoimmune polyglandular syndrome, bronchial asthma, thymoma associated MG. The case report underlines the higher risk of autoimmune disease in patients with one autoimmune disease and suggest that HLA typing analysis may aid to identify diseases susceptible population, and diagnose earlier.

- As the patient had thymoma, I am wondering whether the patient had anti-titin antibody positivity. *** We thank the reviewer for the insight and agree with the comment. Anti-titin antibody was not measured (line 87). In Japan, anti-titin antibody is not routinely measured, and this patient was diagnosed with MG based on positivity of anti-AchR-Ab and result of repetitive nerve stimulation (line 87 “The repetitive nerve stimulation test at 3 Hz performed on the right facial nerve was positive”).

- How the diagnosis of MG was confirmed as they did not mention the single fiber EMG or repetitive nerve stimulation. *** We agree with the suggestion raised by the reviewer. We have added the result of repetitive nerve stimulation (line 87).
- It seems that the patient had isolated ocular MG, I am wondering why they did not tried pyridostigmine. *** We understand the suggestion raised by the reviewer. Pyridostigmine was used as first line therapy in the patient, however due to the adverse events, it was stopped (line 90).

- Moreover it would be better to explain the cause of azathioprine treatment (MG or autoimmune polyglandular syndrome) as in patients with ocular MG, the azathioprine could be second line treatment. The prednisolone dose is also very low, it would be better to explain the rational of treatment strategy. *** We thank the reviewer for pointing this out. For treatment of AIH, mainly azathioprine were required. PSL (10mg) was mainly used for APS-2 and MG. And both azathioprine and PSL were effective for AIH, APS-2, and MG until thymectomy (line 91).

Jonathan Hazlehurst (Reviewer 2): I read this case report which I agree has educational value to the readership with interest and have made a number of comments below.

- Minor comment: some of the grammar is not quite right and it would be good for the handling editor to correct in detail *** We agree with the suggestion raised by the reviewer. A native English editor has revised manuscript again.

- Major: all instances of diagnosed "as" must be changed to diagnosed "with". This may seem subtle but the journal and authors must commit to using person-first language. Detailed comments are below. *** We agree with the suggestion raised by the reviewer. We have corrected to [Diagnosed with].

- Abstract Please changed diagnosed "as" to diagnosed "with" in the this paragraph as a commitment to person first language. *** We agree with the suggestion raised by the reviewer. We have corrected to [Diagnosed with].

-A 52-year-old woman with autoimmune hepatitis (AIH) and bronchial asthma (BA) had been diagnosed as APS-2; autoimmune Addison's disease (AD), and Hashimoto's thyroiditis (HT) 5 months previously, and underwent prednisolone (PSL) treatment. She then noticed ptosis, and was diagnosed as thymoma-associated myasthenia gravis (MG)"The below conclusion is not clear. Are the authors suggesting that APS-2 and AIH are complications of thymoma-associated MG. Please revise this sentence and clarify exact point being made. “This case therefore suggests common endocrinological and autoimmune aspects of APS-2 with AIH in thymoma-associated MG, which are considered to be extremely rare complications."

*** We agree with the comment. We have revised the sentence to clarify the point in the abstract (line 38).

- Background

Please include prevalence of MG and AIH for additional context to this case report.
*** We agree with the suggestion raised by the reviewer. We have inserted the context in line 55.

- Case report "(Figure not shown). Based on these findings, she was diagnosed as APS-2." Please include details of PTH and calcium and also why comment on a figure that is not shown. Either include or delete (Figure not shown) *** We thank the reviewer with the comment. We have included the levels of PTH and Ca, and deleted (Figure not shown)(line 78).

- Why prednisolone rather than hydrocortisone? Is there data around use of pred preferentially versus hydrocortisone in APS2?-this needs comment as will be of interest to those of us more familiar with hydrocortisone in Addison's with limited experience of APS2 and would add to the educational value of the case report. *** We have explained the reason of using PSL rather than hydrocortisone in line 80.

- Please include a comment around developing MG despite being on prednisolone. Is there any data around this? It strikes me as unusual but I could be wrong. Is there anything in the literature about people developing MG who are on suppressive doses of glucocorticoids for other reasons? *** We truly agree with the reviewer. We have added the comments and insights about this unusual course in line 119.

- On first presentation the patient had a CT abdomen and the adrenal glands were commented on. Was the chest imaged at the same time? Was there any evidence of thymoma at this point?

*** We thank to the reviewer for clinical important comment. Unfortunately, on first presentation, chest CT was not done, and thymoma was not clear.

- "Normalized ACA levels...." Is this true or simply a result of immunosuppression lowering antibody titers? *** We thank the reviewer for the insight and agree with the comment. We have added more description of course of ACA in line 98.

- I would recommend additional detail interpreting the below text. This is currently an information dense list that is not very accessible for the general reader. Need to include why HLA typing was done? What added information did HLA typing provide? Did it influence the care?

*** We thank the comments raised by the reviewer. 1) Since multiple autoimmune diseases developed in a patient, HLA typing as a common immunological factor was evaluated. 2) HLA typing test would provide various disease-risk and disease-protective alleles. Therefore, early prediction and intervention of the disease are possible. And those information will help patient care in the follow-up, and, susceptible HLA allele for APS-2 should be clarified in the future (line 102 and line 131)

- And of course mostly of the subtypes listed below what are the implications in terms of association with disease. This could be demonstrated within a table. "And she had HLA-A*11:01/24:02, B*39:01/51:01, C*07:02/14:02, DRB1*04:05/11:01, DRB3*02:02,
DRB4*01:03, DQA1*03:03/05:05, DQB1*03:01/04:01, DPA1*01:03/02:02, and DPB1*02:01/05:01.

*** We agree with the comment. We have built the new table for HLA typing analysis (Table 2)

- Recommend change BA to bronchial asthma as this will be read by the causal endocrine reader and they won't be familiar with BA for bronchial asthma. *** We have corrected accordingly.

- "HLA typing analysis may aid to identify diseases susceptible population, and to diagnose earlier those entities" This sentence is very broad and I'm not sure what it adds. If the authors are going to place great importance on the HLA typing in this case then they need to discuss the HLA information in far greater detail! *** We have deleted the sentence in previous version of Line 138.

- Other Figure 1: I think the arrows on the abdominal CT of the adrenals have moved very slightly on formatting and need correction. *** We have corrected accordingly.