Peer Review File

Article information: https://dx.doi.org/10.21037/shc-22-15

Reviewer A

Comment 1: Line 81/82: "Notably, his disease worsened when prednisone doses fell below 10 milligrams, necessitating higher doses that successfully reduced tumor size". Please advise what "his disease" refers to: status of thymoma or status of myasthenia gravis. "successfully reduced tumor size" has to be revised (it is too premature to conclude increasing the dose of prednisone did this).

Reply: We agree that "his disease" was not adequately specific.
Changes in text: Therefore, we have changed this to "his tumor burden increased" as serial CT scans doses showed interval increase in his thoracic tumor burden with lower prednisone doses. Page 4, line 101-102.

Reply: We also realize that "successfully reduced tumor size" implies well-founded causality, which we have not established.

Changes in text: Therefore, we amended this statement to indicate higher doses of prednisone "were associated with tumor size reduction".
Page 4, line 102-103.

Comment 2: If there are only a handful of spontaneous remission in juvenile MG cases+thymoma, please provide a table (include type of thymoma, other circumstances which could have led to remission)

Reply: We appreciate this suggestion regarding a table. However, we realize that further clarification is warranted here. Spontaneous remission of juvenile MG without surgery or immunosuppressive therapies has been reported in several studies. That itself is not novel. The study by Arroyo et al (2022), which we have now included as a reference in this article, actually includes a table of studies from 1960 – 2020 of JMG patients who achieved SR. In total, there have been less than 40 patients with generalized juvenile myasthenia gravis who have achieved spontaneous remission.

The following are key distinctions between our case and studies to date:
1. Spontaneous remission has been reported in mild to moderate disease. The child in this report has severe disease, compatible with Stage 4-5 MG given his hospitalization for myasthenic crisis.
2. There do not appear to be any reports of spontaneous remission with prednisone in children who had disease progression post-thymectomy. There are scattered reports in adults.
3. Minimally invasive thymectomy was not an option for children in many of the

older studies. Therefore, this report highlights not just the occurrence of remission following prednisone, but sheds light on possible thymectomy outcomes in children.

Changes in text:
We have elected to describe in narrative format how many patients have previously been reported to achieve spontaneous remission. Page 2 Line 46

We have also outlined how our report is distinct as noted in the reasons above. Page 2 Line 52-55, 59-60; Page 8 186-189

Comment 3:"First line therapy for JMG, similar to the adult MG, involves an acetylcholinesterase inhibitor, such as pyridostigmine in this case" >> pyridostigmine is the only acetylcholinesterase inhibitor available to use, so please revise this statement

Change in text: This statement has been revised to “pyridostigmine, an acetylcholinesterase inhibitor.” Page 5, line 124

Comment 4:Please delete "unfortunately" throughout the manuscript

Change in text: We have deleted “unfortunately” in the manuscript.

Comment 5:Lines 52/53, please delete " In consultation with the pediatric neurology team"

Change in text: This phrase was deleted.

Comment 6:Line 123:" and muscle-specific tyrosine kinase (MuSK)" >> as there is strong evidence that thymus does NOT play a role in the pathogenesis of MuSK MG, please modify/revise this sentence.

Reply: We have reviewed evidence on the link between the thymus and MuSK MG and agree that this link is not well supported by recent studies. Moreover, anti-MuSK was not checked in this patient.
Change in text: Therefore, we have deleted this phrase from that sentence. Page 6, line 150

Comment 7:Please advise what is the hypothesis (pathophysiology) behind the spontaneous remission of thymoma in juvenile thymoma + MG, how many similar cases where disease went to remission after prednisone.

Reply: Thank you for this comment. To our knowledge there is no prior case of metastatic thymoma in a patient with JMG who achieved spontaneous remission.

There appear to be around 40 cases total of JMG in which spontaneous remission has been documented (chart in Arroyo et al). However, many of these studies are older and do not include information on which patients were treated with prednisone. In fact, our review of these studies showed that none clearly describe spontaneous resolution specifically after prednisone only.

Changes in text: We have therefore included references to spontaneous resolution in adult MG with metastatic disease.

Page 2 Line 46-47"Additionally, spontaneous remission of JMG has been reported less than 40 patients in the literature, though the overwhelming majority had mild disease-severity or bulbar predominant myasthenia (HH)."

Page 2 Line 52-55 "There are scattered reports of metastatic thymoma in adult MG improving with high dose steroids (III, JJ, KK). However, invasive metastatic thymomas are extremely rare in the pediatric population and have not been well characterized."

The pathophysiology for spontaneous remission is unknown, but we have discussed a possible mechanism per our review of available literature.

Page 7 line 174-183 "The mechanism of spontaneous remission in myasthenia gravis is not understood. In vivo studies have suggested that there may be innate adaptions to the neuromuscular junction that can occur over time that cause decreased binding of acetylcholine receptor antibodies (BB). However, there is no evidence that immunotherapies augment this change. However, several studies have concluded that certain patient characteristics of JMG make one more likely to achieve spontaneous remission."

Reviewer B

Comment 1: Please confirm that he was only on Prednisolon when the tumors shrunk (No sunitinib)

Change in text: We have clarified that sunitinib was stopped prior to steroid therapy.
Page 4, line 96

Comment 2: Please use a preoperative CT image.

Change in text: We have included a pre and post operative CT image as part of Figure 1.

Comment 3: Please refer adult references as there are more case series and

detailed information.

Reply: We have included several more references that describe adult MG and thymoma data. These are highlighted in the references section at the end of the document. Some of the most relevant studies are those that showed metastatic thymoma response to steroids in adult MG and what characteristics appear to predict spontaneous remission in MG patients.
Changes in text: Some examples include references 5, 8, 9, 10, 23

Comment 4: Please state possible reasons behind this unexpected effect.

Reply: Thank you for this comment. The pathophysiology of spontaneous remission is unknown, but we have discussed a possible mechanism per our review of available literature.

Change in text: Page 7 line 174-183 "The mechanism of spontaneous remission in myasthenia gravis is not understood. In vivo studies have suggested that there may be innate adaptions to the neuromuscular junction that can occur over time that cause decreased binding of acetylcholine receptor antibodies (BB). However, there is no evidence that immunotherapies augment this change. However, several studies have concluded that certain patient characteristics of JMG make one more likely to achieve spontaneous remission."

Reviewer C

In this case report, the authors tried to describe a spontaneous resolution of a thymoma that recurred after a thymectomy with prednisone. I appreciate the effort of all the authors of this manuscript regarding this rare condition. According to the literature that about 30–50% of thymoma patients have been reported to develop Myasthenia Gravis, while 10–20% of MG patients have thymoma. Mediastinal and pleural recurrence remains a significant clinical problem, especially for patients with advanced and incompletely resected thymoma. Surgical treatment of recurrent thymoma is technically challenging and has been reported to be effective in only one-third of patients. Due to the above issues, the relevance of this case report is important.
The authors have written it clearly and included all the sections for the manuscript. Unfortunately, I have noticed some major issues that need be explained and revised. Also, the manuscript has some minor issues that need to be revised

Major issues to be revised are listed below:
Comment 1: Page 2, under the heading Introduction – I would suggest adding some literature in terms of incidence of thymomas in pediatric JMG whether JMG occurs in patients with thymoma or patients with JMG have thymoma.

Reply: Thank you for this suggestion. We have added this to the introduction.
Changes in Text:
"Studies suggest thymomas occurs in about 1-2% of JMG patients (3, 4), far less than in the adult myasthenia population (10-30%) (5). Thymomas themselves are often associated with paraneoplastic syndromes, with myasthenia gravis occurring over 50% of the time, though this data is limited to adults (6)." Page 2 Lines 40-43

Comment 2: Page 2, under the introduction – please report if there any previously described cases like this in pediatrics and if not, are there any cases in adults that were treated with post thymectomy recurrence with steroids. Based on quick literature search, I found these references which the authors might use

Qi G, Liu P, Dong H, Gu S, Yang H, Xue Y. Metastatic Thymoma-Associated Myasthenia Gravis: Favorable Response to Steroid Pulse Therapy Plus Immunosuppressive Agent. Med Sci Monit. 2017;23:1217-1223. Published 2017 Mar 9. doi:10.12659/msm.902442
Kirkove C, Berghmans J, Noel H, van de Merckt J. Dramatic response of recurrent invasive thymoma to high doses of corticosteroids. Clin Oncol (R Coll Radiol). 1992 Jan;4(1):64-6. doi: 10.1016/s0936-6555(05)80783-6. PMID: 1736985.

Reply: We greatly appreciate this suggestion and the references provided. We have added this information to our introduction and have re-emphasized in our conclusion the lack of data on metastatic thymoma treatment with steroids.

Changes in Text: "Additionally, spontaneous remission of JMG has been reported less than 40 patients in the literature, though the overwhelming majority had mild disease-severity or bulbar predominant myasthenia." Page 2, lines 46-47

Page 2, lines 52-55 "There are scattered reports of metastatic thymoma in adult MG improving with high dose steroids. However, invasive metastatic thymomas are extremely rare in the pediatric population and have not been well characterized."

Comment 3: Page 2, the introduction should talk about what is different in this case compared to previous cases out there that warrants publication

Reply: We appreciate the reviewer's comment and have accordingly added statements in both the introduction and conclusion to emphasize the unique features of this case. This includes but is not limited to the following:

1. Spontaneous remission has been reported in mild to moderate disease. The child in this report has severe disease, compatible with Stage 4-5 MG given his hospitalization for myasthenic crisis.

2. There do not appear to be any reports of spontaneous remission with prednisone in children who had disease progression post-thymectomy. There are scattered reports in adults.
3. Minimally invasive thymectomy was not an option for children in many of the older studies. Therefore, this report highlights not just the occurrence of remission following prednisone, but sheds light on possible thymectomy outcomes in children.

Changes in Text: Page 2 Line 55-60 "In this report, we describe a rare case of severe JMG and metastatic thymoma that responded to steroid therapy, highlighting the potential role of corticosteroids for JMG and thymoma refractory to thymectomy.

Page 7-8 Lines 177-187 "However, several studies have concluded that certain patient characteristics of JMG make one more likely to achieve spontaneous remission. These include mild disease, young age of onset (pre-adolescent), and perhaps ocular MG (24). While this patient ultimately developed recurrence post-thymectomy, it is unclear if his debulking impacted his eventual spontaneous remission once prednisone was started, as spontaneous remission in the minimally-invasive thymectomy era has not been well characterized in JMG."

Comment 4: Page 3, Line 61, please mention if the child received any steroids as a part of initial therapy and if not the reasons why steroids were not considered.

Reply: We agree this required clarification. It appears the pediatric neurology and heme/onc teams chose IVIG over prednisone in this case given progressive symptoms. Their rationale was a more aggressive treatment approach. There may have also been an intent to decrease pre-operative risk by avoiding steroids, however we cannot confirm this given the surgical plan was not finalized at that point.

Changes in text: "Corticosteroid treatment was deferred given progressive dyspnea and fatigue, creating a need for more aggressive treatment. Instead, he…"
Page 3, line 74 - 76

Comment 5: Line 69, please mention if the child was also discharged on steroids?

Reply: The patient was not discharged on steroids, only pyridostigmine maintenance.
Changes in text: "He did not receive corticosteroids on discharge."
Page 4, line 89

Minor issues to be revised are listed below:

Comment 6: Page 1, line 29- "This case additionally underscores the varied

outcomes patients with juvenile myasthenia gravis have to treatment" -need to be revised to "this case additionally underscores the varied outcomes in patients treated for juvenile myasthenia gravis."

Reply/Changes in text: Thank you for this feedback. We have amended the sentence as recommended. Page 1-2, lines 29-30

Comment 7: Page 2, under case presentation, line 48, please consider removing the age of the child and saying something like school age child or young adolescent

Reply/Changes in text: We have substituted "school-aged" for the age of the patient. Page 3, line 64

Comment 8: Page 3, line 81, please describe what the disease worsening means if the patient has myasthenic crisis symptoms or something else

Reply/Changes in text: This has been changed to specify that the patient's thoracic tumor burden increased. Page 4, line 101

Comment 9: Page 3, line 83, please describe if the child developed any complications from steroid therapy

Reply: We have included weight gain and GERD as the patient's side effects of ongoing steroid therapy.

Changes in text: Page 4-5, line 102-109 "He has overall tolerated his prednisone regimen, although has experienced a nearly 20% increase in his weight, as well as gastroesophageal reflux that has been controlled with famotidine."

Comment 10: Page 4, under discussion, line 97, 99, 106 need references
Changes in text: References have been added for these sentences.