Author’s response to reviews

Title: Untreated primary hypothyroidism with simultaneous rhabdomyolysis, pericardial effusion, and sudden sensorineural hearing loss: a case report

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Author’s response to reviews:

Dear Editor,

We sincerely appreciate your kind email and thoughtful consideration of our manuscript. We are pleased that you are interested in our paper, and we hope that we have answered all the reviewer’s questions adequately. A detailed response to each of their comments is provided below. For your convenience, the changes in the revised manuscript are indicated red colored text.

We understand that the final acceptance depends on satisfactory resolution of these issues. We hope that the revised manuscript is now suitable for publication in BMC Endocrine disorders. We're looking forward to a positive decision from you again.

Respectfully,
<Reply to editor's comments>

1. Please clearly state how this case is novel and what contribution it would make to medical knowledge.

Reply) The most unique point of our report is the concurrent rare complications with rhabdomyolysis with acute kidney injury, moderate pericardial effusion, and sudden sensorineural hearing loss in the patient with untreated hypothyroidism. Our study reminds that timely diagnosis and appropriate treatment is essential in patients with hypothyroidism. To clarify this as editor’s comment, we modified the first paragraph (line 129, page 8) and last paragraph (line 200, page 11) in discussion and conclusions section, as follows:

“Within this context, this report has shown simultaneous rare complications accompanying rhabdomyolysis, pericardial effusion, and sudden sensorineural hearing loss in the patient with untreated hypothyroidism. This case reminds physicians of the importance of timely diagnosis and proper treatment in hypothyroidism patients. Moreover, we should keep an eye on the critical complications, albeit uncommon, like rhabdomyolysis, pericardial effusion, and sudden sensorineural hearing loss in untreated hypothyroidism patients. ”

“Our case report underlines the importance of appropriate diagnosis and treatment of hypothyroidism and suggests that it is reasonable to scrutinize thyroid function in patients with unexplained hearing loss and pericardial effusion as well as rhabdomyolysis.”
<Reply to reviewer’s comments>

1. Reviewer #1 Mirjana Kocova

General comment: There are no novelty in this case report. Obviously, it is untreated patient with a Hashimoto thyroiditis with a development of well-known complications. Patients with a simultaneous appearance of mentioned symptoms and some others have been previously described in the literature (see also Kocova et al. JPEM 2015). The moderate interest in publication of this article might be the severe hearing loss, however, there are also some additional data needed.

Title: Hypothyroidism in this patient was untreated at least for a year after the diagnosis. Since it has characteristics of Hashimoto thyroiditis which develops slowly, previous symptoms might have been unrecognized even much longer. Any overt hypothyroidism becomes severe if untreated for a long time. Therefore, instead of "severe" in the title should be replaced with "untreated"

Reply) We totally agree with the reviewer’s comments. Hypothyroidism, especially for Hashimoto’s thyroiditis usually progresses slowly, and the patient in this case already diagnosed with hypothyroidism one year before the serious manifestations with no appropriate treatment. Therefore, the adjective “Aggressive” may not be suitable to this case. In response to the reviewer’s comments, we changed the title, as follows;

“Untreated primary hypothyroidism with simultaneous rhabdomyolysis, pericardial effusion, and sudden sensorineural hearing loss: a case report”

1. Clinical presentation of the patient correspond to classical myxedema and this term should be used in the case description.

Reply) According to the reviewer’s suggestion, we modified second paragraph in case presentation section (line 77, page 6) to describe myxedema manifestations, as follows:

“General physical examination revealed dry skin, neck vein distension, nontender diffuse goiter around the neck, and myxedema with puffy face, bilateral periorbital and lower extremities edema. His pulse rate was 52 beats/minute, blood pressure was 114/82 mmHg, respiratory rate was 20 breaths/minute, and his body temperature was 37.1°C. Muffled heart sounds without fine crackle were also detected.”
2. The increase of creatinine is probably the effect of rhabdomyolysis rather than acute kidney disease associated with hypothyroidism as described. In favor of this comment is the slight and short lasting increase of creatinine corrected fast after decrease of CK. It has been described and has to be clarified in the discussion.

Reply) We entirely agree with reviewer’s opinion. Thyroid function has been known to play important roles in kidney development as well as renal physiology, such as water and sodium hemodynamics. There are also several reports about renal impairment in hypothyroidism. However, for our case, increased creatinine was more likely induced by rhabdomyolysis rather than untreated hypothyroidism itself. As reviewer’s comments, creatinine was normalized in a short time accompanied by CK decline. To clarify this, we modified 4th paragraph in case presentation section (line 107, page 7) and added descriptions in discussion and conclusion section (line 159, page 10), as follows:

“On consecutive laboratory tests, creatine kinase as well as lactate dehydrogenase began to decrease on hospital day (HD) 3 and continued to decline to 1,530 IU/L and 1,508 IU/L on HD 7, respectively. Creatinine also started to decrease by 1.11 mg/dL on HD 7 accompanied by creatine kinase decline.”

“Furthermore, acute kidney injury in our case could be induced by rhabdomyolysis rather than hypothyroidism itself. Although hypothyroidism is known to affect renal impairment, increased creatinine was normalized in a short time after fluid resuscitation, consistent with creatine kinase decline, suggesting that decreased renal function was more likely associated with rhabdomyolysis than hypothyroidism.”

3. Statin therapy in this patient appears in the manuscript first in the discussion. It should be given in the case description first together with the data on lipidogram.

Reply) In response to the reviewer’s comment, we attached initial lipid profile in case presentation section (line 86, page 6), as follows:

“total cholesterol 222 (130-240) mg/dL, low density lipoprotein cholesterol (LDL-c) 136 (50-160) mg/dL, high density lipoprotein cholesterol (HDL-c) 74 (40-85) mg/dL, and triglycerides 127 (35-200) mg/d.”

4. Pericardial effusion before and after treatment should have been quantified (measured)

Reply) According to the reviewer’s opinion, we added the measured pericardial effusion before treatment (line 93, page 7), and post treatment (line 119, page 8) in case presentation section, as follows:
“...and transthoracic echocardiography revealed a moderate amount of pericardial effusion (posterior 15 mm) with preserved left ventricular systolic function (55%–60%; Fig. 1c).”

“No pericardial effusion appeared on transthoracic echocardiography (Fig. 1d).”

5. Acute hearing loss appeared one year after the diagnosis of hypothyroidism and might be a coincidence (no MRI or other tests have been performed to exclude a series of possible factors for predominantly one sided hearing loss). Hearing loss in patients with hypothyroidism as described by the largest series appears usually bilaterally at a subclinical level even at the onset of hypothyroidism (cit 17). The therapy applied does not guarantee healing, so it is not unusual for one sided hearing loss to remain, although authors present it as very unusual. One sided hearing loss in this patient, might be a coincidence and causing significant discomfort, a contributing reason for asking the repeated consultation in this patient with longstanding myxedema. It should be clarified and discussed in detail (see and cite Plontke SK, GMS Curr Top Otorhinolaryngol Head Neck Surg 2017;16, published online 2018 doi: 10.3205/cto000144).

Reply) Actually, we performed brain CT and CT angiography at the emergency center to rule out the other causes affecting dizziness, sluggish speech, and unilateral hearing loss. Brain CT showed no abnormal findings and brain CT angiography revealed focal atherosclerotic mild stenosis in the right cavernous intracranial artery without other vascular aneurysms or vascular malformations. After admission, we tried to perform additional image studies like brain MRI to find other causes related to unilateral hearing loss. But, unfortunately, the patient refused further brain image studies obstinately due to the economic reasons.

And we indeed respect the reviewer’s opinion that most of the sudden sensorineural hearing loss is idiopathic sensorineural hearing loss commonly affecting unilateral hearing loss and metabolic disorders, including hypothyroidism, usually involve bilateral hearing loss. We also concede that no response to levothyroxine therapy may reflect that hearing loss was not induced by hypothyroidism. However, hypothyroidism is known for a risk factor of sudden sensorineural hearing loss, we thought it was more plausible to surmise that sudden hearing loss in our case, which occurred during other untreated hypothyroidism-related symptoms were exacerbating, was more likely associated with hypothyroidism. And previous report also described that “unilateral symptoms can be observed with those finding like vascular, metabolic, autoimmunological or inflammatory causes (Plontke et al. CMS Curr Top Otorhinolaryngol Head Neck Surg. 2017;16)”. Recently, Premkumar et al. presented a patient who had unilateral hearing loss with longstanding hypothyroidism and had no hearing improvement after treatment (Indian J Otolaryngol. 2016;22(1):56-58). Previous studies also reported about 70% of patients with hypothyroidism-related hearing loss recovered after treatments (Anand et al. Acta otolaryngol. 1989;108:83-87, Van’t et al. Q J Med. 1979;48:361-367).
As reviewer’s comments, we herein modified discussion and conclusion section (line 178, page 10) and added recommended reference, as follows;

“However, metabolic disorders including hypothyroidism usually involve bilateral hearing loss [31]. Additional brain computed tomography (CT) and brain CT angiography conducted to find out other causes related to unilateral hearing loss did not detect any significant findings, and further brain magnetic resonance imaging could not be performed due to the patient’s refusal. Although we cannot completely exclude the possibility that the sensorineural hearing loss was not induced by hypothyroidism, it is more plausible to speculate that sudden sensorineural hearing loss was associated with untreated hypothyroidism in this patient who already have experienced hypothyroidism-related symptoms and complications like rhabdomyolysis and pericardial effusion.”


6. Biochemical data are given only for a period of 20 days and TSH is still high. Although some data about the hearing after a year have been given, no data on thyroid function at that time are presented.

Reply) In response to the reviewer’s suggestion, we appended the thyroid function results at 3 months and 1 year after discharge in the case presentation section (line 117, page 8), as below;

“His thyroid function was normalized at 5 months (TSH 0.10 μIU/mL, free T4 1.60 μIU/mL) and remained euthyroid status until one year after discharge (TSH 0.54 μIU/mL, free T4 1.52 μIU/mL).”

7. Table: to large, only abnormal data should be included. Data on the lipids should be given since the patient is taking statins as a possible cause for rhabdomyolysis.

Reply) As suggested by the reviewer, we modified the table more concisely, excluded with normal values (Platelet, serum sodium, serum potassium, calcium, phosphorus, albumin, and total bilirubin) and included with lipid profiles (total cholesterol, LDL, HDL and Triglyceride).

8. Figures: Unusual combination of different findings, pre and post therapy findings should be combined.

Reply) According to the reviewer’s suggestion, we recombined and added figure legends and figures, as follows:
“Figure 1. Image findings of the patient. Chest radiography shows cardiomegaly without pleural effusion at initial admission (a) and decreased cardiomegaly after discharge (b). Transthoracic echocardiography shows moderate pericardial effusion at initial admission (c) and completely recovered pericardial effusion at one-year later (d).

Figure 2. Pure tone audiometry displayed the presence of unilateral (left side) profound sensorineural hearing loss at initial diagnosis (a) and remained hearing loss at one-year after discharge (b).

Figure 3. Transverse view of thyroid sonography revealed marked heterogenous echotexture of both thyroid glands.”

According to the recombination of figures, we changed all the figure labels in case presentation section and colored in red.

2. Reviewer #2 Swayamsidha Mangaraj

The authors describe an interesting case of hypothyroidism with atypical presentations. Here are few suggestions for the authors.

1. Since, hypothyroidism due to Hashimoto's thyroiditis is a chronic autoimmune disease, the adjective "aggressive" doesn't seem befitting to it. Yes, the manifestations may be sometimes acute and severe during initial presentation. Hence, in my opinion, in the title "Aggressive manifestation/presentation of primary hypothyroidism with simultaneous rhabdomyolysis, pericardial effusion, and sudden sensorineural hearing loss: a case report" would be more apt. Similarly the line 171 of page 10 "Herein, we report for the first time a case of aggressive hypothyroidism with concurrent rhabdomyolysis with acute kidney injury, pericardial effusion, and sudden sensorineural hearing loss" should be replaced with "Herein, we report for the first time a case of hypothyroidism presenting with concurrent rhabdomyolysis with acute kidney injury, pericardial effusion, and sudden sensorineural hearing loss.

Reply) We fully respect with reviewer’s comment. Typically, hypothyroidism due to Hashimoto’s thyroiditis is a slowly progressive autoimmune disease, whereas a small number of patients with hypothyroidism experience severe initial manifestations. Therefore, the adjective “Aggressive” may not be suitable to this case report. Our patient, especially, had one-year untreated period before the appearance of severe manifestations, we modified our title, as follows:

“Untreated primary hypothyroidism with simultaneous rhabdomyolysis, pericardial effusion, and sudden sensorineural hearing loss: a case report”
And we also changed the last paragraph in discussion (line 198, page 11), as follows:

“Herein, we report for the first time a case of untreated hypothyroidism with concurrent rhabdomyolysis with acute kidney injury, pericardial effusion, and sudden sensorineural hearing loss.”

2. Some minor typographical error needs correction. 1.alanine aminotransferase 357 (3-45) IU/L, 2.aspartate aminotransferase 278 (3-45) IU/L Above parameters values are missing in main text in line 84 and 85 ,page 6,though reported in Table.

Reply) We’re sorry for the carelessness. According to the reviewer’s comment, we corrected the typographical errors (line 84, page 6), as follows:

“alanine aminotransferase 357 (3-45) IU/L, aspartate aminotransferase 278 (3-45) IU/L”

3. Figure legends Figure 2. (A) Pure tone audiometry displayed the presence of unilateral (left side "AACE/ATA")

Reply) We corrected the figure legends (line 321, page 19) and additionally, we recombined the figures before and after treatments according to the other reviewer’s suggestion, as follows:

“Figure 1. Image findings of the patient. Chest radiography shows cardiomegaly without pleural effusion at initial admission (a) and decreased cardiomegaly after discharge (b). Transthoracic echocardiography shows moderate pericardial effusion at initial admission (c) and completely recovered pericardial effusion at one-year later (d).

Figure 2. Pure tone audiometry displayed the presence of unilateral (left side) profound sensorineural hearing loss at initial diagnosis (a) and remained hearing loss at one-year after discharge (b).

Figure 3. Transverse view of thyroid sonography revealed marked heterogenous echotexture of both thyroid glands.”

4. thyroid sonography showed diffusely enlarged "gland" not glands. Line 94 ,page 7

Reply) According to the reviewer’s comment, we corrected the text (line 97, page 7), as follows:

“, and thyroid sonography showed diffusely enlarged gland with a heterogenous echotexture and decreased vascularity”
5. Although hypothyroidism can manifest with conductive, mixed or sensory neural hearing loss, the importance of sudden sensory neural hearing loss (SSNHL) as manifestation of hypothyroidism is relatively lesser known. The author's manuscript highlights this atypical complication of hypothyroidism. Following lines may be added in discussion section to highlight the importance of thyroid dysfunction in evaluation of sudden sensory neural hearing loss from one of the cited articles of authors. Thyroid dysfunction can be found in patients presenting with SSNHL, with one report of a 15% rate of hypothyroidism (Heman-Ackah et al., 2010; Narozny et al., 2006). Kuhn M, Heman-Ackah SE, Shaikh JA, Roehm PC. Sudden sensorineural hearing loss: a review of diagnosis, treatment, and prognosis. Trends Amplif. 2011;15:91-105.

Reply) We totally agree with the reviewer’s idea with highlighting the importance of thyroid dysfunction in sudden sensorineural hearing loss. According to the reviewer’s suggestion, we edited the sentences and added references (line 174, page 10), as follows:

“The most common causes are infectious diseases such as HIV, mycoplasma infection, or syphilis followed by otologic trauma or vascular, hematologic, or metabolic disorders such as hypothyroidism and diabetes mellitus [29]. Thyroid dysfunction can be found in patients presenting with sudden sensorineural hearing loss, with one report of a 15% rate of hypothyroidism [30].”


6. The authors have discussed the potential role of hypothyroidism and statin use in precipitating rhabdomyolysis. The potential risk of rhabdomyolysis in hypothyroidism due to concurrent statin use should be stressed in text. Few lines can be added to text for benefit of general readership of journal highlighting this important clinical lesson. Can be added to para 1 of page 9. Statin therapy and untreated hypothyroidism may synergistically enhance the risk of myopathy and rhabdomyolysis in patients as reported in literature.[reference cited below] References Yeter E, Keles T, Durmaz T, Bozkurt E. Rhabdomyolysis due to the additive effect of statin therapy and hypothyroidism: a case report. Journal of medical case reports. 2007;(1):130. Tokinaga K, Oeda T, Suzuki Y, Matsushima Y: HMG CoA Reductase Inhibitors might cause high elevations of creatine phosphokinase in patients with unnoticed hypothyroidism. Endocrine Journal 2006, 53:401-405

Reply) I entirely support the reviewer’s suggestion with the potential synergetic effects of hypothyroidism and statin use. According to the reviewer’s comments, we added the text and references (line 153, page 9), as follows:
“For this reason, we deduced that the main cause of rhabdomyolysis was primary hypothyroidism. However, there is also a possibility that statin therapy and untreated hypothyroidism may synergistically enhance the risk of myopathy and rhabdomyolysis in patients as reported in the literature [22, 23].”


3. Reviewer #3 Mustafa Altay

I read with great interest the manuscript named as "Aggressive primary hypothyroidism with simultaneous rhabdomyolysis, pericardial effusion, and sudden sensorineural hearing loss: a case report". I think it will be publishing without revision.

Reply) We sincerely appreciate your decision.