Date of submission 2022/12/31

Dear BPG Editorial Office, World Journal of Clinical Cases

We wish to re-submit the manuscript titled "Thyrotoxicosis in patients with a history of Graves' disease after SARS-CoV-2 Vaccination (Adenovirus vector vaccine): Two case reports "The manuscript ID is: 80759.

We appreciate the time and effort you and the reviewer have dedicated to providing insightful feedback on ways to strengthen our paper. We have try our best to incorporate your feedback and hope that these revisions persuade you to accept our submission. All of our revisions are identified in the paper with the blue font. The responses to all of the reviewer's and editor's comments are given below.

Thank you for the consideration. We look forward to hearing from you.

Sincerely, Rong Rong Luo Integrated Medicine Far Eastern Memorial Hospital No. 21, Sec. 2, Nanya S. Rd., Banqiao Dist., New Taipei City 220 , Taiwan (R.O.C.) Phone: +886 9 12455182 Fax: +886 2 8966-5567 Email address: agelinro@gmail.com

# **Reviewer comment**

Reviewer #1: Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing) **Conclusion:** Minor revision Specific Comments to Authors: The case report manuscript entitled "Thyrotoxicosis in patients with History of Graves' disease after SARS-CoV-2 Vaccine (Adenovirus vector vaccine): Two case reports" (Manuscript ID: 80759 World Journal of Clinical Cases) by Dr. Yan and Dr. Luo concisely describes two cases with underlying Graves' disease (GD) in remission wich developed thyrotoxicosis that underwent COVID-19 vaccination. A relationship between COVID-19 vaccination and the onset of thyroid dysfunction in patients with underlying Graves' disease in remission has been hypothesized. COVID-19 vaccination induced thyroid dysfunction, but the pathophysiology is unknown. I recommend a minor revision. I have several comments for improving the manuscript General comments 1. I strongly recommend improving the introductive section by introducing more notions on SARS-CoV-2 pandemic and thyroid dysfunction. Since data on thyroid dysfunction after receiving the SARS-CoV-2

vaccine have been published, they can be included in this section alongside supporting references. For completeness, if present, notions on SARS-CoV-2 infection and thyroid dysfunction should be included, authors can check (DOI: 10.1210/endocr/bqab004) 2. The quality of figures 2 and 4 should be improved 3. Terms such as "she" should be avoided throughout the text 4. Authors should include the ethical authorization 5. Have vaccine boosts doses been performed during the follow up? 6. References in this style "(1) (2) etc..." should be moved before commas/periods Minor observations Line 71 this reference on SARS-CoV-2 infection should be included (DOI: 10.3390/microorganisms10061193) Line 94 the hospital name should be detailed. Line 154 better "the patient received" Lines 184-186 English should be improved

## The response to the reviewer #1

#### Language Quality

**Reply:** The revised manuscript had been corrected by the "Editage" English Editing Service.

# **Specific Comments:**

**Comment 1:** I strongly recommend improving the introductive section by introducing more notions on SARS-CoV-2 pandemic and thyroid dysfunction. Since data on thyroid dysfunction after receiving the SARS-CoV-2 vaccine have been published, they can be included in this section alongside supporting references. For completeness, if present, notions on SARS-CoV-2 infection and thyroid dysfunction should be included, authors can check (DOI: 10.1210/endocr/bqab004)

**Reply 1**: Thank you for this suggestion.

(Please see the lines 78-87 of the revised manuscript, and reference (4)).

Although over 13 billion SARS-CoV-2 vaccine doses have been administered worldwide according to WHO statistics<sup>1</sup>), there has been concern about the rapid development, authorization, and marketing of the vaccines which was required for the pandemic, one of which is thyroid dysfunction. Thyroid dysfunction can happen when certain viral infections occur. A previous review disclosed three potential mechanisms of the SARS-CoV-2 viral infection to cause thyroid dysfunction — nonthyroidal illness syndrome from infection, hypothalamic-pituitary-adrenal axis dysfunction due to hypothalamus/pituitary injury and thyroid cell destruction caused by direct thyroid cell infection<sup>[4]</sup>.

4. **Chen W**, Tian Y, Li Z, Zhu J, Wei T, Lei J. Potential Interaction Between SARS-CoV-2 and Thyroid: A Review. Endocrinology. 2021;162(3) bqab004 [PMID: 33543236 DOI: <u>10.1210/endocr/bqab004</u>]

**Comment 2:** The quality of figures 2 and 4 should be improved **Reply (2):** Thank you for kind reminder. We have tried our best to improve the image quality. We now refer to figures 3 and 4.

**Comment 3:** Terms such as "she" should be avoided throughout the text **Reply (3):** Please see the revised manuscript. We now refer to Case 1 or 2 or 'the patient'

**Comment 4:** Authors should include the ethical authorization **Reply (4):** Thank you for kind reminder! We have included the following statements at the end of the article

**Informed consent statements:** Written informed consent was obtained from the patients for publication of the case report and accompanying images.

#### **Statement of Ethics**

The study was granted an exemption from requiring ethics approval by the Research Ethics Review Committee of the Far Eastern Memorial Hospital.

**Comment 5:** Have vaccine boosts doses been performed during the follow up? **Reply (5):** Both patients received vaccine boosters smoothly. We detailed the outcome follow up. Case 1 received Novavax Nuvaxovid® COVID-19 vaccine and case 2 received Moderna as booster.

(Please see the lines 204-205 and 212-213 of the revised manuscript.)

The patient received the Novavax Nuvaxovid® COVID-19 vaccine as booster on August 24, 2022. No discomfort was reported during the follow-up visits and free-T4 level 1.060 ng/dL; TSH 1.43 IU/mL on November, 2022.

On September 20, 2022, the patient received a Moderna booster and her thyroid function tests on October 14, 2022 revealed a free-T4 level of 1.49 ng/dL; TSH 1.180 IU/mL.

**Comment 6:** References in this style "(1) (2) etc…" should be moved before commas/periods **Reply (6):** Thank you for kind reminder!

#### **Minor observations**

**Comment 1:** Line 71 this reference on SARS-CoV-2 infection should be included (DOI: 10.3390/microorganisms10061193)

**Reply (1):** Thank you for this suggestion.

(Please see the lines 74-77 of the revised manuscript, and reference (2)).

Two mainstay diagnostic methods have been adopted —one is molecular diagnostic tenique which takes 2-4 hours with higher specificity and sensitivity, and the other is immunological diagnostic technique which generally considered inexpensive and more rapid(2).

2. **Rotondo JC**, Martini F, Maritati M, Caselli E, Gallenga CE, Guarino M, et al. Advanced Molecular and Immunological Diagnostic Methods to Detect SARS-CoV-2 Infection. Microorganisms. 2022;10(6) [PMID: 35744711 DOI: <u>10.3390/microorganisms10061193</u>]

**Comment 2:** Line 94 the hospital name should be detailed. **Reply (2):** Thank you for this suggestion. (Please see the lines 110-111 of the revised manuscript.) As the symptoms progressed, she visited the Far Eastern Memorial Hospital emergency department on July 31, 2021

**Comment 3:** Line 154 better "the patient received" Lines 184-186 English should be improved **Reply (3):** Thank you for kind reminder! The revised manuscript had been corrected by the "Editage" English Editing Service.

Reviewer comment Reviewer #2: Scientific Quality: Grade B (Very good) Language Quality: Grade A (Priority publishing) Conclusion: Accept (General priority) Specific Comments to Authors: The authors presented two cases about hyperthyroidism and thyroid storm after SARS-Cov-2 vaccination. The authors provided very significant data, as few cases have addressed this topic in the past. There are some minor comments should be addressed.

#### The response to the reviewer #2

**Language Quality Reply:** The revised manuscript had been corrected by the "Editage" English Editing Service.

#### **Specific Comments:**

**Comment 1:** line 97: time of onset of case 2 is unclear. I think a more specific time of onset would be more valuable for similar cases.

Reply (1): Thank you for this suggestion.

(Please see the lines 113-114 of the revised manuscript.)

The patient received her first dose of the AstraZeneca vaccine for SARS-CoV-2 on June 11, 2021, and began to have palpitations about two weeks later.

However, we failed to identify the specific date. Our case 2 said that about two weeks after the vaccination the symptoms made her uncomfortable.

**Comment 2:** Graves' disease has a high recurrence rate after drug therapy. Are there other predisposing factors for case 2 recurrence? please add details **Reply (2):** Thank you for kind reminder.

We detailed the positive and negative findings of case 2 that we examined in the outpatient visiting.

(Please see the lines 113-121 of the revised manuscript.)

The patient received her first dose of the AstraZeneca vaccine for SARS-CoV-2 on June 11, 2021 and began to have palpitations about two weeks later. The accompanying symptoms include a lump in the throat, hand tremors, dyspnoea, fatigue, increased bowel movements but no abdominal pain, nausea nor vomiting. There was no cough, sputum, sore throat, and no fever. Owing to the pandemic and fear of interhospital infection, the patient self-purchased propranolol to control her heart rate; however, there was no improvement and she began to be breathless when talking in August 2021. Finally, the patient made an appointment and presented to the endocrinology outpatient department on August 24, 2021

During the pandemic, Far Eastern Memorial Hospital required that all patients undergo rapid antigen testing for COVID-19 and chest films, especially in those with airway symptoms including fever, sore throat, cough, runny nose, dyspnea, myalgia, and diarrhea. Case 2 had some warning signs for COVID-19 including a lump in the throat, dyspnea, and increase bowel movements, therefore, we performed rapid antigen testing for COVID-19 and took a chest flim for her on the same visit.

(Please see the lines 159-161 and line 171-173). The rapid antigen test was negative, and the chest film was normal.

The rapid antigen testing for COVID-19 was performed also as the patient had warning signs including dyspnoea and increase bowel movements and was negative. Electrocardiography revealed sinus tachycardia with a heart rate of 114 beats per minute (Fig. 2). The chest X-ray was normal. Thyroid ultrasonography revealed heterogeneous and hypoechoic echotexture with increased vascularity (Fig. 4).

<u>Reviewer comment</u> Reviewer #3: Scientific Quality: Grade B (Very good) Language Quality: Grade B (Minor language polishing)

#### Conclusion: Minor revision

**Specific Comments to Authors:** Great cases identifying unusual side effect of covid vaccines. This should be a diagnosis of exclusion, I would recommend adding more context about how other possibilities were ruled out. Why this could not have been due to a simple viral infection or triggered by any other factors.

## The response to the reviewer #3

#### Language Quality

**Reply:** The revised manuscript had been corrected by the "Editage" English Editing Service.

## **Specific Comments:**

**Comment:** Great cases identifying unusual side effect of covid vaccines. This should be a diagnosis of exclusion, I would recommend adding more context about how other possibilities were ruled out. Why this could not have been due to a simple viral infection or triggered by any other factors.

## **Reply:** Thank you for suggestion.

Case 1 presented with progressive dyspnea and palpitation. She identified symptom development after vaccination. We initially checked complete cell counts, kidney function, coagulation profile for thromboembolic event, cardiac markers for possible acute coronary syndrome, and urine and stool tests to identify possible infection and the results were normal.

During the pandemic, Far Eastern Memorial Hospital required that patient underwent rapid antigen testing for COVID-19 and chest films, especially in those with airway symptoms including fever, sore throat, cough, runny nose, dyspnea, myalgia, and diarrhea. Case 1 did have some warn signs, therefore, she received rapid antigen testing for COVID-19 and chest film accordingly. The rapid antigen test was negative, and the chest flim reported non-specific findings in both lung zones and normal heart size. (Please see the lines 152-153 and 165-166 of the revised manuscript.) The rapid antigen testing for COVID-19 was performed due to patient warning signs

including dyspnea, dizziness, myalgia and diarrhoea was negative.

# A chest film was taken which revealed non-specific findings of both lung zones and the heart size was within normal limits.

Concerning case 2, we did fail to identify a specific date of symptom onset. Case 2 recognized that about two weeks after the vaccination, the symptoms made her uncomfortable.

We also detailed the positive and negative findings of case 2 that we examined during the outpatient visit.

(Please see the lines 113-121 and 139-141 of the revised manuscript.)

The patient received her first dose of the AstraZeneca vaccine for SARS-CoV-2 on June 11, 2021 and began to have palpitations about two weeks later. The accompanying symptoms include a lump in the throat, hand tremors, dyspnoea, fatigue, increased bowel movements but no abdominal pain, nausea nor vomiting. There was no cough, sputum, sore throat, and no fever. Owing to the pandemic and fear of interhospital infection, the patient self-purchased propranolol to control her heart rate; however, there was no improvement and she began to be breathless when talking in August 2021. Finally, the patient made an appointment and presented to the endocrinology outpatient department on August 24, 2021

**Case 2:** Physical examination revealed hyperactivity, neck was supple without tenderness, distal tremors in both hands, and tachycardia. Her blood pressure was 17.7/12.0 kPa and heart rate was 109 beats per minute.

Case 2 also had warning signs for COVID-19 including a lump in the throat, dyspnea, and increase bowel movements, therefore, we also performed rapid antigen testing for COVID-19 and took a chest film for her on the same visit.

(Please see the lines 159-161 and line 171-173 of the revised manuscript). The rapid antigen test was negative, and the chest film was normal.

The rapid antigen testing for COVID-19 was performed as the patient had warning signs including dyspnea and increase bowel movements and was negative.

**Case 2:** Electrocardiography revealed sinus tachycardia with a heart rate of 114 beats per minute (Fig. 2). The chest X-ray was normal. Thyroid ultrasonography revealed heterogeneous and hypoechoic echotexture with increased vascularity (Fig. 4).

# EDITORIAL OFFICE'S COMMENTS

# (1) Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision. Language Quality: Grade B (Minor language polishing) Scientific Quality: Grade B (Very good)

Reply: Thank you for this information.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, the author(s) must provide the Signed Consent for Treatment Form(s) or Document(s). Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

**Authors' reply:** Thank you for kind reminder. The manuscript is being revised according to the Peer-Review Report, Editorial Office's comments, and the Criteria for Manuscript Revision by Authors.

For the Signed Consent for Treatment Form(s) or Document(s), the study was granted an exemption from requiring ethics approval by the Research Ethics Review Committee of the Far Eastern Memorial Hospital. We upload IRB approval file as 80759-Supplementary Material

We generated the figures and pictures, and they are original. We added the copyright information: Copyright ©The Author(s) 2022. to the bottom right-hand side of the picture in PowerPoint (PPT).

The three-line tables have been supplemented and the article highlights were added to the latest cutting-edge research results. According to your suggestion, we utilized the RCA database for our literature search. It has the advantages of wider and fast document collection to find the latest highlight articles to further improve our manuscript.