

Letter to the Editor: Before Blaming SARS-CoV-2 Infection or Vaccination for Takotsubo, Differentials Should be Ruled out

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Dear Editor,

We read with interest the article by Rahimi et al.¹ about a 67-year-old female with symptomatic SARS-CoV-2 infection beginning 10 days prior to admission, administration of the second dose of the Moderna anti-SARS-CoV-2 vaccine four days prior to admission, and admission for respiratory insufficiency (tachycardia, tachypnoea, and hypoxigenation) without fever or cough. Examination for sudden chest pain on hospital day two revealed Takotsubo syndrome (TTS). Myocardial infarction was ruled out by coronary angiography. Decreased systolic function improved within three weeks of hospitalization, but the overall outcome was not provided. The study was appealing but raised concerns.

Whether TTS was due to the SARS-CoV-2 infection or due to SARS-CoV-2 vaccination was not discussed. Since both occurred before the suspected onset of TTS and both have been reported as causes of TTS,^{2,3} it is crucial to delineate whether one or both were causative. It also should be considered whether TTS was triggered by respiratory insufficiency (there was severe hypoxigenation), which can cause severe anxiety, and whether TTS occurred prior to hospitalization or prior to SARS-CoV-2 vaccination.

Since SARS-CoV-2 infections or vaccinations can be complicated by myocarditis,^{3,4} the exclusion of myocarditis by cardiac magnetic resonance imaging with contrast medium or endo-myocardial biopsy is crucial. We should be informed of the results of creatine-kinase (CK), CK-MB, and pro-brain natriuretic peptide (proBNP) serum levels. Since the patient had an “irregular tachycardia”, we should be informed whether this was classified as sinus-arrhythmia, supraventricular arrhythmia (particularly atrial fibrillation), or ventricular arrhythmia. Knowing the type of arrhythmias is essential as treatment varies between them. We should know whether TTS also was seen on transthoracic echocardiography or only on ventriculography. According to the description, echocardiography revealed apical hypokinesia, but no apical ballooning.¹ After how many days did apical ballooning resolve?

Since the onset of TTS remains unclear, we should know the results of the electrocardiogram (ECG) at admission, specifically whether upslanting ST elevation already was present on hospital day one.

We should know if pulmonary embolism has been ruled out by spiral CT with contrast medium or if the patient just received a plain CT scan

of the lungs. Was there any evidence of acute right ventricular strain on echocardiography?

A limitation of the study was that no reference limits for blood tests were specified.¹ Another limitation was that the cardiovascular risk profile was not reported in addition to arterial hypertension. We should know if the patient had diabetes, hyperlipidemia, a history of stroke or myocardial infarction, or if she was smoking. There was no information about the treatment that the patient received for TTS.

Overall, the interesting study had limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. The diagnosis of TTS requires the exclusion of various differential diagnoses, including myocarditis.

REFERENCES

- Rahimi O, Varada N, Palma C, Al Taweel O, Lei K, Hawwass D, Ahsan C. Takotsubo cardiomyopathy in a vaccinated patient with severe COVID-19. *Kans J Med* 2022; 15:255-256. PMID: 35899060.
- Solis JG, Carrizales-Sepúlveda EF, Vera-Pineda R, Morales-Rendón EJ, Ortíz-Corona JJ, Flores-Ramírez R. Takotsubo cardiomyopathy and COVID-19: A case report and literature review. *Curr Cardiol Rev* 2022; [online ahead of print]. PMID: 35984028.
- Stewart C, Gamble DT, Dawson D. Novel case of takotsubo cardiomyopathy following COVID-19 vaccination. *BMJ Case Rep* 2022; 15(1):e247291. PMID: 35042734.
- Rubens M, Ramamoorthy V, Saxena A, et al. Hospital outcomes among COVID-19 hospitalizations with myocarditis from the California state inpatient database. *Am J Cardiol* 2022; S0002-9149(22):00854-2. PMID: 36127182.

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Author Response: Before Blaming SARS-CoV-2 Infection or Vaccination for Takotsubo, Differentials Should be Ruled out

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In response to the Letter to the Editor by Dr. Finsterer and Dr. Stollberger, we submit the following information.

1. Whether Takotsubo syndrome (TTS) was due to the SARS-CoV-2 infection or due to SARS-CoV-2 vaccination was not discussed.

Response: Based on the information provided, TTS was suspected to both the acute COVID-19 infection and possibly the vaccine. As documented in our case, IL-6 induced inflammation from the acute viral infection likely caused TTS,¹ but as also cited by Fearon et al.², there are cases of vaccine induced TTS, which based on our patient's timeline makes this differential possible.

2. It also should be considered whether TTS was triggered by respiratory insufficiency (there was severe hypoxigenation), which can cause severe anxiety, and whether TTS occurred prior to hospitalization or prior to SARS-CoV-2 vaccination.

Response: Although this is a possibility, the underlying cause of the hypoxigenation and anxiety would be the COVID-19 infection and/or the COVID-19 vaccine.

3. Since SARS-CoV-2 infections or vaccinations can be complicated by myocarditis,^{3,4} the exclusion of myocarditis by cardiac magnetic resonance imaging with contrast medium or endo-myocardial biopsy is crucial. We should be informed of the results of creatine-kinase (CK), CK-MB, and pro-brain natriuretic peptide (proBNP) serum levels.

Response: No cardiac MRI was available to assist with diagnosis, but given the severe troponin elevation with no signs of coronary ischemia, the likely cause of a hs-troponin > 3,000 ng/L is myocarditis. No CK-mb or CK levels were collected as hs-troponin is a better barometer for myocardial tissue damage.

4. Since the patient had an “irregular tachycardia”, we should be informed whether this was classified as sinus-arrhythmia, supraventricular arrhythmia (particularly atrial fibrillation), or ventricular arrhythmia. Knowing the type of arrhythmias is essential as treatment varies between them.

Response: It was atrial fibrillation that was paroxysmal and resolved by discharge. Given the elevated CHADVASC score, the patient was discharged on anticoagulation. This was not placed in the report as it was not in relation to the TTS and given it had resolved with treatment for the inflammatory response was likely stress induced as well. This could be another area to consider for a future separate report.

5. We should know whether TTS also was seen on transthoracic echocardiography or only on ventriculography. According to the description, echocardiography revealed apical hypokinesia, but no apical ballooning.¹ After how many days did apical ballooning resolve?

Response: Apical hypokinesia is synonymous with ballooning in the setting of basal wall hyperkinesia and it was noted in the report¹ that the findings were collected by a transthoracic echocardiogram. The resolution was after 16 days, which was omitted as it was not relevant for the outcome of the report.

6. Since the onset of TTS remains unclear, we should know the results of the electrocardiogram (ECG) at admission, specifically whether upslanting ST elevation already was present on hospital day one.

Response: Although not noted in the original manuscript, there were no ST elevations on admission as could have been inferred, as the patient was admitted on BiPAP without being sent for cardiac angiography, which is standard of care if the patient was found to have ST elevations with signs of cardiopulmonary distress.

7. We should know if pulmonary embolism has been ruled out by spiral CT with contrast medium or if the patient just received a plain CT scan of the lungs.

Response: The report stated CT chest with contrast was negative for pulmonary embolism.¹ This was a spiral CT as that was the indication for getting the CT.

8. Was there any evidence of acute right ventricular strain on echocardiography?

Response: No strain was noted.

9. A limitation of the study was that no reference limits for blood tests were specified.

Response: Standard normal values are used at our laboratory. The findings reported were significantly elevated such that any laboratory normal value could be inferred.

10. Another limitation was that the cardiovascular risk profile was not reported in addition to arterial hypertension.

Response: Risk profile was to be inferred by the reader given the patient's past medical history noted by the report.¹ Arterial hypertension was noted by stating the patient had a history of hypertension.

11. We should know if the patient had diabetes, hyperlipidemia, a history of stroke or myocardial infarction, or if she was smoking.

Response: None was reported as she did not have any of these conditions. Given the report was on cardiac disease, these would be reported if positive.

12. There was no information about the treatment that the patient received for TTS.

Response: Given the TTS was suspected to be secondary to either acute COVID-19 infection or post-vaccination, then treatment would be COVID-19 infection driven. As noted, she received steroids, remdesivir, and evaluated for tocilizumab.¹

REFERENCES

- ¹ Rahimi O, Varada N, Palma C, et al. Takotsubo cardiomyopathy in a vaccinated patient with severe COVID-19. *Kans J Med* 2022; 15:255-256. PMID: 35899060.
- ² Fearon C, Parwani P, Gow-Lee B, Abramov D. Takotsubo syndrome after receiving the COVID-19 vaccine. *J Cardiol Cases* 2021; 24(5):223-226. PMID: 34539938.
- ³ Stewart C, Gamble DT, Dawson D. Novel case of takotsubo cardiomyopathy following COVID-19 vaccination. *BMJ Case Rep* 2022; 15(1):e247291. PMID: 35042734.
- ⁴ Rubens M, Ramamoorthy V, Saxena A, et al. Hospital outcomes among COVID-19 hospitalizations with myocarditis from the California state inpatient database. *Am J Cardiol* 2022; S0002-9149(22):00854-2. PMID: 36127182.