Author’s response to reviews

Title: Myopericarditis and exertional rhabdomyolysis following an influenza A (H3N2) infection

Authors:

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Author’s response to reviews: see over
Sheryl Ramos  
on behalf of Mr. Nathaniel Nazareno  
Journal Editorial Office  
BioMed Central  
Dear Editor:

Thank you for giving us the opportunity to respond to the reviewer’s and editor's comments in this article entitled "Myopericarditis Provoked by Exertional Rhabdomyolysis: Influenza A (H3N2) to Blame". Our responses to the issues raised by the reviewers and editor are detailed below. At the same time, we have made changes to the manuscript in accordance with the reviewers’ suggestions.

Sincerely yours,

Jenq-Shyong Chan, MD
**Reviewer #1: Specific Responses:**

**OVERALL REPLY:** We thank the reviewer for their obvious in depth reading and questions, we found the insights gained useful and have responded in detail below. Boldfaced comments are yours, with our responses below and insertions in the text in smaller italic. Note that the responses are also highlighted in the main manuscript so they are more easily found. We apologise in advance for any misconstrued comments.

<table>
<thead>
<tr>
<th>1. The authors stated that “Myopericarditis provoked by exertional rhabdomyolysis” in title and discussion. However, there is no apparent evidence regarding rhabdomyolysis causing myopericarditis in this patient. As influenza A can develop myopericarditis as well as rhabdomyolysis, there may be coincidence of both diseases with some time-lag. Title may be better to change to “Myopericarditis and exertional rhabdomyolysis following an influenza A (H3N2) infection.”</th>
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<tr>
<td><strong>Reply –</strong></td>
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<tr>
<td>The authors apologize for having the reviewer inconvenience and agree with the reviewer that there is no apparent evidence regarding rhabdomyolysis causing myopericarditis in this patient. We have changed the title to “Myopericarditis and exertional rhabdomyolysis following an influenza A (H3N2) infection”. We also agree that there may be coincidence of both diseases with a time lag and thus we have added this sentence in the discussion section.</td>
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</table>

This concern is addressed in **discussion as Paragraph 3**

Cardiac involvement in influenza occurs usually during the first week after the onset of influenza symptoms [17]. This may result from direct viral invasion or from the host immune-mediated inflammatory pathology: the immunological dissonance usually plays a major role in the later phases of infection, even in the absence of viral genome [1]. In our case, myopericardial damage occurred later in the course of infection, on the tenth day after the onset of influenza symptoms, and was associated with exertional rhabdomyolysis. More intriguingly, the patient’s clinical manifestations and echocardiographic images also progressed in parallel with the increase in CPK concentration. We consequently assume that this cardiac disorder was provoked by exertional rhabdomyolysis, which may be due to the profound injury caused by inflammatory mediators to the heart, predisposing it to develop influenza myopericarditis (Fig. 2). Alternatively, there may be coincidence of both diseases with a time lag. Further studies are needed to elucidate the molecular mechanisms associated with these clinical phenomena.

<table>
<thead>
<tr>
<th>2. Indeed, there is possibility that rhabdomyolysis provoked myopericarditis in this patient. Patients with rhabdomyolysis and myocarditis have ever been reported. These reports should be added in the references of your paper.</th>
</tr>
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<tbody>
<tr>
<td><strong>Reply –</strong></td>
</tr>
<tr>
<td>The authors appreciate the reviewer’s concurrence about our assumption. Meanwhile, we have added preliminary reports of rhabdomyolysis and myocarditis in the references of our paper.</td>
</tr>
</tbody>
</table>

This concern is addressed in **discussion as Paragraph 2**

Influenza is an acute febrile illness caused by influenza viruses. Most infections are uncomplicated and the illness is usually limited to symptoms of upper respiratory infection in combination with several constitutional symptoms, including headache, lethargy, and myalgia. However, some patients are at risk of severe illness and fatal complications affecting multiple organ systems [9]. Various complications of influenza A infection have been reported in the pulmonary, neurological, renal, cardiac and muscular systems [10-12].

<table>
<thead>
<tr>
<th>3. The authors mentioned a role of inflammatory cytokines including TNF-alfa on development of myocardial injury. Did the authors measure inflammatory cytokines in this patient?</th>
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<td><strong>Reply –</strong></td>
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</table>
The authors apologize for not measuring TNF-alfa during the patient’s hospitalization period. We only checked C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR). The CRP level and ESR were initially slightly elevated but had normalized 7 days later.


Reply –

The authors apologize for having the reviewer inconvenience and we have corrected the Style of all references.

Reviewer #2: Specific Responses:

1. Change mentions of nasopharyngeal "smear" to nasopharyngeal wash samples.

Reply –

The authors apologize for having the reviewer inconvenience and we have corrected the errors in abstract and case presentation.

This concern is addressed in abstract and case presentation as Paragraph 2

Influenza A (H3N2) virus infection was confirmed by polymerase chain reaction analysis of nasopharyngeal wash samples. Other possible infective and autoimmune causes were excluded. Patient recovered completely with anti-inflammatory therapy and the supportive care.

Cultures of blood samples tested negative, and viral studies were negative apart from detecting influenza A (H3N2) virus by polymerase chain reaction analysis of nasopharyngeal wash specimens.

2. Briefly review other viral myocarditides and the influence of exercise in general on this outcome. Some additional references and discussion is warranted.

Reply –

The authors appreciate the reviewer’s suggestions and we have briefly reviewed other viral myocarditides and the influence of exercise in general on this outcome. Meanwhile, additional references and discussion are added in our paper.

This concern is addressed in discussion as Paragraph 1

Myopericarditis, or inflammation of the myocardium and pericardium, can present with an overlap of the symptoms of myocarditis (flu-like symptoms such as fever, fatigue and myalgias) and pericarditis (sharp or pleuritic chest pain that is relieved with sitting forward and worsened by laying back) [1]. In clinical practice both pericarditis and myocarditis coexist because they share familiar causative agents, mainly cardiotropic viruses (Table 1) [2-6]. Enteroviruses, especially group B coxsackieviruses, appear to be the major implicated agents. The term “myopericarditis” indicates a primarily “pericarditic syndrome” and it is responsible for the majority of cases. The inflammatory process is usually self-limited without overt sequelae and can occur as seasonal epidemics, especially coxsackieviruses and influenza. However, preliminary studies have shown that vigorous exercise can markedly accelerate viral myopericarditis and enhance the inflammatory process [7, 8].
Cardiac involvement in influenza occurs usually during the first week after the onset of influenza symptoms [17]. This may result from direct viral invasion or from the host immune-mediated inflammatory pathology; the immunological dissonance usually plays a major role in the later phases of infection, even in the absence of viral genome [1]. In our case, myopericardial damage occurred later in the course of infection, on the tenth day after the onset of influenza symptoms, and was associated with exertional rhabdomyolysis. More intriguingly, the patient’s clinical manifestations and echocardiographic images also progressed in parallel with the increase in CPK concentration. We consequently assume that this cardiac disorder was provoked by exertional rhabdomyolysis, which may be due to the profound injury caused by inflammatory mediators to the heart, predisposing it to develop influenza myopericarditis. Further studies are needed to confirm this hypothesis. We have changed the title to “Myopericarditis and exertional rhabdomyolysis following an influenza A (H3N2) infection”. We also agree that there may be coincidence of both diseases with a time lag and thus we have added this sentence in the discussion section.

This concern is addressed in discussion as Paragraph 3.

Common: Uncommon:

<table>
<thead>
<tr>
<th>Common:</th>
<th>Uncommon:</th>
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<tbody>
<tr>
<td>Coxsackievirus</td>
<td>Parainfluenza</td>
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<tr>
<td>Adenovirus</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Cytomegalovirus</td>
<td>Varicella</td>
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<tr>
<td>Echovirus</td>
<td>Mumps</td>
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<tr>
<td>Influenza</td>
<td>Rubella</td>
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<tr>
<td>Epstein–Barr virus</td>
<td>Rubella</td>
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<tr>
<td>Herpesvirus</td>
<td>Poliomyelitis</td>
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<tr>
<td>Hepatitis virus</td>
<td>Rhinovirus</td>
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<tr>
<td>Parvovirus</td>
<td>Vaccinia (smallpox vaccine)</td>
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<td></td>
<td>Variola</td>
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<td>Other</td>
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* Viral myopericarditis is usually a self-limited disease and can occur as seasonal epidemics, especially coxsackievirus B and influenza.

Editor's Comment: Specific Responses:

1. "The reviewers rightly point out the difficulty in asserting that rhabdomyolysis was the CAUSE of the cardiomyopathy in this patient, and suggest that you be more circumspect in reaching this conclusion.

Reply –

The authors apologize for having the reviewers inconvenience and agree with the reviewers that it is difficult to assert that rhabdomyolysis was the CAUSE of the cardiomyopathy in this patient. However, our patient developed influenza myopericarditis on the third day after the onset of exertional rhabdomyolysis. Reports in the literature have indicated that vigorous exercise can markedly accelerate viral myopericarditis and enhance the inflammatory process. More intriguingly, the patient’s clinical manifestations and echocardiographic images also progressed in parallel with the increase in CPK concentration. We consequently assume that this cardiac disorder was provoked by exertional rhabdomyolysis, which may be due to the profound injury caused by inflammatory mediators to the heart, predisposing it to develop influenza myopericarditis. Further studies are necessary to confirm this hypothesis. We have changed the title to “Myopericarditis and exertional rhabdomyolysis following an influenza A (H3N2) infection”. We also agree that there may be coincidence of both diseases with a time lag and thus we have added this sentence in the discussion section.

2. They also note that similar case reports exist, and should be included in your literature review.

Reply –
The authors appreciate the reviewer’s suggestion and we have added preliminary reports of rhabdomyolysis and myocarditis in the references of our paper.

This concern is addressed in discussion as Paragraph 2.

Influenza is an acute febrile illness caused by influenza viruses. Most infections are uncomplicated and the illness is usually limited to symptoms of upper respiratory infection in combination with several constitutional symptoms, including headache, lethargy, and myalgia. However, some patients are at risk of severe illness and fatal complications affecting multiple organ systems [9]. Various complications of influenza A infection have been reported in the pulmonary, neurological, renal, cardiac and muscular systems [10-12].
REFERENCES

17. Puzelli S, Buonaguro FM, Facchini M, Palmieri A, Calzoletti L, De Marco MA, *et al*: Cardiac tamponade and heart failure due to myopericarditis as a presentation of...