

To reviewer 1,

Thank you for taking the time to review this report with great care. We appreciate the opportunity to resubmit our paper. We have addressed your concerns as much as possible and would greatly appreciate your review of our revised manuscript.

Your case is interesting and informative. However, there are many points that should be clarified and corrected. The followings are my suggestions. Overall - Overall is well-written with some minor grammar errors. - The patient's data was incomplete in many aspects including clinical presentations, physical examinations, basic investigations, and differential diagnoses. - The differential diagnoses and supporting information are somewhat unreasonable. - The pathognomonic/important imaging findings (including echo, CT, and MRI) were not appropriately demonstrated. 1 Title, abstract, introduction -

2. Case presentation 2.1 Chief complaint, history, and present illness - Please detail the onset of the patient presenting symptoms.

Based on your comments, we have revised his symptoms as follows: **The patient reported a transient loss of consciousness and falls while walking in the morning after breakfast. He regained consciousness immediately.**

2.2 Past illness, personal and family history - Please provide more information about the patient's past medical history, particularly medications for AF and DM. Because these medications may cause TLOC e.g., rate/rhythm control drug (arrhythmia), anticoagulant (hemorrhage), and hypoglycemic agent (hypoglycemia), etc.

Based on your comments, we have added the following information:

**The patient was receiving direct oral anticoagulants and amiodarone for paroxysmal atrial fibrillation and dipeptidyl peptidase 4 inhibitor and sodium-glucose cotransporter 2 inhibitor for diabetes mellitus.**

2.3 Physical examination - The physical examinations are not complete, especially in the cardiovascular system, which is the system of involvement. - Authors stated that 'Fever,

jugular venous distension, and bilateral marked leg edema were noted, suggesting heart failure or cardiac tamponade. From the given examinations, they were not enough to diagnose cardiac tamponade. Important information e.g., heart sounds, friction rub, and pulsus paradoxus should be mentioned. Moreover, fever is not a sign of tamponade. - From history and examination, can constrictive pericarditis be differentiated in this case? - Other examinations, particularly the respiratory (to see if there was concomitant left-sided heart failure) and neuro signs (to exclude neurologic cause of TLOC) are also important and should be reported.

Based on your comments, we have added the following findings:

The results of his physical examination were as follows: height, 1.58 m; weight, 51.6 kg; body mass index, 20.59 kg/m<sup>2</sup>; blood pressure, 91/53 mmHg; pulse rate, 92 beats/min and irregular; oxygen saturation in room air, 97%; body temperature, 37.9 °C; and respiratory rate, 16 breaths/min. At the time of the visit, the patient's level of consciousness was clear, and no obvious neurological abnormalities were observed. Mild anemia was observed in the ocular conjunctiva. Jugular venous distension was marked. On auscultation, the heart sounds were irregular but well audible, and there was no clear heart murmur or pericardial friction rub. In the lung field, normal breath sounds were present with no rales. There were no abnormal findings in the abdomen. Bilateral marked leg edema was noted.

2.4 Laboratory examination - Since the patient had a fever, a septic workup results should be described.

Based on your comments, we have added the results of the culture as shown below.

Blood and urine cultures were negative for sepsis. A close examination for collagen disease was negative, as was a quantitative test for tuberculosis.

2.5 Imaging examination - The basic cardiovascular investigation, namely electrocardiogram, should be mentioned. - Echocardiography is an important first-line investigation in patients with suspected cardiac tamponade and heart failure. Therefore, detailed echocardiographic findings including specific signs of tamponade should be described. - The given on-admission ultrasound cardiographic findings (pericardial effusion with normal left ventricular ejection fraction (LVEF)) could not exclude cardiac tamponade. To be more specific, cardiac tamponade can present with pericardial effusion and normal LVEF. - Amount and location of pericardial effusion should be specified. Because they had an influence on further investigation and management decisions. - Other than T1W, T2W, and gadolinium-enhance

T1W images, many MRI sequences and findings are valuable in the diagnosis of cardiac/pericardial mass, e.g., perfusion images (to see tumor vascularity), T1W with fat suppression images (to exclude pericardial lipoma), late gadolinium enhancement images (to see contrast pharmacokinetic in mass), and advanced images if available (native T1 mapping, T2 mapping, ECV mapping, etc.) which were not mentioned in the present manuscript. - MRI is one of the best noninvasive tools for tissue characterization, although it could not make a definite diagnosis, it should give some clues for differential diagnosis. -

Based on your comments, we have added the findings of ECG and UCG as shown below.

Electrocardiography showed the presence of atrial fibrillation.

Regarding pericardial effusion, mild to moderate pericardial effusion was seen in all circumferential areas but seemed slightly more common in the posterior LV (Figure 2A). There was no evidence of right ventricular or atrial collapse or septal bounce, which was not supportive of the presence of cardiac tamponade or constrictive pericarditis.

Regarding the results of MRI, the specific imaging and/or analyses you pointed out might have helped in differentiation, and we did not perform the MRI examination after listing sufficient differential diseases and providing imaging conditions. In addition, some analyses cannot be performed with our MRI equipment. We have added this to our list of “points for improvement” in the Discussion section.

Other than T1W, T2W, and gadolinium-enhanced T1W images, many MRI sequences and findings are valuable in the diagnosis of cardiac/pericardial masses, such as perfusion images (to see tumor vascularity), T1W with fat suppression images (to exclude pericardial lipoma), and advanced images if available (native T1 mapping, T2 mapping, ECV mapping, etc.). Although the specific imaging and/or analyses might have helped in differentiation, we did not perform the MRI examination after listing sufficient differential diseases and providing imaging conditions. In addition, some analyses cannot be performed with our MRI equipment.

Why Gallium scintigraphy was needed in this patient should be explained. - If the present information was not enough, would it be better to perform an 18F-FDG PET scan in this patient?

As you commented, 18F-FDG PET seems superior to gallium scintigraphy in identifying inflammation. Nevertheless, we do not have FDG-PET equipment at our hospital. It is difficult under the Japanese insurance system for hospitalized patients to have FDG-PET performed at other facilities. Thus, in the present case, 18F-FDG PET was not performed, which could have provided more clinical information. We have added the following comments as “points for improvement” in the Discussion section.

Second, in the present study, we performed gallium scintigraphy; however, 18F-FDG PET has been established as the standard examination for malignancies, and it seems superior to gallium scintigraphy in identifying inflammation. Nevertheless, we do not have FDG-PET equipment at our hospital. It is difficult under the Japanese insurance system for hospitalized patients to have FDG-PET performed at other facilities. Thus, in the present case, 18F-FDG PET was not performed, which could have provided more clinical information.

There are many locations and methods to get a tissue diagnosis as described in the text. However, the most appropriate way and location for this patient should be discussed. - In my opinion, a pericardial biopsy might be an effective method with acceptable risk to get a tissue diagnosis. At that time, a definite diagnosis was not made. What if the diagnosis was a treatable disease? -

Based on your comments, we completely agree with your opinion that pericardial biopsy seems to be an effective method for making a final diagnosis of PMPM.

Why should EGD and colonoscopy be performed in this patient should be discussed in detail. They cannot totally exclude intra-abdominal primary cancer. Besides, the benefits of EGD and colonoscopy in critically ill patients might not be worth their risks.

We completely agree with your comments, and we have added the following comments as “points for improvement” in the Discussion section.

First, in this case, a close examination of the gastrointestinal tract was performed to rule out malignant disease of the gastrointestinal tract. Nevertheless, this examination alone was not sufficient and may have placed an additional burden on the patient.

- Again, second echocardiography should provide more information. The given findings (E/A ratio, LVEF, and LVEDD) were not enough to support the restrictive physiology.

Based on your comments, we have added a more detailed description of the echocardiographic findings, as follows:

Furthermore, UCG on the 23<sup>rd</sup> day after admission showed mass-like echogenicity at the apex, which was not present at the time of admission (Figure 2B, C). The E/A ratio was increased to 1.55, and the deceleration time was 140 msec on regular sinus rhythm, indicating progression of the restrictive disorder. The left ventricular end-diastolic diameter was large (40 mm), and the LVEF was slightly decreased (66%). The degree of pericardial effusion remained unchanged.

3. Final diagnosis - Although the final diagnosis could not be made, the probable and the most likely diagnosis could still be differentiated. - This patient presented with TLOC. It should be discussed the cause and mechanism of TLOC. - In the examination part, it was described that cardiac tamponade was suggestive; on the other hand, in the imaging part, the authors excluded tamponade from echocardiographic results. Was TLOC in this patient associated with tamponade?

Based on your comments, we have added possible mechanisms for TLOC.

The transient loss of consciousness may have been caused by diastolic dysfunction due to pericardial disease, dehydration due to fever and inflammation, and decreased cardiac output due to the appearance of paroxysmal atrial fibrillation.

4. Treatment - I am not sure that concomitant hypotension in the text described the patient on admission or during the hospital course. If it was on admission, the most appropriate treatment should be an intravenous fluid replacement, because the provisional diagnosis at that time was cardiac tamponade. - Authors stated 'The cause of death was thought to be septic shock due to infection or cardiac tamponade, but a definitive diagnosis could not be obtained. This is confusing whether the patient had tamponade or not. The information was inconsistent throughout the manuscript (physical exam suspected tamponade, while echo was not, and then tamponade was taught as the cause of death). I hope these comments will be helpful in improving your manuscript.

We have described the case over time to provide a better understanding of its course and treatment.

To reviewer 2

Thank you for your positive comments. We have revised our manuscript according to your comments.

*This manuscript reports a case of primary malignant pericardial mesothelioma (PMPM), which is extremely rare in clinical practice. The subject presented with transient loss of consciousness and falls. Ultrasound cardiography and computed tomography showed cardiac enlargement and a high density of pericardial effusion at admission. Cardiac magnetic resonance imaging and gadolinium contrast-enhanced T1-weighted images showed thick staining inside and outside the pericardium. The patient died of septic shock due to pneumonia and received an autopsy. Pathological test refer to the diagnosis of PMPM. The paper was valuable for differential diagnosis of similar conditions.*

*The languages need to be polished in some places. For example: 1. ""Multiple lung metastases were the differential"", this sentence is confusing. 2. ""but this may have been because autopsy was performed approximately 60 h after death (Table 1). ""*

According to your comments, we have deleted some words with confusing meanings, and we have changed other words to make their meanings easier to understand.

**An autopsy of this case was performed 60 hours postmortem, and this time course may have affected the immunostaining results (Table 1).**