Peer Review File

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Reviewers' Comments

Comment 1: (Reviewer A) 1-a. the marginally elevated troponin is not in line with the clearly increased NT-proBNP value - this could be a clue directing into something else than AL cardiac amyloidosis. Please also cite and discuss pmid 31359320 & 32653441 on this matter.

Reply 1: Thank you for the valuable suggestions and comments. We have modified our text as advised (see Page 11, line 193 to Page 12, line 202). These modifications include a reply to other reviewers' comments.

Changes in the text: (A new paragraph has been added to Page 11, line 193) Although many CA-like features were seen in the patient, some results were consistent with cardiac conditions other than CA. In addition to the normal FLC ratio, the extremely elevated serum NT-proBNP level (12,631 pg/mL), despite the slightly high troponin T level (0.054 ng/mL), may be more indicative of cardiomyopathy associated with POEMS syndrome than of CA. However, no studies on POEMS syndrome have documented such a discrepancy between NT-proBNP and troponin T levels (Table 1) (19–22). Although NT-proBNP and troponin T have been used to estimate the clinical severity and prognosis of CA (23*), these are not diagnostic markers of CA. On the other hand, in their review, Oerlemans et al. suggested that disproportionally high levels of NT-proBNP and chronically elevated troponin T at low levels with normal coronary angiography may be a red flag for CA (24**).

*Reference 23: PMID 32653441.
**Reference 24: PMID 31359320.

Comment 2: (Reviewer A) 1-b. Please elucidate more on the MRI results: what to expect from the T1/ECV values in this patient; does it make AL-CA more or less likely? the illustration on late gad is actually not fitting with amyloidosis.

Reply 2: We did not perform T1 mapping before chemotherapy because it is not an examination routinely conducted by cardiologists of our hospital. We only performed T1 mapping after one cycle of chemotherapy with melphalan and dexamethasone. Therefore, the findings of T1/ECV had little value for diagnosing CA. Instead, we added the result of T1/ECV to the Discussion as the reviewer advised (see Page 12, line 204-206).

Changes in the text: (Changes are underlined) … red flag for CA (24). <u>Additionally, the cardiac MRI findings of our patient may have been equivocal and not highly specific for CA. T1 mapping, which was performed after administration of MD,</u>

showed a normal extracellular volume (ECV, 24.1%). However, the T1/ECV value was not useful for differential diagnosis because the value may have affected by the chemotherapy. To definitely exclude CA, …

Comment 3: (Reviewer A) 1-c. c. Please more boldy state that for diagnosis of AL amyloidosis, a tissue biopsy confirmation is necesssary in all cases before chemotherapy initiation. so in this case the outcome would be that i) other biopsies should be obtained to confirm; or ii) the suspicion will get lower and lower, pointing to POEMS as alternative explanation.
Reply 3: We have modified our text as advised (see Page 20, line 206-209), and we added the results of other biopsies to Page 7, line 121 to Page 8, line 122.
Changes in the text: (Changes are underlined)
(Page 20, line 206-209) … the chemotherapy. To definitely exclude CA, myocardial biopsy is necessary in all cases for whom chemotherapy of plasma cell dyscrasias is planned, even when biopsy results from other organs are compatible with amyloidosis.
(Page 7, line 121 to Page 8, line 122) … amyloid proteins either (Figure 3). Additional biopsies from the skin, subcutaneous fat, and iliac bone marrow failed to detect any amyloid deposits. However, the cardiologist …

Comment 4: (Reviewer B) 1. Has nerve conduction study/electromyogram (NCS/EMG) ever been done for this patient? Demyelinating changes on NCS/EMG make the peripheral neuropathy diagnosis more confirmative in this case.
Reply 4: Thank you for the valuable suggestions and comments. We performed NCS several times but did not conduct EMG. However, NCS detected no electrical signal from his affected nerves, probably due to nerve edema or damages associated with POEMS syndrome. We added the result of NCS to the text, Page 7, line 107-108 as follows.
Changes in the text: (Changes are underlined) … feet. A nerve conduction study failed to detect any electrical signal from the nerves of the patient's legs. A plain chest X-ray…

Comment 5: (Reviewer B) 2. Has the pathological finding of inguinal lymph node biopsy been particularly reviewed for Castleman like changes? Castleman-like pathology of lymph node can be seen in POEMS syndrome and can be an important differential point from primary AL amyloidosis.
Reply 5: There was no specific finding including Castleman-like features in the lymph node biopsy. We have modified our text to answer the reviewer's question (see Page 6, line 87).
Changes in the text: (Changes are underlined) … no specific features suggestive of

Castleman disease. IgG-lambda-type M protein …

Comment 6: (Reviewer B) 3. Are the "small red nodules" on the skin consistent with hemangioma? If so, I would prefer to use the latter term in description.
Reply 6: We have modified our text as advised (see Page 6, line 92 and Page 7, line 104).
Changes in the text: (Changes are underlined)
(Page 6, line 92) … polyneuritis, ~~red nodules~~ hemangiomas at the chest skin, …
(Page 7, line 104) …, and several small ~~red nodules~~ hemangiomas on the chest skin. …

Comment 7: (Reviewer B) 4. Are there any osteosclerotic changes seen on the systemic CT scan?
Reply 7: There was no osteosclerotic changes on the whole-body CT scan. We have modified the text accordingly (see Page 6, line 85-86).
Changes in the text: (Changes are underlined) … in Figure 1A. No osteosclerotic change was detected by the CT scan. An inguinal lymph node biopsy…

Comment 8: (Reviewer B) 5. The patient received a decent dose of radiotherapy (50 Gy) to his plasmacytoma but did not have clinical response. However, when looked at Figure, a significant decline of serum VEGF (from 5150 to 2670 pg/mL) actually happened after radiotherapy. Of note, the clinical response after radiotherapy could be delayed compared to biochemical response. Therefore, the "rapid response" to 1 cycle of MD may be a consequence to prior radiotherapy also, as MD was given closely after radiotherapy. I would prefer the authors to discuss this point.
Reply 8: As the reviewer pointed out, the radiotherapy might have partially contributed to the improvement of CHF. However, his CHF symptoms, such as edema and pleural effusions progressed despite the conventional therapy for CHF during radiotherapy. As CHF is a rare complication in patients with POEMS syndrome, no reliable data is available concerning a latency between improvement of CHF and radiotherapy. In addition, it is unclear whether or not the severity of CHF correlates with serum VEGF levels in patients with POEMS syndrome. Based on these thoughts, we have modified our text as follows (see Page 10, line 177 to Page 11, line 179).
Changes in the text: (Changes are underlined) … CHF. Although radiotherapy might have partially contributed to the improvement of the CHF, this possibility seems unlikely because his CHF progressed during radiotherapy despite the fact that the serum VEGF level decreased by half. Starting treatment with …

Comment 9: (Reviewer B) 6. How is the serum free light chain (sFLC) of this patient? sFLC is a critical test to help differentiating POEMS from primary AL

amyloidosis, as most POEMS patients have a preserved ratio, while primary AL case always show abnormal sFLC ratio with elevated dFLC.

Reply 9: We have added the lab data of serum free light chain to the text (see Page 7, line 118-119) and discussed its interpretation (see Page 11, line 194 to Page 12, line 198).

Changes in the text: (Changes are underlined)

(Page 7, line 118-119) … 0.054 ng/mL, respectively. The concentration of serum free light chain (FLC) lambda-type and FLC ratio were 46.0 mg/L (reference range; 5.7-26.3 mg/L) and 1.43 (reference range; 0.26-1.65), respectively. On the other hand, …

(Page 11, line 194 to Page 12, line 198) … other than CA. In addition to the normal FLC ratio, the extremely elevated serum NT-proBNP level (12,631 pg/mL) despite the slightly high troponin T level (0.054 ng/mL), may be more indicative of cardiomyopathy associated with POEMS syndrome than of CA. However, no studies on POEMS syndrome have documented such a discrepancy between NT-proBNP and troponin T levels (Table 1) (19–22). Although NT-proBNP and …

Comment 10: (Reviewer B) 7. Is there elevated systolic pulmonary arterial hypertension on the echocardiogram?

Reply 10: We added additional findings of UCG to the text (see Page 8, line 124-127).

Changes in the text: (Changes are underlined; the same as the response to **Comment 17**)

… all typical of CA. Pulmonary hypertension (PH), a frequent complication of POEMS syndrome (7), was not initially suspected because pulmonary valve regurgitation was not detected and tricuspid regurgitation was too trivial to measure by UCG. On the other hand, …

Comment 11: (Reviewer B) 8. The sensitivity of endomyocardial biopsy is not ideal, and the cardiac MRI finding in this patient is mild that not highly specific for cardiac amyloidosis. I would prefer the authors to discuss this point.

Reply 11: The limited sensitivity of endomyocardial biopsy had been discussed in the Discussion section of the original manuscript (see Page 12, line 210). However, as the reviewer pointed out, we recognized the cardiac MRI findings was relatively mild in this patient. We have modified our text as advised (see Page 12, line 202-206).

Changes in the text: (Changes are underlined; the same as the response to **Comment 2**)

… for CA (24). Additionally, the cardiac MRI findings of our patient may have been equivocal and not highly specific for CA. T1 mapping, which was performed after administration of MD, showed a normal extracellular volume (ECV, 24.1%). However, the T1/ECV value was not useful for differential diagnosis because the

value may have affected by the chemotherapy. To definitely exclude CA, …

Comment 12: (Reviewer B) 9. Overall, the clinical picture is consistent with POEMS rather than AL. But this two conditions do co-exist in rare circumstance (Am J Hematol. 2010 Feb;85(2):131-2), which should be mentioned in the discussion.
Reply 12: We added a new sentence as advised to page 10, line 160-162.
Changes in the text: (Changes are underlined; the same as the response to **Comment 13**)
… those of CA. In addition, this hypothesis was supported by the facts that CHF was a rare complication in patients with POEMS syndrome and that CA and POEMS syndrome could coexist (1,9). Although these …

Comment 13: (Reviewer C) 1. Please provide the reasons that the authors have suspected cardiac amyloidosis in this patient who have previously identified solitary plasmacytoma of bone through bone biopsy and was suspected to have the POEMS syndrome in a previous hospital.
Reply 13: As described in the first sentence of the Discussion section of the original manuscript, we suspected cardiac amyloidosis (CA) because several non-invasive examinations revealed findings compatible with CA and POEMS syndrome is rarely complicated by heart failure. In addition, CA and POEMS syndrome can coexist as was reported previously (Am J Hematol 2010;85:131-2). To clarify the reasons, we have modified our text as follows (see Page 10, line 160-162).
Changes in the text: (Changes are underlined; the same as the response to **Comment 12**)
… those of CA. In addition, this suspicion was supported by the facts that CHF was a rare complication in patients with POEMS syndrome and that CA and POEMS syndrome could coexist (1,9). Although these …

Comment 14: (Reviewer C) 2. It is presumed that the authors had paid attention to the patient's heart-related tests and made light of other symptoms and findings related with the POEMS syndrome. This limitation should be commented on the discussion.
Reply 14: Our statements may have been misleading because we focused on CHF of the patient in this manuscript. We originally diagnosed our patient to have POEMS syndrome, and suspected that the patient's CHF was not due to POEMS syndrome but to CA. In other words, we suspected co-existence of POEMS syndrome and CA. To make this point clearer, we have revised the manuscript in response to **Comment 13** (see Page 10, line 160-162) and this comment (see Page 9, line 155-156).
Changes in the text: (Changes are underlined) …, CHF due to amyloid cardiomyopathy that occurred concurrently with POEMS syndrome was initially suspected …

Comment 15: (Reviewer D) #1. If the authors performed biopsy examination from other sites, e.g., stomach, rectum, and salivary glands, the information would be provided.
Reply 15: We performed biopsies from the skin and subcutaneous fat. Both were negative for amyloid deposit. We have modified our text as advised (see Page 7, line 121 to Page 8, line 122).
Changes in the text: (Changes are underlined; the same as the response to **Comment 3**)
… either (Figure 3). Additional biopsies from the skin, subcutaneous fat, and iliac bone marrow failed to detect any amyloid deposits. However, …

Comment 16: (Reviewer D) #2. Are there some other possible etiologies that present CA-like manifestations? For comprehensive differential diagnosis, other possible etiologies should be described. Also, the reasons why the authors excluded the etiologies should be briefly discussed.
Reply 16: We did not come up with other diseases than CA as a cause of his CHF because many examination results were typical for CA-like features. We have modified our text as advised (see Page 10, line 164-166).
Changes in the text: (Changes are underlined) … amyloid deposits. However, we did not diagnose any conditions other than CA before chemotherapy because most of the test results were compatible with CA-like features. CA is usually …

Comment 17: (Reviewer E) The most important critique is the diagnosis of the presenting case. As mentioned by authors, CHF is a rare complication in patients with POEMS syndrome. Generally, pulmonary hypertension is more frequently concomitant with POEMS syndrome, contrary to heart failure. Previous literature showed that pulmonary hypertension has been reported to occur in 27% of unselected patients with POEMS syndrome (Haematologica. 2013;98(3):393-398). In addition, there are a several reports with successful reversal of pulmonary hypertension concomitant with POEMS by immunomodulation therapy. Therefore, the RHC data should be presented to evaluate the LV filling pressure was elevated, confirming left-sided heart failure. The findings of pitting edema, elevated NT-pro-BNP and mild impairment of ejection fraction (even they did not mention LVEF or RVEF) were not adequate enough to exclude the possibility of the diagnosis of pulmonary hypertension.
Reply 17: In the report the reviewer quoted (Haematologica. 2013;98:393-8), pulmonary hypertension (PH) was defined as systolic PAP≥ 50 mmHg according to the peak tricuspid regurgitant flow identified by Doppler echocardiography. Following this definition, in our case, PH was ruled out because the peak tricuspid

regurgitant flow was too trivial to be measured and no pulmonary valve regurgitation was detected. However, the RHC showed the mean pulmonary arterial pressure was high at 27 mmHg. Therefore, we have modified our text as advised (see Page 8, line 124-131).

Changes in the text: (Changes are underlined) … all typical of CA. Pulmonary hypertension (PH), a frequent complication of POEMS syndrome (7), was not initially suspected because pulmonary valve regurgitation was not detected and the tricuspid regurgitation was too trivial to measure by UCG. On the other hand, right heart catheterization revealed elevated mean pulmonary arterial pressure (27 mmHg), diastolic pulmonary arterial pressure (18 mmHg), and pulmonary capillary wedge pressure (15 mmHg). However, the patient's low pulmonary vascular resistance (1.96 Wood units) and low diastolic pressure gradient (3 mmHg) suggested that his PH was caused by left heart disease (8).

Comment 18: (Reviewer E) In addition, authors described the symptom of neuropathy such as difficulty in raising toes and walking, but never mentioned dyspnea on exertion before and after treatment. If the diagnosis were consistent with heart failure, the symptom of dyspnea should be described in detail.

Reply 18: He did not complain dyspnea on exertion throughout his clinical course. This is probably because he had been mostly bedridden due to lower legs' paralysis. We have modified our text as suggested (see Page 6, line 96-97).

Changes in the text: (Changes are underlined) … ejection fraction. He had no dyspnea on exertion because he was mostly bedridden due to paralysis of the lower legs. His symptoms were …