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Handling Editor: Dr.Jin-Lei Wang

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Dear Dr. Wang,

We thank you for this opportunity to resubmit a revised version of our manuscript entitled '**Emphysematous thrombophlebitis caused by a misplaced central venous catheter: A case report**'. We also thank the reviewers for their helpful comments. We have revised the manuscript based on these comments and provide point-to-point responses on the appended pages. In the revised manuscript, revised/added content is highlighted in yellow for convenience.

Issues and responses

Reviewer #1:

1. **Issue:** (1) Why do you think the catheter is misplaced? Either the subclavian (where it was inserted) or the internal jugular (where it was found) are both acceptable.

(2) Did you use imaging when inserting the catheter initially?

Response: Thank you for these helpful comments. We speculate that the tip of the CVC was implanted via subclavian access towards the head rather than caudally toward the junction of the SVC and right atrium. This may have occurred because physicians at the original treating hospital did not performance CVC insertion under imaging guidance. Further, CVC catheter tip position was not assessed by chest X-ray after the operation. It

is recommended that the catheter tip be positioned at the junction of the superior vena cava (SVC) and right atrium as the high blood flow and lack of blood reflux minimize the risk of thrombosis. Further, positioning the tip outside the atrium prevents arrhythmia. Improper positioning of the catheter tip has been reported to strongly increase the risk of CRT.

All of these points have been added to the revised Discussion.

Revision: (1) Discussion: The term 'misplacement' refers to migration of the CVC tip to an improper position^[13]. It is recommended that the CVC catheter tip be positioned at the junction of the superior vena cava (SVC) and right atrium^[14], a location with high blood flow to reduce the risk of thrombosis but still lying outside the atrium, thereby preventing arrhythmia^[15]. In the current case, the tip of the CVC was implanted via subclavian access towards the head rather than caudally toward the junction of the SVC and right atrium. Improper positioning of the catheter tip has been reported to greatly increase the risk of CRT due to reflux of blood ^[4]. We speculate that the relatively slow blood flow in the IJV and reflux of blood across the distal tip of the misplaced CVC resulted in CRT.

(2) Further, CVC catheter tip position was not assessed by chest X-ray after the operation.

2. **Issue:** Line 67. This may be a small and insignificant point but occasionally emphysematous thrombophlebitis is iatrogenic. Every time interventional radiology injects a substance to obstruct peripheral bleeding. Also, when spaces (abscesses, cavities, vessels) are irrigated there is the risk.

I am not sure this should even be mentioned in the paper though.

Response: In this case, no interventional vascular therapy was performed using the CVC access. Therefore, we do not think this case of emphysematous thrombophlebitis can be attributed to iatrogenic factors.

3. **Issue:** Line 151. You note.... neurological rehabilitation treatment.... But what were his neurological deficiencies and were any related to the thrombophlebitis or all to the stroke?

Response: The patient presented with spontaneous right basal ganglia hemorrhage and thrombosis in the right IJV. Limb weakness was present in the left upper and lower limbs but not in the right, so we think that the right basal ganglia hemorrhage and thrombosis in the right IJV may both contribute to left limb weakness.

Revision: At this time, the patient was fully conscious but exhibited left limb weakness due to stroke and emphysematous thrombophlebitis, and so was transferred from the ICU to a general ward for neurological rehabilitation.

Reviewer #2:

1. **Issue:** History of past illness: Was the patient diabetic? It is more common in diabetics, hence pls mention it.

Response: Thank you for your careful review and helpful critique. The patient was not diabetic. We have added this information to the case description.

Revision: The patient had a 7-year history of poorly controlled hypertension and did not have diabetes.

2. **Issue:** Physical examination: How was the diagnosis of septic shock made? Pls mention the lactate levels.

Response: The patient suddenly developed fever, tachycardia, and hypotension. Physical examination revealed right neck swelling accompanied by redness, tenderness, and a warm sensation. Arterial blood gas analysis suggested metabolic acidosis with elevated lactic acid. These findings combined with other laboratory and imaging results indicated septic shock. We have added arterial blood gas and lactic acid measurement results to the revised case description.

Revision: Physical examination: These findings combined with other laboratory and imaging results indicated septic shock.

Laboratory examinations: Arterial blood gas measurements were as follows: pH, 7.30; PaCO₂, 33mmHg; PaO₂, 108mmHg; lactate, 3.8mmol/L; HCO₃⁻, 16.8 mmol/L.

3. **Issue:** Laboratory examination: What were the renal function parameters? As the patient was in shock, and was also given vancomycin, which is nephrotoxic, it is important to know the KFT.

Response: The patient's renal function parameters were normal. We have included this information in the revised 'Laboratory examinations' section.

Revision: Laboratory examination: Alternatively, renal function parameters were normal.

4. **Issue:** Treatment: Please mention the sensitivity pattern for *Staphylococcus cohnii*.

Response: The isolated *Staphylococcus cohnii* was sensitive to vancomycin.

Revision: The S. cohnii strain isolated by blood culture demonstrated moderate sensitivity to vancomycin (minimum inhibitory concentration of 1 mg/L).

5. **Issue:** Discussion: Please revise the following statement "We suggest that the relatively slow of the blood flow in the IJV may contribute to CRT in this patient."

Response: We have changed the wording to avoid ambiguity.

Revision: We speculate that the relatively slow blood flow in the IJV and reflux of blood across the distal tip of the misplaced CVC resulted in CRT.

6. **Issue:** Discussion: "The most common causative pathogen for CVC-BSI is *Staphylococcus*⁽³⁾..." Please mention the other pathogens which may cause a similar picture.

Response: *Klebsiella pneumoniae* and *E. coli* may also produce gas and cause similar clinical manifestations.

Revision: Other pathogens such as *Klebsiella pneumoniae* and *E. coli* may also cause similar clinical manifestations due to gas production.

7. **Issue:** Discussion: Would recommend using some recent guidelines like doi: 10.5005/jp-journals-10071-G23183

Response: We have cited some recent guidelines.

8. **Issue:** Figure 2: May be omitted as it offers no new information.

Response: The timeline clearly illustrates the clinical course and is recommended by the journal guidelines for case reports. We believe that Figure 2 should not be omitted.

Reviewer #3:

1. **Issue:** (1) Line 80: How many days before being transferred to your hospital?

(2) Line 98: It's unclear to what "symptom onset" is referred, i.e., to symptoms that were present at your hospital or to the symptoms that the patient presented when he was admitted to the local hospital? Please modify.

(3) Line 99: typo mistake.

(4) Line 107: typo mistake.

(5) Line 109: It is stated that CT scan was not performed due to the critical state (line 103). When was this CT scan obtained? Soon after? Please

clarify.

(6) Line 111: was this the initial diagnosis or the definitive diagnosis?

Please clarify.

(7) Line 166: typo mistake.

Response: Thank you for these helpful comments.

(1) The patient was transferred to our institution two days after surgery performed in the local hospital.

(2) "Symptom onset" refers to the symptoms present at our hospital, including hypotension, fever and swelling in the right neck.

(3, 4) These have been corrected.

(5) CT scans were not obtained immediately due to the critical status of the patient. The patient's hypotension was improved by fluid resuscitation. A subsequent CT scan was performed afterwards on the same day.

(6) We now state that emphysematous thrombophlebitis is the 'definitive diagnosis' throughout the revised manuscript.

We modified the sentences on lines 99, 107 and 166 accordingly.

Revision: (1) Two days later, the patient was transferred to the intensive care unit (ICU) of our hospital for further critical care.

(2-3) After the onset of neck symptoms, blood analysis revealed leukocytosis ($13.69 \times 10^9/\text{L}$) and elevated inflammatory markers including C-reactive protein (75.9 mg/L) and procalcitonin (5.8 ng/mL).

(4) Also, ultrasonography revealed that the misplaced CVC had been placed into the IJV rather than into the ideal position of superior vena cava (SVC) through the right subclavian vein approach and was surrounded by gas bubbles, manifesting as hyperechoic lines with dirty shadowing and comet-tail artifacts (Figure 1, Panel C and D).

(5-6) The patient's hypotension was improved by fluid resuscitation. A subsequent CT scan was performed afterwards on the same day and also confirmed air bubbles surrounding the CVC in the right neck (Figure 1, Panel E), and septic emphysematous thrombophlebitis induced by a misplaced CVC and septic shock was definitively diagnosed.

(7) In the current case, we suggest that emphysematous thrombophlebitis may be attributed to emergency surgery, absence of anticoagulant use, insertion without ultrasound assistance, and misplacement of the CVC tip from the right subcalvian vein into the IJV^[4,12].

Best regards
Dr. Xing