

## SPECIFIC COMMENTS TO AUTHORS

I praise the authors for their informative manuscript. The context will probably be of interest to the readers of the journal. However, a revision is required before I could recommend it for acceptance. Overall, I find two main pitfalls in this article.

First, it lacks adequate detail concerning the non-orthopedic portions, i.e., those related to the presentation and management of the pulmonary thromboembolic disease. The treatment section needs further detail on the treatment of the embolism. Since 'conservative treatment' is a keyword of your manuscript; so, information about it will be eloquent.

*A: Thanks very much for your suggestion. We have included more non-orthopedic portions in case, including the related clinical manifestations, drug dosage, and result of certain laboratory test in the revised version.*

Second, a proper presentation and pertinent details of the timeline of events (a vital component of this paper) is missing. Please rewrite so that the reader can visualize the entire patient care process from the first day of contact to the last day of follow-up. Were the CT scans repeated after the 5th post-op day? Include all instances when lab and radiologic evaluation ensued and their findings. Please consider the inclusion of a tabular representation of vital status, ECG, oxygen saturation, radiologic, and laboratory findings in a date- or day-wise manner.

*A: Thanks for your suggestion. We have summarized the vital signs, ECG, oxygen saturation, radiologic, and laboratory findings in Table 1 in order to gain a better understanding. (Table 1)*

Additionally, I would suggest the inclusion of a flow diagram showing the entire chain of events in detail (preferably with colors). Please add colored markers where possible on all radiologic images and explain them in the caption. Please include the date (or day number) when such images were taken.

A: Thanks for the kind suggestion. We have added a timeline flow chart in the manuscript (Figure 4) and colored markers on the figures to indicate the important signs. Besides, we also included the date in the figure legend section.

A lot of information in the discussion section would be a better fit for the introduction section. I recommend rewriting the discussion section in a much concise manner. Please make the discussion writing more relevant to the case you reported rather than keeping it in general.

A: Thanks for your kind advise, we have revised the discussion section in order to make it more informative and more concise.

Additionally, I recommend addressing the following points in your paper:

1. The predisposing factors that might have increased the odds of the thromboembolic complication.

A: Thanks for the question regarding risk factors for cement embolism. Known risk factors for PCE include thoracic spine instrumentation, spinal metastases, more instrumented levels, and more total cement volume. In the case we presented here, the patient did not have the risk factors mentioned above. However, the patient was diagnosed with osteoporosis, which might also be considered as a risk factor for cement embolism.

2. How did your treatment vary from identical orthopedic cases (in detail)? Discuss the dosages of medications used.

A: Thanks for raising the important question regarding our treatment. In this case, the patient was diagnosed with L4-5 isthmic spondylolisthesis. In order to relieve the pain and numbness as well as improve the quality of life, we decided to perform pedicle screw instrumentation to achieve fully reduction of the listhesis. The S1 pedicle was not as osteoporotic as L4/5 and we inserted two bicortical screws into the sacrum. During pedicle insertion into S1, we could feel the resistance was relatively large, guaranteed the anti-pullout force. Therefore, regular pedicle screws were sufficient.

According to the literature in treating pneumonia, a dosage of 500mg/day levofloxacin was used to treat plausible infection [1]. The patient was treated with low molecular weight heparin 5000IU/day for 1 month and switch to 2.5mg/day of warfarin for 6 months after discharge.

[1] **Noreddin AM**, Elkhatib WF. Levofloxacin in the treatment of community-acquired pneumonia. *Expert Rev Anti Infect Ther.* 2010 May;8(5):505-14. [PMID: 20455679 doi: 10.1586/eri.10.35]

3. What about anesthesia? A talk with the anesthesiologists who cared for the patient and a review of their notes may further help building your case.

A: Thanks for your important question. Because of her mild hypertension the patient and thus was classified as ASA 2. Before surgery, the patient was fast for 12 h. She had general anesthesia with an endotracheal tube utilizing standard American Society of Anesthesiology (ASA) monitoring along with intra-arterial blood pressure monitoring and cerebral oximetry. During surgery, SpO<sub>2</sub> remained at 97% to 100% at an FiO<sub>2</sub> of 1.0, and the airway pressure was 21cm H<sub>2</sub>O at double lung ventilation. The blood pressure was maintained at 120-105/75-60 mmHg. Estimated blood loss during surgery was around 800 ml. She accepted 4U red blood cell transfusion and 400 ml plasma transfusion during surgery.

4. How about physiotherapy and ambulation while the patient was inpatient? What type of home care did the patient receive after returning home in line with thromboembolism management? I would like to know in detail.

A: Thanks for the important question regarding an essential part of our therapy. The patient received intermittent pneumatic compression (IPC) on her lower extremity to prevent thrombosis before surgery. After surgery, the patient was asked to stretch and relax the muscle of her lower extremities. A physical therapist assisted the patient with performing flexion and extension activities of her hip and knee joint. The patient complaint about pain in her lower extremities and surgical region, therefore no ground

activities have been carried out yet. After the commencement of cement embolism, the patient was nursed sitting up regularly and was atomized to clear airway secretions twice daily.

After the patient was discharged, the patient received routine thromboembolism management by switching anticoagulation therapy from LMWH to warfarin. Evidence showed that after 6 months of coumarin therapy, the foreign object is endothelialized and the risk of further embolism are seemly abolished [1, 2]. Therefore, 2.5mg daily warfarin was prescribed to the patient for 6 months with close monitoring of international normalized ratio (INR) every month. Routine CT scan was conducted once a year to monitor the change of cement emboli.

[1] **Krueger A**, Bliemel C, Zettl R, Ruchholtz S. Management of pulmonary cement embolism after percutaneous vertebroplasty and kyphoplasty: a systematic review of the literature. *Eur Spine J.* 2009;18(9):1257-1265. [PMID: 19575243 DOI: 10.1007/s00586-009-1073-y]

[2] **Schmidt R**, Cakir B, Mattes T, Wegener M, Puhl W, Richter M. Cement leakage during vertebroplasty: an underestimated problem? *Eur Spine J.* 2005;14(5):466-473. [PMID: 15690210 DOI: 10.1007/s00586-004-0839-5]

5. The type of experts involved in the management of the patient and their role.

A: We consulted with a respiratory expert, a cardiologist, and a vascular surgeon immediately after the patient suffered from the decrease in oxygen saturation. The respiratory expert performed a physical examination on the patient thoroughly and started mask oxygen therapy immediately. The respiratory expert also advised ventilator-assisted ventilation if necessary. Besides, the respiratory expert suggested that we should evaluate the status of the patient by CT scan or CTPA scan. We treated the patient with antibiotics at his suggestion.

The cardiologist evaluated the cardiac function of the patient. He suggested that the patient did not require cardiac surgery for the time being but monitoring of cardiac function is necessary.

After consultation with the vascular surgeon, we did not consider percutaneous retrieval of the cement emboli because of its small and scatter feature. But the vascular surgeon was also prepared to remove the embolus if the patient presented with progressive dyspnea or other emergencies.

6. State the limitations of your paper, if any. I have additional comments in the manuscript file itself. Thank you.

A: The paper has some potential limitations. Firstly, the case is very rare complication of bone cement augmentation. Therefore, we lack sufficient experience in treating the patient. We treated the patient according to reported cement embolism cases and the advice of experts from different discipline, but we are not certain whether it is also applicable to other patient suffer from the same complication. Secondly, we did not perform some in-detail test such as ventilation/perfusion positron emission tomography to evaluate regional lung functional impairment. In the follow-up stage, the patient was simply accessed with chest plain radiography or CT but not spirometry.

Thanks for your very careful comments in the manuscript, we have revised these contents according to your annotation.

## SPECIFIC COMMENTS TO AUTHORS

This interesting case report was very informative about the CAPSI procedure and the risks of cement embolism, which were not known to me. I feel it would be of interest to general and respiratory physicians who might see presentation with emboli, but not be familiar with the procedure or the (small) risk of such an event. The case was reasonably well described and the past literature on presentation and management of cement emboli was clearly presented in a table. There were a few instances where the English was not quite right, but it was understandable and the deficit more stylistic than anything else. I did have a few questions which the authors might be able to answer to improve their manuscript.

1. Did the patient receive anti-embolic measures such as stockings and prophylactic dose low molecular weight heparin in the peri-operative period? This would be an important standard of care.

A: Thanks for the important question. The patient did not receive prophylactic LMWH treatment before surgery because of the concern for bleeding. Researchers suggested that the benefits and potential risks of the use of LMWH before spine surgeries. As you mentioned, the benefit of anti-embolic measures includes the decreased incidence of thrombosis and thromboembolic complications. However, the application of LMWH may increase the incidence of incision bleeding and spinal epidural hematoma [1]. In the case we present here, the patient did not have a history of venous thromboembolism (VTE) or a high-risk factor for VTE. According to the research by Keeling et.al., patients with (1) VTE within the previous 3 months or of very high risk, (2) previous stroke/TIA in the last 3 months, or (3) mechanical heart valve might consider bridging with heparin treatment before surgery [2]. Although the patient did not receive preoperative LMWH, she did receive intermittent pneumatic compression (IPC) on her lower extremity to prevent thrombosis before surgery.

[1] **Zeng XJ**, Peng H. Prevention of Thromboembolic Complications After Spine Surgery by the Use of Low-Molecular-Weight Heparin. *World Neurosurg.* 2017;104:856-862.

[PMID: 28529056 DOI: 10.1016/j.wneu.2017.05.050]

[2] **Keeling D**, Tait RC, Watson H; British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. *Br J Haematol.* 2016;175(4):602-613. [PMID: 27714755 DOI: 10.1111/bjh.14344]

**2. Mention is made of 'elevation of markers of myocardial infarction'. Which ones? If this was troponin then this is known to be elevated in large PE, such that it is a prognostic marker. It would be useful to be specific and show the levels. The severity of the embolism could also be described using a clinical score (eg PESI).**

A: Sorry for the ambiguity in the terms of 'elevation of markers of myocardial infarction'. Several markers for myocardial infarction including creatine kinase (CK, 219 U/L), lactate dehydrogenase (LDH, 293 U/L), and myoglobin (MYO, 78.4 ug/L) elevated 2 hours after the drop of oxygen saturation. However, the level of troponin I (aTnI) remained a relatively low level (0.01 ug/L).

Thanks for the suggestion, we have included PESI and sPESI scoring system in the case presentation section to help evaluating the severity of pulmonary embolism.

3. If the mechanism of embolism is obstruction by cement itself, how does LMWH work to treat the event? Is there secondary thrombus around the cement? This would be helpful to clarify for the reader, especially as it might determine length of treatment with anticoagulation after the event.

A: Thanks for the thought-provoking question. From our perspective, LMWH may prevent the formation of secondary thrombus, which is softer and of greater mobility than cement emboli. Computed tomography did not reflect secondary emboli around the cement 5 days after the symptom appears. Therefore, we thought LMWH treatment successfully prevented the emergence of further embolism.

4. The patient was also treated for infection - I can imagine that cement might be an inflammatory stimulus, and that this could cause similar features to infection - is this a known problem? Is there any possibility of this being the mechanism rather than a post operative hospital acquired pneumonia? What measures to prevent HAP were taken?

(eg chest physio, nursing sitting up where possible)

A: Thanks for the question regarding our treatment procedure. Combining the factor that the patient presented with the symptom of fever, elevated WBC and diffuse exudation in the both lungs, we considered the possibility that the patient might have developed hospital acquired pneumonia and started antibiotic treatment. Before levofloxacin treatment, sputum culture was conducted but the result was negative. Therefore, it is relatively difficult to determine in which mechanism that leads to the symptoms of pneumonia. Previous cases of bone cement embolism have also reported pneumonia-like symptoms, which have improved with antibiotic treatment [1]. However, it remains unclear whether cement emboli exert an inflammatory stimulus and caused the symptoms of pneumonia. More evidence is needed to determine the role of antibiotic therapy in treating cement embolism.

In the case we presented here, the patient was nursed sitting up regularly and was atomized to clear airway secretions twice daily.

[1] **Chang CH**, Keng LT, Ko JC. Cementing an unwanted relationship. *Thorax*. 2017;72(8):766. [PMID: 27852957 DOI: 10.1136/thoraxjnl-2016-209475]

5. In the discussion the risk factors for cement embolisation are listed - which of these were present in the patient whose case is described? What preventative measures might be taken in a high risk patient requiring CAPSI? Would IVC filter be relevant? Presumably this would prevent embolisation of fragments to the lung.

A: Thanks for the question regarding risk factors for cement embolism. In the case we presented here, the patient did not have the risk factors mentioned above. However, the patient was diagnosed with osteoporosis, which might also be considered as a risk factor for CAPSI.

IVC filter might be the only viable measures to prevent cement embolism as you mentioned. Several surgeons have applicated IVC filter as a viable measure to prevent cement embolism in high-risk patients [1]. However, IVC filter insertion requires extra mini-invasive surgery. Considering cement embolism is a very rare complication

following CAPSI, we did not implant IVC filter as a routine procedure to prevent cement embolism. Due to the limited reported cases of cement embolism, there is no evidence that other preventive measures can reduce the incidence of cement embolism.

[1] **Edwards C 2nd**, Blight A, Kim K, Edwards C Sr. Polymethylmethacrylate Entrapped in Inferior Vena Cava Filter After a Scheuermann Kyphosis Revision Surgery. *Spine Deform.* 2015;3(6):604-607. [PMID: 27927563 DOI: 10.1016/j.jspd.2015.03.004]