Author’s response to reviews

Title: A lung cancer patient with deep vein thrombosis: A case report and literature review

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Author’s response to reviews:

Dedong Cao, M.D. (Reviewer 1):

This case report presents a lung cancer patient with deep vein thrombosis. Though several treatments were used, the surgery of left thigh amputation was performed eventually.

Comment: Did they perform biopsy after the surgery? What is the main components of the thrombosis? Is it a tumor plug?

Response: Thank you for your comment. Yes, a biopsy of the thrombosis was done after the surgery, confirming that it was a blood clot rather than a tumor plug. Grossly, the thrombus was in the shape of the vessel, dark and red. Microscopically, aggregated RBCs and platelets could be seen. Besides, given the characteristics of hematogenous metastasis, it might be unlikely for a tumor plug to present within the femoral vein, which drains blood from the lower extremity, in the setting of primary lung cancer.

Case presentation section, line 16, page 6:

Venous duplex ultrasonography indicated deep vein thrombosis (DVT) of left femoral vein by detecting noncompressibility of the thrombosed vein with reduced blood flow. Compression of left femoral artery caused by thrombosed vein was also noticed (Figure 3).

Case presentation section, line 13, page 7:
“…The post-surgery biopsy indicated the thrombosis was a blood clot. …”

Markus Knott (Reviewer 2):

Thank you for letting me review this interesting case and literature review.

Your literature review is quite good. Nevertheless I agree with you that there is a need of a detailed guideline concerning cancer patients and prophylaxis /therapy of Thrombosis.

Upon reading the case, some major questions arised:

Comment 1: Why did you choose ASS + Warfarin + LMWH triple combination? What was the reasonable behind this selection apart from guidelines?

Response 1: Thank you for the comment. ACCP recommends the use of heparin and Vitamin K antagonists (VKA) as the initial anticoagulation of acute DVT of the leg. Studies have demonstrated that a combination of heparin in addition to VKA is superior to VKA therapy alone. Also, in patients with a high clinical suspicion of acute VTE, the use of parenteral anticoagulants is suggested while awaiting the results of diagnostic tests. Aspirin was used for its anti-platelet effect.

Discussion section, line 5, page 11:

Aspirin, warfarin and LMWH were used as the initial treatment in this case. ACCP recommends the use of heparin and vitamin K antagonist to treat patients with a high suspicion of acute DVT while waiting for the results of diagnostic tests. Aspirin was used empirically as an anti-platelet agent.

Comment 2: As there is a worsening described after four days, did you rule out a HIT? This could, in worst case, explain the thrombogenesis despite every effort. What did you do with the Anticoagulation? Continued or stopped?

Response 2: Thank you for your comment. To the best of our knowledge, for HIT to be diagnosed, one with proven thrombosis must present with a significant fall in platelet 5-10 days after the commencement of heparin treatment. In this case, however, the patient didn’t show a significant fall in platelet, making the diagnosis of HIT less likely. Still, we became aware that HIT should be included in the differentials.

Discussion section, line 21, page 10:
Differential diagnosis includes heparin-induced thrombocytopenia (HIT), Antiphospholipid Syndrome and warfarin necrosis. For HIT to be diagnosed, patients with proven thrombosis must present with a significant fall in platelet 5-10 days after the commencement of heparin treatment[19]. In this case, however, the patient didn’t show a significant fall in platelet, making the diagnosis of HIT less likely.

Comment 3: I was missing descriptive coagulation lab values. You stated that coagulation was in normal range. Which parameters did you evaluate at the beginning? Prothrombin time, INR, aPTT, Protein C / S? Specialized coagulation lab? Was there any sign of change during the worsening of the Thrombosis?

Response 3: Thank you for your comment. Coagulation lab values have been added into the manuscript. D-dimers, TT, PT, fibrinogen, APTT and INR were evaluated at the first time. Among them, D-dimers, PT, APTT and INR were abnormally high. These values were progressively lowering after the amputation surgery, but D-dimers, PT and INR were still higher than the upper limit of normal.

Case presentation section, line 10, page 6:

8 days after the initiation of chemotherapy, the right hip pain was alleviated. 2 days later, the patient described he felt distending pain in the left lower limb. Coagulation lab tests were as follows.

Table 2. Coagulation lab results of the patient

<table>
<thead>
<tr>
<th>Description</th>
<th>Result</th>
<th>Unit</th>
<th>Ref int</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimers</td>
<td>27.53↑</td>
<td>ug/ml</td>
<td>0.0-0.5</td>
</tr>
<tr>
<td>TT</td>
<td>15.2</td>
<td>s</td>
<td>10.3-16.6</td>
</tr>
<tr>
<td>PT</td>
<td>14.2↑</td>
<td>s</td>
<td>9.8-12.8</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2.92</td>
<td>g/l</td>
<td>2.00-4.00</td>
</tr>
<tr>
<td>APTT</td>
<td>32.9</td>
<td>s</td>
<td>25.1-36.5</td>
</tr>
<tr>
<td>INR</td>
<td>1.17↑</td>
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TT: thrombin time; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio, Ref int: reference interval.
Comment 4: I was missing the medical history of the patient. Apart from smoking and no tuberculosis, unfortunately nothing is said about it. Did the patient have any history of thrombosis in the past? Other underlying diseases?

Response 4: Thank you for the comment. We added more information into the past history section. The patient’s past history was otherwise unremarkable and there was no history of thrombotic events.

Case presentation section, line 5, page 5:

Past history revealed the patient had a smoking history for 30 pack years but was otherwise unremarkable. The patient denied any history of tuberculosis infection or thrombotic events. The level of tumor markers is shown in Table 1.

Comment 5: No further pictures of the venous Thrombus obstructing the Artery is shown. Was the artery obstructed other than compression? Where there other diagnostics apart the CT-Angio?

Response 5: Thank you for the comment. The venous duplex ultrasonography (figure 3) demonstrated that there was no blood flow in the left femoral vein, and the left femoral artery was compressed. We modified the figure and its legend by adding two arrows pointing to the anomalies.

Case presentation section, figure 3, line 2, page 7:

Figure 3. Venous duplex ultrasonography indicated absence of blood flow in the thrombosed left femoral vein (solid arrow) and compression of the left femoral artery (dashed arrow). The diameter of the vein examined was still considerably broad when compressed.

Comment 6: Did you rule out an extensive Antiphospholipid Syndrome?

Response 6: Thank you for the comment. Extensive Antiphospholipid Syndrome is a hypercoagulable state caused by autoantibodies, the diagnosis of which requires the detection of autoantibodies. There might be a possibility that Antiphospholipid Syndrome was an etiology of the DVT event in our case. Unfortunately, this case was from several years ago, and the corresponding physician didn’t order a lab test on Antiphospholipid Syndrome according to the collected clinical data. Further, the patient had denied any history of VTE event, stroke or other autoimmune diseases before, making it less likely for Antiphospholipid Syndrome to be a cause, given that the VTE event was chronologically after an underlying malignancy. Still, Antiphospholipid Syndrome is a condition worth our attention when treating cancer patients with VTE events. We appreciate you for raising this point to us.
Discussion section, line 25, page 10:

……The diagnosis of Antiphospholipid Syndrome, an autoimmune disease, requires the detection of autoantibodies. Although lab tests concerning this disease were not ordered by corresponding physicians, a lack of any history of thrombotic events or autoimmune defects makes Antiphospholipid Syndrome a less likely etiology……

Comment 7: Did you rule out Warfarin necrosis?

Response 7: Thank you for your comment. Warfarin necrosis is caused by the vitamin K-antagonist effect of warfarin. It not only inhibits Factor II, VII, IX, X, but also decreases protein C, an anticoagulant. The larger the dose is, the more the imbalance of the inhibition becomes, resulting a hypercoagulable state. However, concomitantly administrated heparin or LMWH can prevent warfarin necrosis because they take a different mechanism. In this case, LMWH was administrated with warfarin, lowering the possibility of warfarin necrosis to occur. Still, warfarin necrosis is worth our attention when treating patients with VTE events, as the narrow therapeutic window needs physicians’ close eyes on the state of patients.

Discussion section, line 29, page 10:

……The risk of warfarin necrosis is normally reduced by concomitantly administrated heparin, because heparin takes a different mechanism than warfarin.

I would additional do a literature research if anywhere is a description of a DVT Thrombus compressing an artery.

Shailesh Advani, MD, PhD (Reviewer 3):

Comment 1: Introduction: Lines 10-13 provide references; Provide in detail: literature on smoking and VTE. It remains inconclusive from this introduction; Need English Edits throughout

Response 1: Thank you for your comment. We added a reference for line 10-13 to support the relationships between VTE and smoking.

Reference section:

We also consulted a native English speaker specializing in language editing to improve the English language.

Background section, line 10, page 3:

Lung cancer remains the leading cause of cancer-related mortality globally, with tobacco intake as the main known risk factor. More than 85% of……

Background section, line 15, page 3:

……Despite a known correlation between VTE and lung cancer, a comprehensive guideline of the prophylaxis and treatment for patients with lung cancer who develop VTE is still needed due to the limited number of studies conducted on the matter.

Background section, line 21, page 3:

Additionally, we reviewed and discussed current guidelines for cancer patients with VTE to find ways that might improve prognostic outcomes.

Case presentation section, line 26, page 3:

A 53-year-old male was hospitalised because of pain in the right hip that was ongoing for 3 months. On physical examination, positive signs included the enlargement of his right supraclavicular lymph node of 0.5cm * 0.5cm, and overt tenderness in his right groin with no mass palpated. The patient had a symmetric chest and breathing sounds of both lungs were clear on auscultation and no rales or crackles were heard. The abdomen was soft without any tenderness of rebound pain, bowel sounds were normal, and there was no redness or swelling found in any limbs.

Case presentation section, line 2, page 8:

……Thus, amputation of the left thigh was eventually performed.

Conclusion section, line 18, page 11:

Cancer patients, especially those whose cancer originates in the lung, are……

Comment 2: Case Presentation: Give more details about pathological and clinical characteristics of this lung cancer patient, if possible
Response 2: Thank you for your comment. We have added more pathological and clinical information into the manuscript.

Case presentation section, line 5, page 5:

Past history revealed the patient had a smoking history for 30 pack years but was otherwise unremarkable. The patient denied any history of tuberculosis infection or thrombotic events. The level of tumor markers is shown in Table 1.

Case presentation section, Line 13, page 6:

8 days after the initiation of chemotherapy, the right hip pain was described to be alleviated by the patient. 2 days later, the patient described he felt distending pain in the left lower limb. Coagulation lab tests were as follows.

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Line 18 page 6:

Venous duplex ultrasonography indicated deep vein thrombosis (DVT) of left femoral vein by detecting noncompressibility of the thrombosed vein with reduced blood flow. Compression of left femoral artery caused by thrombosed vein was also noticed (Figure 3).

Comment 3: Discussion: Give details about why treatment did not work in this patient.
Response 3: Thank you for the comment. We added more details discussing potential factors that cause treatment failure.

Discussion section, line 16, page 10:

Some factors might reduce the effect of treatment. The lung cancer in this patient was in the late phase, spreading throughout both lungs. Failure to notice the thrombotic event early caused delayed treatment. Additionally, the patient also had many risk factors predisposing VTE, like smoking, bed rest and high coagulability caused by the malignancy. All these factors might explain why treatment did not work.