



SIMULTANEOUS PULMONARY EMBOLISM WITH CARDIAC TAMPONADE AND REPETITIVE ISCHEMIC STROKE AS VASCULAR COMPLICATIONS OF LUNG CANCER: A CASE REPORT AND SYSTEMATIC LITERATURE REVIEW

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SUMMARY – It is known that patients with lung cancer have a considerably higher incidence of cardiovascular complications that lead to venous or arterial events, and malignant pericardial effusion can often be observed due to pericardial metastases. Simultaneous occurrence of cardiac tamponade and venous thromboembolism almost always happens in patients with lung malignancy. Our case report describes a patient with concurrent pulmonary embolism and cardiac tamponade as the initial manifestation of lung cancer, which, apart from pericardiocentesis and symptomatic therapy, was treated at long term with a direct oral anticoagulant (apixaban). Therapy was well tolerated by the patient and there were no bleeding complications related to primary disease and anticoagulant treatment. The course of the disease was complicated by repetitive strokes, which were treated with mechanical thrombectomy. Because of this scenario, a systematic review of the literature was conducted, listing all available case reports of patients with the simultaneous occurrence of cardiac tamponade and pulmonary embolism. In all patients, the underlying condition was lung malignancy, often as the first manifestation of the disease. This is a relatively rare event, and the approach to long-term treatment varied from case to case in the absence of valid guidelines. Our case demonstrated that, in the light of new studies and guidelines, apixaban represented a safe and effective treatment option even in patients at a high risk of bleeding.

Key words: *Lung cancer; Cardiac tamponade; Pulmonary embolism; Direct oral anticoagulant; Apixaban*

Introduction

Simultaneous occurrence of pulmonary embolism and cardiac tamponade is exceptionally rare and poses a significant diagnostic and therapeutic challenge. Both conditions are life-threatening emergencies that can present with overlapping clinical features. Prompt recognition and appropriate management are crucial to improve patient outcomes.

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Case Report

A 73-year-old female patient was admitted to our hospital with a three-day history of progressive dyspnea. The patient was tachypneic and hypotensive. Initial evaluation revealed tachycardia, low peripheral oxygen saturation (SpO₂ 89%), and mildly dilated jugular veins. Electrocardiography displayed sinus tachycardia with an 'electrical alternans' pattern (Panel A1/ black box) and prominent low voltage QRS complexes (Fig. 1A, black arrows). Imaging studies revealed bilateral segmental pulmonary embolism (Fig. 1B, red arrows), and an extensive pericardial effusion with echocardiographic signs of tamponade (Fig. 1B, blue arrows). Hemodynamic stability was obtained with emergency pericardiocentesis. After pericardial drain extraction, low molecular weight heparin (LMWH, dalteparin in a dose of 100 IU/kg, twice daily) was introduced and switched to apixaban (5 mg, twice daily) after seven days, in addition to corticosteroids

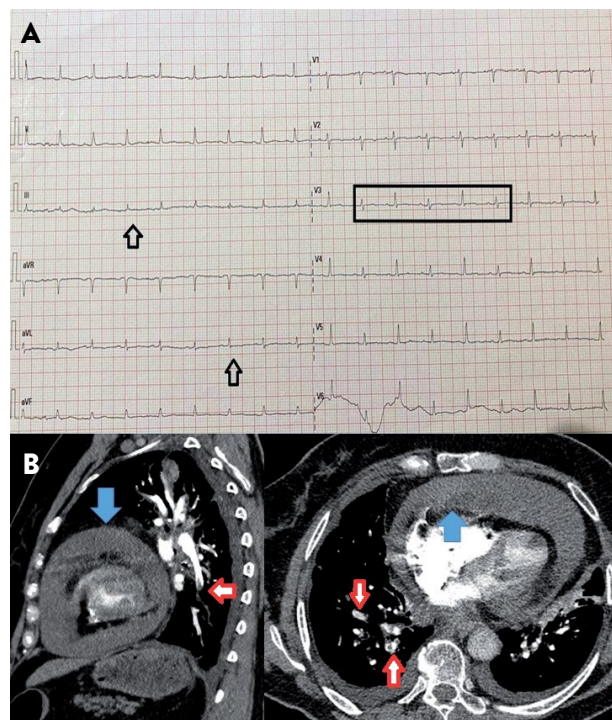


Fig. 1. (A) Electrocardiogram showing 'electrical alternans' pattern; (B) computed tomography scan showing pericardial effusion (blue arrows) and pulmonary embolism (red arrows).

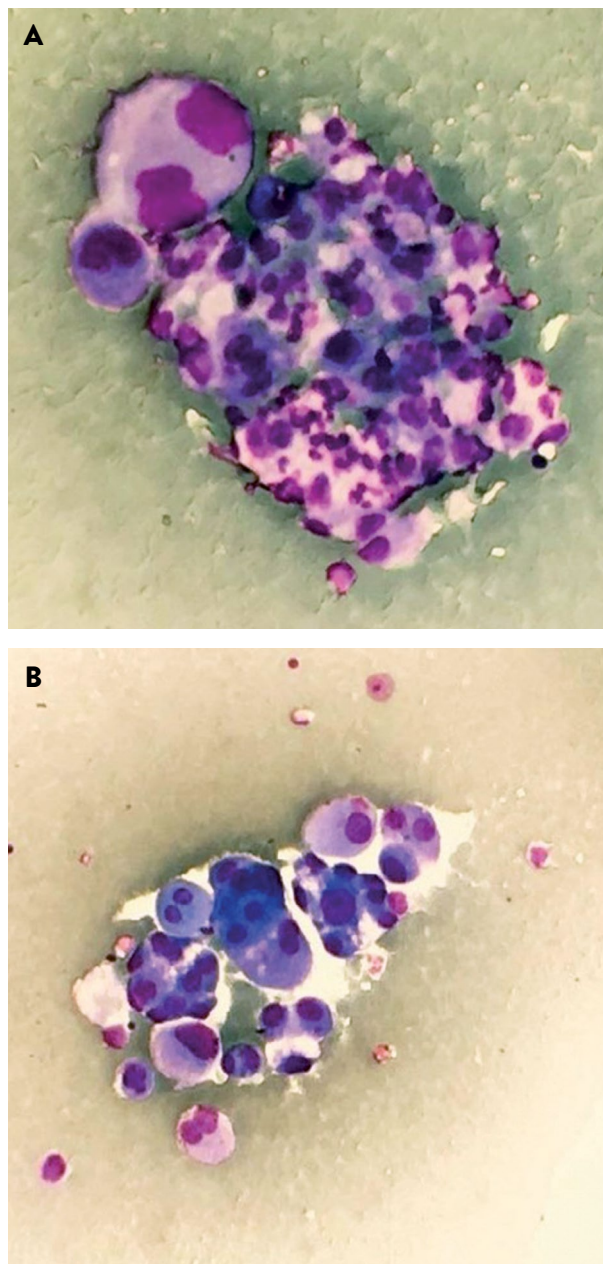


Fig. 2. Cytologic finding of cells isolated from pericardial fluid.

(methylprednisolone 32 mg once daily with a subsequent 'step-down' approach) and colchicine (0.5 mg twice daily). There were no signs of deep vein thrombosis on duplex ultrasound. Cytologic analysis of pericardial fluid confirmed metastatic adenocarcinoma cells (Fig. 2), but no primary site of malignancy was found

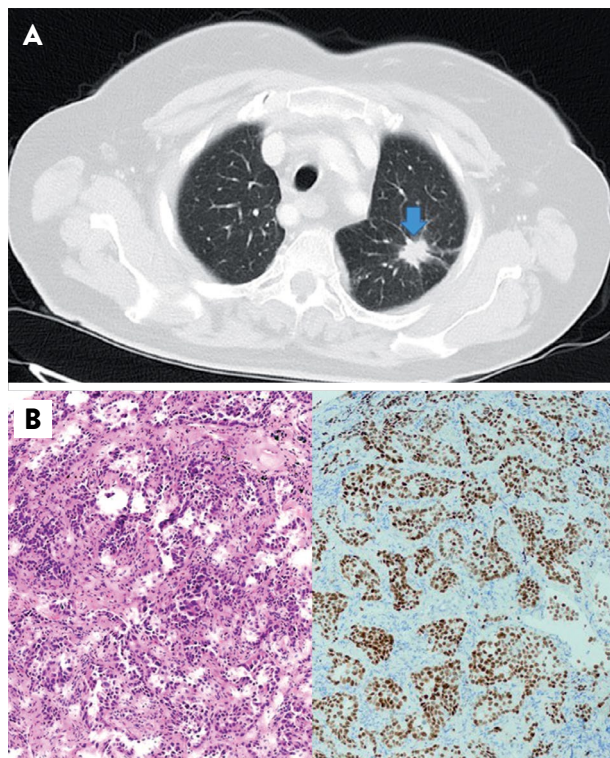


Fig. 3. (A) Computed tomography scan showing lung cancer (blue arrow); (B) histopathologic analysis of a lung biopsy specimen.

on imaging. The patient underwent chemotherapy with paclitaxel and carboplatin, which was well tolerated. Subsequent echocardiography showed no recurrence of pericardial effusion. However, a 3-month follow-up computed tomography (CT) scan revealed a 'star-like' pulmonary lesion (Fig. 3A, blue arrow), and CT-guided biopsy confirmed primary pulmonary cancer (Fig. 3B). Two weeks later, the patient experienced an ischemic stroke with minor neurological disability, and magnetic resonance imaging demonstrated multiple supra- and infratentorial leptomeningeal metastases without bleeding complications. No carotid stenosis was found on carotid Doppler ultrasound. Monitoring of heart rhythm and Holter electrocardiography (ECG) did not record any supraventricular arrhythmias, including atrial fibrillation. Despite ongoing apixaban therapy, another ischemic stroke occurred within the next month, with acute occlusion of the left anterior cerebral artery (Fig. 4A, arrows) that was treated successfully with mechanical thrombectomy (Fig.

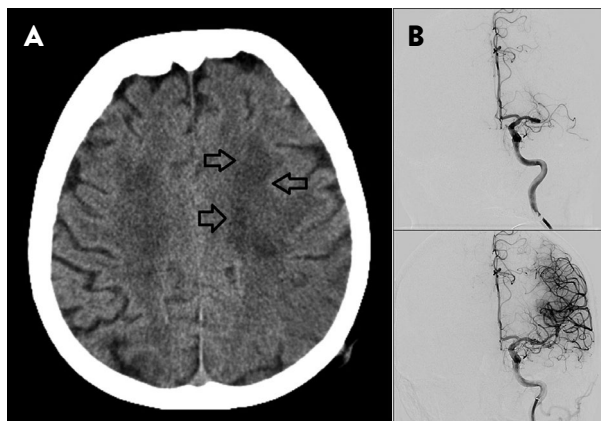


Fig. 4. (A) Computed tomography scan showing acute ischemic stroke; (B) angiography with occlusion of the left anterior cerebral artery and finding after mechanical thrombectomy.

4B) followed by dual antiplatelet therapy (acetylsalicylic acid and clopidogrel). Due to the patient's poor general condition and the non-significant impact on further treatment modalities and course, transesophageal echocardiography to exclude right-to-left shunt was not performed. Despite appropriate management, the patient eventually succumbed to the disease during the next month.

Ethical issues

The data used in this case study were reviewed by the Ethics Committee of the Sestre milosrdnice University Hospital Center, Zagreb. Since the patient deceased and the family or legal representatives were unavailable, the case was reviewed by the Legal Department of the Sestre milosrdnice University Hospital Center at the meeting held on January 23, 2024, based on whose decision the use of anonymized patient data in this case study was approved (available on reasonable request).

Discussion

The prevalence of lung cancer is on a rise worldwide. Evidence for the association between lung cancer and arterial complications, including ischemic stroke and coronary disease, is increasing¹. In lung cancer patients, cerebrovascular disease is recognized as the second most common complication in the central nervous

system, significantly impacting patient outcomes. According to available data so far, lung cancer patients have a significantly higher risk of developing cerebrovascular events, both ischemic and hemorrhagic. The pathophysiological basis of these complications is likely multifactorial, with the most commonly mentioned factors being coagulopathy caused by the tumor itself, atherosclerosis, and cardioembolism². Prevention of these events is still a subject of debate, considering the simultaneous occurrence of both pro-coagulant and pro-hemorrhagic states in lung cancer patients, and clear guidelines are not yet available.

On the other hand, due to their hypercoagulability, patients with malignancy are at a greater risk of developing venous thromboembolism, occurring in almost 15% of patients with cancer³. Concomitant pericardial effusion with tamponade and pulmonary embolism are found almost exclusively in patients with cancer and pose a diagnostic and therapeutic dilemma. Malignancy represents a high-bleeding risk state *per se*, and anticoagulation and thrombolysis should be avoided in hemorrhagic pericardial effusion⁴. Also, pericardiocentesis is relatively contraindicated in a state of (iatrogenic) coagulopathy. On the other hand, venous

thromboembolism, if left untreated, carries a high mortality risk. Our case shows the management of a patient with a simultaneous existence of high bleeding and a high pro-thrombotic state which goes beyond guidelines and daily clinical practice.

In order to consolidate and compare the experiences published so far, we performed a literature search of the PubMed and Scopus databases for articles published up to December 2022 with case reports of patients with simultaneous, non-traumatic pulmonary embolism and tamponade in malignancy. The following key words were used: „cardiac tamponade“, „pericardial effusion“, „pulmonary embolism“, „venous thromboembolism“, „malignancy“, and „cancer“. No language restrictions were applied, and reference lists of all included case reports were manually searched for other potential eligible studies. Nine cases were found (one paper was excluded from our review because tamponade and pulmonary embolism did not occur simultaneously but several months apart) and are shown in Table 1⁵⁻¹³.

In the nine patients included in our review, the median age at the diagnosis was 51 (range 25-63) years and 2/9 (22%) were males. Eight out of nine patients

Table 1. Baseline data and clinical characteristics

Ref. No.	Case report	Age (yrs)	Sex	Comorbidity	Primary tumor – organ	Primary tumor – histology	Metastases/pericardial metastases	IVC filter placement
5	Jairath <i>et al.</i>	64	F	Diverticulitis/irritable bowel syndrome	Unknown	Non-small cell carcinoma	Yes/yes	Yes
6	Wijesinghe <i>et al.</i>	25	F	Unknown	Lung	Adenocarcinoma	Yes/yes	Unknown
7	Nguyen Ba <i>et al.</i>	36	M	Dyslipidemia	Lung	Sarcomatous carcinoma	Yes/yes	No
8	Barski <i>et al.</i>	53	F	Hypertension/smoking	Lung	Adenocarcinoma	Yes/yes	No
9	Thomas <i>et al.</i>	50	F	Psoriasis/GERD	Lung (suspected)	Adenocarcinoma of UPO	Yes/yes	Yes
10	Akhbour <i>et al.</i>	63	F	None	Lung	Adenocarcinoma	Yes/yes	No
11	Kandasamy	40	F	None	Lung	Adenocarcinoma	Yes/yes	No
12	Huang <i>et al.</i>	48	F	None	Lung	Adenocarcinoma	Yes/yes	No
13	Pazooki and Sherafati	50	M	Smoking	Lung	Adenocarcinoma	Yes/yes	No

IVC = inferior vena cava; GERD = gastroesophageal reflux disease; UPO = unknown primary origin

Table 2. Anticoagulant treatment and outcome data

Ref. No.	Anticoagulation during hospital stay	Anticoagulation – initiation date	Anticoagulation agent	Outcome of acute treatment	Anticoagulation therapy after discharge	Recurrent pericardial bleeding
5	No	/	/	Acute abdomen, stroke, death	/	No
6	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
7	Unknown	Unknown	Unknown	Discharge	Unknown	No
8	No	/	/	Discharged, chemotherapy started	No	No
9	Yes	Postpericardiocentesis day 4	UHF	Renal and liver failure, recovery, discharge	Yes (warfarin)	Yes, after discharge
10	Yes	Unknown	Unknown	Discharge, referred to oncology	Yes (drug unknown)	No
11	Yes	Unknown	Unknown	Discharge, chemotherapy started	Yes (drug unknown)	No
12	Yes	Day 1	UFH	ECMO, death on day 3	/	No
13	Yes	Day 1	UFH	Discharge	Yes (enoxaparin)	No

UFH = unfractionated heparin; ECMO = extracorporeal membrane oxygenation

had a lung cancer diagnosed during hospital stay and one patient had metastatic cells found in the pericardial fluid, but no primary tumor was localized during imaging diagnostics. All patients had documented metastatic involvement of the pericardium. It is known that pericardial metastases are more common than primary cardiac tumors (2.3%–18.3% and 0.001%–0.28%, respectively) and significantly contribute to mortality^{14,15}. Our findings support the results shown in an autopsy review where pericardial metastases were mostly attributed to lung carcinoma (19%–40%), breast carcinoma (10%–28%) and hematologic malignancies (9%–28%), and rarely to gynecologic malignancy^{16,17}.

All patients had a diagnosed cardiac tamponade and pulmonary embolism before initiation of any anticoagulant therapy, and no previous thromboembolic events were reported. All patients were treated with pericardiocentesis, and five of them started with anticoagulation treatment during hospital stay, mostly with continuous infusion of unfractionated heparin. None of them had recurrence of pericardial fluid accumulation during hospital stay. Our patient was treated successfully with LMWH (dalteparin) throughout

the 7-day hospital stay. Either unfractionated or low molecular heparin seems a reasonable option for acute treatment of those patients, due to availability of specific antidote which can be used in case of emergency and hemodynamic deterioration. However, there are available data on the superiority of low molecular heparin *versus* unfractionated heparin in the context of efficacy and safety, as well as a lower risk of heparin-induced thrombocytopenia¹⁸. As a questionable alternative to anticoagulation, two patients were treated with inferior vena cava filter placement soon after pericardiocentesis.

Four out of six successfully discharged patients received long term anticoagulant with warfarin or enoxaparin. One patient treated with warfarin had re-accumulation of pericardial fluid requiring pericardiocentesis. It has been shown that LMWH lowers the risk of recurrent venous thromboembolism by 40% with a major bleeding risk comparable to vitamin K antagonist (warfarin)¹⁹. However, there are arising evidence on safety and efficacy of direct oral anticoagulants, considering that oral administration is more convenient than daily subcutaneous injections.

In the SELECT-D trial, rivaroxaban showed similar efficacy but with more bleeding events (mostly gastrointestinal) in comparison to dalteparin²⁰. The Caravaggio trial demonstrated that apixaban was as effective as LMWH without an increased risk of major bleeding^{21,22}. According to the mentioned data, the NICE (2020) and CHEST (2021) guidelines mark rivaroxaban and apixaban as the first-line therapy over LMWH for cancer-associated thrombosis²³⁻²⁵. We presented the first case of a patient with malignancy and simultaneous tamponade and pulmonary embolism treated with direct oral anticoagulant at long term, without hemorrhagic complication during follow up.

Conclusion

Vascular complications, either arterial or venous, represent a significant challenge in patients with lung cancer and have a substantial impact on their outcomes. It is crucial to accurately diagnose and appropriately treat them, but even then, the results are often not as successful as in patients without malignancies. New therapeutic options should certainly be thoroughly investigated in this vulnerable patient group. It is essential for treatment strategy and monitoring of such patients to be collaborative and multidisciplinary in nature.

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Sažetak

PLUĆNA EMBOLIJA I TAMPONADA SRCA TE PONAVLJAJUĆI ISHEMIJSKI
MOŽDANI UDARI KAO VASKULARNE KOMPLIKACIJE KARCINOMA
PLUĆA: PRIKAZ SLUČAJA I SUSTAVNI PREGLED LITERATURE*N. Kos i M. Vrsalović*

Poznato je kako bolesnici koji boluju od karcinomom pluća imaju značajno veći rizik od kardiovaskularnih komplikacija, uključujući venske i arterijske tromboembolijske događaje. Perikardijalni izljev nastaje kao posljedica zahvaćanja perikarda metastazama i česta je pojava u takvih bolesnika. Istodobna prisutnost tamponade srca i venske tromboembolije dosad je opisana gotovo isključivo u bolesnika koji boluju od maligne bolesti pluća. U ovom slučaju prikazujemo bolesnicu u koje su plućna embolija i tamponada srca bile prva klinička manifestacija karcinoma pluća. Uz perikardiocentezu i simptomatsku terapiju bolesnica je liječena direktnim oralnim antikoagulansom (apiksaban). Terapiju je bolesnica dobro podnijela i nisu zabilježene krvareće komplikacije povezane s osnovnom bolešću niti s antikoagulantnim liječenjem. Tijek bolesti bio je kompliciran ponavljanim ishemijskim moždanim udarima koji su uspješno liječeni mehaničkom trombektomijom. Zbog rijetkosti ovakve kliničke prezentacije provedena je sustavna analiza literature, kojom su obuhvaćeni svi dostupni prikazi slučajeva s istodobnom pojavom tamponade srca i plućne embolije. U svim opisanim slučajevima osnovna bolest bila je karcinom pluća. Ovaj rijedak klinički slučaj pokazuje da unatoč izostanku smjernica za produženo protuzgrušavajuće liječenje bolesnika s venskom tromboembolijom u podlozi zloćudne bolesti s visokim rizikom krvarenja direktni oralni antikoagulans (apiksaban) može biti sigurna i učinkovita terapijska opcija.

Ključne riječi: Karcinom pluća; Tamponada srca; Plućna embolija; Direktni oralni antikoagulans; Apiksaban