

# An unusual case of non-small-cell lung cancer presenting as spontaneous cardiac tamponade

Sarah Joseph, MD, MSc,<sup>a</sup> Hassan Al-Khalisy, MD,<sup>a</sup> Umair Randhawa, MD,<sup>a</sup> John Lazar, MD,<sup>b</sup> and Kathryn Peroutka, MD<sup>c</sup>

Departments of <sup>a</sup>Internal Medicine, <sup>b</sup>Cardiovascular and Thoracic Surgery, and <sup>c</sup>Internal Medicine, Division of Hematology and Oncology, PinnacleHealth Network, Harrisburg, Pennsylvania

**H**emorrhagic pericardial effusion with associated cardiac tamponade as a *de novo* sign of malignancy is seen in about 2% of patients.<sup>1</sup> Consequently, cardiac tamponade is an oncologic emergency and considered a unique presentation of a malignancy.<sup>2</sup> Cancer emergency is defined as an acute condition that is caused directly by the cancer itself or its treatment and requires intervention to avoid death or significant morbidity.<sup>3</sup> The mechanism by which cardiac tamponade is classified as a life-threatening emergency stems from its impairment of right ventricular filling, resulting in ventricular diastolic collapse and decreased cardiac output, which can ultimately lead to death.<sup>4</sup>

We describe the case of a previously healthy woman in her late 40s who was a nonsmoker with no previous risk factors and who presented with a large pericardial effusion and bilateral pulmonary emboli. She was diagnosed with metastatic epidermal growth factor receptor-positive (EGFR-positive) adenocarcinoma of the lung. This case highlights an oncologic emergency as a *de novo* presentation of malignancy.

## Case presentation and summary

A 48-year-old white woman presented to the emergency department with a 2-week history of progressive shortness of breath at rest and exertion, associated with dry cough, night sweats, and mild myalgias. Her medical history was significant for superficial vein thrombosis involving the right greater saphenous vein 4 months before she presented. She was a nonsmoker, with no history of previous smoking or environmental exposure, but her family his-

tory was pertinent for lung cancer in her maternal grandparents.

Her physical examination was positive for sinus tachycardia. Her neck veins were also distended to her jaw at 60 degrees. No lower extremity swelling was noted. The results of an initial electrocardiogram (ECG) were consistent with electrical alternans (Figure 1). They also showed significant collapse of the right ventricle occurring in systole and diastole with swinging motion of the entire heart within the pericardial sac, which was indicative of impending tamponade (Figure 2). A computed-tomography (CT) scan of the chest revealed bilateral pulmonary emboli, bilateral pleural effusions, and a large pericardial effusion (Figure 3). The patient underwent percutaneous pericardiocentesis with drain placement by interventional cardiology and placement of an inferior vena cava filter. At the same time, she also underwent right thoracentesis.

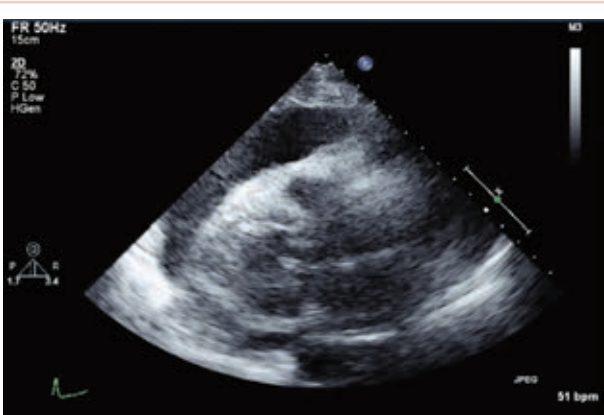
The pericardial fluid was hemorrhagic, and the final immunohistochemistry results demonstrated primary adenocarcinoma of the lung. Immunohistochemistry was positive for thyroid transcription factor 1, the Ber-EP4 antibody, and cytokeratin 7. Cell-block histochemistry from the pleural and pericardial fluids were supportive for adenocarcinoma. While we were waiting for these results, the pericardial drain was pulled on day 3 after placement and a repeat echocardiogram on day 5 showed recurrence of the effusion. We consulted with our thoracic surgery colleagues, and the patient underwent video-assisted thoracic surgery with partial pericardectomy, right middle lobe wedge resection for additional tissue, chest wall biopsies, mechan-

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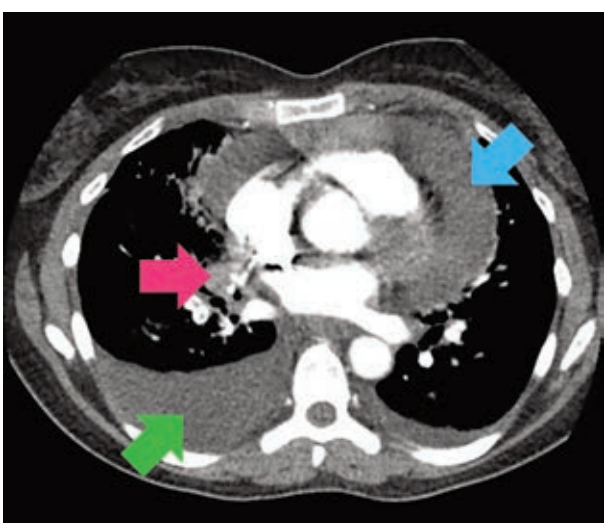
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**FIGURE 1** Electrocardiogram displaying electrical alternans, a characteristic of cardiac tamponade.



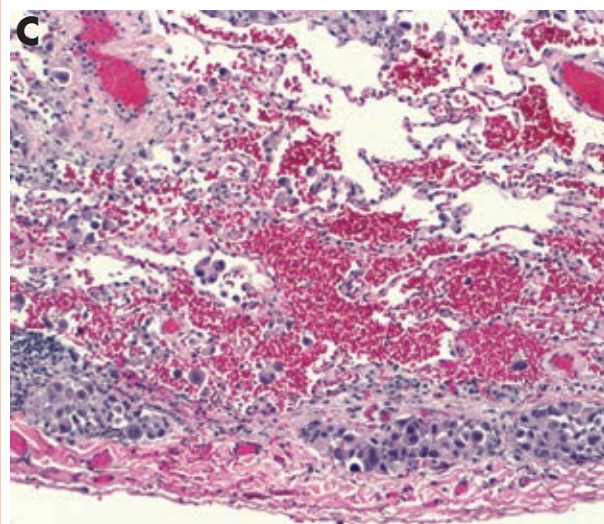
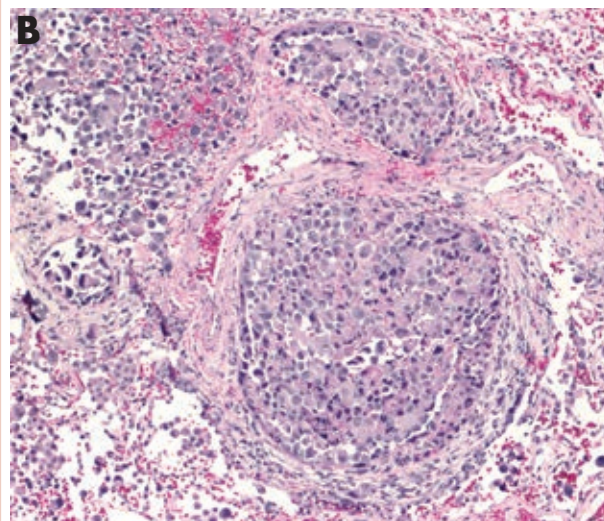
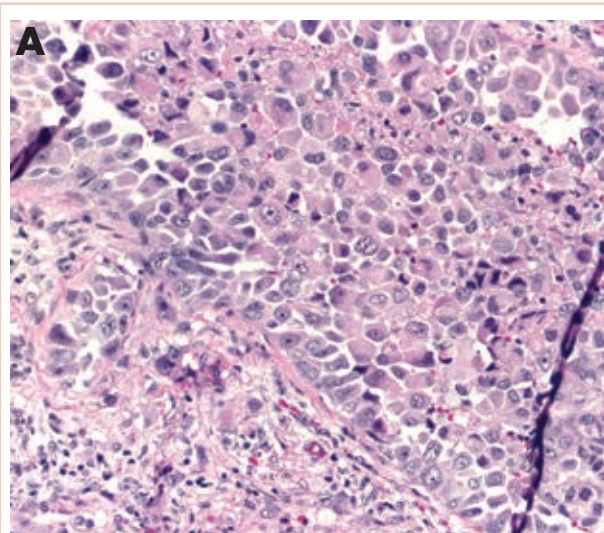
**FIGURE 2** Echocardiogram demonstrating features characteristic of cardiac tamponade.



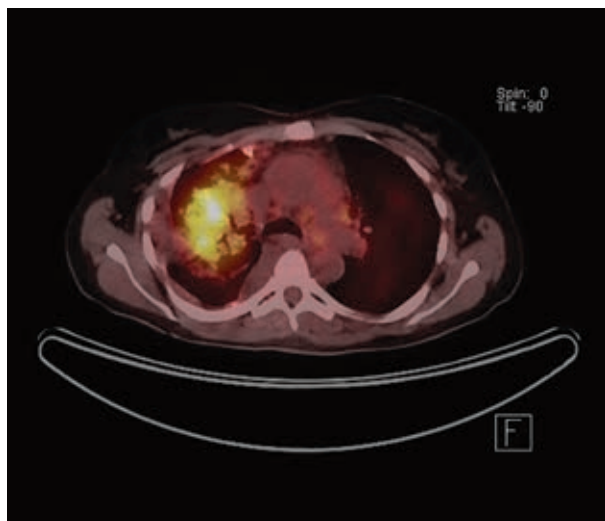
**FIGURE 3** Computed-tomography scan of chest showing cardiac tamponade (blue arrow), pulmonary emboli (pink arrow), and pleural effusion (green arrow).

ical and talc pleurodesis, and placement of a tunneled Aspira catheter. In addition, a biopsy of the right middle lobe was positive for poorly differentiated adenocarcinoma with lymphovascular invasion (Figure 4). Additional testing came back positive for EGFR mutation for L858R substitution mutation on exon 21.

The patient was discharged on day 5 after the procedure. Her Eastern Clinical Oncology Group (ECOG) Performance Status score was 0 (fully active), and she was



**FIGURE 4** Tissue biopsy (100x, H&E stain) demonstrating A, poorly differentiated adenocarcinoma; B, tumor invasion of blood vessels; and C, pleural lymphatic invasion with tumor.



**FIGURE 5** Positron-emission tomography scan highlighting right lung mass.

started on warfarin, titrated to maintain an INR between 2-3 for her bilateral pulmonary emboli.

As an outpatient, she underwent a positron-emission tomography scan for staging purposes. It revealed widespread metastatic disease (Figure 5). In the left upper lobe, innumerable hepatic metastatic lesions, mediastinal adenopathy, left thoracic inlet adenopathy, and bony metastases to the ribs. In addition, a large pericardial effusion was noted. She had a third echocardiogram at that time, which confirmed a large pericardial effusion with early tamponade, which was manifested by transmitral respiratory variation and mild diastolic compromise in the right ventricular free wall. There was also development of a new upper extremity deep-vein thrombosis even though she was on warfarin therapy.

The patient was re-admitted to the hospital and underwent a procedure to create a subxiphoid pericardial window. During this hospital stay, she was started on enoxaparin anticoagulant therapy at 1mg/kg every 12 hours. She was discharged home on day 7 after the procedure, again with an ECOG score of 0, and started on the tyrosine kinase inhibitor erlotinib at 150 mg by mouth daily given the EGFR-positive nature of her adenocarcinoma.

## Discussion

Lung cancer is the leading cause of cancer-related deaths in the United States. In 2015, it was estimated that 221,200 new cases of lung and bronchial cancers would be diagnosed and about 105,590 people would die from lung cancer.<sup>5</sup> About 80% of new lung cancer diagnoses are classified as non-small-cell lung cancer (NSCLC), with more than two-thirds of those cases presenting with advanced disease at the time of diagnosis.<sup>6</sup> In patients with NSCLC, the

most common sites of distant metastasis are bone and the brain, liver, and adrenal glands.<sup>7</sup> Cardiac metastasis is rare, but when it does occur, it is most prevalent in advanced cancers. Li and colleagues have reported that malignant pericardial effusion is found 2.7% of all cancer cases, with an estimated one-third originating from the lungs.<sup>8</sup> It has been estimated the 1-year survival for NSCLC complicated by malignant pericardial effusion is 18.3%, with a median survival of 5 months.<sup>9</sup>

Our patient had an isolated episode of superficial vein thrombosis (SVT) months before her diagnosis of cancer. There is conflicting evidence as to whether she should have been screened for malignancy. Van Doormaal and colleagues investigated the incidence of newly diagnosed malignancies during a 2-year period following an episode of SVT and concluded that a single episode of unprovoked SVT was not associated with an increased risk of malignancy.<sup>10</sup> However, Sørensen and colleagues found an increased risk of cancer diagnosis in patients who had been diagnosed with SVT, particularly within the first year after the SVT diagnosis.<sup>11</sup>

Another question raised by our case was whether we should have anticoagulated her for her bilateral pulmonary embolism, SVTs, and DVTs in light of her hemorrhagic pericardial effusion. In the case of recurrent hemorrhagic pericardial effusion causing tamponade, the safety of anticoagulation is questionable. Yet an acute pulmonary embolism carries significant mortality if left untreated. Thomas and colleagues demonstrated a similar situation in which they first established the stability of the pericardial effusion by echocardiogram, then proceeded with successful anticoagulation treatment of the pulmonary embolisms with heparin, then subsequent warfarin.<sup>12</sup> Initially, our patient was started on warfarin titrated to maintain INR between 2-3, then re-presented with a large pericardial effusion and was started on therapeutic dose of 1mg/kg every 12 hours of enoxaparin due to the progression of her clots.

The National Comprehensive Cancer Network guidelines recommend the use of weight-based unfractionated heparin, low-molecular weight heparin (LMWH), or fondaparinux for at least 5-7 days for treatment of venous thromboembolism (VTE) in cancer patients.<sup>15</sup> At that point, long-term therapy is considered. LMWH use in cancer patients with VTE has been shown to have superior outcomes warfarin, and it is recommended as monotherapy for the first 6 months of long-term treatment as well as for prevention of recurrent VTEs.<sup>15</sup> The 2014 American Society of Clinical Oncology guidelines also recommend LMWH for the first 5-10 days of therapy, followed by long-term anticoagulation for 6 months.<sup>16</sup> Yet patient preference, cost and therapeutic monitoring are also considered; many patients do not like injections with LMWH, however the drawbacks of weekly INR checks with warfarin also influence patient decision. Chronic

treatment of VTE with LMWH has not been evaluated for longer than 6 months in a clinical trial, so continuing with current therapy or changing to warfarin is left to the discretion of the clinician and patient.<sup>15</sup> Warfarin use as a long-term therapy can be problematic for the cancer patient because of the potential difficulties achieving a targeted international normalized ratio of 2-3 given drug-drug interactions with chemotherapeutic agents, malnutrition, and liver dysfunction.<sup>17</sup> In the end, our patient was switched to enoxaparin therapy as there was progression of clots on warfarin.

To our knowledge, there are no guidelines for the optimal management of malignant pericardial effusion that arises from NSCLC. For many years, the surgical pericardial window has been used as an effective means to drain fluid from the heart and prevent its re-accumulation. There have been studies investigating the use of sclerosing or cytotoxic agents to treat effusions, but none have established survival benefit.<sup>8</sup> Moriya and colleagues evaluated the use of intrapericardial administration of carboplatin for controlling malignant pericardial effusion and had promising outcomes that showed reduced rates of re-accumulation of fluid in the pericardium.<sup>13</sup> In the modern molecular era that targets specific mutations, our patient's EGFR mutation allowed for the use of targeted therapy. In the Li case series, 2 patients were found to have benefited from

erlotinib therapy. Both patients were alive at the time of the manuscript submission, 15 and 17 months from treatment respectively.<sup>8</sup>

Another study, the EURTAC (European Tarceva versus Chemotherapy) trial, was an open label phase 3 study which randomized patients diagnosed with NSCLC to receive tarceva or 2 standard chemotherapeutic agents as first-line treatment. The medical progression-free survival was found to be longer in the tarceva arm, 10.4 months compared with 5.2 months in the chemotherapy arm.<sup>14</sup> Based on this trial, the traditional method of treatment with pericardiocentesis followed by intrapericardial chemotherapy agents or sclerosing agents has a dismal survival benefit when compared with emerging therapies. There is hope that molecular targeting agents, such as tarceva in the EURTAC trial will continue to drastically improve survival rates and change treatment guidelines.

## Conclusion

Our case highlights how a malignancy can initially present as a pericardial effusion. As we discovered with our patient, it can be an oncological emergency that requires emergency intervention. In patients with NSCLC, the most commonly found EGFR mutations, as in the case of our patient, were within exon 19 which responds to erlotinib. To date, the patient has been doing well.

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