CASE REPORT

Pulmonary embolism with haemorrhagic pericardial effusion and tamponade: a clinical dilemma

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SUMMARY

The synchronous presentation of a patient with pulmonary embolism (PE) and haemorrhagic cardiac tamponade is uncommon and presents a therapeutic dilemma. Both conditions can be life-threatening and require opposing management strategies. The authors report a 50-year-old woman who presented with abdominal symptoms and subsequent rapid development of dyspnoea and cardiogenic shock. Investigations demonstrated bilateral segmental PEs and a large pericardial effusion causing cardiac tamponade. This large blood-stained effusion was drained urgently. She developed acute kidney injury and acute hepatic injury with synthetic failure. She was initially deemed unsuitable for anticoagulation so an inferior vena cava filter was placed to minimise risk of further PE. When no early re-accumulation of pericardial fluid occurred, a heparin infusion was started to treat the PEs. Pericardial fluid cytology was suggestive of metastatic carcinoma, with the immunophenotype most consistent with metastatic non-small cell lung cancer. She was subsequently treated with the tyrosine kinase inhibitor, erlotinib.

BACKGROUND

This case characterises a rare presentation of metastatic adenocarcinoma with simultaneous haemorrhagic pericardial effusion and pulmonary embolism (PE).

PE, though a common condition, is rare diagnosis without an underlying risk factor for development. In a review of over 1200 patients treated for venous thromboembolism (VTE), over 96% had one or more risk factors.¹ Underlying or occult malignancy alone is an important risk factor, in some studies increasing risk of VTE more than fourfold.²

Acute PE carries a high mortality of up to 30% if left untreated.³ This risk is significantly reduced by prompt initiation of anticoagulant therapy.⁴ It is therefore crucial that anticoagulation is initiated as soon as possible when the diagnosis of PE is made. Indeed treatment may be started empirically when the clinical suspicion of acute PE is sufficiently high.⁵

Anticoagulation should be avoided in acute haemorrhagic pericardial effusion. The development of pericardial effusion is a reasonably common consequence of malignancy, the recognition of which is crucial to facilitate treatment and avoidance of potentially fatal tamponade. Cardiac tamponade is an absolute indication for urgent pericardiocentesis,⁶ though uncorrected coagulopathy is a relative contraindication.

This case highlights a difficult clinical dilemma with regard to the anticoagulation of a patient at high risk for bleeding, yet with multiple segmental PEs where immediate anticoagulation would be conventional practice. The management is further complicated by acute hepatic failure and subsequently raised conventional markers of oagulability (prothrombin time (PT) and international normalised ratio (INR)).

CASE PRESENTATION

A 50-year-old woman was referred to the emergency department by her general practitioner with symptoms of epigastric pain, vomiting and two episodes of diarrhoea. Physical examination revealed generalised abdominal tenderness. She was investigated with a plain film abdominal radiograph, which demonstrated no abnormalities, a chest radiograph which demonstrated no air under the diaphragm but a hilar prominence and a set of routine blood tests which demonstrated deranged liver function: bilirubin 20 µmol/L, alanine aminotransferase (ALT) 95 IU/L and alkaline phosphatase (ALP) 133 IU/L. She received intravenous fluid resuscitation and was discharged home with a medical outpatient clinic appointment booked for the following day to investigate the mildly abnormal liver tests.

She returned to the emergency department the following day with further episodes of vomiting overnight and feeling generally more unwell. On direct questioning she disclosed a history of shortness of breath of recent onset and dry cough and weight loss of 3 kg over the previous month which she attributed to effective dieting. There was no history of fever or night sweats.

Prior to this episode she reported good general health, with a limited exercise tolerance which she ascribed to being unfit. Medical history included gastro-oesophageal reflux disease and psoriasis. She was an ex-smoker with a 30 pack-year history and rarely consumed alcohol. Her regular medication was lansoprazole and ferrous gluconate. She gave a strong family history of cancer: both her mother and sister died from breast cancer in their 40s. Consequently, she underwent regular breast screening, with the most recent mammogram 6 months previously being clear.

The initial working diagnosis was of biliary tree sepsis with acute hepatic failure and she was started on intravenous antibiotics and intravenous crystalloid rehydration. She became acutely unwell overnight, developing oligoanuric acute kidney injury (urine output <25 mL/h) despite fluid resuscitation

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with 2.5 L crystalloid. Repeat liver function tests demonstrated the development of acute hepatic failure with synthetic dysfunction (INR 1.6). She subsequently became acutely dyspnoeic. On examination, she was tachypnoeic (respiratory rate 40/min) despite her chest being clear on clinical examination and maintaining good oxygen saturations (100% on 2 L/min oxygen via nasal cannulae). She was markedly tachycardic (heart rate 130/min) and was peripherally shut down (capillary refill time >3 s), though maintained a blood pressure of 108/67 mm Hg, with diminished pulse volume on inspiration (pulsus paradoxus). The jugular venous pressure was noted to be elevated. The abdomen was mildly distended with epigastric tenderness on deep palpation.

INVESTIGATIONS

An arterial blood gas (taken on 2 L/min supplemental oxygen) demonstrated a partially compensated severe lactic acidosis with no evidence of hypoxia; pH 7.19, pO_2 12.3, pCO_2 2.11, lactate 12.6, base excess -21.1.

The ECG showed sinus tachycardia, and a portable plain film chest radiograph revealed a large cardiac silhouette, despite its anteroposterior projection (figure 1).

Urgent CT of the thorax demonstrated bilateral segmental pulmonary emboli and a large pericardial effusion (figure 2). Immediate transthoracic ECHO confirmed massive pericardial effusion with diastolic collapse of the right ventricular wall, signifying tamponade. She was transferred to the cardiac catheterisation laboratory for immediate pericardiocentesis. In total, 900 mL of heavily blood stained fluid was drained with immediate symptomatic improvement.

Pericardial fluid was sent for biochemistry, microscopy and culture and cytology (figure 3). Ultrasound Doppler of the lower limbs was suspicious for deep vein thrombosis (DVT) but inconclusive.

Full basic haematological and biochemical screens were repeated post-pericardiocentesis. Liver tests demonstrated an acutely elevated: bilirubin 58 $\mu\text{mol/L}$, ALT 3726 IU/L, ALP 132 IU/L, albumin 33 g/L and clotting tests showed: INR 5.5, activated partial thromboplastin time ratio (APTT_r) 1.32 (0.85–1.15), thrombin time 24 s (11–16), consistent with acute hepatic failure.

Figure 1 Plain film chest radiograph (anteroposterior projection) demonstrating enlarged cardiac silhouette.

Figure 2 CT pulmonary angiogram demonstrating a large pericardial effusion (white arrow) and bilateral segmental pulmonary emboli. There is thrombus in the right upper lobe pulmonary artery and segmental branches of the lower lobe artery. There is thrombus in the left upper and lower lobe pulmonary arteries.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a unified cause of PE and a haemorrhagic pericardial effusion in the presence of acute liver and

Figure 3 Pericardial fluid cytology with immunostaining. (A) May-Grünwald-Giemsa stain highlights the presence of a perinuclear vacuole (arrow). (B) Ber-EP4 immunoperoxidase stain confirms the epithelial nature of the cells (this indicates metastatic carcinoma rather than reactive mesothelial cells).

renal impairment include Behçet's disease, systemic lupus erythematosus (SLE) and malignancy of uncertain origin. Further investigations therefore included a blood film, thrombophilia screen and a full autoimmune screen.

Clinically she had no history of malaise, rash, joint pain consistent with either SLE or an associated antiphospholipid syndrome. Nor did she have evidence of haematuria or of haematological features of lupus such as lymphopaenia or anaemia. However, the feature of serositis (pericarditis) together with PE could fit the diagnosis of SLE.

This patient was Caucasian, making the diagnosis of Behçet's disease less likely. There was no history of uveitis, arthralgia or neurological involvement, nor were there mucocutaneous lesions. However, this diagnosis could also explain her gastrointestinal symptoms and serositis.

TREATMENT

The patient's multiorgan failure was supported in intensive care. After placement of the pericardial drain the patient's cardiovascular status improved. However, she still developed anuric kidney injury and an acute hepatic injury with deranged synthetic function. Activated partial thromboplastin time (APTT) mixing studies demonstrated correction of laboratory coagulation abnormalities.

Owing to her significantly raised INR she received fresh frozen plasma prior to insertion of central venous catheters for haemodynamic monitoring and renal replacement therapy. She was given vitamin K 10 mg intravenous once a day for 3 days, with a subsequent correction and maintenance of clotting tests within the normal range.

The risk of further PE was deemed high, but the risk of further life-threatening pericardial haemorrhagic tamponade, particularly in the light of the hepatic synthetic dysfunction, was also judged to be high. An inferior vena cava (IVC) filter was therefore fitted on the second day postdecompensation.

She required continuous haemofiltration on the intensive care unit for anuric acute kidney injury (without anticoagulation of the circuit), and subsequently underwent four sessions of intermittent haemodialysis on the renal unit.

The pericardial drain was removed 24 h after insertion, once drain output was minimal. Interval transthoracic echocardiography was performed 24 and 72 hs after drain removal and demonstrated no recurrence of the pericardial effusion. As liver tests including PT were normalising, the benefits of systemic anticoagulation for prevention of further embolic events were now judged to outweigh the risks of pericardial tamponade. Therefore 4 days after her acute decompensation and pericardial drainage, unfractionated heparin infusion was administered systemically to maintain an APTT of 2–3. After five further days with lack of clinical evidence of bleeding, the heparin infusion was converted to twice daily unfractionated heparin injections of 10 000 units until recovery of renal function.

OUTCOME AND FOLLOW-UP

The patient's autoimmune screen demonstrated antinuclear antigen to be weakly positive with a negative double-stranded DNA antibody, negative anti-neutrophil cytoplasmic antibody (ANCA) and a negative autoimmune liver screen.

Immunohistochemical analysis of the pericardial fluid revealed metastatic carcinoma. There was diffuse strong tumour cell positivity for cytokeratin 7 and throid transcription factor-1, favouring either thyroid malignancy or non-small cell carcinoma of the lung. An ultrasound study of the thyroid demonstrated an avascular nodule with no malignant features, thought to be a

colloid nodule. Cross-sectional imaging was repeated, showing central mediastinal lymphadenopathy. No definite lung lesions were seen, nor liver or bony lesions. She was diagnosed with a metastatic adenocarcinoma with an uncertain primary site (epidermal growth factor receptor (EGFR) mutation positive), though lung was thought to be the most likely diagnosis given her smoking history, central mediastinal lymphadenopathy and spread to affect the pericardium and pleura. Given her EGFR positivity she was started on the tyrosine kinase inhibitor erlotinib (Tarceva) which she tolerated well.

The patient's hepatic function returned to baseline after 7 days. After discharge from the intensive care setting where she received continuous haemofiltration she received four sessions of intermittent haemodialysis. Within 2 weeks of her initial decompensation her renal function improved considerably, producing good volumes of urine, with urea and creatinine returning to their premorbid levels and potassium levels remaining stable.

Fourteen days after pericardiocentesis, interval echocardiography demonstrated reaccumulation of pericardial fluid. She underwent a repeat fluoroscopic pericardiocentesis, with a further 560 mL fluid aspirated. The drain was removed after 24 h. Further interval echocardiography 1 week later showed only minimal residual pericardial effusion with mild pericardial thickening. The patient had no further clinical symptoms of PE.

DISCUSSION

Initial resuscitation in both tamponade and PE has in common the need to support the patient's cardiovascular and respiratory systems, especially in the presence of hepatic failure and kidney injury. However, in this case of concurrent haemorrhagic pericardial effusion producing tamponade, early anticoagulation, the preferred strategy for management of acute PE could not safely be initiated. A non-permanent IVC filter was placed given the initial contraindication to anticoagulation and to prevent recurrence of PE from a DVT. However, British Thoracic Society guidelines do not specifically recommend placement of an IVC filter for the management of suspected PE, indeed filter placement does not seem to affect mortality from PE.⁷

This patient developed acute hepatic failure with synthetic malfunction at the time of decompensation from cardiac tamponade; the aetiology of this was thought to be ischaemic. Importantly though PT and INR values were raised, unlike in raised PT/INR from overanticoagulation with warfarin, this may not put the patient at a great risk of a clinical bleeding episode. Indeed Agarwal *et al*⁸ demonstrate how raised PT/INR levels in patients with acute liver failure do not correlate with thromboelastography parameters. This may be due to reduced synthesis of both procoagulant and anticoagulant proteins (protein C, protein S and antithrombin III) in acute liver failure. This study suggested that coagulation defects in acute liver failure disorders are heterogeneous in nature and may not be predicted from laboratory values such as PT alone.⁸ In this way it is not possible to initiate anticoagulation therapy for PE based on a particular cut-off value for PT or INR.

There are very few similar published cases. Han *et al*⁹ describe a recent case of simultaneous haemorrhagic pericardial effusion and PE presenting in a gentleman 1 month post-traumatic spinal cord injury. Han *et al*'s case differs by aetiology, being traumatic in nature and also because tamponade did not develop. After demonstration of stability of the pericardial effusion by echocardiography, intravenous heparin therapy was successfully initiated for treatment of the PEs, as in our case. Intravenous heparin was then substituted for warfarin therapy

after demonstration of a period of stability with therapeutic heparin administration.

Learning points

- ▶ The symptoms and clinical signs of cardiac tamponade may be non-specific. Other organ failures such as congestive liver and renal impairment may be present secondary to cardiac failure, further complicating diagnosis. One must be highly suspicious in a patient presenting with breathlessness and an enlarged cardiac silhouette on chest radiography.
- ▶ The risks and benefits of anticoagulation must be carefully weighed and continually revisited in cases of concurrent bleeding and clotting tendencies, remembering that laboratory values may not represent clotting tendencies in vivo.
- ▶ Management of such complex patients requires good communication between multiple specialist teams (haematology, cardiology, oncology and respiratory); for a patient in multiorgan failure, this may be best orchestrated in an intensive care unit setting.

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