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CASE REPORT
Heart failure

Acute pulmonary tumour embolism and right systolic dysfunction in a hidden intrahepatic cholangiocarcinoma: case report

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Background Pulmonary tumour embolism is a rare entity that can arise from a wide variety of neoplasms. It can initially manifest as a pulmonary embolism with right heart failure and be refractory to thrombolytic therapy. Cholangiocarcinoma is a rare malignancy that arises from the epithelium of the biliary tree, representing 3% of all the gastrointestinal malignancies, being the intrahepatic cholangiocarcinoma the second most common liver tumour after hepatocellular carcinoma.

Case summary This case regards a patient that presented to our centre with acute pulmonary embolism, deep vein thrombosis, and unrevealing previous medical history. Imaging studies revealed pulmonary embolism, an ovarian mass, and multiple hepatic hypodensities. Throughout the hospitalization, the patient's haemodynamic state and right heart failure worsened, eventually leading to multi-organ failure and death. Post-mortem evaluation revealed cholangiocarcinoma cells on the pulmonary arteries.

Discussion Pulmonary tumour embolism is a rare pathology that can present with acute right heart failure. The diagnosis of occult cancer can be challenging, and the appropriate treatment for this entity remains an unexplored subject.

Keywords Cholangiocarcinoma • Right heart failure • Pulmonary tumour embolism • Case report

ESC Curriculum 2.2 Echocardiography • 2.4 Cardiac computed tomography • 6.4 Acute heart failure • 6.7 Right heart dysfunction • 6.9 Cardiac dysfunction in oncology patients

Learning points

- Pulmonary tumour embolism is a rare entity that can develop pulmonary hypertension and right heart failure.
- Prompt diagnosis of occult cancer can be challenging, and the appropriate treatment for pulmonary tumour embolism remains an unexplored area.

Introduction

Pulmonary tumour embolism (PTE) is a very rare entity. It refers to a group of cells that embolize from a tumour and lodge in the pulmonary circulation, resembling a conventional pulmonary thromboembolism. Patients usually present with acute dyspnoea and tachycardia, and eventual complications such as right heart failure and pulmonary hypertension can occur.[1] Pulmonary tumour embolism must be distinguished

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from pulmonary tumour thrombotic microangiopathy (PTTM), which is a histopathologically different diagnosis. Pulmonary tumour thrombotic microangiopathy occurs secondary to the activation of the coagulation cascade inside the pulmonary circulation, and therefore, a cardinal finding is the elevation of D-dimer.[2]

Pulmonary tumour embolism is commonly diagnosed in autopsies; many patients can be asymptomatic, and a minor number can debut with clinical signs of pulmonary embolism (PE) and right heart failure. The literature reports the major incidence in patients with hepatic, renal, breast, gastric, or gallbladder adenocarcinomas.[3]

Roberts *et al.*[4] described the resistance to recanalization of the PTE with the conventional treatment of PE. Therefore, PTE can lead to progressive and irreversible obstruction of the vascular bed that will be refractory to medical treatment. The appearance of tumour-induced vasoreactivity and persistence of pulmonary artery hypertension after treatment have been hypothesized but remain an incompletely explored area.

Cholangiocarcinoma is a rare malignancy that arises from the epithelium of the biliary tree. It has been associated with chronic liver disease such as cirrhosis, viral hepatitis, primary sclerosing cholangitis, and choledochal cysts. It is more frequently diagnosed incidentally, although some patients might present dull right upper quadrant pain, fullness, weight loss, jaundice, tea-coloured urine, clay-coloured stools, and pruritus, as well as elevated liver function tests and alkaline phosphatase.[5]

Summary figure

Date	Event
October 2019	Unilateral left leg edema
December 7, 2019	Small effort dyspnea
December 15, 2019	Hospital admission, Angiotomography revealed bilateral pulmonary thromboembolism and deep vein thrombosis of the lower extremities. Clinical signs of right heart failure, thrombolysis and anticoagulation treatment were established.
December 18, 2019	Septic shock established, vasopressive and antibiotic therapy were initiated.
December 30, 2019	Imaging findings showed ovarian mass with hepatic metastasis. Persistent thromboembolism with hemodynamic deterioration.
January 4, 2020	Acute kidney injury KDIGO 3 that required hemodialysis treatment.
January 9, 2020	Multiple organ failure refractory to vasopressors, culminating in her death.

Case presentation

A 60-year-old female presented to our centre with acute-onset dyspnoea and palpitations. Pulse oximetry revealed an SaO_2 of 66%, the heart rate was 145 beats per minute, and respiratory rate of 40 respirations per minute. Past medical history revealed unilateral left lower leg oedema, erythema and pain that was noted 4 weeks ago, and New York Heart Association functional class deterioration from grade 1 to grade 3 within a week.

The SaO_2 improved to 88% with supplementary O^2, and the diagnostic assessment was directed towards pulmonary thromboembolism. The computed tomography (CT) pulmonary angiogram revealed acute pulmonary thromboembolism in the lobar branches of the pulmonary arteries (*Figure 1*), deep vein thrombosis of the left lower extremity, and a 10 cm pelvic tumour (*Figure 2*), in the left adnexal region with multicystic appearance and septations.

The patient had signs of right ventricular failure with jugular venous distention, positive hepatojugular reflux, N-terminal prohormone of brain natriuretic peptide of >25 000 pg/mL, troponin I of 186.8 pg/mL, and lactate of 4.3 mmol/L, suggesting hypoperfusion. Thrombolysis with alteplase was performed due to the clinical signs of right ventricular failure, and the patient was intubated due to respiratory insufficiency. The echocardiogram showed a dilated right ventricle, with systolic dysfunction and a severely dilated right atrium, generalized right ventricular hypokinesia, and significant tricuspid regurgitation (*Figure 3*).

The patient presented persistent hypotension, fever, and clinical signs of septic shock. Empiric antibiotics were started, and the blood cultures later revealed *Pseudomonas aeruginosa* infection. Despite fluid infusion and vasopressor therapy, the patient continued to deteriorate; our main suspicion was a concomitant persistent cardiogenic shock due to right ventricular failure.

Because of the adnexal tumour detected on the CT, an oncologic assessment was ordered. Imaging studies including an abdominal ultrasound and computed tomography revealed multiple hepatic lesions suggestive of metastases (*Figure 2*).

In the following days of hospitalization, the patient had a torpid evolution despite haemodynamic and respiratory support measures, eventually developing multi-organ failure and death. Autopsy findings showed an intrahepatic cholangiocarcinoma with vascular dissemination and PTE that resulted in pulmonary infarction and right ventricular failure (*Figures 4* and *5*; see Supplementary material online, *Figure S1*).

Discussion

Cancer is considered an important risk factor for PE, as several characteristics of the disease put patients in a hypercoagulable state and are therefore prone to thromboembolic events.[6] Sun *et al.*[7] found a relative risk of 2 for pulmonary thromboembolism in patients with lung, hepatic, colorectal, or haematopoietic cancers. The hypercoagulable state developed in cancer patients has been attributed to a number of variables such as tissue factor, cancer procoagulant, and increased platelet activity and turnover, as well as the abnormalities of the three components of Virchow's triad frequently seen in patients with cancer. Cancer cells can directly produce tissue factor and cancer procoagulant, which as a consequence activate the coagulation cascade and lead to the formation of thrombi.[6]

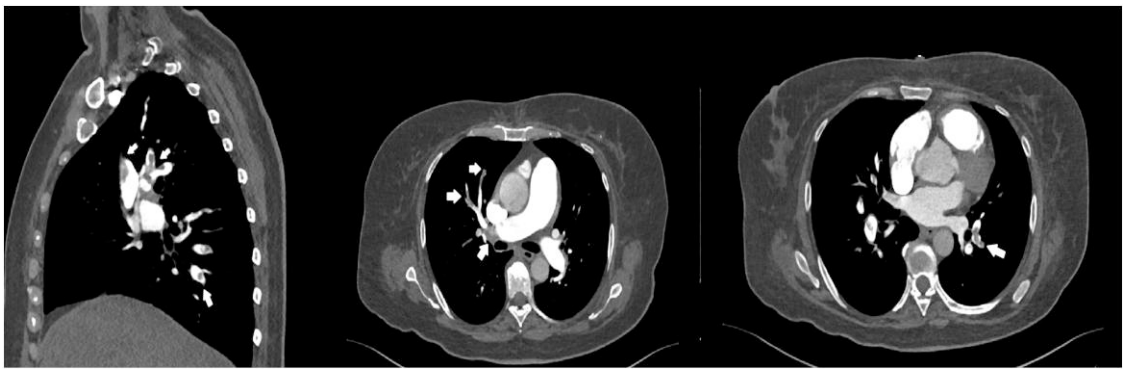

Figure 1 Angiotomography. Arrows show bilateral pulmonary embolisms in the lobar branches of the pulmonary arteries.

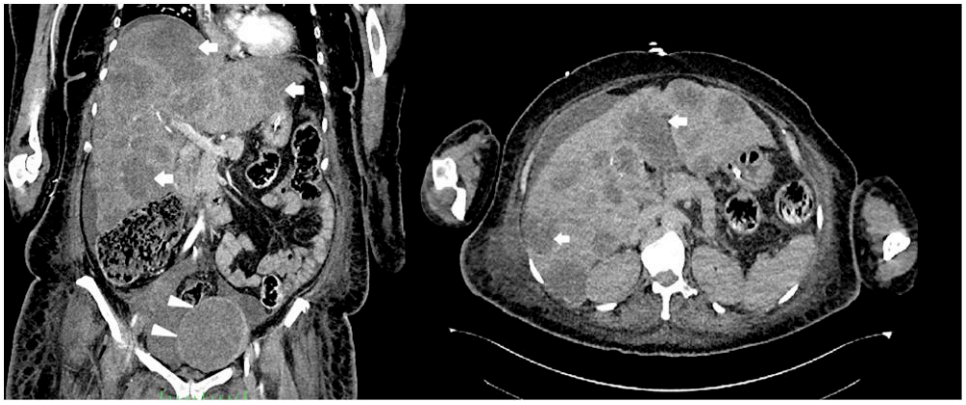

Figure 2 Abdominal computed tomography. Arrows show multiple hypodensities in the hepatic parenchyma suggestive of metastasis. A 10 cm heterogeneous mass was identified in the left adnexal region (arrowheads).

Since patients with cancer present a hypercoagulable state, a PE should be suspected in a patient with the suggestive clinical signs. Apart from the aforementioned, less frequent diagnoses should be kept in mind if the patient does not respond to the appropriate pharmacological therapy. Pulmonary tumour embolism is an infrequent cause of right heart failure and cardiogenic shock in cancer patients. The metastatic cells carry the potential to mechanically obstruct the pulmonary capillaries and transform into a PTTM. Our patient had a D-dimer of 3136 μg/mL. Even if the patient had deep vein thrombosis (DVT), it raises the question of whether the metastatic cholangiocarcinoma cells could have activated the coagulation cascade in the pulmonary vessels and could have played a part in the cardiogenic shock as a result of the rapidly evolving right heart failure.

When our patient arrived at the emergency department, our first diagnostic impression was a pulmonary thromboembolism. The imaging studies confirmed the diagnosis and even showed a DVT of the left lower leg. The patient received treatment with alteplase; nevertheless, the haemodynamic deterioration continued and the cardiogenic shock did not resolve with this measure. At the moment, the clinical picture presented an incredible complexity with multiple differential diagnosis, including the patient developing concomitant septic shock that was treated accordingly; the further scarcity in medical history or previous clinical signs hampered the diagnosis. The post-mortem evaluation revealed a metastatic embolus that resulted in right heart failure and ultimately provoked the death of the patient. In hindsight, a percutaneous interventional approach with mechanical thrombectomy of the pulmonary arteries could have improved the patient's clinical course, and therefore, the main intention of this case report is to highlight the importance of differential diagnosis when the appropriate therapeutics are implemented and the patient does not improve.

The standard care for PTE has not been defined yet; nevertheless, some authors mention that the treatment should target the primary malignancy. Petnak *et al.*[8] relate the increased levels of vascular endothelial growth factor, platelet-derived growth factor (PDGF), and osteopontin in patients with PTE due to prostate cancer. Therefore, a theoretical therapeutic with tyrosine kinase inhibitor for PDGF receptors was proposed. Furthermore, we can only speculate if a prompt diagnosis and early starting of the specific pharmacotherapy could have changed the clinical course of our patient.

Our patient had imaging findings suggesting a primary ovarian tumour with hepatic metastases and DVT. Epithelial adenocarcinoma of the ovary is the most common cause of gynecological cancer death, and many patients are asymptomatic for a period of time. The hypercoagulable state present in adenocarcinoma of the ovary could explain the DVT and the pulmonary thromboembolism; nevertheless, it would

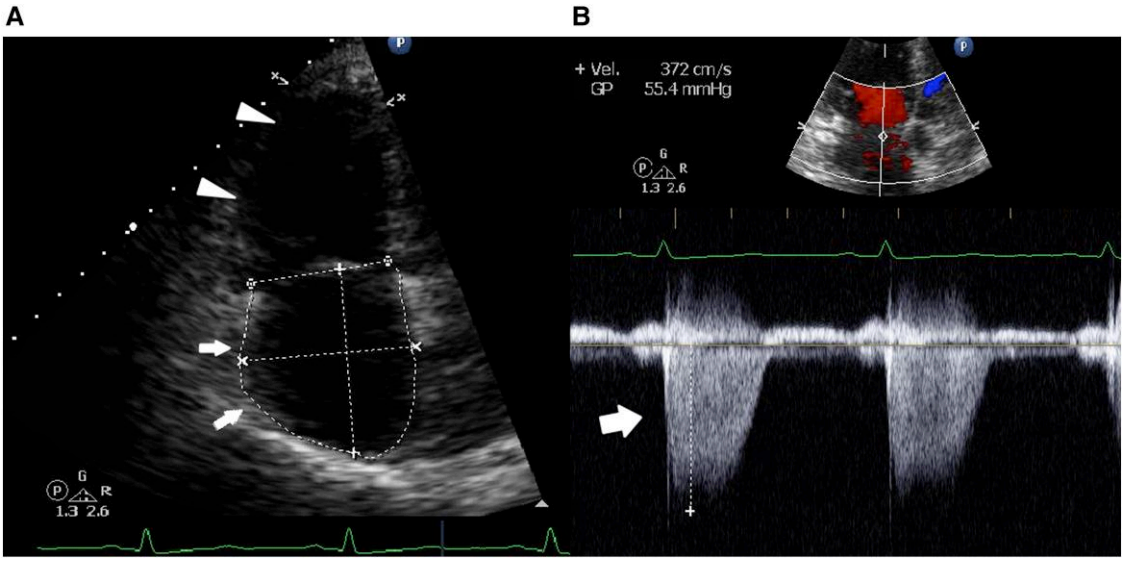

Figure 3 Echocardiogram. (*A*) Four-chamber window showing dilation of the right auricle (arrows) and dilation of the right ventricle (arrowheads). (*B*) Doppler ultrasound: arrow showing significant tricuspid regurgitation.

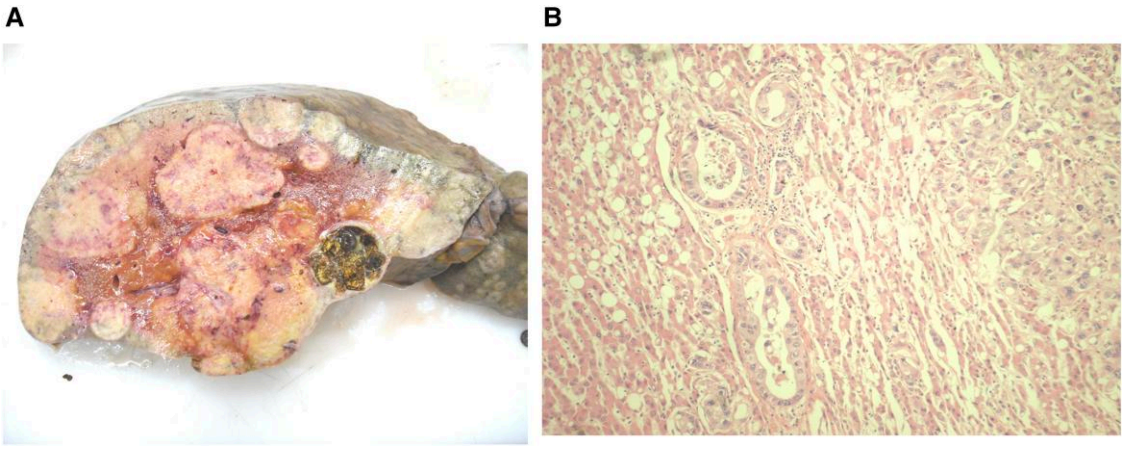

Figure 4 (*A*) Coronal cut surface of the liver: numerous nodules of different sizes are observed, yellowish white that replace the liver parenchyma in ~85%, and these nodules are also observed on the surface where they protrude. In the centre, the cross-sectioned gallbladder contains mixed cholesterol and bile salt stones, which is why yellow and black brown colours alternate. The gallbladder wall is clear and appears not to be infiltrated. (*B*) Histological section of the liver: in the upper right portion of the observer is the neoplasm with a semisolid pattern with glanduloid lights. In the centre, the duct neoplasm limited by simple cuboidal epithelium with nuclear plemorphism showed an intrahepatic cholangiocarcinoma. For comparison, normal hepatocyte cords with steatosis to the observer's left. H/E 20×.

have resolved with alteplase.[9] The therapy did not resolve the obstructive shock because the aetiology of the embolus was not thrombotic but neoplastic. The pathological analysis of the ovary revealed a benign cystic tumour.

Screening for occult cancer has been proposed after an event of non-evoked venous thromboembolism. However, the extent to which clinicians should screen patients for occult cancer remains unclear since randomized controlled trials have shown no improvement in patient outcomes. The current guidelines suggest physicians to individualize diagnostic assessments based on the past medical history, physical examination, and age/gender-specific cancer screening.[10]

The first and foremost thing to keep in mind when assessing a patient with PE and suspicion of an occult malignancy is the fact that the sole hypercoagulable state could lead to a PE and right heart failure, which should be addressed as such. The door for differential diagnosis should remain open especially if the proper therapeutic intervention with plasminogen activators or anticoagulants has been administered and the clinical picture continues to deteriorate.

Imaging studies like the CT angiogram and the ventilation/perfusion lung scan will be able to determine the presence of a PE, with the multifocal dilatation and beading of central or peripheral pulmonary arteries being reported as a characteristic finding of PTE

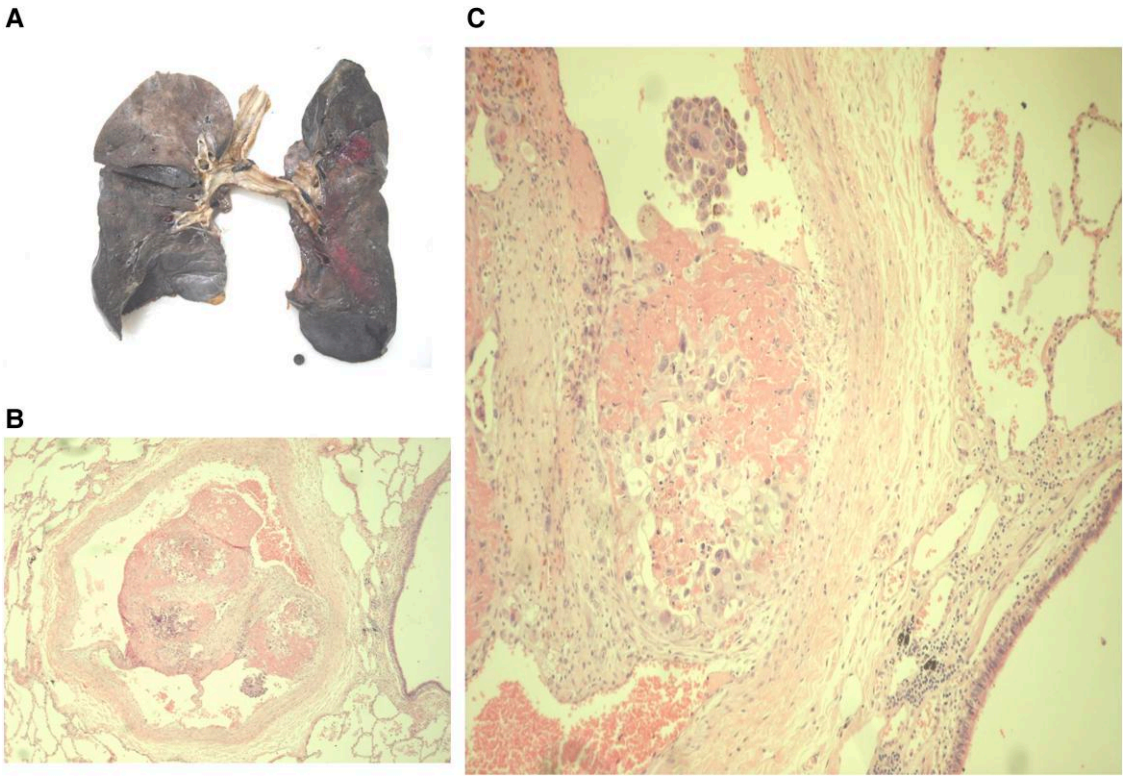

Figure 5 (*A*) Coronal surface of the lungs, which are mostly dark brown due to intense congestion; the right upper lobe is the one that retains its spongy appearance and light brown colour. There is no evidence of infarcts or metastasis. (*B*) Histological section of the pulmonary artery that follows a bronchiole. Note an organizing fibrinous embolus with few cells. H/E 10×. (*C*) Photomicrograph at higher magnification of the tumour embolus, in which nests of malignant neoplastic cells are observed, coming from the liver. H/E 20×.

or PTTM.[4,8] However, the pathological examination of the lungs is still considered the gold standard. Petnak *et al.*[8] suggest that the tissue diagnosis can be obtained via transbronchial or transthoracic CT-guided lung biopsy, and Blanc *et al.*[11] were able to obtain the pathological diagnosis of a thyroid cancer PTE via ultrasound-guided transbronchial needle aspiration.

Roberts *et al.*[4] mention the utility of right heart catheterization and pulmonary artery cytology to confirm the presence of malignancy. The interpretations of these pathology samples can be challenging, especially since cells from the endothelium and megakaryocytes can resemble malignancy. In their study, they were able to find tumour cells that were identical to the tumour cells found on their patient's primary bladder adenocarcinoma. Therefore, the pulmonary artery cytology may provide some utility in establishing the diagnosis, but it should be supported by the patient's clinical history and imaging findings to help guide the pathologist amongst the different probable origins of the occult neoplasia.

Prompt diagnosis of the neoplasia is absolutely necessary, as most authors agree that directly treating the cancer could improve the clinical condition.[8,11] Chung *et al.*[12] mention the utility of utilizing extra corporeal machine for oxygenation (ECMO) on a patient with PTE secondary to choriocarcinoma. The haemodynamic stability that the ECMO provided allowed the patient to undergo the diagnostic workup, the pulmonary thrombectomy, and prompt initiation of chemotherapy that led to the dissolution of PTE in the 2-month follow-up evaluation.

The data regarding the appropriate treatment of this entity are scarce due to how infrequent it presents. Nevertheless, the anecdotal evidence that we possess right now suggests that prompt diagnosis of the neoplasia and life support measures to allow interventions such as specific antineoplastic therapy and pulmonary artery thrombectomy when feasible could present better outcomes in these patients.

Lead author biography

Alejandra Portillo-Romero is a cardiologist currently doing a fellowship in interventional cardiology at the National Institute of Cardiology 'Ignacio Chávez'.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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