CASE REPORT

Breathless: a case of pulmonary tumor thrombotic microangiopathy?

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Abstract
Pulmonary hypertension (PHT) in the ICU is mostly seen in cardiac surgery patients, in patients with acute respiratory distress syndrome or pulmonary embolism. However, there is a broad differential diagnosis. In this case report we present a patient, who rapidly developed PHT with right sided heart failure and who was unresponsive to medical therapy. The diagnosis of "Pulmonary Tumor Thrombotic Microangiopathy (PTTM)" was suspected. PTTM is a fatal, cancer-related pulmonary complication, characterized by progressive dyspnoea, pulmonary hypertension and right-sided heart failure.

Introduction
Pulmonary tumour thrombotic microangiopathy (PTTM) is a rare complication of metastatic cancer, with a prevalence of 1.4%. The clinical presentation is typically of acute dyspnoea and progressive pulmonary arterial hypertension (PHT). PTTM has a very rapid clinical course progressing to death in hours to days, which confounds diagnosis, making it a challenging one. PTTM is a pulmonary phenomenon, first described by Von Herbay in 1990. It is directly caused by multiple non-occlusive microthrombi of cancer cells, which organise and recanalise to pulmonary vasculature leading to fibrocellular intimal thickening, vessel stenosis and increased vascular resistance.[1] This case demonstrates the diagnostic difficulties and scarcity of treatment options in a rare and rapidly fatal cancer-related complication.

Case history
A 58-year-old woman was admitted to the emergency department. She presented after syncope, complaining of acute dyspnoea and pain between the shoulder blades. Past medical history included hypertension, carcinoma of both breasts for which she underwent mastectomy, and chemoradiation therapy. Just weeks prior to presentation she visited her cardiologist with complaints of shortness of breath. Echocardiography, which had been performed prior to her visit, had been unremarkable.

Clinical presentation
Shortness of breath on exertion had been present for seven months. She had no chest pain, no haemoptysis, nausea, vomiting, or abdominal complaints. On initial examination, the patient was tachypnoeic, tachycardic (105 beats/min), and hypertensive (177/123 mmHg), with no notable jugular venous distension. Pulse oximetry measured 85% corresponding to blood oxygen saturation. The lung fields were clear, and no murmurs were heard on cardiac auscultation.

Diagnostics
Laboratory testing revealed a normal blood cell count, troponin T (31 ng/l) and creatine kinase (149 U/l), and an elevated D-dimer of >5000 ng/ml. An ECG showed a right axis, S in I, signs of right atrial strain in V1, new negative T waves in II, III, aVF, and V4–5–6, without significant ST elevations. A chest X-ray was normal, and focused echocardiography revealed no pericardial effusion or dilatation of the ventricles. CT angiography and ventilation/perfusion scan ruled out aortic dissection and pulmonary embolism. Pulmonary parenchyma was normal. Despite multiple diagnostic testing no definite diagnosis could be established, and she was admitted to hospital.

Clinical course
The patient was treated with oxygen, which led to some relief of the dyspnoea. In the following days, she became hypotensive, and oliguric, her extremities cold to touch and her pulse oximetry dropped to 77%. Central venous pressure was elevated, her arterial blood gases: pH 7.43, pO2 9.8 kPa (9.8–13.1 kPa), and pCO2 3.6 kPa (4.7–6.4 kPa). Repeated cardiac ultrasound revealed right ventricular (RV) strain, severely reduced RV function, with an elevated pressure gradient over the tricuspid valve of 64 mmHg. The left ventricular function was normal with no signs of wall motion abnormalities. Pro-BNP measured 10,601 pg/ml. A bedside ultrasound of the extremities ruled out deep vein thrombosis. The patient had obstructive shock...
with PHT of unknown aetiology. Three days after presentation, she was admitted to the ICU. A pulmonary artery catheter was inserted. The first pulmonary artery pressure measured 70/39 mmHg, right atrial pressure 18 mmHg, pulmonary artery occlusion pressure 8 mmHg with a cardiac index of 1.8 l/min/m² and an arterial blood pressure of 102/69 mmHg.

**Therapy**

Treatment with inotropes (dobutamine and milrinone), epoprostenol (PGI₂), and sildenafil was commenced to treat the PHT and improve RV function. The pulmonary artery pressures did not respond to the treatment and the patient developed respiratory failure and hypotension. Norepinephrine was introduced, the patient was intubated and ventilation with nitric oxide was started; nevertheless the clinical status of the patient rapidly deteriorated.

**Right ventricular assistance**

Extracorporeal membrane oxygenation (ECMO) as bridge-to-decision was considered to stabilise the patient, allowing time for diagnostics and consultation regarding the possibility of lung transplantation.

**Differential diagnosis and clinical course**

Other than breast cancer and concurrent treatment, the patient’s medical history did not provide any other clues to the origin of the PHT. Neither did the diagnostic workup. PHT classes II to IV were systematically eliminated. After consulting several PHT specialists, taking into account the patient’s history of cancer class V, PHT with the diagnosis of PTTM seemed most likely. With no treatment options, and the rapid decline in the patient’s clinical status, the decision was made to withhold ECMO and discontinue further supportive treatment. The patient died just one day after ICU admission.

**Post-mortem examination**

The lung parenchyma had a normal appearance with no signs of lobar pneumonia. No thrombi were present in the pulmonary trunk or its branches. Minimal age-related atherosclerosis was present in the coronary arteries and aorta. The heart and other organs showed no macroscopic abnormalities; no primary tumours were found. Haematoxylin and eosin section showed severe dysplastic cells in the blood vessels of the lungs, thyroid, bone marrow, and in between muscle fibres (figure 1). Further immunohistochemical staining was difficult to interpret because of post-mortem changes in the material. The material did test positive for keratin AE1 and 7 and weakly positive for GATA-3 (marker profile of mammary origin), but negative for progesterone and oestrogen receptors (both marker profiles of mammary origin), thyroid transcription factor 1, CDX2, CD138 and CD 6. Accordingly the lesional cells are probably of mammary origin. Unfortunately, Verhoeff-Van Gieson staining did not bring to light intimal thickening.

**Discussion**

PTTM is considered to be extremely rare and the diagnosis notoriously difficult as many findings are non-specific. In most cases it remains a post-mortem diagnosis. Patients present with exertional breathlessness and hypoxia commencing approximately three weeks to six months prior to hospital presentation. Our patient presented in a similar manner. Due to her rapid deterioration, the clinicians were prompted to repeat the cardiac ultrasound which was not part of the initial diagnostics upon presentation. Revelation of RV failure made PHT a more likely diagnosis and further work-up was undertaken (figure 2).
Transthoracic echocardiography images obtained after admission were compared with those taken just six weeks earlier. Standard images were taken in both examinations, revealing RV strain, tricuspid insufficiency grade II-III and sPAP of at least 70 mmHg in the echocardiography after admission, which were not present in the earlier scan. ECG changes, in particular a right axis, were also not present six weeks previously. In PTTM the histopathological diagnosis is the most specific means of diagnosis and may be established by lung biopsy or aspiration cytology. The clinical deterioration of our patient prevented us from performing a lung biopsy. Pulmonary wedged aspiration cytology was part of the diagnostic work-up, but unfortunately failed to be completed.

Currently, the treatment of PHT consists of general measures and supportive therapy, drug therapies such as calcium channel blockers, endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and prostacyclin analogues with definitive treatment being heart-lung transplant. As more PTTM cases are being documented, a few ante-mortem diagnoses have been reported, enabling more aggressive treatment strategies. Abe et al. reported the expression of platelet-derived growth factor (PDGF) A and endothelial growth factor C on cancer cell microthrombi in PTTM. They postulated that these growth factors are related to vascular remodelling, accounting for the appearance of PHT. These insights have provided a new class of drugs that may be effective in treating PHT in PTTM. Imatinib (registered for the treatment of different haematological cancers, hypersensitivity disorders, and gastrointestinal stromal tumours) is an anti-proliferative agent with inhibitory effects of tyrosine kinase on PDGF receptors. It is postulated that down-regulation of the expression of PDGF receptors in tumour cells by imatinib results in increased apoptosis and inhibition of tumour angiogenesis. Results reported in the IMPRES trial are promising, with improvement in haemodynamics and exercise capacity with the use of imatinib in patients with advanced PHT. However, serious adverse events such as congestive heart failure and left ventricular dysfunction were more common with its use. Partial successful treatment with imatinib has mainly been reported among patients with gastric cancer. Effectivity in these cases is expected to be achieved after three months. There have also been cases of patients with breast cancer in whom imatinib therapy was successful in decreasing pulmonary artery pressures within a week. Nevertheless death followed rapidly due to progression of the underlying illness. Ogawa et al. reported a case where a patient with an ante-mortem diagnosis of PTTM was successfully treated for PHT with percutaneous cardiopulmonary support and imatinib.

This patient had been-electively referred for treatment of PHT and did not present with emergency complaints as in our case. Use of imatinib was considered in our case, however deemed not to be a viable treatment option. Despite comprehensive medical therapy the decline in our patient’s clinical status was too rapid to expect a meaningful effect from imatinib therapy. ECMO therapy in combination with imatinib would probably not have led to a more favourable outcome because multi-organ failure syndrome had already developed.

Conclusion
The differential diagnosis of a patient with PHT of unknown origin must entail that of PTTM.
In general, PTTM proves difficult to diagnose for multiple reasons: relatively non-specific symptoms of dyspnoea, often absence of a cancer diagnosis and the rate of clinical decline despite treatment. It thus warrants a high index of suspicion in patients presenting with dyspnoea and unexplained PHT. An early trial of imatinib should be considered part of the treatment strategy, alongside current PHT guidelines. However, PTTM remains a highly fatal disease and the large majority of patients succumb to death shortly after hospital admission due to severe hypoxia. Regrettably we could not ascertain fibrocellular intimal proliferation on post-mortem examination, the hallmark feature in PTTM. Pathological findings, however, combined with the clinical course and diagnostics, has led us to conclude our patient did succumb to PTTM. The antecedent cause for PTTM was that of progressive metastatic breast cancer.

Disclosures
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References