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# Pulmonary tumor thrombotic microangiopathy in a patient with a metastatic urothelial carcinoma

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ABSTRACT

A 78-year-old woman was admitted for acute dyspnoea. One year before, she had been treated with cisplatin and gemcitabine for a high grade urothelial carcinoma. Immunotherapy was discussed 9 months later due the progression of bone metastases but could not be administered before this episode of respiratory distress. There was a major discrepancy between the findings of a limited pulmonary embolism at thoracic tomodensitometry and the severity of a recently developed pulmonary hypertension at echocardiography. The patient presented cardiac arrest on day 6 and post-mortem findings were consistent with diffuse pulmonary tumor thrombotic microangiopathy, a rare complication of urothelial carcinoma.

## Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare entity characterized by progressive dyspnea and eventually fatal pulmonary hypertension in patients suffering from metastatic carcinoma. Association with urothelial carcinoma seems extremely uncommon contrasting with gastric adenocarcinoma. Pulmonary hypertension is the ultimate complication that seems poorly influenced by any therapy and fatality rapidly follows the start of oxygen therapy.

## Case presentation

A 78-year-old woman was diagnosed in early 2019 (one year before the current hospital admission) with a high grade urothelial carcinoma revealed by gross hematuria. Her past medical history was unremarkable, except for osteopenia and nephrolithiasis.

After 4 cycles of induction chemotherapy with cisplatin and gemcitabine, an anterior pelvectomy was performed. Histopathological examination revealed a ypT1N1 stage according to the TNM classification 8th edition. At 9-month follow up, the thoracic and abdominal CT revealed multiple bone condensing metastases in the ribs, spine and pelvis. Urothelial carcinoma relapse was documented by bone biopsy. Immunotherapy with a monoclonal antibody targeting the PD-(L)1 pathway was proposed, pending tumor PD(L)1 expression. Before immunotherapy could be started, the patient was admitted in the Emergency Department with complaints of dry cough and rapidly progressive dyspnoea that had started 3 weeks before, with a rapid worsening over the last two days. Pulse oxygen saturation (SpO2) was only 75% on room air. Chest-X-ray examination was not relevant (Fig. 1). D-dimers were measured at 2459 ng/ml (<500). Other relevant laboratory investigations were: platelet count 157 $\times$ $10^3$/mm$^3$, LDH 1285 IU/L (<250). CT pulmonary angiography showed an inferior right-lobe peripheral pulmonary embolism with a dilated right ventricle (Fig. 2). A transthoracic echocardiogram (TTE) revealed a severe pulmonary hypertension with a tricuspid regurgitation pressure gradient of 73 mmHg compared to the 19 mmHg obtained at the pre-operative TTE in 2019. Despite high-flow oxygen therapy, hypoxia progressed. No reversal of pulmonary hypertension was observed after inhaled nitric oxide therapy (10 ppm). Blood analysis revealed a drop in platelet count (16 $\times$ $10^3$/mm$^3$), undetected levels of haptoglobin, along with a rise in arterial lactate, LDH, schizocytes (>3%) and liver enzymes. The discrepancy between the size of pulmonary embolism and the severity of pulmonary hypertension led to reconsider the initial diagnosis of pure blood clots pulmonary embolism. Anti-PF4 antibodies, ADAMST13 and lupus anticoagulant tests came back negative and the timing seemed off concerning a gemcitabine-related microangiopathy. Thus, the diagnosis of a pulmonary tumor thrombotic microangiopathy (PTTM) was first suggested on day 3 of her ICU stay. A corticosteroids therapy consisting of

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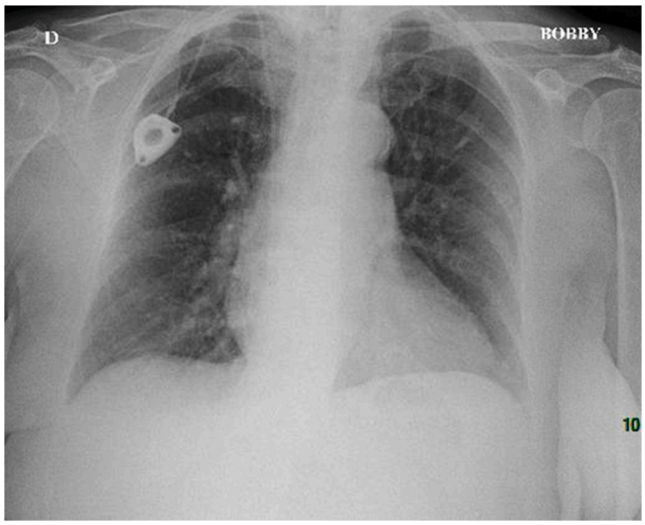


**Fig. 1.** Chest-X-ray on admission.

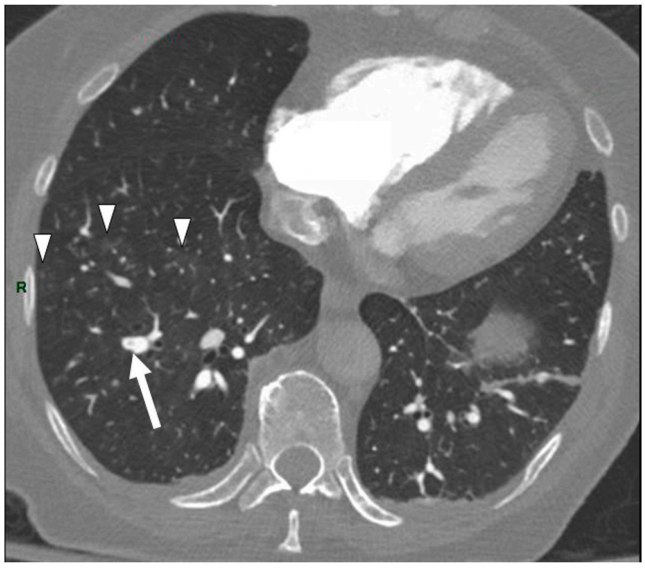


**Fig. 2.** CT pulmonary angiography showing a small pulmonary embolism in a segmental pulmonary artery of the right lower lobe (arrow). Areas of ground glass opacification and centrilobular nodules are depicted in the lower lobes (arrowheads).

methylprednisolone was initiated at 1mg/kg of body weight. Immunotherapy judged futile as PD-1 expression on the bone biopsy specimen came back negative. The patient denied further chemotherapy and presented refractory cardiac arrest on ICU day 6. Post-mortem examination mainly disclosed a nutmeg liver and pulmonary congestion. But, at histology, multiple intravascular tumoral emboli were seen in pulmonary and hepatic vessels. Immunochemistry of pancytokeratin confirmed epithelial origin of tumoral cells. These also expressed vascular endothelial growth factor (VEGF) but not osteopontin (Fig. 3).

## Discussion

The term of pulmonary tumor thrombotic microangiopathy (PTTM) was first introduced in 1989 and referred to a remodelling of the pulmonary circulation consisting of a fibrocellular intimal proliferation of small arteries that will ultimately result in a fatal pulmonary hypertension.[1] In a series of 30 autopsy cases, ante-mortem diagnosis was obtained in only six cases. This was confirmed in a recent literature review, with only 21% of ante-mortem diagnosis.[2] One of the reasons is its mediocre survival rate. In some series, the median survival after diagnosis is of seven months. Patients presenting with hypoxemia requiring supplemental oxygen are surviving only a few days or weeks after presentation. In the present case, respiratory symptoms developed 14 months after the initial diagnosis of urothelial carcinoma and the patient died less than six days after the start of oxygen therapy. While dyspnea is frequently noted to be progressive, the presentation may also be subacute with the progression of pulmonary hypertension. Chest-X-ray examination is often unremarkable. Thoracic computed tomography (CT) does not frequently reveal thrombi or tumor emboli in the pulmonary arteries. The main descriptions of common CT features are mainly referring to PTTM associated with gastric malignancy. They include ground-glass opacities, nodules, septal thickening and mediastinal/hilar lymphadenopathy.

To the best of our knowledge, only six cases of urothelial carcinoma related PTTM have been cited in the literature, but only three of those have been thoroughly described in the English literature.[3,4]

The pathophysiology of PTTM appears complex and involves interactions between tumor cells, endothelial cells, smooth muscle cells, mediators of inflammation (PDGF, VEGF) and tissue repair (osteopontin), and activators of the coagulation system (tissue factor). An interrelationship between PDGF and osteopontin was suggested to be involved in the pathogenesis of PTTM. Osteopontin is predominantly expressed at the protein level in clear cell renal carcinoma when compared to other types of renal tumors. In a recent series of primary renal tumors, osteopontin expression did not correlate with tumor progression or survival. In our observation, expression of VEGF was weak in the metastatic cells and absent for osteopontin. The rapid progression of pulmonary hypertension remains speculative. It could be explained by tumour clusters obstruction of supernumerary arteries (small branches arising from elastic and muscular pulmonary arteries in a perpendicular manner). When secondary tumour emboli are accumulating at the proximal site of the lesion, the PTTM lesion extends to larger proximal trunk with a sudden increase in pulmonary arterial resistance.[5]

Several medications were proposed in PTTM. They included anti-

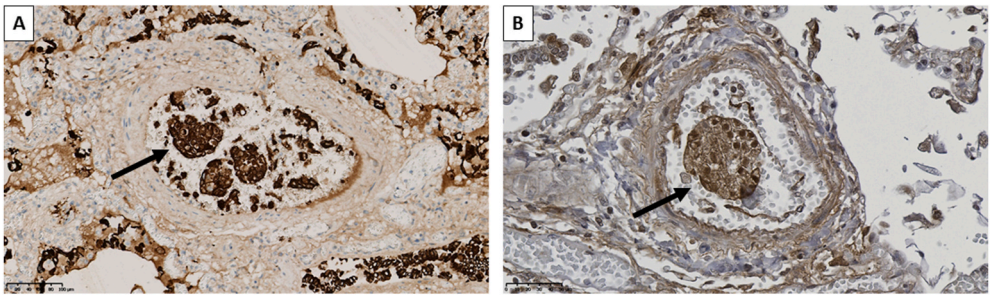


**Fig. 3.** Pancytokeratin staining revealed (arrow) clusters of epithelial neoplastic cells into pulmonary vessels (A, x200). These neoplastic cells also showed (arrow) expression of VEGF in immunochemistry (B, x400).

neoplastic drugs, anticoagulants, diuretics, corticosteroids or specific drugs for advanced pulmonary hypertension. Imatinib, as a PDGF receptor inhibitor, appeared promising in some cases, but further studies are required. A previous trial with inhaled nitric oxide combined with corticosteroids appeared unsuccessful in a patient with metastatic gastric adenocarcinoma.

## Conclusion

In conclusion, PTTM may be regarded as an unusual complication following urothelial carcinoma. Progression to subacute cor pulmonale may be particularly rapid and poorly responsive to anticoagulants or other therapies for advanced pulmonary hypertension.

## Ethical approval

The case report has been approved by our local research ethics committee.

## Consent

Written informed consent was obtained from the patient's relatives for publication of this case report and any accompanying images.

## Authors' contributions

JP drafted the manuscript, JL reviewed the pathological findings, BG reviewed the radiological examination, PFL and PH revised and approved the final version.

## Declaration of competing interest

The authors have no conflicts of interest to declare.

## References

1. von Herbay A, Illes A, Waldherr R, Otto HF. Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. *Cancer*. 1990 Aug 1;66(3):587–592.
2. Godbole RH, Saggar R, Kamangar N. Pulmonary tumor thrombotic microangiopathy: a systematic review. *Pulm Circ*. 2019 Apr-Jun;9(2), 2045894019851000.
3. Parama JK, Hashimoto N, Murota M, et al. Pulmonary tumor thrombotic microangiopathy caused by urothelial carcinoma: an autopsy-proven case of a rare etiology. *Pathol Int*. 2020 Dec;70(12):1037–1039.
4. Wakabayashi Y, Iwaya M, Akita M, Takeuchi W, Yamazaki K, Iijima A. Pulmonary tumor thrombotic microangiopathy caused by urothelial carcinoma expressing vascular endothelial growth factor, platelet-derived growth factor, and osteopontin. *Intern Med*. 2016;55(6):651–656.
5. Sato N, Tasaki T, Noguchi H, Irie K, Nakayama T. The pathological challenge of establishing a precise diagnosis for pulmonary tumour thrombotic microangiopathy: identification of new diagnostic criteria. *Histopathology*. 2019 May;74(6):892–901.