

Pulmonary tumour thrombotic microangiopathy due to adenocarcinoma of the lung. A cause of pulmonary hypertension



To Editor,

Pulmonary tumour thrombotic microangiopathy (PTTM) is a very rare cancer-related pulmonary complication, histologically characterised by fibrocellular subintimal proliferation of small pulmonary arteries and arterioles in patients with metastatic carcinoma and associated with the development of thrombotic microangiopathy (TMA), respiratory failure and *cor pulmonale*,¹ and it is a known cause of severe pulmonary hypertension.² TMA is a disorder characterised by thrombocytopenia, microangiopathic haemolytic anaemia with negative Coombs test, and variable degrees of organ dysfunction.¹

We present the case of a 60-year-old male who had been diagnosed four years previously with carcinoma of larynx treated with surgery and radiotherapy, without evidence of relapse, and who was admitted for dyspnoea, orthopnea, dysphonia and haemoptoic sputum with two weeks of evolution. The physical examination showed the patient to be tachypneic, with a yellowish or icteric hue of the skin and signs of right-sided heart failure. The following were the most relevant complementary examinations. Blood test: platelets $99 \times 10^3 \mu\text{L}^{-1}$; total bilirubin 3.4 mg/dL (as opposed to direct bilirubin, 2 mg/dL); GOT 241 UI/L; GPT 73 UI/L; GGT 787 UI/L; alkaline phosphatase 802 UI/L; ferritin 1457 ng/mL and N-terminal brain natriuretic propeptide 2155 pg/mL. Peripheral blood smear: 7% of schistocytes with negative direct Coombs test, PaO₂ 49.8 mmHg. Radiology and chest computed tomography (CT) angiography showed a pulmonary nodule with ground glass halo and a small calcification and several peripheral ground glass nodular lesions, and hepatomegaly with faint, hypodense, ill-defined, subcentimetre hepatic nodules. There was no evidence of defects in repletion at the level of the pulmonary trunk, principal, lobar and segmental arteries (Fig. 1A). Abdominal echography: hepatomegaly was suggestive of chronic hepatopathy and splenomegaly. Echocardiography: right-sided chamber dilatation with septal displacement, tricuspid insufficiency and severe pulmonary hypertension with preserved left ventricular ejection fraction. Right heart catheterisation: pulmonary arterial pressure 87/22/40 mm Hg; pulmonary capillary wedge pressure 5 mm Hg; cardiac output 7.7 l/min; cardiac index 3.94 l/min/m²; pulmonary vascular resistance 363 dyn/sec/cm⁵. Positron emission tomography: increased uptake at a pulmonary, mediastinal, hepatic and bone level, suggestive of malignancy. Hepatic magnetic resonance with contrast: thrombosis of the left branch of the portal vein, suprahepatic veins threadlike but permeable (Fig. 1B and C).

These data pointed to atypical thrombotic microangiopathy probably secondary to a neoplastic process of pulmonary origin which advanced with pulmonary hypertension. On subsequent days, the patient's clinical deterioration intensified and he presented with anasarca, increased dyspnoea, signs of hepatic encephalopathy, increased anaemia (which

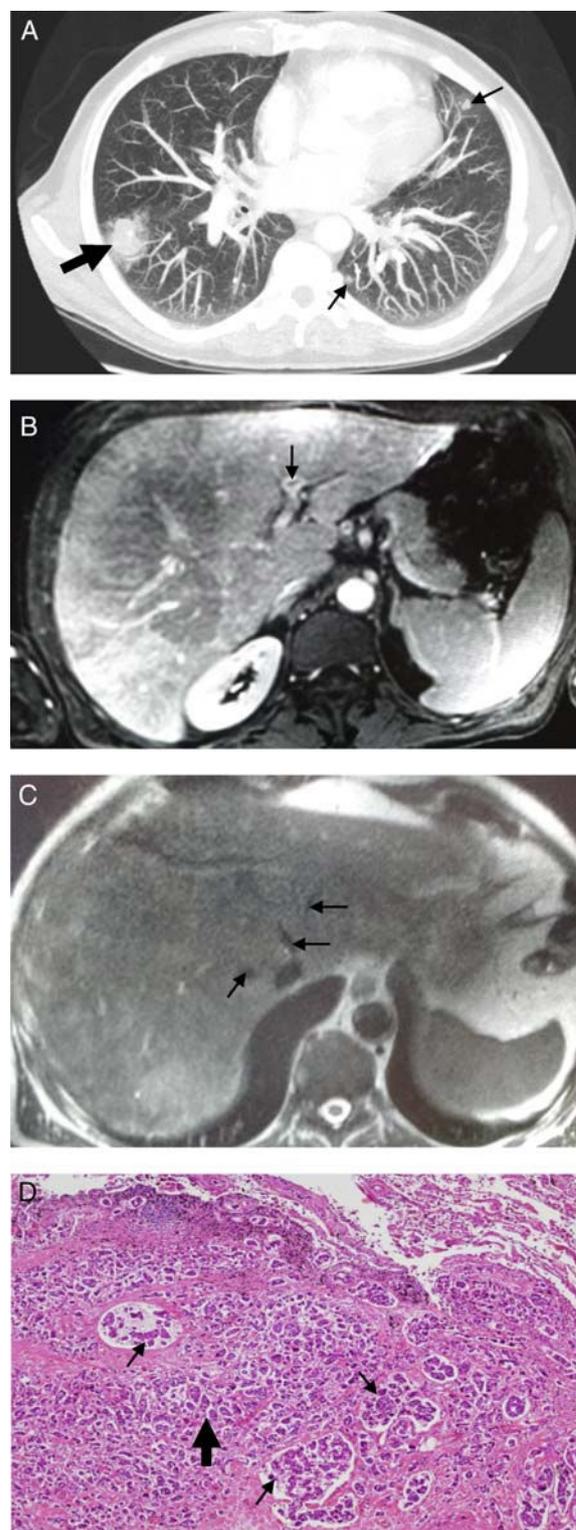


Figure 1 (A) Projection of maximum intensity in the computed tomography of the thorax. It shows a pulmonary nodule with ground glass halo and a small calcification (thick arrow) and several peripheral ground glass nodular lesions (thin arrows). (B) Thrombosis of the left portal vein on magnetic resonance imaging of the liver (sequence T1 with Gadolinium), (C) Narrow, but permeable, suprahepatic veins on magnetic resonance imaging of the liver (FSE T2WI sequence), (D) Micropapillary pattern lung adenocarcinoma (thick arrow) with marked vascular invasion (thin arrows). HE4× (haematoxylin eosin).

required transfusion of red blood cells and fresh-frozen plasma) and severe liver damage. The patient died some days later. The necropsy showed the existence of adenocarcinoma in the right lung, with massive pulmonary vascular embolisation which affected both lungs, mediastinal lymph nodes, heart, both suprarenal (adrenal) glands and liver, with hypertrophy and dilatation of the right cardiac cavities, subendocardial ischaemia, congestive hepatosplenomegaly, bilateral pleural effusion and ascites (Fig. 1D). The cause of death was multiorgan failure related to PTTM.

Diagnosis of PTTM during life is extremely rare.³ Adenocarcinoma of the stomach is the condition most frequently associated with PTTM (52.4% of all described cases), followed by those of the lung (14.3%), breast (9.6%), and a few rarely-reported tumour sites.¹ Disease course tends to be rapidly progressive and may cause pulmonary hypertension, right ventricular pressure-overload and *cor pulmonale*,⁴ or organ dysfunction. In many cases, the presence of TMA is the predominant finding in the clinical scenario and differential diagnosis with thrombotic thrombocytopenic purpura must be made⁵ to avoid initiation of ineffective therapeutic measures, such as plasmapheresis, which would delay diagnosis and might, even, favour microthrombotic formation.^{2,6} Diagnosis during life of this disease has only been achieved in 10 patients on the basis of: transbronchial biopsy (5 cases); video-assisted thoracic surgery (2); CT-guided lung biopsy (1); and pulmonary microvascular cytology using a wedged pulmonary catheter (2).⁷

If diagnosis can be established during life, it should be followed by starting early treatment. Of the only four patients to survive beyond the initial acute phase, one was treated with warfarin, dexamethasone, acetylsalicylic acid and chemotherapy based on fluoropyrimidine (gastric adenocarcinoma).⁷ While the other three patients showed improvement in their pulmonary hypertension after administration of Imatinib, all died due to disease progression.³ Imatinib is an inhibitor of the vascular endothelial growth factor receptor implicated in the pathogenesis of PTTM, which is used in this disease because it has been shown capable of reducing such blood receptor levels.

In brief, in cases of severe, rapidly progressive pulmonary hypertension, differential diagnosis should include PTTM secondary to a neoplasm, particularly if accompanied by haematological alterations that suggest TMA. Although our case was one of pulmonary adenocarcinoma, the most frequent clinical profile is that where the tumours are gastric in origin. In the course of patient's clinical disease, early diagnosis is crucial to enable treatment to be initiated as quickly as possible, since, failing this, prognosis is generally fatal.

Authors' contributions

RA, MET and LV were responsible for the conception and design of the study, and wrote and edited the manuscript. JMAD contributed to the drafting and revision of the manuscript. All authors read and approved the final manuscript.

Funding

This work was performed without funding.

Conflicts of 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;66:587–92.
2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *International Society for Heart and Lung Transplantation (ISHLT)*. *Eur Heart J*. 2016;37: 67–119.
3. Fukuda I, Araki K, Minatsuki S, Fujino T, Hatano M, Numakura S, et al. Imatinib alleviated pulmonary hypertension caused by pulmonary tumor thrombotic microangiopathy in a patient with metastatic breast cancer. *Clin Breast Cancer*. 2015;15:e167–70.
4. Garvin MC, Morse D, Partridge AH, Levy BD, Loscalzo J. Breathless. *N Engl J Med*. 2012;366:75–81.
5. George JN. Thrombotic thrombocytopenic purpura. *New Engl J Med*. 2006;354:1927–35.
6. Vasko R, Koziolok M, Fuzesi L, König F, Strutz F, Müller GA. Fulminant plasmapheresis refractory thrombotic microangiopathy associated with advanced gastric cancer. *Ther Apher Dial*. 2010;14:222–5.
7. Ho AL, Szulakowski P, Mohamid WH. The diagnostic challenge of pulmonary tumour thrombotic microangiopathy as a presentation for metastatic gastric cancer: a case report and review of the literature. *BMC Cancer*. 2015;15:450.

R. Abelleira^{a,*}, M.E. Toubes^a, J.M. Álvarez Dobaño^{a,b}, L. Valdés^{a,b}

^a *Pneumology Department, Hospital Clínico-Universitario, Santiago de Compostela, Spain*

^b *Interdisciplinary Pneumology Research Group, Santiago de Compostela Health Research Institutions (Instituto de Investigaciones Sanitarias de Santiago de Compostela/IDIS), Santiago de Compostela, Spain*

* Corresponding author.

E-mail address: romina.abelleira.paris@sergas.es (R. Abelleira).

Available online 24 December 2017

<https://doi.org/10.1016/j.rppnen.2017.11.008>
2173-5115/

© 2017 Sociedade Portuguesa de Pneumologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).