


From the authors:

We thank M. Merad and coworkers for their comments. Indeed there have been at least eight reported cases of pulmonary tumour thrombotic microangiopathy (PTTM) since ours was submitted in early 2015, including cases in other major respiratory journals [1], emphasising that PTTM may not be such a rare condition. Indeed, it is being increasingly recognised both by oncologists and pulmonary hypertension physicians alike. Of over two hundred case reports or series of PTTM now cited on PubMed, the majority relate to adenocarcinomas, mainly gastric in origin, but also oesophageal, colorectal, pancreatic or lung, and more rarely breast, bladder and ovarian. Autopsy studies suggest a prevalence of 3% in gastric cancer [2]. Despite increasing recognition, however, most cases remain a post mortem diagnosis. The presence of undiagnosed malignancy must therefore be borne in mind when physicians assess new cases of pulmonary hypertension.

Early diagnosis is clearly important. We agree with the authors’ hypothesis that identification of pathways involved in the pathogenesis of PTTM may improve survival by allowing targeted therapy. In addition to the vascular endothelial growth factor and platelet-derived growth factor pathways there is evidence for dysregulated intravascular coagulation as indicated by activation of tissue factor and raised D-dimer. As well as increased awareness, we also need an improvement in diagnostic accuracy.

In a new patient presenting with pulmonary hypertension of unknown cause, undiagnosed malignancy should be in the differential diagnosis. The clinical features of PTTM include non-specific signs of pulmonary hypertension but may include symptoms and signs of malignancy in other organs. In terms of blood tests, the role of common tumour markers is not established in the routine work-up of a new patient with suspected pulmonary hypertension. Importantly, the presence of a raised D-dimer with an absence of filling defects seen on computed tomography pulmonary angiography [3] is described in PTTM. Ventilation–perfusion scanning, however, may demonstrate distal and non-segmental diffuse perfusion abnormalities [4]. Conventional pulmonary angiography may show occlusion of distal vessels but without abrupt narrowing or intravascular webs suggestive of chronic thromboembolic pulmonary hypertension [5]. High-resolution computed tomography findings are non-specific but may demonstrate ground glass opacification, mosaicism (reflecting small vessel occlusion) [5], small pulmonary nodules (due to fibrointimal thickening), diffuse shadows [6], consolidation, tree-in-bud [7] and interlobular septal thickening (when pulmonary vein or lymphatics are involved). Interestingly, the recent European Society of Cardiology/European Respiratory Society pulmonary hypertension guidelines suggest that computed tomography is useful in many respects, but does not emphasis the potential role for computed tomography (and/or ultrasound) of the abdomen and pelvis to assess for malignancy [8]. Indeed, as previously highlighted previously in this journal, computed tomography should pick up malignancy in rapidly progressive new cases of pulmonary hypertension [9]. The presence of signs of pulmonary veno-occlusive disease on high-resolution computed tomography (including interstitial oedema with diffused central ground-glass opacification and thickening of interlobular septa) in a patient with likely
PTTM may suggest the involvement of pulmonary veins and lymphatics. This was indeed the case in our reported cases, in which rapid deterioration was evident and pulmonary vasodilators poorly tolerated. Pulmonary vein involvement in PTTM may therefore represent a subgroup within the classification of pulmonary veno-occlusive disease [10]. The use of 18-fluorodeoxyglucose-positron emission tomography (CT-PET) has been reported to be helpful in of PTTM [7, 11] but the resolution of small vessels involved may be insufficient in some cases. Importantly, one would not want to perform a lung biopsy, given the high risk of pulmonary haemorrhage in patients with pulmonary hypertension and the likely poor tolerance to anaesthesia and sedation. The role of bronchoscopy is not routine in these patients for similar reasons. However, as has been successfully reported [5], pulmonary hypertension physicians should consider the use of pulmonary artery wedge aspiration of blood for cytological analysis of tumour cells at the time of right heart catheterisation. Perhaps this should be considered a more routine test, as this opportunity may be missed if the diagnosis is not anticipated. These cells may allow identification of potentially treatable pathways as discussed by the authors.

We believe an important way to improve outcomes in this devastating pulmonary vascular complication of cancer would be to set up a prospective international registry. This could be set up to determine efficacy and safety of anticoagulation, pulmonary hypertension therapies, and the role of novel anti-remodeling treatments including tyrosine kinase inhibitors (TKIs). We agree with our colleagues in Paris that although the experience of TKI in non-malignant PAH must be appreciated, PTTM may represent a condition with few other treatment options where their use should be formally studied.

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Earlier diagnosis and international registries may improve outcomes in pulmonary tumour thrombotic microangiopathy http://ow.ly/V74EI

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References