Pulmonary tumour thrombotic microangiopathy in a young man: clinical and immunohistochemical characterisation of a rare complication of gastric signet-ring cell carcinoma

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INTRODUCTION

Thrombotic microangiopathies (TMA) are characterised by thrombocytopenia, mechanical haemolytic anaemia and microvascular thrombosis. The two main TMA are thrombotic thrombocytopenic purpura (TTP) and the haemolytic uraemic syndrome. TTP is caused by reduced activity of the von Willebrand factor (VWF)-cleaving protease ADAMTS13. Patients with TTP and deficient ADAMTS13 activity in plasma have highly platelet-reactive forms of ultralarge molecular weight VWF multimers[1]. Haemolytic uraemic syndrome is caused by a bacterial gastrointestinal infection or complement dysregulation[2]. Pulmonary tumour thrombotic microangiopathy (PTTM) is a cancer-related TMA of unknown pathogenesis. It affects mainly the lung, where tumour cell microemboli and fibrocellular proliferation are found in the microvasculature, resulting in rapid and fatal pulmonary hypertension[3]. Recently, mediators such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) have been shown to play a role in PTTM and some patients have been successfully treated with combination therapy including a PDGF receptor antagonist and chemotherapy, plasma exchange being ineffective. We describe a fatal case of PTTM associated with signet-ring cell carcinoma in a young man.

CASE REPORT

A 41-year-old man was admitted to another hospital for lumbar pain, fatigue and weight loss. Full-body contrast-enhanced computed tomography (CT) revealed osteolytic lesions of the spine and enlarged mediastinal and perigastric lymph nodes. Blood analyses showed anaemia (haemoglobin 8 g/dL) and mild thrombocytopenia (platelet count 131×10^9/L) with normal white blood cells (WBC). The prothrombin time and activated partial thromboplastin time were normal, and the D-dimer concentration was 3,522 ng/mL. To investigate the anaemia he underwent colonoscopy that was negative and gastroscopy with excision of a polyp. After a week, laboratory tests showed worsening thrombocytopenia (platelet count 28×10^9/L) and haemolytic anaemia (haemoglobin 5.4 g/dL) with increased lactate dehydrogenase (2,123 U/L), haptoglobin consumption and peripheral erythroblastosis (increased up to 79.8/100 WBC). Coombs' test was negative, schistocytes were detected in the peripheral blood smear. D-dimer increased up to 14,464 ng/mL and fibrinogen was 156 mg/dL. Absence of kidney damage excluded

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haemolytic uraemic syndrome. With the suspicion of TTP the patient was transferred to our specialised unit. On admission he had tachypnoea and tachycardia with no neurological symptoms. He was hypoxaemic (pO_2 68 mmHg), requiring oxygen support at 2 L/min. Blood tests confirmed microangiopathic haemolytic anaemia with thrombocytopenia (haemoglobin 6.2 g/dL, platelets 11×10^9/L). ADAMTS13 activity was normal (52%), thus excluding TTP. Bone marrow biopsy was performed, but aspiration resulted in a dry tap. The patient was treated with fresh-frozen plasma, red blood cell transfusions and plasma exchange given his rapid clinical deterioration. Three days later, rapid severe respiratory failure occurred, so he was transferred to the intensive care unit. Chest CT revealed millimetric centrilobular nodules and interlobular septal thickening, suggesting lymphangitic carcinomatosis. Echocardiography showed right ventricle enlargement with pulmonary artery systolic pressure (PAPs) of 65 mmHg. In the next few hours, his clinical condition worsened further, with development of acute right heart failure (PAPs 80 mmHg) and the need for endotracheal intubation. The patient died a few hours later. Bone marrow biopsy showed signet-ring cells of possible gastrointestinal origin. Post-mortem examination confirmed poorly cohesive gastric carcinoma with multi-organ metastases. PTTM was confirmed by fibrocellular intimal proliferation of the pulmonary arterioles (**Figure 1**) and tumour emboli in lymphatic vessels. By immunohistochemistry, tumour cells found in the stomach, lungs and brain were positive for VEGF and, to a lesser extent, for PDGF (**Figure 2**). Renal parenchyma showed post-mortem tubular autolysis and focal glomerulosclerosis; there was no evidence of tumour metastases, vascular thrombi, or alterations of blood vessels. In plasma samples collected before plasma exchange, VWF antigen was markedly increased up to 733% (normal values 55-165%), and the platelet-dependent VWF activity (VWF:GPIbR) was 405% (normal values 53-168), being associated with a reduction of high molecular weight VWF multimers, increase of low and intermediate molecular weight multimers but absence of ultralarge multimers[4] (*Online Supplementary* **Figure S1**).

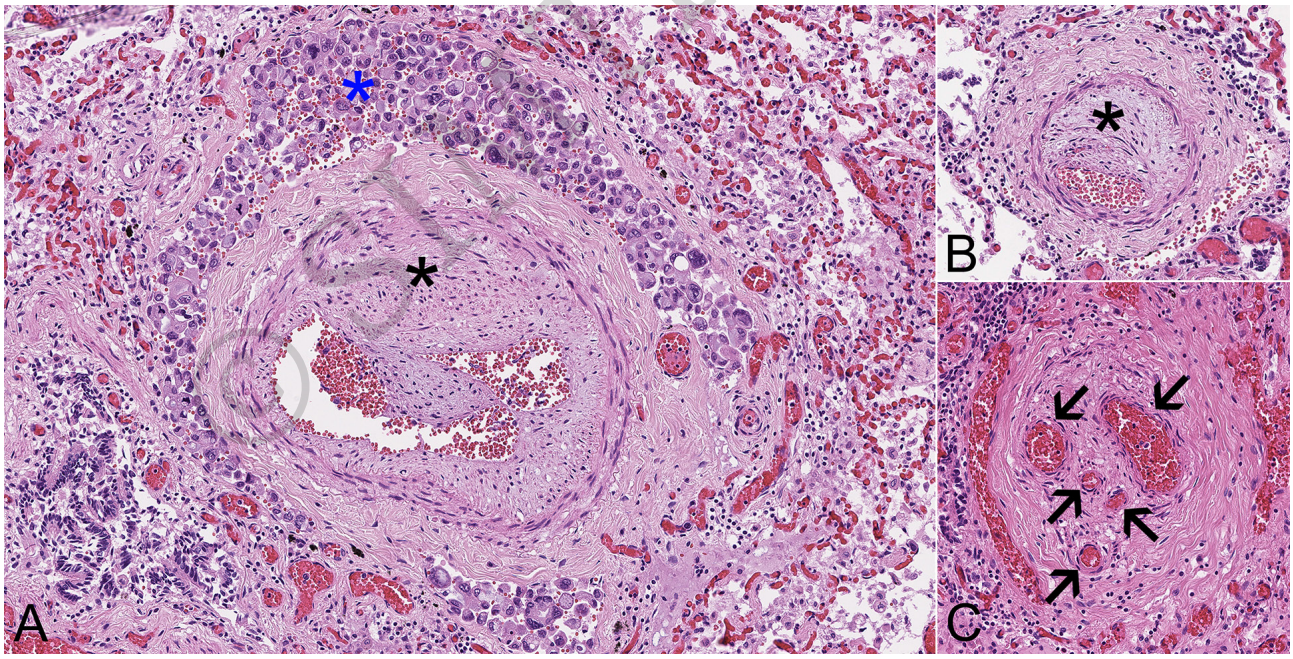

Figure 1 - Pulmonary histopathological findings
(A) A thrombus of metastatic gastric adenocarcinoma, poorly cohesive with signet-ring phenotype can be seen in a lymphatic vessel (blue asterisk) surrounding an arteriole with intimal proliferation and fibrosis (black asterisk). **(B, C)** Smaller arterial vessels also showed eccentric parietal proliferation (**B**, asterisk) and revascularisation (**C**, arrows).

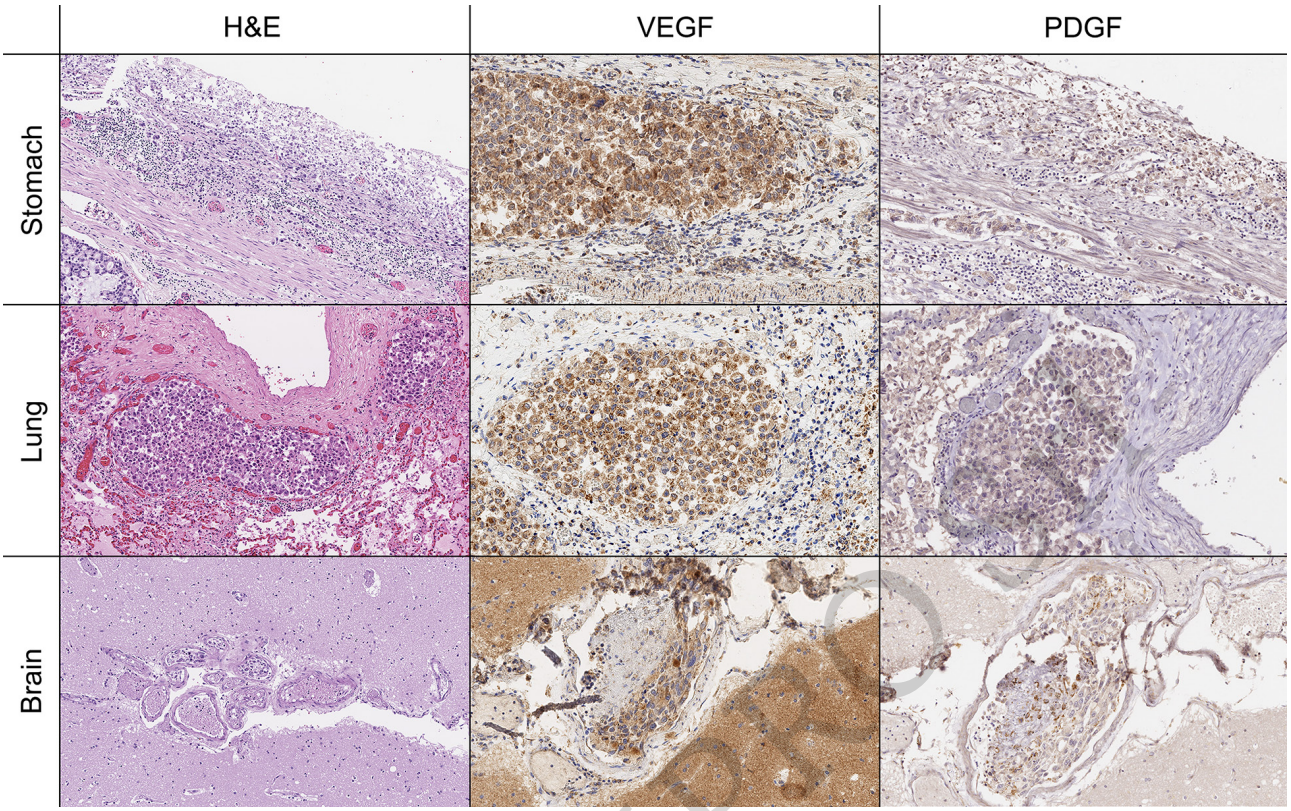

Figure 2 - Expression of VEGF and PDGF evaluated with immunohistochemistry in primary and metastatic gastric adenocarcinoma, poorly cohesive with signet-ring differentiation
In the stomach, the tumour consists of scattered malignant cells which infiltrate the gastric wall and lymphatic vessels. The lung shows diffuse metastases, in particular within the lymphatic system. The brain shows focal presence of metastatic cells admixed with macrophages within the lumen of subpial blood vessels. Strong, diffuse positivity for VEGF can be noted in the primary tumour and its metastases in the lung and brain. Faint positivity for PDGF is also present in all three sites. H&E: haematoxylin and eosin; VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor.

DISCUSSION

PTTM is a rare disorder often associated with gastric adenocarcinoma, but also reported in lung, breast and ovarian carcinomas among others[5,6]. PTTM has been increasingly reported recently, but ante-mortem diagnosis remains challenging, because of the non-specific presentation and rapid progression of the disease towards severe pulmonary hypertension. It is crucial to suspect PTTM in a patient with TMA and normal ADAMTS13 levels, even if cancer has not yet been proven. In our case, weight loss, osteolytic lesions and erythroblastosis suggested cancer-associated TMA[7,8]. Chest CT scan revealed the typical radiological alterations of PTTM, namely centrilobular pulmonary nodules and septal thickening, and the echocardiogram confirmed rapid worsening of pulmonary hypertension.

The pathogenesis of PTTM is unclear. Tumour cells are supposed to stimulate endothelial cells with activation of the coagulation cascade and inflammation, leading to intimal and fibromuscolar proliferation in pulmonary vessels[9]. Postulated mediators implicated in PTTM include tissue factor, VEGF, PDGF and osteopontin[10]. In our case, post-mortem analysis confirmed PTTM, showing intimal thickening of small arteries and tumour emboli in lymphatic vessels only of the lung. Immunohistochemical staining for VEGF was more marked than that of PDGF, as previously reported. In our patient, plasma levels of VWF:Ag and VWF:GPIb-R were increased as described in TTP and metastatic cancer, but

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ADAMTS13 levels were normal. The larger multimeric forms of VWF were reduced as during acute TTP. We speculate that one of the possible mechanisms involved in this microangiopathy was the interaction of platelets with the released VWF, resulting in the consumption of platelets and ultralarge VWF multimers. These aggregates can clog microvessels contributing to the mechanism of the disease. The reduction in larger VWF multimers has also been described in other TMA associated with metastatic tumours[11].

In conclusion, this report of PTTM elucidates the role of VWF in microangiopathy, with significantly elevated VWF but normal ADAMTS13. Because VWF released by the stimulated endothelium is highly thrombogenic, especially for high molecular weight multimers, the alteration of the VWF/ADAMTS13 axis was probably the cause of the consumption of ultralarge multimers and platelet GPIb interaction causing a hypercoagulable state with high risk of thrombosis. At variance with TTP, plasma exchange is ineffective in PTTM. Chemotherapy might be an effective treatment, but requires early detection of the underlying tumour, which is rarely feasible due to the rapidly progressive course of disease, as in our case. Recent reports suggest that the use of therapy targeting PDGF or VEGF (such as imatinib and bevacizumab) can dramatically improve pulmonary hypertension and prolong survival[12].

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Keywords: *carcinoma, signet ring cell, ADAMTS13 protein, platelet-derived growth factor, von Willebrand factor.*

DISCLOSURE OF CONFLICTS OF INTEREST

FP reports speaker fees from Roche, Sanofi, Sobi and Takeda, outside the submitted work. The other Authors declare no conflicts of interest.

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