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<td>Author(s)</td>
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Pulmonary thrombotic microangiopathy caused by gastric carcinoma

Tatsuo Yokomine, Hiroshi Hirakawa, Eisuke Ozawa, Kenichiro Shibata, Toshiyuki Nakayama

ABSTRACT

Pulmonary tumour thrombotic microangiopathy (PTTM) is characterised by wide spread tumour emboli along with fibrocellular intimal proliferation and thrombus formation in small pulmonary arteries and arterioles. PTTM is a rare but fatal complication of carcinoma, but the pathogenesis remains to be clarified. An autopsy case of PTTM caused by gastric adenocarcinoma is described, in which tumour cells in the PTTM lesion had positive immunoreactivity for platelet-derived growth factor (PDGF) and PDGF receptor (PDGFR), and proliferating fibromuscular intimal cells also showed expression of PDGFR. In addition, the overexpression of PDGF was detected in the alveolar macrophages. These findings suggest that PDGF derived from alveolar macrophages and from tumour cells may act together in promoting fibrocellular intimal proliferation. To the best of the authors’ knowledge, the possible involvement of activated alveolar macrophages in PTTM has not been previously reported.

DISCUSSION

Hervay et al speculated that attachment of tumour cell emboli may damage endothelial cells and release PDGF in PTTM. The currently held mechanism of PTTM is that tumour cells occlude the small arteries and arterioles, and also activate coagulation systems and release inflammatory mediators and growth factors. However, the molecular mechanism and associated factors in PTTM remain to be determined.

PDGF is a key mediator in proliferation and migration of smooth muscle cells and fibroblasts. In the presenting case, PDGF, PDGFR, and phosphorylated Src expression were found in tumour cells in a PTTM lesion. These suggested an autocrine function of PDGF in the cancer cells.
**Figure 1** (A) Stenosis and obstruction of many pulmonary arteries and arterioles are shown. Bar, 1000 μm. (B, C) A pulmonary artery showing fibrous thickening of intima and fibrin thrombus (B: H&E stain; C: elastic van Gieson stain). (D) Intimal proliferating fibromuscular cells are positive for α-smooth muscle actin. (E, F) Fibrin thrombus with (E) or without (F) adenocarcinoma cells. Immunoreactivity of pancytokeratin antibody (AE1/AE3) is indicated in the carcinoma cells (F). (E) Arrowheads indicate cancer cells in the vessel. (B–F) Bar, 100 μm.

**Figure 2** (A) Carcinoma cells and endothelial cells are immunopositive for platelet-derived growth factor (PDGF)-A. (B) Alveolar macrophages show the overexpression of PDGF-A in the PTTM lesion. (C) Carcinoma cells, endothelial cells and fibromuscular cells are immunopositive for PDGF-B. (D, E) The expression of PDGF receptors (PDGFRs) (PDGFR-α (D); PDGFR-β (E)). PDGFR-α and -β were detected in tumour cells and fibromuscular cells. PDGFR-α were detected in endothelial cells. (F) Immunoreactivity of phosphorylated Src was found in the tumour cells. (A, C, D, E, F) Arrowheads indicate cancer cells in the vessel. (A–F) Bar, 100 μm.
Take-home messages

► Pulmonary tumour thrombotic microangiopathy (PTTM) is a rare pulmonary complication seen in patients with metastatic carcinomas.
► Clinically, patients with PTTM often present with progressive dyspnoea and severe pulmonary hypertension, and develop acute right side heart failure.
► PTTM is characterised by multiple tumour microemboli associated with proliferation of intimal fibromuscular cells and the formation of fibrin thrombi in the small pulmonary arteries and arterioles.
► Activated alveolar macrophages in the PTTM lesion contributed cooperatively with tumour cells and had a critical role in the onset and/or progression of PTTM via expression of PDGF.

alveolar macrophages and PDGFR in intimal mesenchymal cells in the pulmonary arterial wall. Our findings suggest that activated alveolar macrophages in the PTTM lesion contributed cooperatively with tumour cells to proliferation of fibromuscular cells and had a critical role in the onset and/or progression of PTTM via expression of PDGF.

Competing interests None.

Ethics approval This study was conducted with the approval of the Nagasaki University.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES