


Pulmonary tumor thrombotic microangiopathy with thrombus in pulmonary artery caused by diffuse sclerosing variant of thyroid papillary adenocarcinoma: A case report

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Abstract

Pulmonary tumor thrombotic microangiopathy (PTTM) is a fatal disease associated with malignant tumors that progresses to pulmonary hypertension. Gastric cancer is the most common cause, followed by breast cancer and lung cancer, whereas PTTM due to thyroid cancer has not been reported. In addition to pulmonary obstruction by tumor embolism, tumor cells stimulate endothelial cells to release angiogenic factors, which induce remodeling of pulmonary arteries and veins and lead to lymphatic obstruction. There is limited information on the relationship between thrombus and PTTM. We herein report an autopsy case with PTTM which was caused by diffuse sclerosing variant of thyroid papillary adenocarcinoma, in which differential diagnosis included the acute phase of chronic thromboembolic pulmonary hypertension.

KEYWORDS

pulmonary hypertension, pulmonary tumor thrombotic microangiopathy, thyroid cancer

CASE DESCRIPTION

A previously active 44-year-old man presented with presyncope for 3 days. There were no abnormalities during annual medical examination. He visited another hospital because of fainting (Day 0). At that visit, he was conscious with the following vital signs: blood pressure, 99/75 mmHg; heart rate, 110 beats/minute; SpO₂, 93% under ambient air. He was admitted with cardiopulmonary shock due to pulmonary hypertensive (PH) determined by echocardiography and went

into circulatory failure 2 h later. Hemodynamic parameters obtained with emergent right heart catheterization were as follows: pulmonary arterial pressure (PAP) (systolic/diastolic [mean]), 83/35 (60) mmHg; pulmonary arterial wedge pressure, 8 mmHg; mean right atrial pressure, 15 mmHg; cardiac index, 1.3 L/min/m²; and pulmonary vascular resistance, 21.6 Wood units. Dobutamine and oxygen were initiated immediately after circulatory collapse. Despite treatment, circulatory, and respiratory failure progressed rapidly and subsequent cardiac arrest required

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ventilator support and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) on Day 3. The interval between cardiac arrest and VA-ECMO initiation was approximately 20 min. On Day 3, he was transferred to our hospital and hypothermia therapy was initiated. Laboratory data on Day 3 were as follows: aspartate transaminase, 2302 IU; alanine transaminase, 2564 IU; estimated glomerular filtration rate, 37.9 ml/min/1.73 m²; d-dimer, 44.9 µg/ml; brain natriuretic peptide, 832 pg/ml; thyroid-stimulating hormone, 0.0786 µU/ml; free T₃, <1.5 pg/ml; and free T₄, 0.93 ng/dl. These results suggested liver and renal dysfunction due to circulatory failure, thrombus formation, and central hypothyroidism. Lung perfusion scintigraphy could not be performed; however, reconstruction of computed tomography (CT) images obtained in the previous hospital revealed multiple thrombi in bilateral pulmonary arteries. Acute pulmonary embolism or acute pulmonary embolism with chronic thromboembolic pulmonary hypertension (CTEPH) was considered as the cause in the absence of other PH signs. No solid tumors were observed on CT, but enlarged paraaortic lymph nodes were present. Hypoxic encephalopathy was considered as the cause of central hypothyroidism. Heparin (16,800 U/day), oral macitentan (10 mg once/day), and inhaled nitric oxide (40 ppm) were initiated.

On Day 8, PAP was reduced to 73/36 (46) mmHg under VA-ECMO (3.1 L/min) with a d-dimer level of 11.8 µg/ml. On Day 12, VA-ECMO was successfully withdrawn following further PAP improvement to 50/27 (30) mmHg. On Day 13, he was extubated and nitric oxide was stopped. Despite improvement in hemodynamics and respiratory state, he remained unconscious following sedative discontinuation. Hypoxic encephalopathy was considered based on a flattened electroencephalogram. His family did not consider further treatment, and the patient died on Day 29.

On autopsy, the right and left lungs weighed 980 and 725 g, respectively, with congestion, but there were no thrombi in the main pulmonary arterial branch. The diffusely swollen thyroid gland did not have clearly identifiable nodules. There were no abnormalities in other organs. Pathological examination revealed pulmonary edema and alveolar hemorrhage in bilateral lungs, and pulmonary artery exhibited intimal thickening and recanalization with tumor cell embolization. Tumor cells exhibiting the characteristics of those in the pulmonary artery were found in thyroid gland parenchyma and vasculature. The tumor cells were positive for thyroglobulin and cytokeratin 7 and negative for cytokeratin 20 and thyroid transcription factor-1, suggesting thyroid gland as the origin. Pathological diagnosis

was PTTM due to diffuse sclerosing variant of thyroid papillary adenocarcinoma (DSVTPC) with thromboembolism in pulmonary artery resembling CTEPH (Figure 1).

DISCUSSION

In the present case, DSVPTC accompanied only by histological changes was a potential cause of PTTM, which mimicked the CTEPH with well-organized thrombus in pulmonary arteries on enhanced CT. Anticoagulant therapy and pulmonary dilators improved PH and enabled the withdrawal of mechanical support.

Poorly differentiated gastric cancer is a cause of PTTM, but thyroid cancer leading to PTTM has not been reported.¹ In an autopsy study, 16.7% of patients with gastric cancer exhibited PTTM features.² While poorly differentiated cancers are a frequent cause of PTTM, 85% of thyroid cancers are well-differentiated follicular cancers with a relatively good prognosis and a 10-year survival rate of 93%.³ DSVTPC is an aggressive variant with increased rates of recurrence, metastasis, and poor prognosis.⁴ DSVTPC, which comprises 6% of all papillary carcinomas,⁵ is characterized by diffuse thyroid gland enlargement without nodules, which hinders diagnosis. DSVTPC typically develops at a younger age and is usually complicated with Hashimoto's disease,⁵ vascular invasion, and lymph node metastasis.⁴ In the present case, the laboratory data and electroencephalogram revealed central hypothyroidism due to hypoxic encephalopathy and pathological findings of Hashimoto's disease were absent. Fine-needle aspiration cytology, which is useful for the diagnosis of thyroid cancer, does not necessarily reflect overall abnormalities in the thyroid gland. The present patient did not have thyroid nodules; therefore, thyroid carcinoma was not suspected. Positron emission tomography and aspiration cytology are used to diagnose primary thyroid lesions.⁶ Multimodality approaches may be considered for early identification and intervention of primary lesions leading to PTTM in the absence of a solid tumor.

The main cause of PTTM is remodeling of pulmonary arteries responding to cytokines released from tumor cells, and not tumor occlusion.⁷ However, the histological findings in the present case revealed recanalization in the organizing thrombus in the pulmonary artery, suggesting CTEPH. Additionally, there were obvious thrombi in segmental arteries on CT. These atypical PTTM findings mimicked the acute pulmonary embolism with CTEPH. The thrombotic tendency of thyroid carcinomas remains controversial. Cancer is associated with an overall increased of

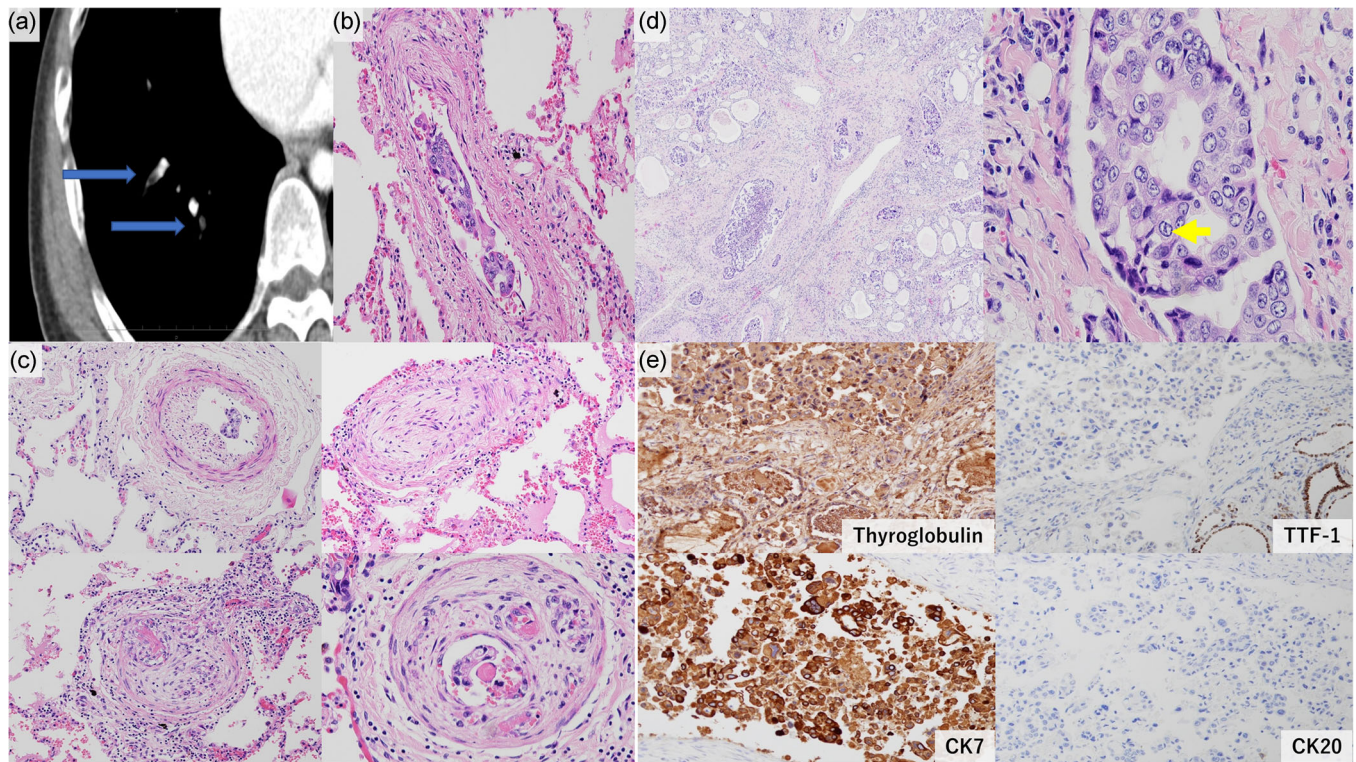


FIGURE 1 (a) Contrast-enhanced computed tomography at the time of diagnosis showing embolism in the subsegmental branch of pulmonary artery. (b) Postmortem pathological examination shows pulmonary edema and pulmonary alveolar hemorrhage in bilateral lungs and intimal thickening and recanalization with tumor cell embolization in both pulmonary arteries. (c) Pulmonary artery intimal thickening and thrombus recanalization. (d) Tumor cells exhibiting the characteristics of those in the pulmonary artery observed in the parenchyma and vasculature of the thyroid gland. Left: low-magnification ($\times 20$) image showing tumors in the vasculature and parenchyma. Right: high-magnification ($\times 200$) image showing characteristics of papillary carcinoma including nuclear grooves, frosted nuclei, and intranuclear cytoplasmic inclusions. (e) Tumor cells are positive for thyroglobulin and cytokeratin 7 and negative for cytokeratin 20 and thyroid transcription factor-1.

venous thromboembolism; however, data on the association between thyroid cancer and thrombus are limited. Medullary thyroid carcinoma can lead to a hypercoagulable state by elevating serotonin levels and increasing platelet aggregation capacity.⁸ Papillary carcinoma may also cause thrombosis.⁹ Heme oxygenase-1 upregulation in thyroid cancer cell lines increases the function of fibrinogen *in vivo* and *in vitro*.¹⁰ However, further confirmation in various thyroid cancer types, including aggressive variants, at various stages is warranted due to insufficient information.

We herein presented a patient who was diagnosed with PTTM due to DSVPTC without nodules using pathological assessment at autopsy to illustrate the possibility of a prothrombotic phenotype in PTTM which might require differential diagnosis including pulmonary embolism and CTEPH.

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CONFLICT OF INTERESTS

Yoshihisa Nakano and Takahisa Kondo were in the endowed Department of Actelion Pharmaceuticals Japan (now Janssen Pharmaceutical K.K.) until March 2021. All other authors have no conflict of interest to disclose.

ETHICS STATEMENT

We obtained a written consent from the patient's father.

AUTHOR CONTRIBUTIONS

Masahiro Yoshida, Ryo Imai, Yoshihisa Nakano, and Shiro Adachi examined the patient. Masahiro Yoshida, Kenichiro Yasuda, Itsumure Nishiyama, Deoksu Kim, Yuta Tsuyuki, and Shiro Adachi collected the data, drafted the manuscript, and revised the manuscript. Shiro Adachi, Takahisa Kondo and Toyoaki Murohara critically reviewed and revised the

manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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