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Case report

Long-term survival of a patient with uterine cancer-induced pulmonary tumor thrombotic microangiopathy following treatment with platinum-based chemotherapy and bevacizumab: A case report

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ABSTRACT

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare but fatal cancer-related disease. Owing to its non-specific findings, aggressive course, and lack of established treatment guidelines, only a few cases of antemortem diagnosis in long-term survivors have been reported. We aimed to report a case of uterine cervical cancer induced PTTM that was suspected based on pulmonary hypertension and successfully treated using combination chemotherapy despite of delayed diagnose. It is important to be aware that PTTM should be suspected when respiratory failure occurs in patients with unexplained pulmonary hypertension. Multidisciplinary treatments including molecular targeted therapies might be effective treatment options.

1. Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare and fatal cancer-related disease that was first proposed by von Herbay and colleagues in 1990 [1]. It is characterized by acute progressive respiratory failure, along with pulmonary hypertension caused by pulmonary tumor embolism and fibrocellular intimal proliferation of small pulmonary arteries and arterioles. Owing to the rapid progression to respiratory and heart failure, most patients diagnosed with PTTM die within several weeks. The antemortem diagnosis of PTTM is challenging and relies on many nonspecific clinicopathological findings [2]. Therefore, most cases of PTTM (79%) are diagnosed only during postmortem examination [3], and only a few case reports of long-term survival exist [4–11]. The most common primary malignancy associated with PTTM is gastric cancer; however, various other types of cancers may cause PTTM as well [12]. There has been only one case report of uterine cervical cancer causing PTTM [13], although there are no case reports of patients experiencing long-term survival.

The pathogenesis of PTTM has not been well established, and therapeutic interventions are directed at treating the primary tumor. PTTM treatment may involve surgical resection, systemic chemotherapy, radiation therapy, or any combination thereof [9]. Some cytokines may contribute to progressive PTTM, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and osteopontin, all of which are associated with macrophage recruitment and fibrointimal proliferation [14]. Some case reports have shown that the survival of patients can be prolonged by the administration of molecular targeted agents, including bevacizumab (a VEGF receptor inhibitor) and imatinib (a PDGF receptor inhibitor) [4–8].

This report provides the first description of long-term survival in a patient with PTTM caused by uterine cervical cancer. In this case, PTTM was suspected based on the presence of pulmonary hypertension and was successfully treated via combination chemotherapy (platinum-based chemotherapy and bevacizumab).

Abbreviations: PTTM, pulmonary tumor thrombotic microangiopathy; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; GGO, ground glass opacity; CT, computed tomography; BAL, bronchoalveolar lavage; PAP, pulmonary arterial pressure; EBUS-TBLB, endobronchial ultrasound-guided transbronchial lung biopsy; PET–CT, positron emission tomography–computed tomography; PAWP, pulmonary arterial wedge pressure; FDG, fluorodeoxyglucose (^{18}F).

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2. Case presentation

A 66-year-old Japanese woman presented to Kameda Medical Center, a tertiary care and teaching hospital with 925 inpatients beds, due to dyspnea that had started the previous month. She had a past medical history of hypertension, diabetes mellitus, and dyslipidemia. She had no history of smoking or alcohol abuse, and she had no familial history of connective tissue or hematological diseases. She had not come into contact with any animals, including birds. Chest radiography, performed at our hospital four years previously, had revealed no abnormalities.

Upon physical examination, her blood pressure was 136/58 mmHg, and her heart rate was 83 beats/min. Her oxygen saturation level was 90% (room air), her respiratory rate was 20 breaths/min, her body temperature was 36.7 °C, and her body mass index was 34. Her mucous membranes were moist, and her nasopharynx and oropharynx had no ulcerations or exudates. Cardiac examination revealed normocardia, with prominent P2 sounds and a regular rhythm without murmurs. Tachypnea was noted. Inspiratory crackles were present in both lungs. No wheezing or rhonchi were present. No clubbing, cyanosis, or edema of the arms, hands, legs, or feet was noted. The abdominal, musculoskeletal, neurologic, and cutaneous examinations were normal. Arterial blood gas quantification showed type 1 respiratory failure (Table 1). Chest radiography revealed diffuse reticular and ground-glass opacities (GGO) in both lungs. Chest computed tomography (CT) demonstrated a bilateral mosaic attenuation pattern, with enlarged pulmonary arteries and patchy GGOs with consolidation (Fig. 1 A). There was no evidence of pulmonary embolism detected via contrast-enhanced CT performed on the following day.

The patient began treatment with a new medication (sitagliptin) for diabetes mellitus two months before presentation; therefore, we initially suspected a drug-induced lung disease, hypersensitivity pneumonia, or nonspecific interstitial pneumonia. On the next day of hospitalization, we stopped all of her medications and advised antigen avoidance. On the 7th day of hospitalization, bronchoalveolar lavage (BAL) was performed. BAL revealed increased numbers of inflammatory cells (Table 1), although the other findings were not specific and the BAL fluid cultures and cytology were negative. Her respiratory failure did not improve with the cessation of medications and antigens; therefore, we initiated the administration of prednisolone (40 mg/day: 0.5 mg/kg ideal body weight) on day 8. However, even after the start of steroid therapy, her respiratory status and CT findings did not improve; in fact, they continued to worsen, despite the subsequent administration of pulse steroid therapy (methylprednisolone: 1000 mg) with tacrolimus treatment (Fig. 1 B). Transthoracic echocardiography on day 10 revealed pulmonary hypertension, with findings that included a transtricuspid pressure gradient of 45 mmHg, flattening of the interventricular septum, right atrial enlargement (57 mm × 45 mm), estimated mean pulmonary artery pressure (PAP) of 27 mmHg, mild tricuspid and pulmonary regurgitation, and preserved ejection fraction of 67%. Therefore, we suspected PTTM and subsequently performed endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB), pulmonary perfusion scintigraphy, positron emission tomography–computed tomography (PET–CT), and right heart catheterization to confirm pulmonary hypertension, identify the primary tumor, and diagnose PTTM. The EBUS-TBLB revealed no malignant cells; however, arteriole stenosis with fibrous intimal thickening was observed (Fig. 3 A–B). Pulmonary perfusion scintigraphy revealed multiple small peripheral perfusion defects in both lungs (Fig. 2 A). PET–CT showed fluorodeoxyglucose (FDG) accumulation in the lungs,

Table 1
Laboratory tests.

Arterial blood gas (Room air)			Biochemistry			Bronchoalveolar lavage		
pH	7.436		TP	7.5	g/dL	Cell count	375000	/mL
$PaCO_2$	41.5	mmHg	Alb	3.9	g/dL	Neutrophils	1	%
PaO_2	49.2	mmHg	T-bil	0.5	mg/dL	Lymphocytes	5	%
HCO_3^-	27.3	mEq/L	AST	25	U/L	Macrophages	94	%
Base excess	2.8	mEq/L	ALT	20	U/L	CD4/CD8 ratio	0.41	
Glucose	114	mg/dL	LD	240	U/L			
			CK	54	U/L	Immunology		
Hematology			ALP	261	U/L	IgG	1442	mg/dL
WBC	7300	/μL	γ-GTP	22	U/L	IgA	246	mg/dL
Neutro	65.7	%	Na	141	mEq/L	IgM	96	mg/dL
Eosino	3	%	K	4.7	mEq/L	C3	132	mg/dL
Baso	0.8	%	Cl	103	mEq/L	C4	36.4	mg/dL
Mono	5.2	%	Ca	9.6	mg/dL	RF	10	IU/mL
Lymph	25.3	%	P	4	mg/dL	Anti-CCP antibody		negative
Atypical-Lymph	0	%	BUN	12	mg/dL	Anti-nuclear antibody	<40	Index
RBC	558×10^4	/μL	sCr	0.61	mg/dL	Anti-Smith antibody		negative
Hb	16.1	g/dL	eGFR	73.98	mL/min/1.73m^2	Anti-SS-A antibody		negative
Ht	49.1	%	CRP	1.77	mg/L	Anti-Scl 70 antibody		negative
Plt	29.0×10^4	/μL	BNP	103.5	pg/mL	Anti-U1RNP antibody		negative
			IGRA		negative	Anti-centromere antibody	<5	Index
Blood coagulation			β-D-glucan	<5	pg/mL	PR3-ANCA	<1.0	U/mL
PT-INR	1.01		ACE	13.5	U/L	MPO-ANCA	<1.0	U/mL
APTT	24.8	Sec	KL-6	490.5	U/mL	HIV-1/2 antibody		negative
Fibrinogen	463	mg/dL	sIL-2R	556	U/mL			
FDP	3.2	μg/mL						
D-dimer	1.5	μg/mL						

WBC: white blood cells, Neutro: neutrophils, Eosino: eosinophils, Baso: basophils, Mono: monocytes, Lymph: lymphocytes, RBC: red blood cells, Hb: hemoglobin, Ht: hematocrit, Plt: platelets, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, TP: total protein, Alb: Albumin, T-bil: total-bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, LD: lactate dehydrogenase, CK: creatine kinase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltransferase, BUN: blood urine nitrogen, sCr: serum creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, BNP: brain natriuretic peptide, IGRA: interferon gamma releasing assay (QuantiFERON®-TB Gold Plus), ACE: angiotensin-converting enzyme, KL-6: Krebs von den Lungen-6, sIL-2R: soluble interleukin-2 receptor, CD4/CD8 ratio: cluster of differentiation 4/cluster of differentiation 8 ratio, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, RF: rheumatoid factor, Anti-CCP antibody: anti-cyclic citrullinated antibody, Anti-SS-A antibody: anti–Sjögren's-syndrome-related antigen A antibody, Anti-Scl 70 antibody: anti-scleroderma and 70 kD immunoreactive fragment antibody, Anti-U1RNP antibody: anti-U1-ribonucleoprotein antibody, PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, HIV-1/2 antibody: human immunodeficiency virus 1/2 antibody.

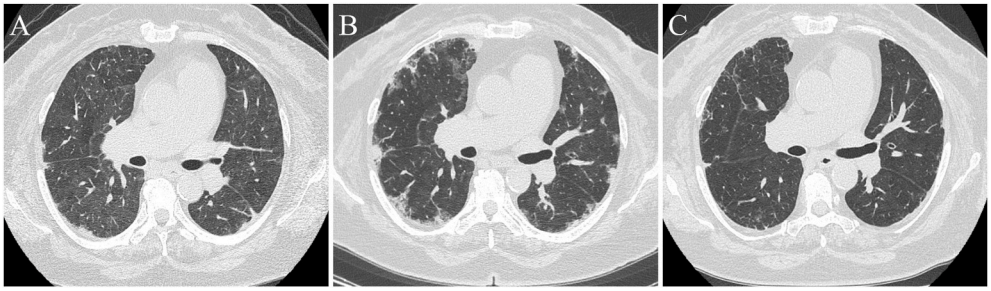

Fig. 1. Chest CT findings at the time of admission (A), after the administration of a corticosteroid and tacrolimus (B), and after six cycles of chemotherapy (C). Conventional CT of the chest revealing mosaic attenuation, with patchy GGOs and a slight subpleural consolidation at the time of admission (A). Even after initiating steroid and tacrolimus therapy, GGOs and consolidation worsen (B). Mosaic attenuation, GGOs, and consolidation in both lungs are improved after chemotherapy (C). CT: computed tomography, GGO: ground-glass opacity.

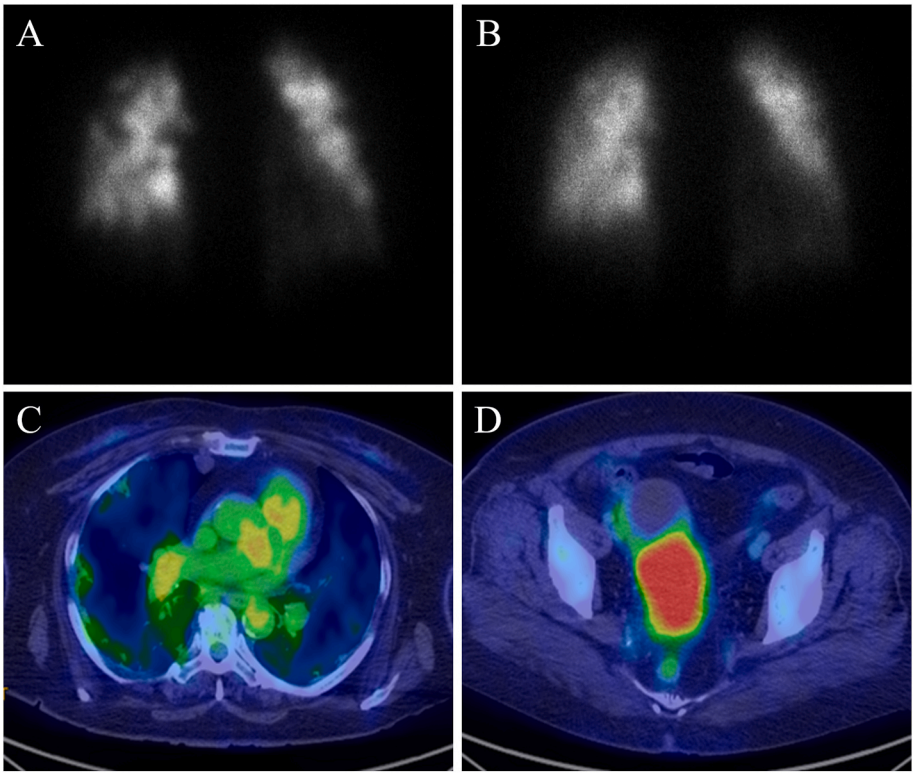

Fig. 2. Pulmonary perfusion scintigraphy findings before chemotherapy (A) and after chemotherapy (B). PET–CT findings used to diagnose uterine cervical cancer (C–D). Pulmonary perfusion scintigraphy showing multiple small peripheral perfusion defects in both lungs (A). The defects are improved after chemotherapy (B). PET–CT revealing FDG accumulation with consolidation in both lungs (C) and in the uterine cervix (D). PET–CT: Position emission tomography–computed tomography, FDG: Fluorodeoxyglucose (^{18}F).

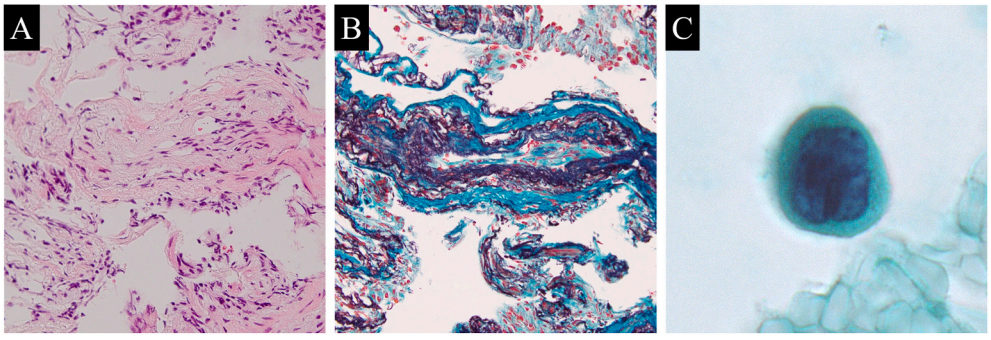

Fig. 3. EBUS-TBLB reveals pulmonary arteriolar stenosis by fibrointimal proliferation of fibroblasts and collagen (A–B). Only a single cell consistent with the characteristics of squamous cell carcinoma can be identified in the cytologic smears of pulmonary arterial blood aspirated from a catheter in the wedge position (C). EBUS-TBLB: endobronchial ultrasound-guided transbronchial lung biopsy. (A: Hematoxylin and eosin staining at × 200, B: Elastica-Masson staining at × 200, C: Papanicolaou staining at × 1000).

with consolidation, as well as in the uterine cervix (Fig. 2 C–D). Right heart catheterization indicated pulmonary hypertension (mean PAP: 28 mmHg) without elevated pulmonary artery wedge pressure (PAWP: 9 mmHg). Cytologic smears of pulmonary wedge arterial blood exhibited only a single atypical cell, characterized by a large, grooved nucleus containing coarsely granular chromatin, dense, round cytoplasm, and high nuclear/cytoplasmic ratio; these findings were compatible with the characteristics of squamous cell carcinoma (Fig. 3 C).

Based on these findings, we suspected that the uterine cervical cancer caused PTTM. We consulted a gynecologist, and uterine cervical cancer was finally diagnosed on the 45th day of hospitalization. Chemotherapy was initiated immediately after diagnosis (1st course:

carboplatin [AUC5] + paclitaxel [175 mg/m^2], 2nd course onwards: carboplatin [AUC5] + paclitaxel [175 mg/m^2] + bevacizumab [15 mg/kg]) under strict informed consent requirements. The patient was discharged on the 60th day of hospitalization. After initiation of chemotherapy, the patient's respiratory status and radiological findings (assessed by chest CT and pulmonary perfusion scintigraphy) improved concomitantly with a reduction in the size of the tumor (Fig. 1 B–C, Fig. 2 A–B). She received chemotherapy every three weeks for a total of 18 weeks (six total courses). Although chemotherapy had to be discontinued due to grade 1 epistaxis, no serious side effects were noted. After six courses of chemotherapy, the patient achieved complete remission from uterine cervical cancer. The patient is still alive and is followed up at our hospital regularly. She has recovered well from respiratory failure, and her condition has improved, even six months after the end of treatment. Currently, the patient only requires oxygen administration upon exertion, at a flow rate of 1 L/min.

3. Discussion

3.1. Clinical discussion

We reported a case of PTTM in a patient with uterine cervical cancer. PTTM was suspected due to the presence of pulmonary hypertension, and long-term survival was achieved using a combination treatment of platinum-based chemotherapy with bevacizumab, a VEGF inhibitor. This case provides two important recommendations.

Firstly, PTTM should be considered when patients display unexplained pulmonary hypertension with respiratory failure. The diagnosis of PTTM is challenging due to its rarity and its associated nonspecific initial findings. Therefore, it is important to suspect the condition whenever appropriate and relevant. One systematic review revealed that the common symptoms of PTTM were cough (85%), dyspnea (94%), hypoxemia (95%), and pulmonary hypertension (89%), with common CT features being GGOs (82%) and nodules (86%) [3]. Other CT features depended on the etiology of the primary tumors (tree-in-bud, septal thickening, mediastinal adenopathy, etc.) [3]. These symptoms and CT findings are nonspecific and might be observed in other respiratory diseases as well. Pulmonary hypertension seems to be an unusual and specific finding in our case. Pulmonary hypertension is usually the result of an underlying cause, such as heart failure or chronic pulmonary disease, and it is classified into five groups based on the etiology and mechanism [15]. The 2015 European Society of Cardiology and European Respiratory Society Guidelines have classified PTTM within subgroup 5.4 of the current classification of pulmonary hypertension [16]; however, this classification does not necessarily provide insight into managing such patients. In our case, the patient did not have any previous history of chronic respiratory disease, heart disease, genetic disease, pulmonary hypertension, collagen disease, or massive pulmonary embolism. Therefore, we suspected that her pulmonary hypertension was unusual, and additional tests were recommended.

Secondly, VEGF might be a target for the treatment of PTTM. Although the pathogenesis of PTTM has not been clearly established, the main etiology of PTTM is characterized by tumor microemboli associated with fibrointimal proliferation [14]. Cancer cell attachment is hypothesized to cause endothelial cell damage, activating coagulation mechanism and initiating proliferation through the release of cytokines and growth factors, including tissue factor, VEGF, and PDGF. This can contribute to the progression of the occlusion of the pulmonary vessels, resulting in increased pulmonary vascular resistance [17]. Previous reports have supported this idea through immunohistochemical studies, observing that tissue factor, VEGF, and PDGF are important molecules in the pathogenesis of PTTM [12,17].

Several questions remain unanswered in this case. Firstly, PTTM is fulminant, and the mean time from the onset of symptoms to death is only one month [14]. However, in this case, the patient had survived for about two months before receiving any chemotherapy. According to a previous systematic review [3], the average values associated with right heart catheterization in PTTM cases are a mean PAP of 48 mmHg (median: 48 mmHg, range: 34–70 mmHg) and a PAWP of 15 mmHg (median: 12 mmHg, range: 6–35 mmHg). In this case, the pulmonary hypertension and heart failure experienced by the patient was milder (mean PAP: 28 mmHg, PAWP: 9 mmHg) than that in previous reports. This mild pulmonary hypertension may have contributed to the long-term survival of this patient. Secondly, we cannot completely rule out the possibility of other complications associated with respiratory failure, such as infectious diseases or other diseases that would benefit from corticosteroid administration. However, the patient was not prescribed any antibiotics during the course of treatment, and her respiratory failure progressed even after we discontinued all other drugs and initiated steroid treatment. Therefore, we believe that any potential involvement of infectious microorganisms and other diseases would have been minimal or non-existent.

3.2. Imaging discussion

The perfusion scintigraphy showed multiple small, wedge-shaped perfusion defects in both lungs, which are characteristic of PTTM and suggest the presence of lesions in the blood vessels [18]. After chemotherapy treatment, mosaic attenuation, GGOs, and consolidation observed in the chest CT had improved, as did the defects observed in pulmonary perfusion scintigraphy. These imaging findings were compatible with the diagnosis of PTTM.

3.3. Pathologic discussion

We performed lung biopsies to search for tumor emboli within the pulmonary arterioles, along with fibrocellular intimal proliferation, as these are characteristic of PTTM [19]. However, we could not find any tumor emboli; therefore, we performed catheterization of the right side of the heart, which can not only determine the severity of pulmonary arterial hypertension but can also confirm the presence of tumor cells. Cytologic examination of blood aspirated through a pulmonary artery catheter in the wedge position may help diagnose PTTM, although it is challenging [20]. We could not confirm the presence of tumor cells in the histopathology of the lung biopsy specimens, although we did find an atypical cell in the blood aspirated from a pulmonary artery catheter that was consistent with the characteristics of squamous cell carcinoma. Considering this as well as the other findings, the patient's condition was conclusively diagnosed as PTTM.

3.4. Brief review of literature

In our case, the patient experienced long-term survival of PTTM following treatment with combination chemotherapy (platinum-based chemotherapy with bevacizumab). Adding bevacizumab might contribute to an enhanced therapeutic effect, which is supported by several case reports showing long-term survival is possible following PTTM through administration of molecular targeted agents, including bevacizumab (a VEGF inhibitor) and imatinib (a PDGF inhibitor) [4–8]. However, there is insufficient data to generate effective strategies for PTTM treatment because of its fulminant presentation and grave prognosis. Comprehensive studies are therefore needed to elucidate the effects of these molecular targeted agents.

4. Conclusion

In conclusion, it is important to be aware that various types of cancers may cause PTTM. We should consider PTTM when we see respiratory failure patients with unexplained pulmonary hypertension. Molecular targeted agents including bevacizumab might be a treatment option for PTTM; however, further research is needed for confirmation.

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Declarations of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of competing interest

The authors have no conflicts of interest declare.

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