in vivo *32*: 337-343 (2018)
doi:10.21873/invivo.11243

Pulmonary Tumor Embolism Due to Squamous Cell Carcinoma of the Uterine Cervix: A Case Report

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Abstract. *Background/Aim: We report on a case of pulmonary tumor embolism caused by squamous cell carcinoma of the uterine cervix. Patients and Methods: A 60-year-old female diagnosed with stage IVB (cT4N1M1) squamous cell carcinoma of the uterine cervix was admitted to our institution with a chief complaint of progressive dyspnea that developed within a few days after admission. Results: A chest CT scan showed dilated pulmonary arteries, right ventricular enlargement and mosaic ground-glass opacities in both lungs. An echocardiogram revealed elevated right ventricular pressure and a floppy mass in the right ventricle. Pulmonary tumor embolism was highly suspected. However, she died from respiratory failure on the fourth day after admission. Autopsy revealed diffuse tumor emboli in bilateral pulmonary arteries and arterioles. Conclusion: Pulmonary tumor embolism should be considered when patients with malignant disease develop unexplained dyspnea, hypoxemia, and pulmonary hypertension.*

Pulmonary tumor embolism is a rare and fatal complication in cancer patients. It leads to progressive clinical manifestations including respiratory failure, pulmonary hypertension, right heart failure, and sudden death (1). Generally, tumor embolism is more common in patients with adenocarcinoma compared to other histological types (2). This report describes a case in which a patient with squamous cell carcinoma of the uterine cervix developed pulmonary tumor embolism and followed a fatal clinical course within a few days after the onset of symptoms, along with multimodal diagnostic imaging and autopsy findings.

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Key Words: Pulmonary tumor embolism, uterine cervical cancer, autopsy.

Case Presentation

Clinical findings. A 60-year-old female visited a local clinic with a chief complaint of continuous genital bleeding. She was referred to our institution with suspected cervical cancer. Pelvic examination revealed an easily bleeding mass occupying the external uterine orifice, with bilateral parametrial and lower vaginal infiltration. Magnetic resonance imaging (MRI) revealed a large tumor in the uterine cervix that had invaded into the uterine corpus, bilateral parametria, vagina, rectum, and bladder (Figure 1). MRI also showed multiple enlarged pelvic lymph nodes. Computed tomography (CT) revealed multiple low-density lesions in the liver, suggesting liver metastases. A biopsy of the cervical mass revealed a keratinizing squamous cell carcinoma of the uterine cervix, and the patient was diagnosed with stage IVB (cT4N1M1) cervical cancer. One week later, she developed progressive dyspnea, cyanosis, tachycardia (105 beats per minute), and tachypnea (30 breaths per minute). Her peripheral capillary oxygen saturation was 80-85%, and her blood pressure and body temperature were normal. No abnormal findings were noted on auscultation of both lungs. Arterial blood gas analysis showed alkalemia (pH 7.482), decreased levels of arterial oxygen tension (PaO_2, 54.9 mmHg), arterial carbon

Table I. *Laboratory data on admission.*

Hematology & Coagulation		Biochemistry		Blood gas analysis	
WBC	11530/μ	TP	6.3 g/dl	pH	7.482
RBC	425×10^4/μ	Alb	3.4 g/dl	$PaCO_2$	21.8 mmHg
HGB	14.4 g/dl	CK	186 U/L	PaO_2	54.9 mmHg
HCT	42.4%	AST	51 U/L	BE	–7.5 mmol/L
MCV	99.8 fl	ALT	28 U/L	HCO_3	15.9 mmol/L
MCH	33.9 pg	LDH	443 U/L	SaO_2	87.9%
MCHC	34.0 g/dl	ALP	625 U/L	AG	16.5 mmol/L
D-dimer	1.71 μg/ml	Cr	0.90 mg/dl		
FDP	4.4 μg/ml	BUN	12 mg/dl		
PT	12.7 sec	Na	133 mEq/L		
PT-INR	1.11	K	5.2 mEq/L		
APTT	31.5 sec	CRP	3.36 mg/dl		

WBC: White blood cell count; RBC: red blood cell count; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscle volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; FDP: fibrinogen degradation products; PT: prothrombin time; INR: international normalized ratio; APTT: activated partial thrombin time; TP: total protein; Alb: albumin, CK: creatine phosphokinase, AST: alanine aminotransferase; ALT: alanine transaminase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase, Cr: creatinine; BUN: blood urea nitrogen; Na: sodium; K: potassium; CRP: c-reactive protein, $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; BE: base excess; HCO_3: bicarbonate; SaO_2: oxygen saturation in arterial blood; AG: anion gap.

dioxide tension ($PaCO_2$, 21.8 mmHg), bicarbonate (15.9 mmol/l), and base excess (-7.5 mmol/L), and an elevated anion gap (16.5 mmol/l), suggesting type I respiratory failure, respiratory alkalosis, and metabolic acidosis. Laboratory tests showed elevated D-dimer, C-reactive protein, white blood cell count, and creatinine levels (Table I). Contrast enhanced CT of the chest showed dilation of pulmonary artery trunk, dilated peripheral pulmonary artery branches, right ventricular enlargement and mosaic ground-glass opacities in both lungs, suggesting possible pulmonary hypertension, while defects of enhancement in major pulmonary arteries were not observed (Figure 2a and b). Echocardiogram revealed elevated right ventricular pressure estimated to be 88 mmHg and a floppy mass in the right ventricle (Figure 3), which was suspected to be a thrombus or vegetation. Based on these findings, it was highly likely that the patient developed multiple microscopic pulmonary tumor emboli. Her condition rapidly deteriorated on the fourth day after admission, and she died from respiratory failure.

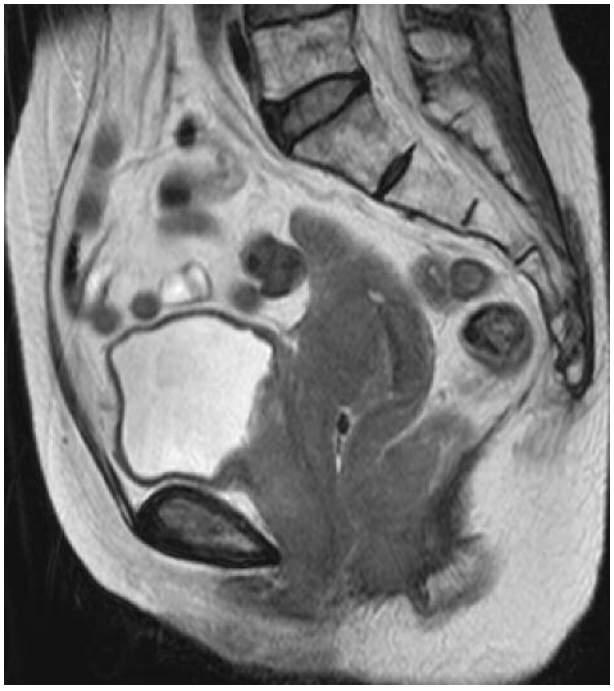
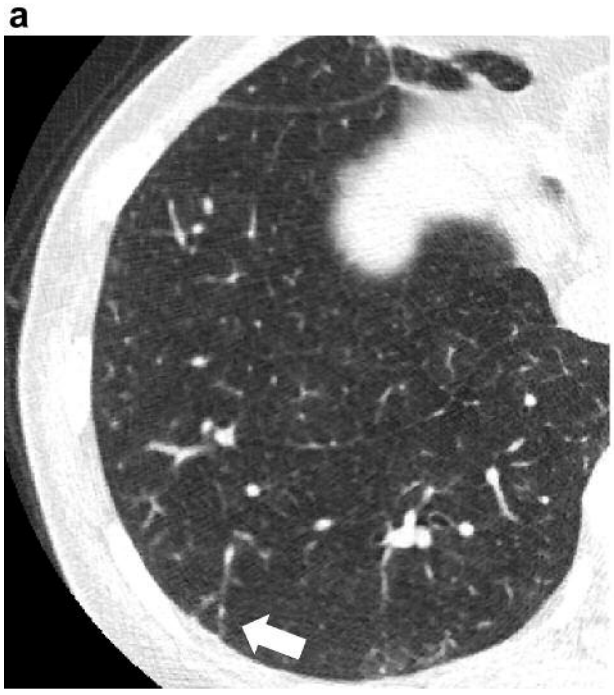


Figure 1. *MRI of the pelvis at diagnosis. T2 weighted MRI at diagnosis showed a bulky tumor in the uterine cervix that had invaded the surrounding organs.*

Pathological findings. An autopsy was performed with consent from the patient's family. A white solid tumor occupied the uterine cervix with ambiguous borders between surrounding normal structures such as the uterine corpus, vagina, rectum, and bladder (Figure 4a). The tumor was externalized on the bladder wall and had invaded into the lamina propria of the rectum. Tumor embolism was observed in bilateral pulmonary arteries without evidence of direct invasion to pulmonary parenchyma (Figure 4b). A metastatic tumor was found in the papillary muscle of the right ventricle (Figure 4c). Tumor embolism was also observed in the portal vein (Figure 4d). Hemorrhagic infarctions were



observed in the lower lobes of both lungs, and the lung parenchyma was congested with loss of aeration. There was no pleural effusion. Bloody fluid (50 ml) was present in the pericardial cavity. Her liver weighed 1,540 g and had multiple metastatic nodules. Her kidneys, pancreas, spleen, adrenal glands, gastrointestinal tract, and thyroids were normal. Her brain was not examined.

Histologically, tumor cells had oval nuclei and eosinophilic cytoplasm and were arranged in restiform nest with the interstitial reaction. Keratinization and intercellular bridges were present, leading to a diagnosis of squamous cell carcinoma (Figure 4e). The tumor had invaded blood vessels and infiltrated lymph vessels (Figure 4f). Diffuse tumor emboli were found in pulmonary arterioles (Figure 4g). The arteriole walls had a normal structure. Although intimal organizations and stenoses were partially observed along with micro tumor emboli, most of vascular intimae were normal. Blood clot formation were not observed.

These findings were consistent with the diagnosis of diffuse tumor embolism in bilateral pulmonary arteries and arterioles, which were considered the direct cause of death.

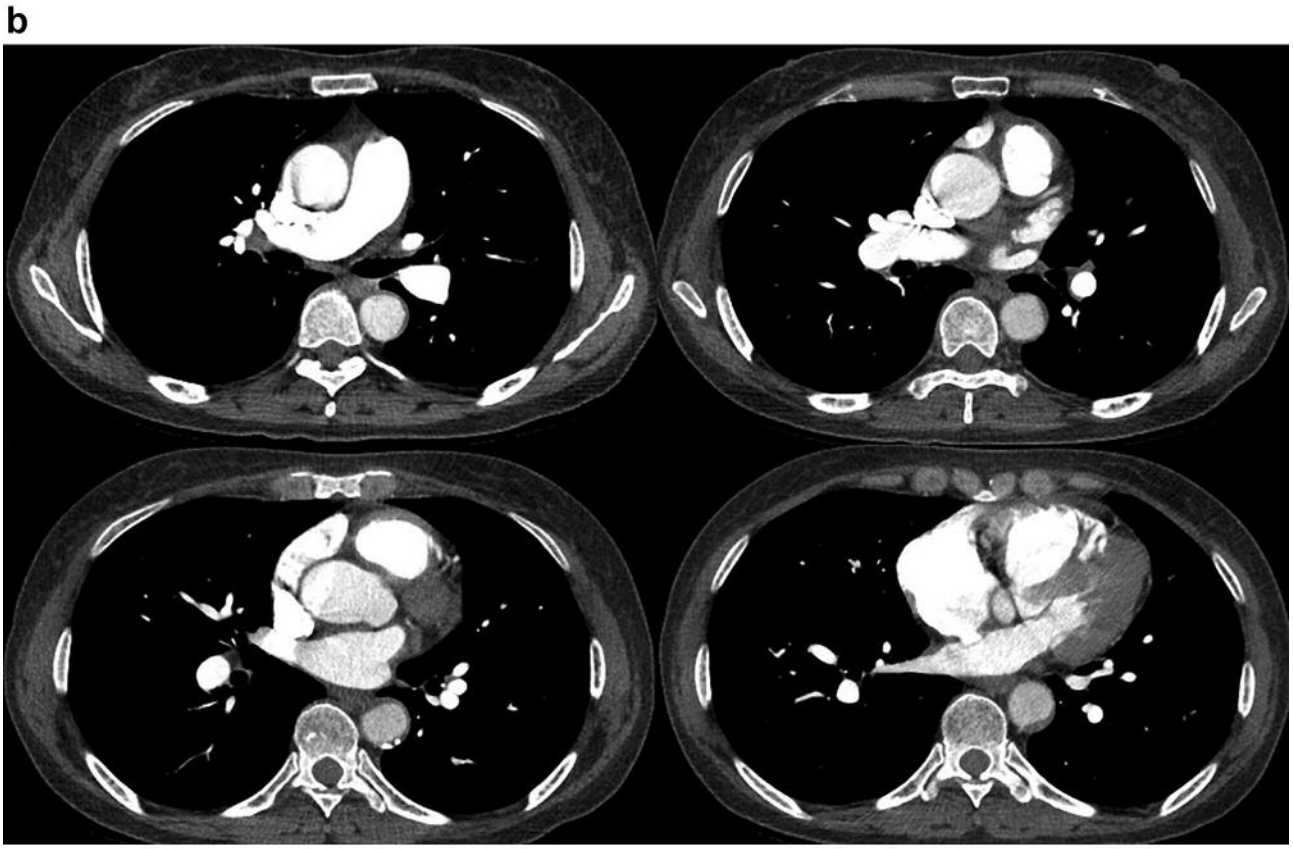


Figure 2. *Chest CT images at the onset of progressive dyspnea. a. Mosaic ground-glass opacities and dilated peripheral artery branches (white arrow) were observed in chest CT with lung window settings; b. Contrast-enhanced CT scan of the chest in the arterial phase showed no filling defects in pulmonary arteries, while dilation of pulmonary artery trunk and right ventricular enlargement were observed.*

Table II. *Previous reports of pulmonary tumor embolism due to cervical cancer.*

Author	Age	Initial stage	Histological type	Diagnostic modality for tumor embolism	Cardiac metastasis	Treatment of tumor embolism	Time to death from tumor embolism	Time to death from initial diagnosis
Senzaki *et al*. (7)	28	IB	SCC	Autopsy	+	Chemotherapy	ND	17 months
Byun *et al*. (8)	32	IIA	SCC	Chest CT	+	Surgery and chemotherapy	13 months	32 months
Inamura *et al*. (9)	58	IB1	SCC	Chest CT	+	Surgery	4 months	47 months
Borsaru *et al*. (10)	42	IVB	SCC	Chest CT	+	Surgery	ND	ND
Iwaki *et al*. (11)	49	ND	SCC	Autopsy	+	Chemotherapy and radiotherapy	2 months	2 months
Nakao *et al*. (12)	57	IIIB	SCC	Chest CT	+	None	2 months	12 months
Caballero *et al*. (13)	52	IVB	AD	Mini-thoracotomy	+	None	ND	ND
Mohammed *et al*. (14)	64	IIIB	SCC	ND	+	Radiotherapy	3 days	7 months
Nesser *et al*. (15)	81	ND	SCC	Autopsy	+	None	3 days	5 years
Present study	60	IVB	SCC	Autopsy	+	None	4 days	23 days

ND: No data; SCC: squamous cell carcinoma; CT: computed tomography; AD: adenocarcinoma.

Discussion

Pulmonary tumor embolism is a rare and fatal complication of cancer, with an incidence ranging from 0.2% to 26% (2-4). Sakuma *et al*. reported higher incidence rates for large cell carcinoma, hepatic cell carcinoma, and adenocarcinoma, compared with other histological types (2). By primary site, incidence rates were higher for breast, stomach, lung, and liver cancers (1), which may be related to their proximity to the heart and lungs. In general, cervical squamous cell carcinoma tends to metastasize through the lymphatic pathway (5) and rarely causes cardiac metastasis or pulmonary tumor embolism. In the present case, metastatic tumors were found in the portal vein, right ventricle, and pulmonary arteries, suggesting that the primary tumor metastasized through the venous circulation. The fatal clinical course of this patient might have been due to this rare mechanism of metastasis.

Clinically-diagnosing tumor embolism is generally difficult, especially in patients with small arterial emboli. Goldhaber *et al*. reviewed 73 autopsy cases with malignant tumors and pulmonary embolism, including 56 with major pulmonary thrombotic embolism (PTE) and 17 with pulmonary tumor embolism, and reported that although 45% of patients with PTE were correctly diagnosed, only 6% of those with tumor embolism were correctly diagnosed (6). Microscopic pulmonary tumor embolism shows nonspecific radiographic findings, which include focal interstitial opacities, effusions, and increased vascular markings (1). In such cases, pulmonary tumor embolism may only be found by autopsy. In the present case, tumor embolism was not directly diagnosed by imaging but was highly suspected based on indirect findings such as acute onset type I respiratory failure, dilatation of peripheral pulmonary arteries, mosaic ground-grass opacities in chest CT images, significant pulmonary hypertension, presence of a mass in the right ventricle, and elevated right ventricular pressure. Pulmonary tumor embolism in cervical cancer has been reported mostly in patients with cardiac metastasis (Table II) (7-15), suggesting that pulmonary tumor embolism should be considered in the differential diagnosis of patients with findings that suggest cardiac metastasis, even in the absence of typical imaging findings (*e.g*., perfusion defects in major pulmonary arteries).

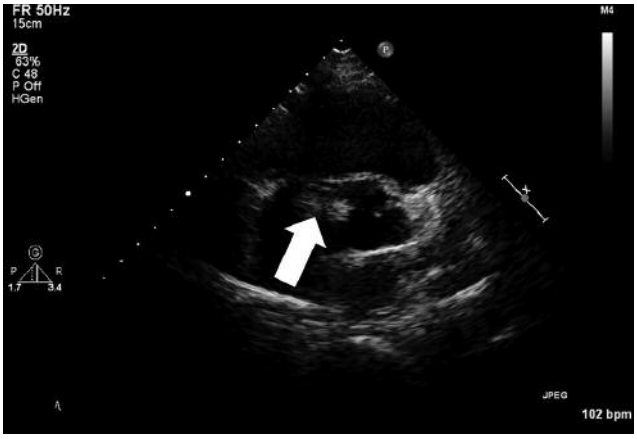


Figure 3. *Echocardiogram finding at the onset of progressive dyspnea. Echocardiogram in the four chamber view revealed a floppy mass in the auriculoventricular valve (white arrow).*

The present case took a fatal course within a few days after admission, as the patient's symptoms rapidly progressed. This is consistent with previous reports (Table

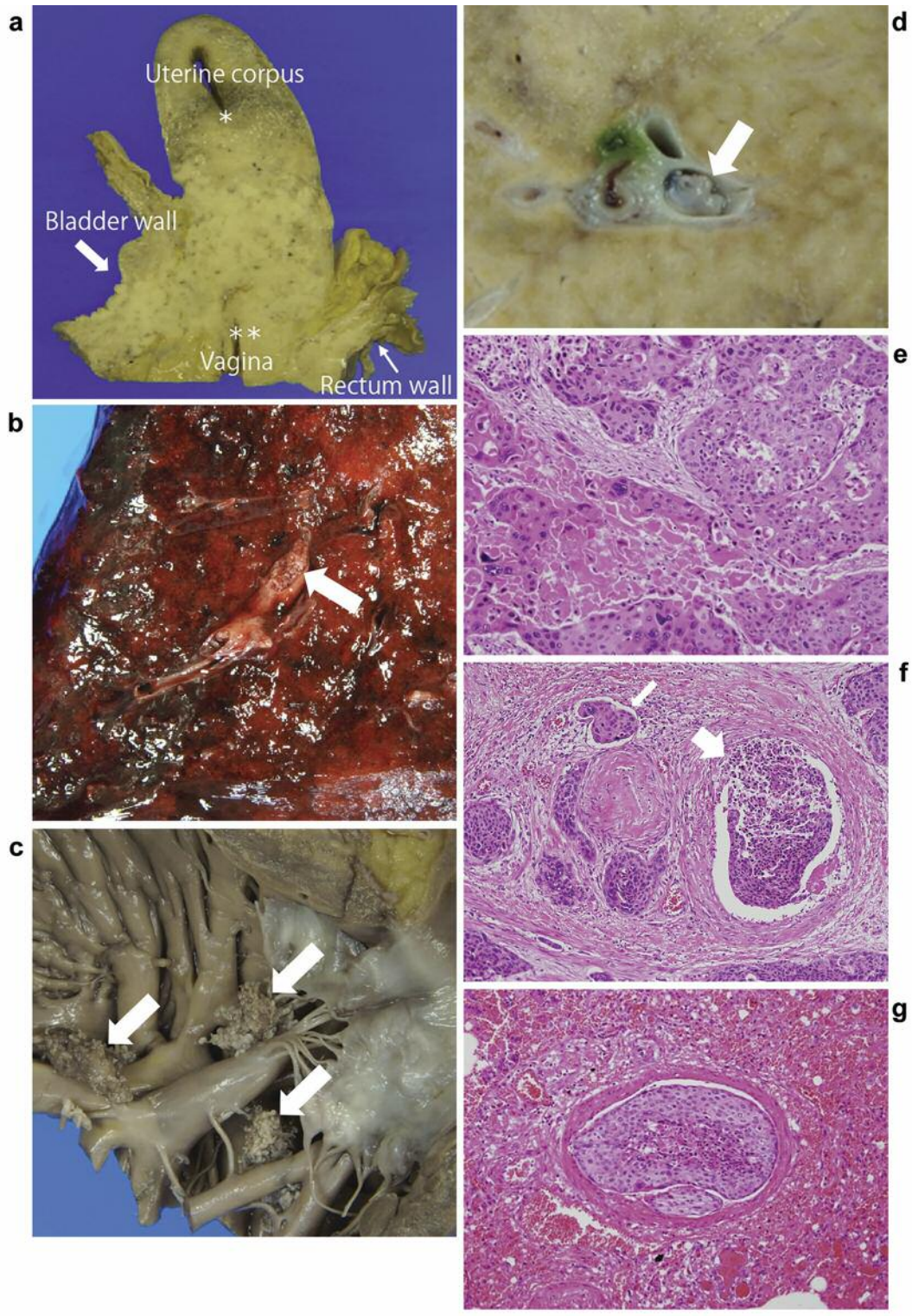


Figure 4. *Histopathological findings of the specimens at autopsy. a. The large tumor arose from the uterine cervix. The white homogenous tumor invaded the uterine corpus (*), vagina (**), posterior wall of the bladder (thick arrow), and anterior wall of the rectum (thin arrow); b. Tumor embolus was found in the pulmonary artery (white arrow); c. The metastatic tumor adhered to the papillary muscle in the right ventricle (white arrows); d. Tumor embolus was found in the portal vein (white arrow); e. Malignant squamous cells showed small round to oval nuclei and amphiphilic to eosinophilic cytoplasm; f. Tumor cells invaded the blood vessel (thick arrow) and lymphatic vessel (thin arrow); g. Viable tumor cell clusters were found in the pulmonary artery. The arterial wall had a normal structure. No intimal proliferation or blood clot formation was observed.*

II) suggesting that most patients with untreated tumor embolism progressed to death within a few days, whereas patients who received treatment survived for 2-13 months. Despite the rapid progression of symptoms, our patient showed no specific chest CT findings. Caballero *et al*. (13) reported a case in which a patient with pulmonary tumor embolism followed an acute clinical course; chest CT images revealed interstitial infiltrates that indicated carcinomatous lymphangitis and diffuse alveolar damage. In our case, non-specific CT findings suggested the cause of death to be microcirculatory impairment due to microscopic pulmonary tumor emboli, rather than interstitial damage.

Pulmonary tumor thrombotic microangiopathy (PTTM), characterized by fibrocellular intimal proliferation in small pulmonary arteries and activation of the coagulation system at the surface of tumor emboli should be considered as the differential diagnosis in patients with cancer suffering from pulmonary hypertension and rapidly progressive dyspnea (16). Although microscopic examination showed partial intimal thickening and stenoses similar to PTTM, the overwhelming majority of micro tumor emboli were observed, and they were considered to be the major cause of death. Extensive and diffuse pulmonary micro tumor emboli might have caused a rapid progression of respiratory failure as is the case with PTTM.

Microscopic pulmonary tumor embolism may be diagnosed more accurately with ventilation-perfusion scanning than other tests such as chest radiograph and CT scan (1). Chen *et al*. reported that perfusion defects caused by tumor emboli are characteristic in that they are more numerous, symmetric, and peripheral than those of thrombotic emboli (17). Sostman *et al*. and Crane *et al*. reported the superior diagnostic ability of lung scintigraphy when compared to other diagnostic modalities (18, 19). However, the safety of lung scintigraphy in patients with pulmonary hypertension is controversial. Some reported that patients with pulmonary hypertension developed fatal pulmonary complications following injection of macroaggregated albumin (20, 21). The use of other diagnostic modalities, such as right heart catheterization, pulmonary wedge aspiration cytology, and CT-guided lung biopsy with mini-thoracotomy have been reported (1, 13). In the present case, because respiratory failure progressed rapidly within a few days after the onset of symptoms, invasive examinations could not be performed. If patients with malignant disease develop unexplained hypoxemia and pulmonary hypertension, the above-mentioned diagnostic modalities should be considered, and if the condition allows, appropriate treatment should be initiated.

Although pulmonary tumor embolism caused by uterine cervical cancer is rare, this report completes multimodality diagnostic imaging and autopsy findings, and would be useful for the diagnosis of pulmonary micro-tumor embolism.

Conclusion

We reported multimodality diagnostic imaging and autopsy findings of diffuse pulmonary tumor embolism in a patient with squamous cell carcinoma of the uterine cervix. Pulmonary tumor embolism should be considered if patients with malignant disease develop rapidly progressive dyspnea.

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Received December 14, 2017
Revised January 12, 2018
Accepted January 15, 2018