

[CASE REPORT]

Concomitant Pulmonary and Cerebral Tumor Embolism and Intracardiac Metastasis from Bladder Cancer

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Abstract:

An 82-year-old woman with a history of bladder cancer presented with dyspnea and loss of consciousness. Contrast-enhanced computed tomography revealed pulmonary embolism, and emergency thrombus aspiration therapy was performed, but the thrombus was not aspirated. Echocardiography showed mobile masses in the heart and a right-to-left shunt due to a patent foramen ovale (PFO). Magnetic resonance imaging showed multiple cerebral infarctions. Surgical thrombectomy and PFO closure were performed, and the patient was diagnosed with intracardiac metastasis of bladder cancer based on intraoperative histopathology. This is a rare case of concomitant pulmonary and cerebral tumor embolism and intracardiac metastasis from bladder cancer.

Key words: pulmonary tumor embolism, paradoxical embolism, patent foramen ovale, intracardiac metastasis, pulmonary artery aspiration cytology

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Introduction

In patients with patent foramen ovale (PFO), when the right atrial pressure exceeds the left atrial pressure, a right-to-left shunt occurs. Embolic sources shift from the right heart system to the left heart system through the PFO and cause embolism in the systemic arterial system (1-3).

Malignant tumors are known to cause organ damage due to embolism, in addition to direct organ damage. Paradoxical embolism and pulmonary tumor embolism (PTE) affect the patient's prognosis. PTE is associated with a mortality rate of 8% (4). Autopsies of patients with solid tumors revealed PTE in 3-26% of the cases (5). The majority of PTEs are caused by breast, lung, and stomach cancers. However, in a previous study, 3 of 109 patients with solid tumors had PTE due to bladder cancer (4). In addition, metastatic malignant tumors are relatively common among heart tumors, although cardiac metastasis of bladder cancer is rare.

We herein report a case of PTE complicated by paradoxi-

cal embolism due to PFO and intracardiac metastasis of bladder cancer, which was diagnosed by an intraoperative examination.

Case Report

An 82-year-old woman with gross hematuria visited our urology department and was diagnosed with invasive bladder cancer. She had never been diagnosed with congenital heart disease or embolism. She underwent total cystectomy with ileal conduit surgery and postoperative radiation therapy. Computed tomography (CT) was performed two months after the operation, and neither relapse nor metastasis was observed. Six months after the operation, she visited our hospital for transient loss of consciousness and persistent dyspnea.

On admission, her blood pressure was 88/46 mmHg, pulse rate was 132/min, and oxygen saturation was 74% in room air. The D-dimer level was 14.7 µg/mL (<1.0 µg/mL), and transthoracic echocardiography (TTE) showed normal

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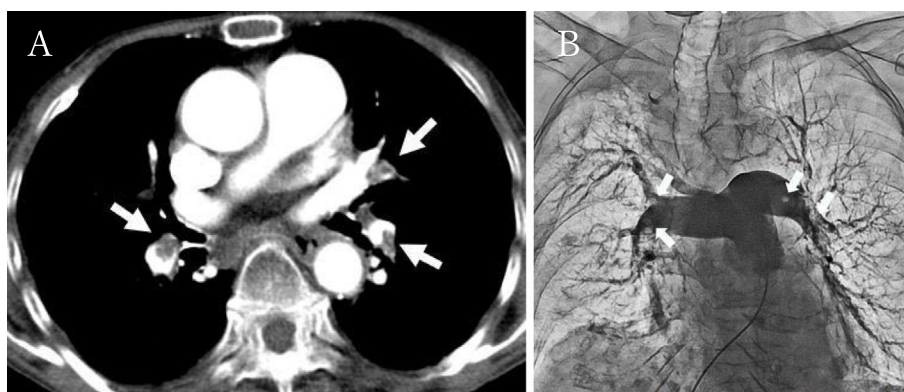


Figure 1. (A) Contrast-enhanced computed tomography image of the chest showing filling defects in both pulmonary arteries (arrow). (B) Pulmonary angiography showing filling defects in the left main pulmonary artery and both branches.

left ventricular wall motion and flattening of the interventricular septum. Contrast-enhanced CT showed filling defects in the bilateral pulmonary arteries (Fig. 1A) and right ventricular dilatation. No thrombus was found in the limbs or pelvic veins. We diagnosed her with pulmonary embolism (PE) with obstructive shock. Despite treatment with fluid therapy and dopamine in the emergency room, her systolic blood pressure was approximately 60 mmHg, and no improvement was observed.

Given her advanced age, thrombolytic therapy had a high risk of bleeding; therefore, thrombus aspiration therapy was performed. Selective pulmonary angiography via an AXESS 7-Fr JR4.0 [Asahi Intecc (Thailand)] revealed defects in the left main pulmonary artery and branches. Thrombus aspiration therapy was performed using this catheter directed to the left pulmonary artery, but the thrombus was not aspirated. We did not advance an AXESS 7-Fr JR4.0 (Asahi Intecc) in the right pulmonary artery; instead, we used a 5-Fr JR4.0 (Asahi Intecc) in the right pulmonary artery. Subtraction angiography also demonstrated defects in the right upper and lower pulmonary branches, but no thrombus was removed (Fig. 1B).

After attempting thrombus aspiration, right heart catheterization was performed, showing a pulmonary artery pressure of 31/21(26) mmHg. When the patient's vital signs stabilized, we abandoned aspiration. In addition, coronary angiography did not reveal any significant stenosis of the coronary artery.

Continuous infusion of unfractionated heparin, 5,000 units of intravenous bolus, and continuous infusion of 1,000 units/h were started after the catheter examination, and the activated partial thromboplastin time (aPTT) was maintained between 1.5 and 2.5 times the control values.

On the third day after admission, TTE showed a mobile mass on the mitral valve and mitral chordae tendineae, which moved between the left atrium and the left ventricle (Fig. 2A). A mobile mass was also observed in the tricuspid valve of the chordae tendineae (Fig. 2B). Furthermore, there was flattening of the interventricular septum (Fig. 2C), and pulmonary hypertension with a right ventricular systolic

pressure (RVSP) of 59.6 mmHg was detected. Transesophageal echocardiography (TEE) revealed a PFO 4 mm in diameter, a right-to-left shunt, and a mass in the right atrium that straddled the PFO (Fig. 2D). The mass attached to the mitral valve was 35 mm×10 mm in size and moved back and forth between the left ventricle and the aorta beyond the aortic valve (Fig. 2E).

Although no significant neurological disorders were observed, magnetic resonance diffusion-weighted imaging of the brain (Fig. 3) showed scattered hyperintensities in the bilateral cerebral hemispheres and cerebellum, and we diagnosed multiple cerebral infarctions. The structure attached to the mitral valve was mobile, and since it could lead to further embolism, we decided to perform emergent surgical removal of the mass in the heart and PFO closure on the fourth day.

An intraoperative examination revealed a white mass in the left ventricle, which did not appear to be blood clots. The PFO was 5 mm in diameter and located in the upper part of the fossa ovalis. A string-like structure straddled the PFO. This string-like structure and the mass on the left ventricle were able to be easily removed. However, the mass on the tricuspid chordae tendineae and right atrium were firmly adhered, and we were unable to completely excise them. An intraoperative histopathological analysis revealed that the masses within the tricuspid chordae tendineae and right atrium were urothelial carcinoma, suggesting intracardiac metastasis of bladder cancer. After as much of the tumor as possible was removed, the PFO was closed.

On a postoperative pathological examination (Fig. 4), the mass found in the heart was determined to be metastasis of high-grade urothelial carcinoma. Given her poor general condition, chemotherapy after the operation was not initiated. Postoperative TTE showed no mass in the left atrium and ventricle, but it revealed a new mobile mass in the right atrium (Fig. 5A) and inferior vena cava (Fig. 5B). Despite intensive treatment, she died on the eighth day because of multiple organ failure.

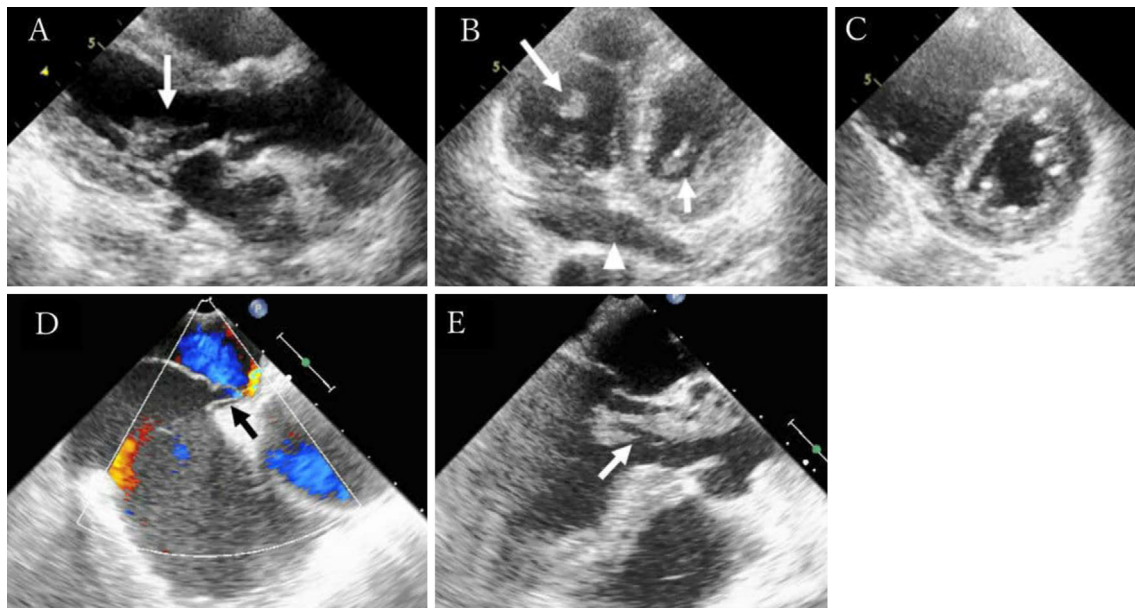


Figure 2. Transthoracic echocardiogram on the third day. (A) Parasternal long-axis view. The image demonstrated a mass on the mitral valve and mitral chordae tendineae (arrow). (B) Homogenous spherical mass on the mitral valve and tricuspid chordae tendineae (arrow) and expansion of the coronary sinus (arrowhead). (C) Parasternal short-axis view. This indicated dilatation of the right ventricle and flattening of the interventricular septum. Transesophageal echocardiography on the fourth day after admission. (D) View obtained at 60°. A blood flow indicated the presence of a right-to-left shunt due to the patent foramen ovale (PFO). The linear structure (arrow) in the right atrium straddled the PFO. (E) The view was obtained at 130°. It demonstrated the mobile mass (arrow) attached to the mitral valve moving back and forth between the left ventricle and the aorta beyond the aortic valve.

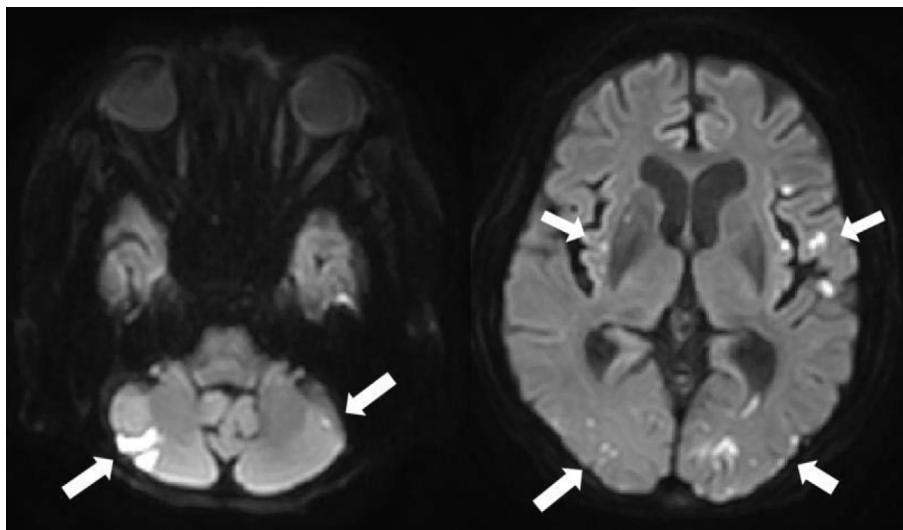


Figure 3. Magnetic resonance diffusion-weighted imaging of the brain showing scattered hyperintensities in the bilateral cerebral hemispheres and cerebellum (arrows).

Discussion

This is a rare case of PTE due to bladder cancer with paradoxical embolism and intracardiac metastasis, which was diagnosed by an intraoperative pathological examination.

PFO is present in 25-30% of individuals (2, 3). Some strokes of unknown origin may be caused by paradoxical embolism due to PFO (1). Although observing a thrombus straddling the PFO is difficult, some cases are detected by echocardiography (6-11). In the present case, we considered there to be a high possibility of tumor embolism rather than

thromboembolism, including Trousseau syndrome. We found that the tumor had spread from the right atrium to the left atrium via the PFO by TEE. In addition, contrast-enhanced CT did not indicate any other sources of embolus; brain magnetic resonance imaging did not demonstrate any stenosis of the intracranial or cervical arteries and showed cerebral infarcts scattered in various blood vessel regions. Although she had atrial fibrillation, TEE did not show any thrombus in the left atrial appendage thrombus, and we could not find any thrombus in the heart during intraoperative observation. Based on the above findings, we were able to diagnose PE and paradoxical embolism caused by the tumor.

In this case, we consider there to have been two types of tumors in the patient's heart: the tumor straddling the PFO and on the mitral valve, and the tumor in the right atrium and on the tricuspid valve. The tumor straddling the PFO and on the mitral valve was deemed to have invaded the heart due to the normal blood flow, and not due to intracar-

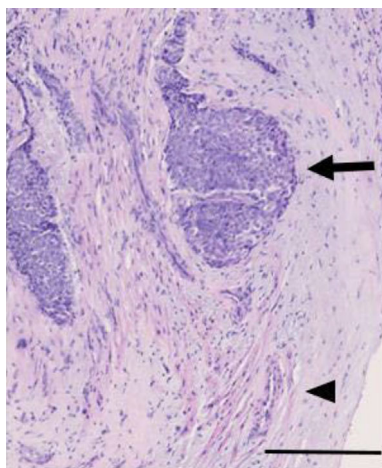


Figure 4. Postoperative pathological examination showing high-grade urothelial carcinoma infiltration (arrow) in the cardiac muscle tissue (arrowhead, $\times 50$, scale bar=0.25 mm).

diac metastasis. We suspect that the PE provoked a high pulmonary artery pressure, and the right atrial pressure exceeded the left atrial pressure, which created a right-to-left shunt through the PFO. In addition, the mass in the left heart and the mass straddling the PFO were easily removed during surgery, and we did not observe any infiltration into the cardiac tissue on a pathological examination. These findings suggest that these masses just drifted to the left heart and that there was no intracardiac metastasis. In contrast, the tumor in the right atrium had involvement with the heart because the pathological examination revealed urothelial carcinoma infiltration of the myocardium.

Metastatic heart tumors are relatively common among heart tumors, and a study on autopsies of 1,900 patients with cancer reported cardiac metastases in 8% of the patients (12). In a previous report, the proportion of metastatic tumors was shown to be high in lung cancer, breast cancer, and hematological tumors (13). However, intracardiac metastasis of bladder cancer is rare.

Tumor-bearing patients generally have a high risk of thrombosis, and it is important to determine the source of the embolism. In the present case, we were unable to confirm whether the PE had been caused by the tumor or thrombus because we could not perform an autopsy or any other pathological examinations. However, we consider the PE in this case to have been caused not by the thrombus but rather by the tumor for the following reasons. First, we confirmed the mobile mass of the bladder cancer in the right atrium and at the ventricle during the operation, and it had a high risk of drifting to the pulmonary arteries and provoking PE. Second, we were unable to aspirate any thrombus during thrombus aspiration therapy. If an embolus is a thrombus, we generally can aspirate some thrombus pieces in most cases. Third, the patient had started continuous infusion of unfractionated heparin after thrombus aspiration therapy, and the aPTT was maintained between 1.5 and 2.5 times that of the control. The D-dimer level decreased from 14.7 $\mu\text{g/mL}$ to 1.5 $\mu\text{g/mL}$, but her RVSP remained high, and

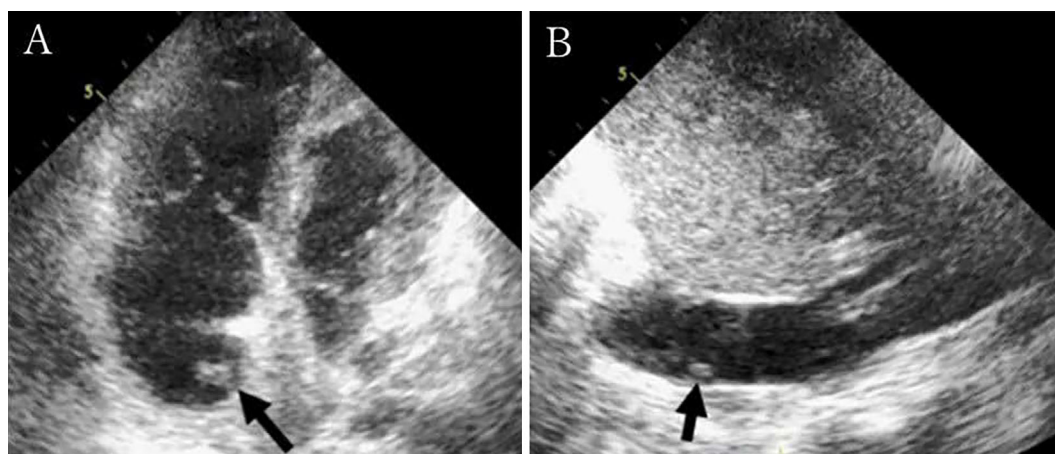


Figure 5. Four-chamber view (A) and parasternal view (B) of transthoracic echocardiography after the surgery (6 days after admission). They indicated new mobile masses in the right atrium and inferior vena cava (arrow). They were not found immediately after the operation.

we observed no improvement in the right heart overload.

In the present case, we detected the tumor embolism by rapid intraoperative histopathology. However, we might have been able to confirm the diagnosis earlier by pulmonary artery aspiration cytology. Pulmonary artery aspiration cytology is a method of diagnosing blood cytology aspirated from a Swan-Ganz catheter wedged into the pulmonary artery. Although filling defects in the pulmonary arteries on contrast-enhanced chest CT and peripheral blood deficits in pulmonary perfusion scintigraphy are suggestive findings of PTE, pathological evidence is required for a definitive diagnosis (4, 14).

In previous case reports, pulmonary artery aspiration cytology was useful for the diagnosis of PTE (4, 14-18), and pulmonary tumor thrombotic microangiopathy (PTTM) has been reported to be diagnosed with a sensitivity of 80-88% and a specificity of 82-94% (19). In the present case, for the early diagnosis, a cytodagnosis of the aspirated blood from the pulmonary artery should have been performed when thrombus aspiration therapy was performed.

Furthermore, autopsies of patients with solid tumors revealed PTE in 3-26% of the cases (5); therefore, in cases of PE with not only bladder cancer but also a history of malignant tumors, PTE is possible, and pulmonary artery aspiration cytology is recommended.

In summary, this is a rare case of PTE complicated by paradoxical embolism due to PFO and intracardiac metastasis of bladder cancer. An intraoperative pathological examination confirmed that the embolisms were caused by bladder cancer. The most important point is that, in patients with a history of cancer, the possibility of tumor embolism as well as thromboembolism should be considered. For the early diagnosis of PTE, pulmonary artery aspiration cytology may be considered if PE occurs in patients with a history of malignancy, which is not limited to bladder cancer.

The authors state that they have no Conflict of Interest (COI).

References

- Windecker S, Stortecky S, Meier B. Paradoxical embolism. *J Am Coll Cardiol* **64**: 403-415, 2014.
- Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* **59**: 17-20, 1984.
- Meissner I, Whisnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. *Mayo Clin Proc* **74**: 862-869, 1999.
- Roberts KE, Bena DH, Saqi A, Stein CA, Cole RP. Pulmonary tumor embolism: a review of the literature. *Am J Med* **115**: 228-232, 2003.
- Tamura A, Matsubara O. Pulmonary tumor embolism: relationship between clinical manifestations and pathologic findings. *Nippon Kyobu Shikkan Gakkai Zasshi (Jpn J of Thorac Dis)* **31**: 1269-1278, 1993 (in Japanese, Abstract in English).
- Sattar A, Win TT, Schevchuck A, Achrekar A. Extensive biatrial thrombus straddling the patent foramen ovale and traversing into the left and right ventricle. *BMJ Case Rep* **2016**: 216761, 2016.
- Shang X, Li D, Qiu Q, et al. First direct evidence of a patent foramen ovale (PFO): a large thrombus straddling the foramen ovale. *Eur Heart J* **37**: 782, 2016.
- Faustino A, Costa G, Providência R, Paiva L. Impending paradoxical embolism with a thrombus crossing a patent foramen ovale. *BMJ Case Rep* **2012**: 006662, 2012.
- Nemoto A, Kudo M, Yamabe K, Yozu R. Successful surgical treatment for a thrombus straddling a patent foramen ovale: a case report. *J Cardiothorac Surg* **8**: 138, 2013.
- Mascarenhas V, Kalyanasundaram A, Nassef LA, Lico S, Qureshi A. Simultaneous massive pulmonary embolism and impending paradoxical embolism through a patent foramen ovale. *J Am Coll Cardiol* **53**: 1338, 2009.
- Rinaldi JP, Latcu DG, Saoudi N. Real-time 3-dimensional transesophageal echocardiography for the diagnosis of a thrombus straddling the patent foramen ovale. *J Am Coll Cardiol* **55**: e7, 2010.
- Silvestri F, Bussani R, Pavletic N, Mannone T. Metastases of the heart and pericardium. *G Ital Cardiol* **27**: 1252-1255, 1997.
- Goldberg AD, Blankstein R, Padera RF. Tumors metastatic to the heart. *Circulation* **128**: 1790-1794, 2013.
- Fukuoka M, Kimura K, Kimura A, et al. Pulmonary tumor embolism 18 years after surgery for Paget's disease of the breast. *Nihon Rinsho Geka Gakkai Zasshi (J Jpn Soc Clin Surg)* **78**: 1236-1242, 2017 (in Japanese, Abstract in English).
- Kitamura A, Nishimura N, Jinta T, et al. A case of pulmonary tumor thrombotic microangiopathy diagnosed by transbronchial lung biopsy and treated with chemotherapy and long-term oxygen and anticoagulation therapies. *Case Rep Pulmonol* **2013**: 259080, 2013.
- Masson RG, Krikorian J, Lukl P, Evans GL, McGrath J. Pulmonary microvascular cytology in the diagnosis of lymphangitic carcinomatosis. *N Engl J Med* **321**: 71-76, 1989.
- Ishiguro T, Takayanagi N, Baba Y, et al. Case series of pulmonary tumor embolism and intravascular lymphoma: evaluation of the usefulness of pulmonary microvascular cytology. *J Intern Med* **55**: 2679-2684, 2016.
- Yamakawa H, Yoshida M, Yamada M, et al. Pulmonary tumor thrombotic microangiopathy associated with urothelial carcinoma of the urinary bladder: antemortem diagnosis by pulmonary microvascular cytology. *Clin Case Rep* **3**: 735-739, 2015.
- Keenan NG, Nicholson AG, Oldershaw PJ. Fatal acute pulmonary hypertension caused by pulmonary tumor thrombotic microangiopathy. *Int J Cardiol* **124**: e11-e13, 2008.

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