Case Series of Pulmonary Tumor Embolism and Intravascular Lymphoma: Evaluation of the Usefulness of Pulmonary Microvascular Cytology

Takashi Ishiguro¹, Noboru Takayanagi¹, Yuri Baba¹, Naho Kagiyama¹, Takashi Miyamoto², Makoto Mutoh², Yoshihiko Shimizu³ and Yutaka Sugita¹

Abstract

Pulmonary tumor embolism (PTE) and intravascular lymphoma cause rapidly progressive deterioration and an antemortem diagnosis is difficult. The usefulness of pulmonary microvascular cytology (PMC) in the diagnosis of these disorders has been reported in sporadic case reports. We retrospectively evaluated the records of 7 patients with tumor cells in the pulmonary microvasculature (4 with PTE and 3 with malignant lymphoma) who underwent pulmonary microvascular cytology. Two of the 4 patients with PTE and 2 of the 3 patients with malignant lymphoma (all 3 had intravascular metastasis) had positive PMC results. These findings suggested that PMC may be useful in the diagnosis of these disorders.

Key words: pulmonary microvascular cytology, pulmonary tumor embolism, pulmonary hypertension, intravascular lymphoma, pulmonary wedge aspiration cytology

(Intern Med 55: 2679-2684, 2016) (DOI: 10.2169/internalmedicine.55.6855)

Introduction

Malignant diseases do not uncommonly metastasize to the lungs because the pulmonary microvascular bed is anatomically well suited to serve as a filter and theoretically can entrap circulating tumor cells (1). In several conditions, however, tumor cells can metastasize and rapidly grow in the pulmonary microvasculature. Such conditions include pulmonary tumor embolism (PTE) and intravascular lymphoma (IVL), a subset of diffuse large B-cell lymphoma (DLBCL). These disorders have a poor prognosis and early diagnosis is required (2, 3), but antemortem diagnosis is difficult because radiological abnormalities are often not observed. In addition, patients with these disorders are often accompanied by pulmonary hypertension, thrombocytopenia, and severe respiratory failure, which limit the applicable methods of diagnosis.

It has been reported that pulmonary microvascular cytology (PMC), a procedure in which blood is obtained from the pulmonary microvasculature via a Swan-Ganz catheter, can detect tumor cells in the pulmonary microvasculature (4), suggesting that PMC is a useful method for diagnosing PTE and IVL. To our knowledge, however, the usefulness of PMC other than as reported by Masson et al. (4) has been addressed in only a few case reports (5-10) and small case studies (11). Therefore, in the present study, we assessed its usefulness in patients with tumor cells in the pulmonary microvasculature.

Case Report

We retrospectively studied the records of 7 patients with PTE (n=4), IVL (n=2), and DLBCL with intravascular metastasis (n=1) who underwent PMC from 2007 to 2014. Four of these cases have been reported previously (7, 8, 12, 13). The present study was approved by the ethical committee of the Saitama Cardiovascular and Respiratory Center (No. 2014032, approved on March 16th, 2015).

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Received for publication November 17, 2015; Accepted for publication January 13, 2016

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Table. Characteristics; Results of Tests Performed on Admission, to Detect Tumor Cells, and from PMC; and Prognosis of Patients who Underwent PMC.

| Case No. | Age/Sex | Initial symptoms (duration from initial symptoms to admission) | Diagnosis of pulmonary disease | RVSPa | Pulmonary artery pressureb | Arterial blood gas analysis pH/PaCO2/PaO2 (condition) | Platelets (×10^4/μL) | Tests performed to detect tumor cellsd | Hospital day performed | Amount of blood sampled | Results | Chemotherapy and prognosis | Autopsy |
|----------|---------|---------------------------------------------------------------|--------------------------------|-------|----------------------------|-----------------------------------------------|---------------------|---------------------------------------|----------------------|--------------------------|---------|-------------------------------|---------|
| Case 1  | 82/F   | Dyspnea, chest pain (9 days)                                  | PTE by breast cancer          | 57    | 60/20/33                   | 7.43/29.7/58.4 (ambient air)                  | 18.5                | BAL, PMC                             | 10                   | 20                       | Carcinoma | Patient refused chemotherapy and died on the 21st hospital day. | Yes     |
| Case 2  | 65/M   | Dyspnea (27 days)                                             | PTE (PTTM) by unknown primary site | 79    | 60/33/44                   | 7.46/26.9/50.8 (ambient air)                  | 2.7                 | BMA, PMC, TBLB                      | 2                    | 20                       | No malignancy | No chemotherapy but died 10 months from initial symptoms. | No      |
| Case 3  | 76/M   | Dyspnea, dry cough (32 days)                                  | PTE by gastric cancer         | 51    | 37/10/21                   | 7.44/36.7/66.2 (ambient air)                  | 27.4                | BAL, TBLB, PMC                      | 36                   | 20                       | No malignancy | Chemotherapy was not performed because of the severity of the patient's general condition. Died on the 14th hospital day. | Yes     |
| Case 4  | 82/F   | Dyspnea (47 days)                                             | PTE by unknown primary site   | 58    | 55/11/25                   | 7.47/34.2/60.7 (ambient air)                  | 20.3                | PMC                                  | 1                    | 10                       | Non-small cell carcinoma | Patient refused chemotherapy and died on the 37th hospital day. | No      |
| Case 5  | 68/M   | Dyspnea, night sweats, fever (14 days)                        | IVL                            | c     | 40/14/23                   | 7.44/33.6/64.4 (5 L/min, nasal canula)       | 8.2                 | BMA, skin biopsy, PMC               | 9                    | 50                       | Lymphoma    | Improved via chemotherapy, but died 9 months later from initial symptoms. | No      |
| Case 6  | 77/F   | Dyspnea, fever, headache (5 days)                             | Pulmonary metastasis by DLBCL of splenic origin | 30    | No recordings              | 7.47/33.5/58.8 (ambient air)                  | 5.3                 | BAL, skin biopsy, BMA, PMC          | 6                    | 20                       | Lymphoma    | Chemotherapy was performed but deteriorated to death on the 15th hospital day. | Yes     |
| Case 7  | 78/M   | Dyspnea, night sweats, fever (13 days)                        | IVL                            | 49    | 48/12/26                   | 7.49/27.7/50.2 (ambient air)                  | 15.4                | BAL, TBLB, skin biopsy, PMC         | 10                   | 50                       | No malignancy | Improved via chemotherapy and alive (complete remission) at 25 months from initial symptoms. | No      |

PMCCase No. | Initial symptoms (duration from initial symptoms to admission) | Diagnosis of pulmonary disease | RVSPa | Pulmonary artery pressureb | Arterial blood gas analysis pH/PaCO2/PaO2 (condition) | Platelets (×10^4/μL) | Tests performed to detect tumor cellsd | Hospital day performed | Amount of blood sampled | Results | Chemotherapy and prognosis | Autopsy |
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BAL: bronchoalveolar lavage, BMA: bone marrow aspiration, DLBCL: diffuse large B-cell lymphoma, IVL: intravascular lymphoma, PMC: pulmonary microvascular cytology, PTE: pulmonary tumor emboli, PTTM: pulmonary tumor thrombotic microangiopathy, RVSP: right ventricular systolic pressure, SG: Swan-Ganz, TBLB: transbronchial lung biopsy

a) Predicted RVSP measured by echocardiography (mmHg). b) Pulmonary artery pressure measured by Swan-Ganz catheter (mmHg) (systolic/diastolic/mean). c) No findings suggesting elevated RVSP. d) Underlines indicate tests with positive results. e) TBLB was performed after improvement by chemotherapy resulted in the diagnosis of PTTM.
Figure. Cytological findings obtained via pulmonary microvascular cytology. Malignant cells in Case 1 (a), Case 4 (b), Case 5 (c), and Case 6 (d) are presented (Papanicolaou stain). The images in a and c were published previously in References 7 and 8, respectively; the use of these images was permitted by the Japanese Respiratory Society and the Japanese Society of Internal Medicine.

Results

Patient age was 75.4±6.6 (mean ± standard deviation) years, and 4 patients were men. Of the 7 included patients, 4 had pulmonary metastatic cancer [3 with PTE and 1 with PTE (PTTM)], and 3 had DLBCL (2 with IVL and 1 with DLBCL of splenic origin with intravascular metastasis) (Table). None of them had been diagnosed as having malignant diseases when they presented to our hospital. Their chief complaints included dyspnea, fever, or chest discomfort. Duration from the initial symptoms to admission was 5-47 days. Their radiologic (X-ray and computed tomography) findings varied from no evident findings to slightly thickened interlobular septa or widely distributed ground-glass opacities, but they did not include specific characteristics that would lead to a diagnosis. Five of the 7 patients showed elevated right ventricular systolic pressure (≥40 mmHg) measured by echocardiography, and 4 of the 7 showed increased mean pulmonary artery pressure (≥25 mmHg) measured by Swan-Ganz catheter. Five of the 7 patients developed respiratory failure, and 3 of the 7 showed thrombocytopenia (<10.0×10^4 cells/mm³) at presentation. From the clinical courses of acute deterioration, presence of pulmonary hypertension, and laboratory findings, PTE or IVL was suspected in these patients.

Transbronchial lung biopsy (TBLB) could be performed in only 2 patients because of pulmonary hypertension or thrombocytopenia, and the histological findings were diagnostic in these 2 patients. Alternatively, bronchoalveolar lavage was performed in 4 patients, but was not diagnostic in all cases. PMC was performed from the 1st to the 36th hospital day. Among the 4 patients with PTE or PTE (PTTM), PMC results were positive in 2 (50.0%) patients, whereas among the 3 patients with IVL or DLBCL with intravascular metastasis, tumor cells were detected via PMC in 2 (66.7%) patients (Figure). Two of 4 patients whose PMC result was positive received chemotherapy. One of these 2 patients survived until 9 months from initial symptoms, but the other patient deteriorated to death on the 15th hospital day. The other 2 patients died on the 21st and 37th hospital days, respectively, because their general condition was severe and they refused to undergo chemotherapy. Among 3 patients whose PMC result was negative, tumor cells were detected via TBLB (n=2) or bone marrow aspiration (n=1). Two of
these 3 patients received chemotherapy, which improved their condition, and both were discharged. In the 7 patients who underwent PMC, no complications other than slight bleeding at the skin puncture site for catheter insertion were reported.

Discussion

In the present study, we evaluated the usefulness of PMC in patients with pulmonary microvascular tumor cells. Two of the 4 patients with PTE and 2 of the 3 patients with malignant lymphoma (all 3 had intravascular metastasis) had positive PMC results. Overall, 4 (57.1%) of the 7 patients with intravascular metastasis showed positive PMC results.

The objective of PMC is to detect cytological findings from blood obtained from the pulmonary microvasculature via a Swan-Ganz catheter, which is wedged into the pulmonary artery, and thus, the procedure is also reported as "pulmonary wedge aspiration cytology." The usefulness of PMC was first reported in 1979 in a case of amniotic fluid embolism (4). After that, PMC was applied to the diagnosis of fat embolism and lymphangitic carcinomatosis by Masson et al. (16). They reported that PMC showed tumor cells in 7 of 8 patients with cancer accompanying lymphangitic carcinomatosis but in only 1 of 17 patients with cancer without lymphangitic carcinomatosis. In 23 patients without cancer, PMC showed a pseudo-positive result in 1 patient with pulmonary infarction (16). We retrospectively evaluated the records of 7 patients [4 with PTE or PTE (PTTM) and 3 with malignant lymphoma] who underwent PMC. Two of the 4 patients with PTE and 2 of the 3 patients with malignant lymphoma had positive PMC results. Our study had fewer positive results compared with those of Masson et al. (16), but the reason for this was not evident and further study is needed.

PTE is a disorder characterized by the embolization of tumor cells and thrombus to the peripheral arteries (17). PTTM is a subset of PTE in which the histological findings show tumor embolism to the peripheral pulmonary arteries with organized thrombus and intimal fibrosis (15). These conditions accompany rapidly progressive respiratory failure, pulmonary hypertension, or heart failure (13), and in the present study, the duration from the initial symptoms to admission to our hospital was 9-47 days. Previous reports showed a poor prognosis, from several days to months in Japan (13, 18) or from 4 to 12 weeks in other countries (19), and most cases were diagnosed by autopsy. In the present study, with the exception of the patient in Case 2, who improved with chemotherapy and survived until 10 months after initial symptoms, the patients died on the 14th-37th hospital day. These outcomes suggest that an aggressive investigation is required for an early diagnosis (6, 13). However, diagnosis is often difficult because radiological abnormalities of PTE are often not observed. Even if PTE can be suspected, the severe condition of these patients on presentation often prevents the performance of invasive diagnostic procedures. Our results indicate that PMC is useful in such patients. Among our 4 patients with PTE and PTE (PTTM), positive results were obtained in 2 (50.0%) patients. These patients had pulmonary hypertension, poor respiratory condition, and bleeding tendency (thrombocytopenia), but PMC was applicable and useful for the diagnosis of PTE.

We also performed PMC in cases of malignant lymphoma with pulmonary microvascular tumor cells. In 2 of our patients with IVL (8) and IVL-like pulmonary lesions, the patients showed respiratory failure or thrombocytopenia, and their conditions did not allow us to perform a lung biopsy. We instead performed PMC and detected tumor cells, allowing us to make an early diagnosis of IVL and start chemotherapy. To date, in addition to our reported case (8), three other reports of PMC detecting tumor cells of lymphoma have been published (9-11): two were case reports of IVL (9, 10), and the other was a case series of 8 patients with non-Hodgkin’s lymphoma who had pulmonary metastasis. The PMC results were true positive in 4, false positive in 1 (pneumonia), false negative in none, and true negative in 2 patients, suggesting relatively high positivity but whether the term “pulmonary metastasis,” which was described in one study (11) means “intravascular metastasis” is not known.

In our patients who could undergo the procedure, TBLB detected tumor cells, whereas PMC could not. However, in 5 patients whose conditions did not allow the performance of TBLB, PMC was useful in 4 cases to detect tumor cells. Although lung biopsy is the definitive procedure for making the diagnosis of PTE or IVL, the level of morbidity due to such an invasive procedure may be unacceptable in patients whose condition is often very fragile, with pulmonary hypertension, low pulmonary reserve, and bleeding tendency (20-22). PMC can be applicable in such patients, and the usefulness of PMC should be reevaluated.

The PMC results and the subsequent treatment requires discussion. Only one of our 4 PTE patients in whom a diagnosis was established before death could receive chemotherapy. Our 2 patients with positive PMC findings could not receive chemotherapy due to the severity of their general condition and because they refused to undergo chemotherapy, which indicates that an antemortem diagnosis made with PMC did not always lead to chemotherapy treatment. In the future, it is expected that as the use of PMC sampling progresses, earlier diagnoses will allow for the patient’s general condition to be preserved, which will lead to effective chemotherapy, and that the use of a molecular analysis will allow even severely ill patients to receive effective targeted molecular therapy. On the other hand, the usefulness of chemotherapy for IVL has been established, and our 2 patients improved with chemotherapy. Other patients with IVL who were diagnosed with PMC also improved with chemotherapy (9, 10), indicating that a positive PMC result can lead to chemotherapy, which not rarely improves the prognosis in patients with IVL. Our hope is that patients with PTE or...
ILV are diagnosed rapidly by lung biopsy or PMC and that such patients do not lose the chance to receive chemotherapy.

PMC has several limitations. Our results suggest that negative PMC results do not deny the possibility of these disorders. PMC cannot obtain a tissue sample, nor can it diagnose PTTM. Pulmonary artery catheterization is also an invasive procedure, and complications with Swan-Ganz catheterization may develop. For example, inflating the balloon after the catheter is already in the wedge position can result in fatal pulmonary hemorrhage. However, we could perform PMC without complications in patients in whom it was dangerous to perform bronchoscopy.

We tried to obtain 20 to 50 mL of blood via PMC because we thought that the amount of buffy coat was small and the number of evaluable cells was limited when using a 10-mL sample. However, this amount differs from that specified in the original method (4, 14). Our results indicated that the amount of PMC blood sampled tended to be large in patients with positive PMC results, whereas the amount of blood sampled was small in the patients with negative PMC results. The appropriate amount of blood actually required for PMC should be evaluated.

It is expected that more elaborate techniques to diagnose PTE will be developed in the future. Recent advances in the detection of circulating tumor cells have provided non-invasive methods for cancer detection, early diagnosis, molecular analysis, prognosis prediction, and the testing of drug responses (23). Circulating tumor cells are present in much higher numbers in patients with metastatic cancer, and it is expected that these cells can be detected from blood samples in patients with PTE, in which tumor cells rapidly enter the circulation causing embolism of the pulmonary arteries.

Further, applying these newly developed techniques to samples obtained via PMC may be more useful for detecting tumor cells because more tumor cells are captured in the pulmonary microvasculature than in peripheral blood.

It may be difficult to perform lung biopsy including that via bronchoscopy in cases of PTE or ILV with pulmonary hypertension, thrombocytopenia, and severe respiratory failure. Therefore, PMC may be a useful test to detect tumor cells localized to the pulmonary microvasculature in such conditions.

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

Acknowledgement

We thank our colleagues at the Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, for their detailed comments.

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