Subacute pulmonary embolism in a hemodialysis patient, successfully treated with surgical thrombectomy

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Abstract A 53-year-old woman was admitted to our hospital with a 1-month history of gradually progressive resting dyspnea and lumbar backache. For the preceding 6 years, she had received regular hemodialysis for end-stage renal disease caused by autosomal dominant polycystic kidney disease and had taken tamoxifen for 3 years as post-operative chemotherapy for breast cancer. Before admission, the patient's symptoms had been attributed to volume overload, based on right thoracic fluid and leg edema. However, despite volume correction by dialysis therapy, her symptoms had not improved. The patient was transferred to our hospital, where she was diagnosed with subacute pulmonary embolism (PE). Emergent pulmonary thrombectomy was performed using cardio-pulmonary bypass. The patient was discharged from our hospital on post-operative day 23. Recent reports have shown that hemodialysis patients have a relatively higher risk of PE compared with the general population. Our case had additional risk factors for PE: female sex, decreased protein C level, tamoxifen use, and autosomal dominant polycystic

kidney disease. These factors may have had a synergistic effect on the onset of PE.

Keywords ADPKD · Hemodialysis · Pulmonary embolism · Tamoxifen

Introduction

Hemodialysis patients would seem to have a low risk of thrombosis because of uremic platelet dysfunction and the use of anti-coagulation during hemodialysis sessions. However, several clinical studies have found that hemodialysis patients have a higher risk of pulmonary embolism (PE) than the general population, even after adjusting for conventional risk factors [1, 2]. The symptoms of PE are non-specific, but its mortality is high. Dialysis clinicians tend to attribute symptoms of right heart failure in hemodialysis patients to fluid overload. However, we must differentiate PE from other disorders in hemodialysis patients, especially in those with additional risk factors for thromboembolism, such as autosomal dominant polycystic kidney disease (ADPKD) and tamoxifen use.

Case report

A 53-year-old woman was admitted to our hospital because of resting dyspnea and lumbar backache. Her symptoms had gradually worsened over the preceding month. For the previous 6 years, the patient had received regular hemodialysis for end-stage renal disease (ESRD) resulting from ADPKD. Approximately, 3 years before presentation, she had undergone mastectomy with axillary lymph node

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dissection for right-sided breast cancer. Since that time, she had been taking tamoxifen (20 mg/day) as post-operative chemotherapy, and there was no sign of cancer recurrence. The vascular access of the patient was arteriovenous fistula and she had never undergone thrombectomy or other endovascular procedures against obstruction of vascular access for hemodialysis. Initially the patient had experienced mild exertional dyspnea. Chest radiographs at the dialysis clinic showed slight thoracic fluid on the right side, but no consolidation or signs of metastatic tumor. The cause of the woman's symptoms was thought to be volume overload and she underwent volume correction by dialysis therapy. The patient's symptoms did not improve with this treatment, and she was transferred to our hospital for further care.

On admission, the patient's height was 161 cm and her weight was 59 kg (body mass index = 22.8 kg/m^2). Her pulse rate was 110/min and her blood pressure was 84/56 mmHg. Her arterial oxygen saturation was 98 % under oxygen administration (2 L/min). Both of her legs were edematous, with the left worse than the right. Her respiratory and heart sounds were normal, and her palpebral conjunctiva showed no evidence of anemia. The patient did not have hemoptysis, and did not complain of arthralgia or other symptoms of connective tissue disease. Blood tests revealed a slightly increased white blood cell count ($9950/\mu\text{L}$) and elevated C-reactive protein (5.65 mg/dL). Polycythemia ($574 \times 10^4/\mu\text{L}$) was a new finding, and might have resulted from excessive fluid volume depletion and chronic hypoxia. The patient's blood fibrinolysis system was profoundly activated (FDP $70.2 \mu\text{g/mL}$, D-dimer $21.3 \mu\text{g/mL}$), and both anti-thrombin III and protein C plasma levels were decreased (63 and 59 %, respectively).

Electrocardiogram showed sinus tachycardia, with an S wave in lead I, a Q wave in lead III, and a negative T wave in right-sided chest lead. Cardiac ultrasonography revealed dilatation of the right atrium, enlargement of the right ventricle, and elevated pulmonary artery-to-right ventricular pressure gradient (34 mmHg), but no sign of volume loading. In addition, we observed an irregularly shaped and

movable thrombus in the right atrium and the origin of the pulmonary artery. We immediately carried out computed tomography with enhancement, which showed that the thrombus in homogeneously filled the trunk of the pulmonary artery and extended to the bilateral peripheral branches. Multiple, enlarged liver cysts were identified in contact with the inferior vena cava (Fig. 1). We suspected that the thrombus was organized because it had high echogenicity and because approximately 1 month had passed since its onset. Therefore, we made a diagnosis of subacute PE. Because the traditional window for thrombolysis in patients with massive PE is reported to be 2 weeks [3], we decided to perform surgical removal. The patient was started on intravenous heparin (500 U/h) while awaiting surgery. The following morning, the patient's arterial PO_2 was 98 mmHg under 3 L/min of oxygen administration but, her systolic blood pressure had decreased. Emergent pulmonary thrombectomy was performed using cardio-pulmonary bypass. A massive thrombus was surgically removed from the pulmonary artery and right atrium. There were no malignant cells such as breast cancer cells in the thrombus, and its structure was soft and contained little fibrosis (Fig. 2), findings consistent with the subacute clinical course.

On the day following the operation, the patient's respiratory condition returned to nearly normal. Ventilation/perfusion (V/Q) lung scintigraphy was performed on post-operative day (POD) 13. We found V/Q mismatch only in the left lingular segment; the other segments maintained perfusion. Lower limb venous ultrasonography revealed remnant thrombi in the bilateral femoral veins on POD 14. The patient began warfarin therapy (1.5 mg/day) after surgery and a vena cava filter was implanted percutaneously on POD 16 to prevent recurrence of PE. After discharge, the patient did not experience recurrence of PE, but no longer received tamoxifen because of its adverse effect. On POD 71, follow-up computed tomography (CT) scan was performed. There was no recurrence of PE, but the patient's huge liver cysts seemed to compress the inferior vena cava (Fig. 3).

Fig. 1 Chest computed tomography on admission. Computed tomography images of upper (a) and lower chest (b) are shown. The massive thrombus is located in the bilateral pulmonary arteries (arrow). Multiple, enlarged liver cysts were identified in contact with the inferior vena cava (arrowhead)

Fig. 2 Surgical removal of thrombi. The *red* and *soft* thrombi containing little fibrosis are shown, suggesting an acute or subacute course of illness

Fig. 3 Follow-up computed tomography after discharge. The inferior vena cava appears to be compressed by a liver cyst (*arrow*)

Discussion

PE is a common fatal disease, with a prevalence of 62 cases per million in the Japanese population in 2006. The mortality rate of acute PE is reported to be 14 % [4]. PE would seem to be rare in chronic hemodialysis patients, but chronic dialysis can result in a hypercoagulable state by several mechanisms: platelet activation resulting from extracorporeal circulation with less biocompatible membrane, and activated coagulation pathways resulting from uremia [diminished protein C activity, deficient release of tissue plasminogen activator, reduced activity of anti-thrombin III, increased level of lipoprotein (a), and hyperhomocysteinemia] [5, 6]. These mechanisms can contribute to a higher incidence of thromboembolic events in hemodialysis patients. According to Tveit et al., the age-adjusted incidence of PE in chronic hemodialysis patients was 2.34-fold higher than that in the general population in the United States [1]. Kumar et al. reported that the annual frequency of PE among ESRD patients was eight times higher than among individuals with normal kidney function

[2]. In addition, in a large, prospective, population-based study, even non-dialyzed chronic kidney disease patients have an increased risk for venous thrombosis [7].

Our patient had additional risk factors for PE. First, tamoxifen is a selective estrogen receptor modulator and an adjuvant treatment to prevent breast cancer recurrence, with good efficacy and tolerability even in chronic hemodialysis patients [8]. However, tamoxifen has been shown to increase the risk of venous thromboembolism in many clinical trials [9, 10]. Second, among patients with ADPKD, enlarged liver or renal cysts can compress the inferior vena cava, a condition that induces intra-operative inferior vena cava syndrome or obstruction of hepatic venous outflow [11, 12]. Moreover, some case reports of ADPKD have shown thrombotic obstruction in the inferior vena cava, leading to PE [13]. In our patient, enlarged liver cysts that seemed to compress the inferior vena cava were identified in follow-up CT scan after discharge, but we could not confirm their direct effect on venous thrombosis. In a study of 534 ADPKD patients after renal transplantation, thrombotic events were more common than in non-ADPKD patients, and thromboembolic complications were not associated with polycystic liver disease [14]. Further study is needed to clarify the precise mechanisms for the development of thromboembolic events in ADPKD patients.

In the present case, we were able to treat subacute PE in a hemodialysis patient by surgical thrombectomy before her cardiopulmonary condition worsened. Pulmonary thrombectomy was effective treatment for the massive thrombus located in the main pulmonary trunk. In cases where it would be difficult to remove thrombi by medical thrombolytic therapy, we should consider surgical pulmonary embolectomy [15]. Once PE progresses to chronic thromboembolic pulmonary hypertension, it will result in reduced quality of life and lead to a poor prognosis [16].

The natural history of subacute and chronic pulmonary embolism remains to be fully determined. Although the mechanism of progression of pulmonary embolism in this patient is unknown, we suggest that repeated latent thrombosis and progression of thrombosis in the pulmonary arteries might have occurred [17]. The thrombi harvested from the patient contained little fibrosis, which is consistent with this hypothesis.

According to guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis, the duration of warfarin therapy after an episode of acute pulmonary embolism should be 3 months for the patients with risk factors for recurrence [4]. However, there is no evidence of anti-coagulation therapy for ADPKD patients with massive PE. Although, in this case, tamoxifen was stopped just after the operation, warfarin therapy has been continued.

We have described a case of subacute PE in a patient receiving regular hemodialysis therapy. The patient had multiple risk factors for PE (i.e., tamoxifen use, decreased protein C level due to ESRD [18], female sex, and ADPKD). When a hemodialysis patient with many potential risk factors for venous thromboembolism has signs of right cardiac failure, we must consider the possibility of PE even in subacute course. Additionally, the use of tamoxifen could be a substantial risk factor for venous thromboembolism in hemodialysis patients.

Compliance with ethical standards

Conflict of interest Honoraria: Takanari Kitazono (Bayer Pharmaceutical Co., Bristol-Myers Squibb Co., Daiichi-Sankyo Co.), Kazuhiko Tsuruya (Chugai Pharmaceutical Co., Kyowa Hakko Kirin Co.); Takanari Kitazono (Astellas Pharma Inc., Daiichi-Sankyo Co., Eisai Co., Kyowa Hakko Kirin Co., Mitsubishi Tanabe Pharma Co., MSD K.K., Ono Pharmaceutical Co., Otsuka Pharmaceutical Co., Sanofi-Aventis Pharmaceutical Co., Takeda Pharmaceutical Co.), Kazuhiko Tsuruya (Chugai Pharmaceutical Co., Kyowa Hakko Kirin Co., Otsuka Pharmaceutical Co., Takeda Pharmaceutical Co.); Endowed department: Kazuhiko Tsuruya (Baxter).

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