Lung Adenocarcinoma Complicated by Trousseau’s Syndrome Successfully Treated by a Combination of Anticoagulant Therapy and Chemotherapy


Abstract

A 63-year-old woman was diagnosed with advanced lung adenocarcinoma complicated by Trousseau’s syndrome characterized by non-bacterial thrombotic endocarditis, asymptomatic brain infarction, deep venous thrombosis, and low-grade disseminated intravascular coagulation (DIC). The patient’s DIC rapidly became widespread, and multiple micropulmonary embolisms led to severe respiratory failure. She received a blood transfusion and anticoagulant treatment with heparin and recombinant human soluble thrombomodulin, which modestly ameliorated her symptoms, and additional chemotherapy led to tumor shrinkage with concomitant resolution of Trousseau’s syndrome. Although there are no established medical approaches for managing Trousseau’s syndrome, intensive anticoagulant treatment may be effective for improving the patients’ general condition in order for them to be able to undergo subsequent combination chemotherapy.

Key words: disseminated intravascular coagulation, lung adenocarcinoma, pulmonary embolism, recombinant human soluble thrombomodulin, Trousseau’s syndrome


Introduction

Venous thromboembolism is one of the most common complications in cancer patients and is strongly associated with lung cancer (1, 2). Thromboembolism complicated by malignant tumors is known as Trousseau’s syndrome and was originally described by Trousseau in 1865 (3). It is generally recognized to be a fatal condition with a poor prognosis (4). The clinical manifestations of this syndrome vary from deep venous thrombosis (DVT) to disseminated intravascular coagulation (DIC). Trousseau’s syndrome is defined as unexplained thrombotic events that precede the diagnosis of an occult visceral malignancy or appear concomitantly with the tumor (5). We herein describe the case of a 63-year-old woman with lung adenocarcinoma complicated by Trousseau’s syndrome who developed severe respiratory failure due to pulmonary embolism (PE) and was successfully treated with a combination of anticoagulant therapy and chemotherapy.

Case Report

A 63-year-old woman with no history of cigarette smoking was admitted to our hospital with a four-month history of pyrexia. A physical examination performed on admission revealed a low-grade fever with no other significant abnormalities. Her laboratory tests revealed anemia, thrombocytopenia, coagulation abnormality, and a marked increase in tumor marker and Krebs von den Lungen-6 (KL-6) levels (Table). The patient’s coagulation abnormality was suspected to be caused by low-grade DIC; therefore, we initiated heparin treatment via continuous intravenous infusion at a dose of 10,000 U/day.
The patient underwent various imaging examinations for further evaluation (Fig. 1). A chest radiograph showed no abnormalities. Contrast-enhanced computed tomography (CT) of the chest and positron emission tomography demonstrated a 2.5-cm nodule attached to the hilar lymph nodes in the left lower lobe of the lungs and lymphadenopathy of the mediastinum and left axilla. Because primary lung cancer was suspected, a transbronchial biopsy of the left-sided hilar lymph node was performed using ultrasonic bronchoscopy. A mucin-producing adenocarcinoma positive for thyroid transcription factor-1 (TTF-1) on immunohistochemistry was diagnosed on the basis of a histopathological examination. The patient was screened for an epidermal growth factor receptor mutation and anaplastic lymphoma kinase gene translocation, but neither was detected. We made a final diagnosis of lung adenocarcinoma, T1bN3M1b (LYM), Stage IV.

Because the patient’s clinical condition was complicated by a coagulation abnormality, we performed further evaluations for thromboembolic disorders (Fig. 2A-C). Multiple asymptomatic cerebral embolisms were observed on enhanced brain magnetic resonance imaging. A 1-cm vegetation that was determined to be non-bacterial thrombotic endocarditis (NBTE) was demonstrated on the anterior and posterior cusps of the mitral valve by transthoracic echocardiography; these vegetations appeared to be responsible for
adenocarcinoma. with Trousseau’s syndrome associated with advanced lung that point in time. Accordingly, the patient was diagnosed on contrast-enhanced CT, no apparent PE was detected at the multiple cerebral embolisms. Although DVT was evident value, rapidly deteriorated on day 15 of admission (Fig. 3). 

The laboratory findings suggestive of coagulation abnormality, including thrombocytopenia and an elevated D-dimer value, rapidly deteriorated on day 15 of admission (Fig. 3). The patient’s DIC score [Japanese Ministry of Health and Welfare Criteria, 1988 (6)] reached 10 points; therefore, we initiated the intravenous infusion of recombinant human soluble thrombomodulin (rhsTM). The patient was also suffering from rapidly worsening respiratory failure. Although no obvious PE findings were detected on repeat contrast-enhanced chest CT, pulmonary perfusion scintigraphy revealed multiple peripheral perfusion defects (Fig. 2D), thus indicating multiple pulmonary microemboli, and supplemental oxygen therapy was initiated.

In addition to rhsTM and continuous heparin infusion, the patient’s DIC required transfusions of platelet concentrate and fresh frozen plasma. Treatment with rhsTM resulted in partial amelioration of DIC, as demonstrated by a gradual recovery of platelet count and D-dimer levels to normal without any marked improvement of Performance Status 3 (PS, Eastern Cooperative Oncology Group). We considered that the patient’s poor PS was mainly attributable to Trousseau’s syndrome, and the primary approach for the treatment of Trousseau’s syndrome is the elimination of the causative tumor (5). Although adverse events associated with poor PS were suspected, the anti-cancer modality of treatment was selected under informed consent. Accordingly, the patient received combination chemotherapy with carboplatin (AUC 5) and pemetrexed (500 mg/m²) on the 22nd hospital day (Fig. 4). Although adverse events, including grade 3 and 4

![Figure 2. Radiological findings of thromboembolism. (A) A diffusion-weighted image (DWI) window of brain magnetic resonance imaging showed multiple small cerebral embolisms (arrows). (B) Transthoracic echocardiography revealed a 1-cm club-like vegetation indicating non-bacterial thrombotic endocarditis on the anterior and posterior cusps of the mitral valve. (C) Enhanced computed tomography of the lower limbs showed deep venous thrombosis in the vein genus. (D) Lung technegas scintigraphy on day 15 after admission showed no abnormalities, but 99m technetium-labeled macroaggregated albumin lung perfusion scintigraphy revealed multiple peripheral defects.](image)

![Figure 3. Clinical course of the patient’s laboratory data and therapies. DIC: disseminated intravascular coagulation, FFP: fresh-frozen plasma, PC: platelet concentrate, PLT: platelets, rhsTM: recombinant human soluble thrombomodulin](image)
thrombocytopenia [National Cancer Institute - Common Toxicity Criteria (NCI-CTC) Version 2.0], were observed, a total of six courses of chemotherapy were completed, and a partial response represented by a 40% decrease in tumor size (Response Evaluation Criteria in Solid Tumors ver. 1.1) and concomitant disappearance of NBTE and DVT was achieved (Fig. 5). Lung perfusion scintigraphy also demonstrated gradual decreases in the multiple peripheral defects (Fig. 4). No new thromboembolic events of cerebral infarction or PE occurred during the one-year observation period after combination chemotherapy, and the patient is receiving 14 courses of pemetrexed maintenance chemotherapy and subcutaneous heparin injections.

**Discussion**

Trousseau’s syndrome is characterized by spontaneous, recurrent, and often migratory episodes of venous thrombosis with or without arterial embolism due to NBTE in patients with a malignancy (7). Although the molecular mechanism of cancer-related hypercoagulability is not completely understood, thrombosis is considered to be associated with low-grade DIC that might be triggered by the release of tissue factors from malignant cells (5).

The most common sites for cancer occasionally complicated by thromboembolic events include the lung, prostate, breast, colon, and rectum (2). Indeed, patients with lung cancer are at a 20-fold higher risk for the development of DVT compared with the general population (8). In terms of histopathology, patients with lung adenocarcinoma, particularly mucin-producing adenocarcinoma, are at an increased risk for venous thrombosis compared with patients with squamous cell carcinoma (2, 8). Tachihara and colleagues presumed that elevation of markers, such as KL-6, might be a predictive factor for coagulopathy and reflect histopathological subtype (9). Furthermore, the risk of venous thrombosis in patients with distant metastasis is six-fold higher than that in patients that only have local tumor growth (8). In the present case, the risk factors for thromboembolic events included the histopathological appearance of mucin-producing adenocarcinoma, elevated KL-6 levels, and distant metastasis.

Chuang et al. reported that the median survival time (MST) of lung cancer patients with PE was significantly shorter than that of matched control patients (243.5 vs. 327 days, p=0.01) (10). Cestari et al. also reported that lung cancer is the most common primary tumor associated with

**Figure 4.** Clinical course of chemotherapy and lung perfusion scintigraphy findings. CBDCA: carboplatin, KL-6: Krebs von den Lungen-6, PEM: pemetrexed, s.c.: subcutaneous

**Figure 5.** Chest enhanced computed tomography (CT). (A) Before chemotherapy. (B) After 6 courses of chemotherapy. The CT scans showed tumor shrinkage and resolution of lymphadenopathy in the hilum, mediastinum, and axilla.
brain stroke, particularly embolic events, and the MST from the diagnosis of stroke is 4.5 months in cancer patients (11). Several case reports of Trousseau’s syndrome associated with lung cancer have already been published, and most cases demonstrated poor prognoses for several months (9, 12-14).

Although chemotherapy is associated with an increased risk of venous thrombotic events (15, 16), the primary approach for treating Trousseau’s syndrome is the elimination of the causative tumor (5). In the present case, initial treatment with rhsTM, the first gene-spliced thrombomodulin preparation, and heparin to control thromboembolic events improved the patient’s general condition, which led to the successful completion of six subsequent courses of combination chemotherapy. While the clinical efficacy of rhsTM as a part of DIC treatment in patients with Trousseau’s syndrome is not yet established, a phase III clinical trial of rhsTM for DIC demonstrated significant decreases in DIC score and bleeding symptoms compared with standard heparin therapy (17). In addition to anti-coagulant activity, an anti-inflammatory role for rhsTM has been demonstrated via its ability to neutralize high-mobility group box 1 (HMGB1), a representative damage-associated molecular pattern molecule (DAMP) for innate immune responses. Intriguingly, recent papers proposed a role for HMGB1 in tumor progression, including cell growth, cellular invasiveness, and metastasis in lung cancer cells (18, 19). HMGB1 released from necrotic cancer cells may enhance the regrowth and metastasis of remnant cancer cells via activation of the receptor for advanced glycation endproducts (RAGE) (20). Furthermore, it has also been reported that HMGB1 may be a useful clinical marker for evaluating non-small cell lung carcinoma progression and is of potential prognostic value (21). Hence, we speculate that rhsTM is a promising treatment for Trousseau’s syndrome complicated with lung cancer, at least partly via neutralization of HMGB1.

In conclusion, we encountered a patient with Trousseau’s syndrome with near-fatal PE associated with advanced lung adenocarcinoma who was successfully treated with a combination of anticoagulant therapy and chemotherapy. Although there is no established medical approach to extend the survival of patients with Trousseau’s syndrome, we speculate that intensive anticoagulant treatment with rhsTM to control thromboembolic events and DIC, and also possibly for tumor suppression, may improve the general condition of patients and facilitate the completion of subsequent combination chemotherapy.

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

References