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CASE REPORT

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A case of disseminated intravascular coagulation following tumour lysis syndrome due to small cell carcinoma of the lung

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Abstract

A 64-year-old man was diagnosed with small cell lung cancer (SCLC) with multiple bone and liver metastases and bone marrow metastases. Spontaneous tumour lysis syndrome (TLS) was observed before starting chemotherapy with carboplatin, etoposide, and atezolizumab. The tumour further collapsed, and the patient developed disseminated intravascular coagulation (DIC) on day 4 of chemotherapy. The patient was successfully treated with intravenous hydration and rasburicase for TLS and subcutaneous unfractionated heparin for DIC. A large amount of tissue factor may be released in TLS, which could induce DIC. However, to the best of our knowledge, this is the first report of DIC following TLS in a case of SCLC. DIC following TLS in SCLC is a rare but life-threatening oncologic complication. Therefore, clinicians should be aware of this possibility when treating patients with advanced SCLC.

KEYWORDS
disseminated intravascular coagulation, small cell lung cancer, tumour lysis syndrome

INTRODUCTION

The incidence of tumour lysis syndrome (TLS) in haematological malignancies is reported to be 4%–42%.[1] Meanwhile, TLS is considered rare in solid tumours and the incidence of TLS in each solid tumour, including small cell lung cancer (SCLC), is not known. Ongoing progress in cancer therapy has increased the incidence of TLS in solid tumours. The mortality rate for TLS in solid tumours has been reported to be 35%, higher than the 1.9% mortality rate for TLS in haematological malignancies.[2]

SCLC is classified as intermediate risk for TLS.[3] Approximately 20 cases of TLS due to SCLC, including spontaneous TLS, have been reported in literature to date but many cases may have been unreported or overlooked. A large amount of tissue factor (TF) may be released in TLS that can induce disseminated intravascular coagulation (DIC). DIC following TLS has been reported in rhabdomyosarcoma[4] and breast cancer;[5] however, to the best of our knowledge, this is the first report of DIC following TLS in a case of SCLC. Herein, we present the case of a patient diagnosed with spontaneous TLS the day before starting chemotherapy. Chemotherapy further collapsed the tumour, and DIC was diagnosed on the fourth day of chemotherapy.

CASE REPORT

A 64-year-old Japanese man with a 90 pack-year history of smoking, hypertension, and chronic hepatitis C was admitted to a local hospital with a lumbago. Multiple vertebral compression fractures with suspected bone metastases were observed. The patient developed melena after admission and was transferred to our hospital for further examination. The patient's vital signs at the time of transfer showed no abnormalities, and blood test findings were as follows: leukocyte: 10,600/mm^3, haemoglobin: 7.2 g/dL, platelet: 79,000/mm^3, myelocytes: 5.5%, metamyelocytes: 1.5%, erythroblasts: 27%, potassium: 4.0 mmol/L, phosphorus: 4.2 mg/dL, creatinine (Cr): 0.99 mg/dL, uric acid (UA): 7.6 mg/dL, and lactate dehydrogenase (LDH): 1676 U/L. Computed tomography (CT) showed nodular shadows in the left upper lobe of the lung, multiple lymphadenopathies in the left hilum and mediastinum, and multiple metastases in the liver and bone

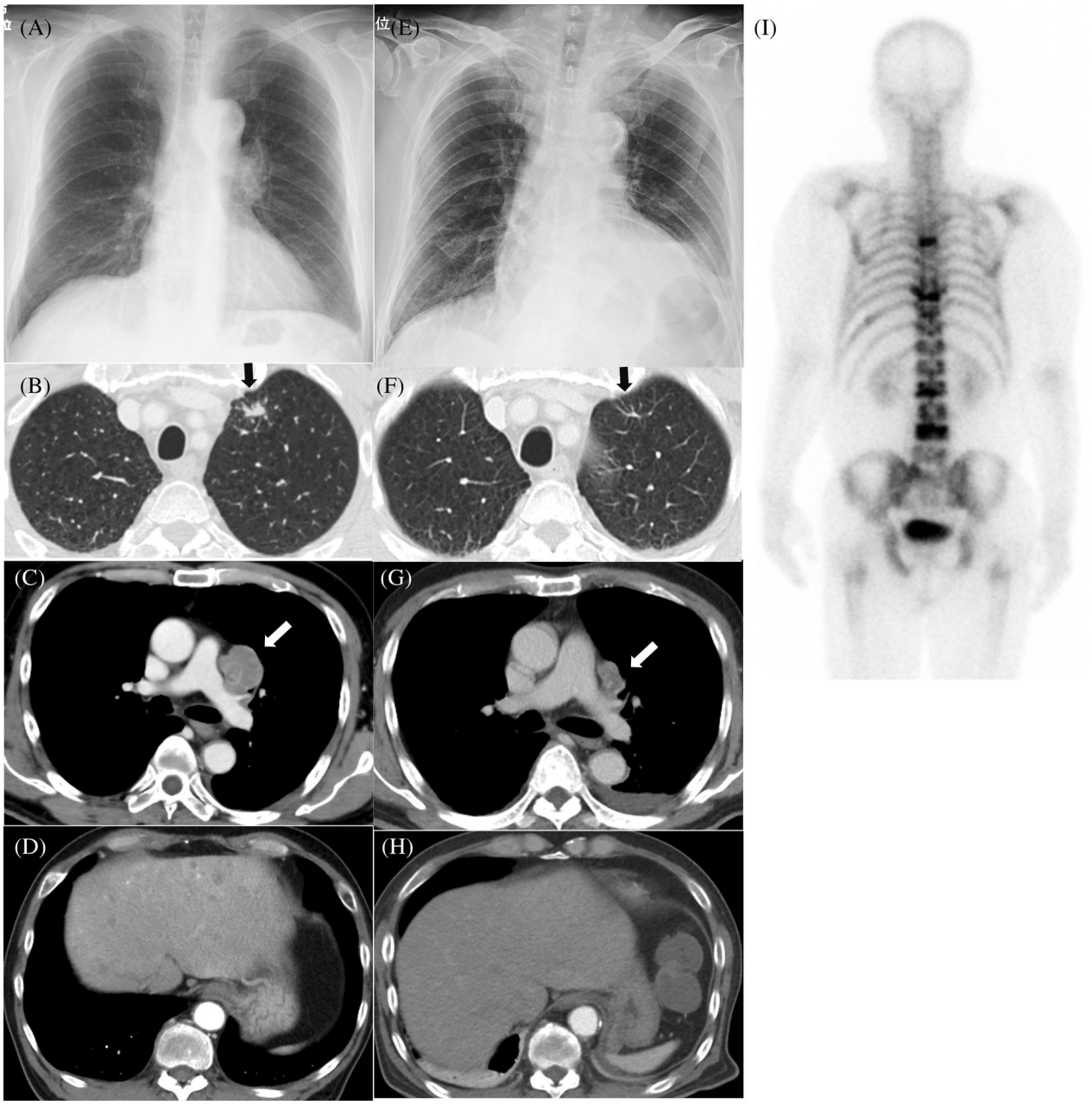
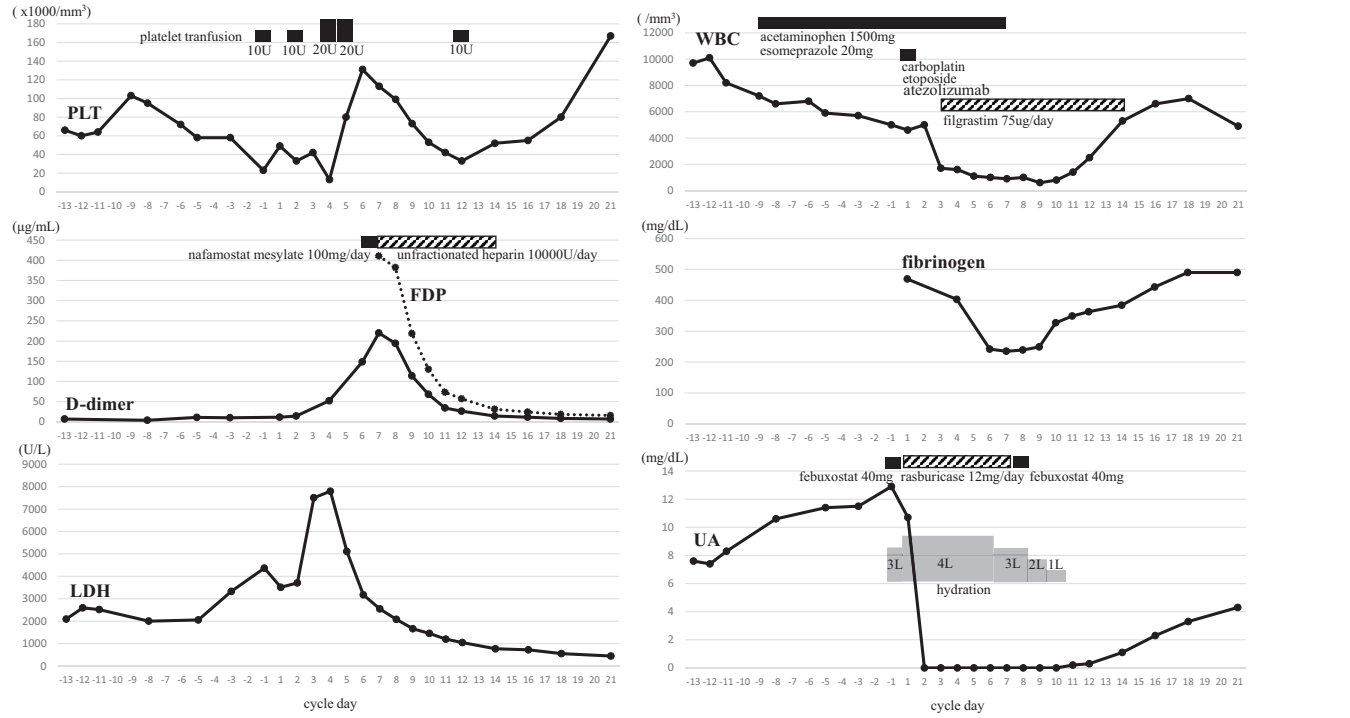


FIGURE 1 Chest X ray of the lung (A), nodule in the lung on computed tomography (CT) (B), mediastinal lymph nodes enlargement on CT (C), and liver metastasis (D). A–D were taken at the time of hospital transfer. E–G were taken on day 21 of chemotherapy. Bone scan performed before chemotherapy (I)

(Figure 1B–D, I). Endobronchial ultrasound-guided transbronchial needle aspiration was performed, and the patient was diagnosed with SCLC. On immunostaining, the tumour cells were diffusely positive for TTF-1, CD56, and synaptophysin, and partially positive for chromogranin A. Based on the peripheral blood examination findings, the patient was clinically diagnosed with bone marrow metastases. Endoscopic examination revealed bleeding from dilated capillaries in the small intestine, but there were no metastatic lesions in the digestive tract. Based on the clinical findings and investigations, the tumour was classified as extensive (T1bN2M1c). Since the day of transfer, the levels of serum LDH and UA had increased. Blood test results 1 day before chemotherapy were LDH: 4366 U/L, UA: 12.9 mg/dL, Cr: 1.42 mg/dL, potassium: 5.2 mmol/L, and phosphorus: 5.3 mg/dL. The patient was diagnosed with spontaneous TLS; therefore, intravenous sodium hydration and oral febuxostat administration were initiated (Table 1). The following day, combination chemotherapy with carboplatin (AUC5), etoposide 100 mg/m^2 (170 mg), and atezolizumab 1200 mg was administered, and febuxostat was switched to intravenous rasburicase 12 mg and continued for 7 days. On day 2 of chemotherapy, after

TABLE 1 Course of TLS, DIC, and white blood cell counts



Abbreviations: DIC, disseminated intravascular coagulopathy; TLS, tumour lysis syndrome.

administering etoposide, the patient had a sore throat and was diagnosed with COVID-19 based on polymerase chain reaction (PCR) findings for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Remdesivir administration was initiated and continued for 10 days. The scheduled etoposide treatment was discontinued on day 3. Dexamethasone 6 mg was administered to treat COVID-19 from days 2 to 6. The severity of COVID-19 remained mild and improved. Calcium polystyrene sulfonate was administered to treat hyperkalaemia. On day 2, precipitated calcium carbonate and alfacalcidol were administered for hypocalcaemia due to TLS and denosumab which was given 1 week before chemotherapy to treat bone metastases. Though TLS was successfully managed, blood tests showed platelet: 13,000/mm^3, D-dimer: 52.1 μg/ml, fibrinogen: 403 mg/dL, and prothrombin time- international normalized ratio (PT-INR): 1.29; thus, the patient was diagnosed with DIC on day 4. Dynamic CT showed no pulmonary thromboembolism or deep vein thrombosis. As the D-dimer level continued to rise, nafamostat mesylate 100 mg/day was administered on day 6. However, as the D-dimer level increased further, 5000 units of subcutaneous unfractionated heparin (UFH) every 12 h was administered on day 7, and the D-dimer levels decreased. Neutropenia occurred on day 3 and filgrastim was administered from days 3 to 14. Considering the possibility of drug-induced neutropenia, rasburicase and acetaminophen were discontinued, and esomeprazole was switched to famotidine on day 7. Both neutropenia and DIC resolved on day 14. The first course of chemotherapy was effective, and the patient was in good general condition. One week before chemotherapy, serum levels of pro-gastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) were 12,800 pg/ml and 686 ng/ml, respectively, which improved to 48.3 pg/ml and 10 ng/ml, respectively on day 21. CT on day 21 showed improved nodular shadows in the left upper lobe of the lung, lymphadenopathy, and multiple liver and bone metastases (Figure 1E–G). Treatment was provided every 3 weeks, and the response after two courses of carboplatin, etoposide, and atezolizumab was evaluated as partial response (PR), close to complete response (CR). After four courses of treatment, the patient maintained PR status close to CR. He has since completed three maintenance courses with atezolizumab 1200 mg every 3 weeks and has not experienced any recurrence to date.

DISCUSSION

To the best of our knowledge, this is the first report of DIC following TLS in a patient with SCLC. The patient had multiple metastases to the liver, bone, and bone marrow. Spontaneous TLS was diagnosed before the initiation of chemotherapy. TLS is considered rare in solid tumours though it may be unreported or overlooked. Although SCLC is classified as an intermediate risk factor for TLS,[3] the incidence of TLS in SCLC is not known. The risk factors for TLS include (1) high tumour cell proliferation rate; (2) chemosensitivity of the malignancy; and (3) large tumour burden, manifested by bulky disease >10 cm in diameter and/or a leukocyte count >50,000/mm^3, a pre-treatment serum LDH more than two times the upper limit of normal, organ

infiltration, or bone marrow involvement.[6] A large amount of TF may be released in TLS, which could induce DIC. TF expression in lung cancer is reported to be independent of histology but increases with cancer progression.[7,8,9,10]

Coagulopathy can occur in COVID-19 patients associated with hyperinflammation. The rate of complication of COVID-19 by DIC has been reported to be 0.6% for survivors and 71.4% for non-survivors.[11,12] The patient underwent a SARS-CoV-2 PCR test because a close contact (his roommate) had tested positive for SARS-CoV-2 on PCR test. The test was performed as a pre-transfer screening to the nursing home. Our patient had not complained of any symptoms before the test, but when asked after his positive result was informed, he said he had been aware of a slight sore throat since the previous day. He had left pleural effusion and atelectasis prior to COVID-19 infection and had been using low flow oxygen, but no apparent pneumonia due to COVID-19 developed. Considering the presence of immunodeficiency due to the cancer-bearing condition, remdesivir was administered for 10 days. The patient's COVID-19 remained mild and cured. Therefore, we considered the DIC to have occurred due to the TLS, though COVID-19 might have had some effect on the coagulopathy.

Although we successfully managed the patient's TLS and DIC, we reviewed our treatment and discussed the following points: (1) Allopurinol should have been administered on the day of transfer when the patient's serum UA level was 7.6 mg/dL. (2) The administration of rasburicase for 7 days might have been excessive treatment for the patient's TLS, which then led to prolonged leukopenia. (3) Nafamostat, rather than heparin, was initially administered for DIC on day 6 in consideration of bleeding from the small intestine; however, we switched to heparin the following day because of insufficient efficacy. If UFH had been administered earlier, the patient could have recovered from DIC sooner and would not have required platelet transfusion. (4) The discontinuation of etoposide on day 3 may have resulted in some suppression of tumour lysis and a reduction in the severity of TLS.

DIC following TLS is a rare but serious life-threatening complication that clinicians need to be aware of when treating patients with advanced SCLC.

AUTHOR CONTRIBUTIONS

Saeko Takahashi: the patient's physician and primary author. Tomohiro Takehara, Tetsuo Tani, Kota Ishioka, and Seiji Madoiwa were involved in intensive care management and review of the work and final improvement of the article.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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