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Lung adenocarcinoma complicated by left atrial thrombus during chemotherapy with immune checkpoint inhibitor after thoracic chemoradiotherapy: a case report

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ABSTRACT

We report the case of a 72-year-old man diagnosed with left lower lobe lung adenocarcinoma (cT2aN3M0 stage IIIB) exacerbated by multiple liver metastases and meningeal dissemination after completing 10 courses of durvalumab followed by chemoradiation therapy. The patient was treated with nivolumab, ipilimumab, carboplatin, and pemetrexed combination therapy for stage 4 non-small cell lung cancer. After completion of the two courses, efficacy evaluation CT findings revealed the therapeutic effects of treatment on meningeal dissemination and liver metastasis; however, a thrombus was observed in the left atrium. The patient was treated with heparin and warfarin. CT scan images on day 14 of treatment showed shrinkage of the thrombus. Thrombosis after immunotherapy is a rare adverse event. So far, intracardiac thrombosis with this regimen has not been reported, and there is no established treatment. Since thoracic radiation therapy and treatment with immune checkpoint inhibitors for lung cancer patients improve their prognosis, it is expected that their frequency of use will increase in the future. We report this investigation to accumulate more cases of this condition.

Keywords: immune checkpoint inhibitor, left atrial thrombus, lung adenocarcinoma, thoracic chemoradiotherapy

Introduction

In recent years, treatment for advanced lung cancer has evolved, and long-term survival has become possible with the use of radiation therapy, cell-mediated anticancer drugs, molecular targeted drugs, and immune checkpoint inhibitors. However, adverse events caused by the combination of these therapies can sometimes be a serious problem. We report a case of thrombus formation in the posterior wall of the left atrium after chemoradiation therapy, followed by combination therapy with immune checkpoint inhibitors and cytotoxic anticancer agents, for non-small cell lung cancer. Thrombosis in the posterior wall of the left atrium after radiotherapy or anticancer chemotherapy is considered extremely rare and will be presented with literature review.

Case report

The patient was a 72-year-old male, who used to smoke 20 cigarettes/day between the ages of 20 and 54 years. He had a history of bilateral inguinal hernias at the age of 64 years, diabetes at 67 years, atrial fibrillation and heart failure at 70 years, and

early-stage gastric cancer and arteriosclerosis obliterans at 71 years. He was taking dabigatran 300 mg/day for atrial fibrillation. Nodular shadows in the lower lobe of the left lung and enlarged mediastinal lymph nodes were noted on Computed tomography (CT) when the patient was diagnosed with early-stage gastric cancer. Thoracoscopic right mediastinal lymphadenectomy and left exploratory thoracotomy were performed because the diagnosis could not be made by bronchoscopic biopsy, and N3 lymph node metastasis was found. He was diagnosed with lung cancer (adenocarcinoma pT2aN3M0 stage IIIB), and chemoradiotherapy (left lung + mediastinum total 60 Gy/30 fr, weekly carboplatin + paclitaxel) was performed. Treatment resulted in a partial response, and a total of 10 courses of durvalumab were administered as additional treatment. The primary lesion was scarred, and the lymph node metastases remained scarce; however, 6 months after the start of treatment, CT findings showed multiple liver metastases and meningeal dissemination, which led to the progression of the disease. He then received nivolumab, ipilimumab, carboplatin, and pemetrexed combination therapy. After two courses of treatment, CT scan images showed efficacy of treatment for meningeal dissemination and liver metastasis, but thrombus formation along the posterior wall of the left atrium was observed. Then, he was admitted to our hospital for thrombosis treatment.

The following baseline characteristics were observed on admission: performance status 0; height 168.7 cm; weight 68.0kg; BMI 23.8kg/m^2; body temperature 36.6°C; blood pressure 155/73 mmHg; pulse 61/min, irregular; SpO_2 97% (room air); and absence of superficial lymphadenopathy. No respiratory rales were heard, and no heart murmur was noted. There were no specific findings of the abdomen. Blood examination revealed elevated levels of the brain natriuretic peptide (BNP) (106.7 pg/mL) and D-dimer (3.37 μg/mL), but BNP did not significantly change compared to that of his previous data. In addition, activated partial thromboplastin time (APTT) was prolonged (48.0 s), due to dabigatran.

Electrocardiogram findings showed atrial fibrillation and complete right bundle branch block.

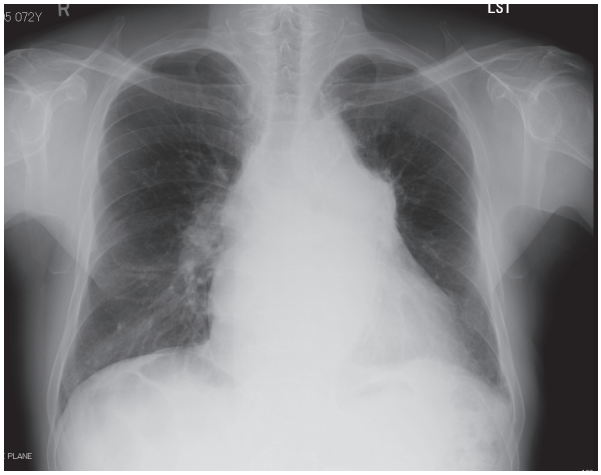

Figure 1. Chest radiograph finding showing enlargement of the left hilar region and cardiomegaly

Chest radiography results showed enlargement of the left hilar region and cardiomegaly (Fig. 1). A contrast-enhanced CT scan of the chest showed a thrombus in the posterior wall of the left atrium (Fig. 2A, B, C). A thrombus of approximately 6 cm in length was identified on echocardiography. Cardiac function was unchanged with a left ventricular ejection fraction of 62% compared to that before the start of lung cancer treatment. The site of thrombus formation in the left atrium coincided with the site of irradiation during thoracic radiotherapy for the primary lesion of lung cancer (Fig. 3A, B, C). In conclusion, it was considered an adverse event due to lung cancer treatment based on his clinical course and findings. The anticancer therapy was discontinued, and the patient was treated with continuous heparin administration while suspending dabigatran. After 14 days of treatment, the thrombus was reduced. His therapy was then modified to oral warfarin, while maintaining a prothrombin time-international normalized ratio (PT-INR) of 1.6 to 2.6.

Discussion

Thrombosis during cancer treatment is a common medical complication, and the risk of venous thromboembolism in cancer patients is 4 to 20 times higher than in non-cancer patients[1]. The number of patients with cancer-related thrombosis

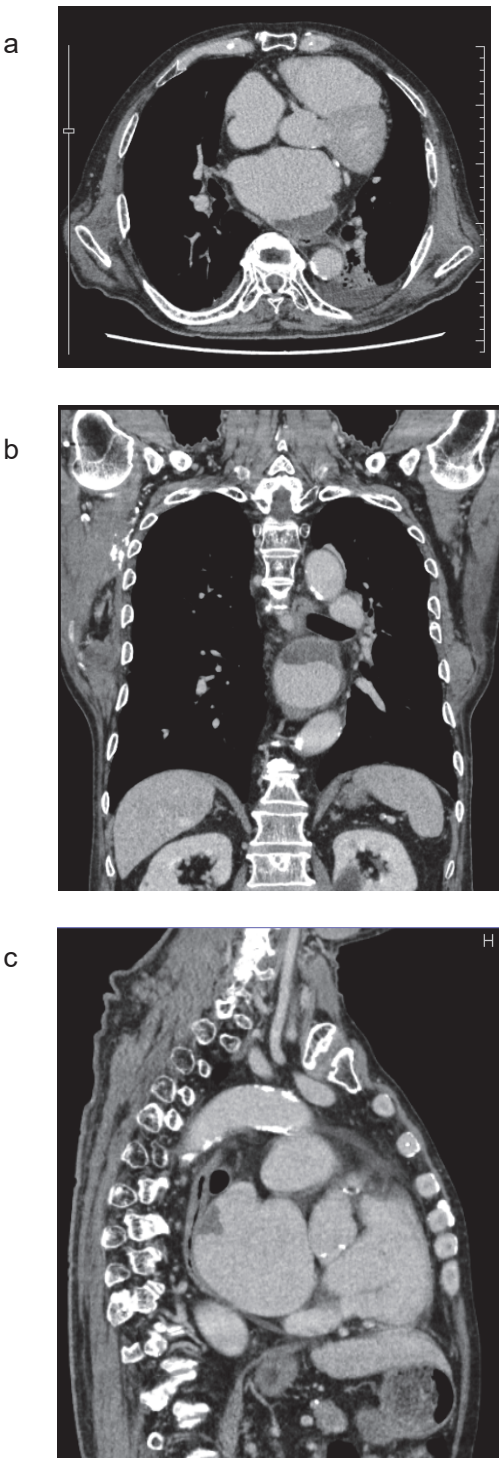

Figure 2. A contrast-enhanced computed tomography image of the chest showing a thrombus in the posterior wall of the left atrium ([A] axial view, [B] coronal view, [C] sagittal view)

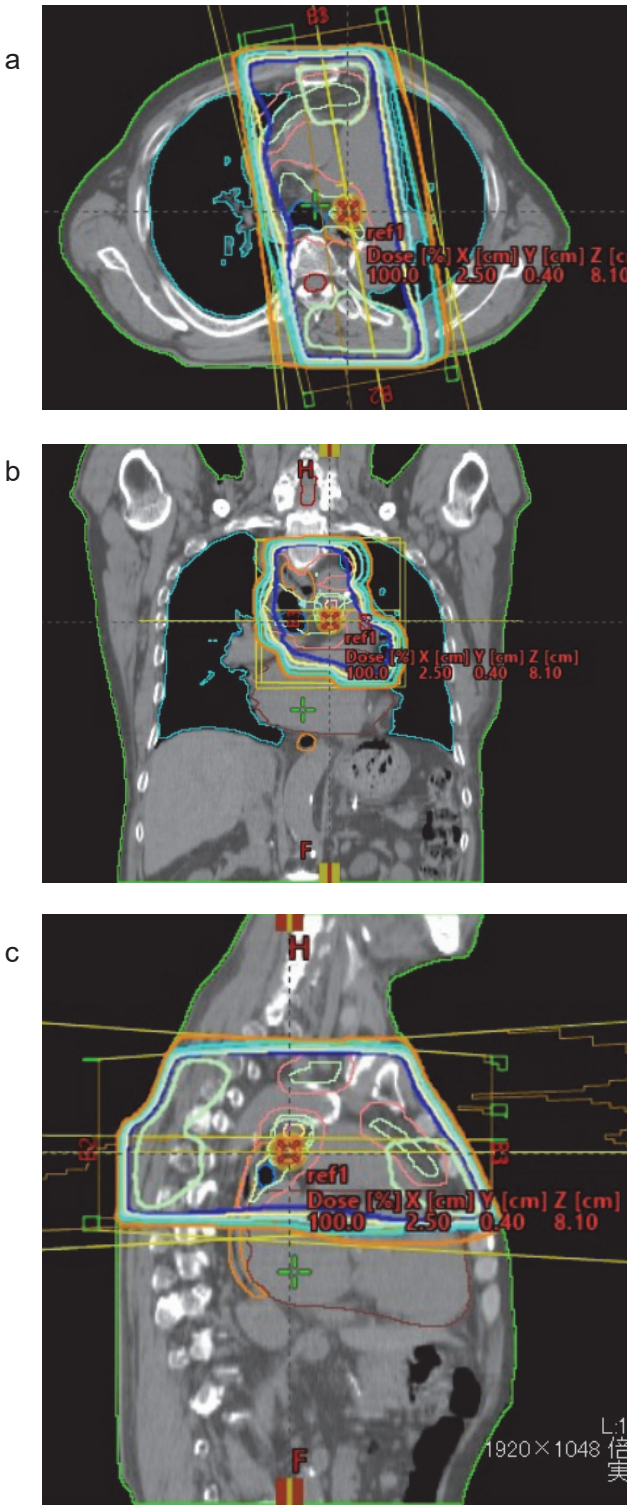

Figure 3. Irradiation plan for radiation therapy of lung cancer. The site of thrombus formation in the left atrium coincided with the site of irradiation during thoracic radiotherapy for the primary lung cancer tumor. ([A] axial view, [B] coronal view, [C] sagittal view)

is increasing each year and the prognosis is poor[1]. In this case, thrombus formation was observed in the posterior wall of the left atrium during the course of nivolumab, ipilimumab, carboplatin, and pemetrexed combination therapy even though the patient was taking direct oral anticoagulants to prevent thrombosis caused by atrial fibrillation. It has been reported that more than 90% of left atrial thrombi in patients with atrial fibrillation originate from the left atrial appendage[2]. Thrombus in the posterior wall of the left atrium, as in this case, is extremely rare. This location coincided with the irradiation site of the initial radical thoracic radiation therapy, suggesting that the thrombus was related to radiation. In a study that investigated thrombosis occurring in the pulmonary arteries during radiation therapy to malignant tumors, all pulmonary artery thrombosis was located within the radiation therapy[3]. Previous reports have shown that radiation-induced NO production, a component of the DNA damage response in vascular endothelial cells, causes chronic inflammation and may be involved in cardiovascular disease after radiation exposure[4]. In addition, ionizing radiation generated in radiotherapy increases the production of reactive oxygen species, causing DNA and mitochondrial damage and increased apoptosis[5]. Radiation has also been reported to increase the release of inflammatory cytokines and chemokines and increase the expression of adhesion molecules[5]. In this case, the thrombus was formed in the site that coincided with the area with a high dose of radiotherapy. Moreover, the left atrial appendage, where thrombosis is more frequent, was outside the area with a high dose of radiation. These findings reveal that the thrombus formation in this case was caused by the combination of high-dose exposure to the posterior wall of the left atrium during the initial thoracic radiotherapy and the modification of local immunity by administration of multiple immune checkpoint inhibitors.

After administration of immune checkpoint inhibitor, several reports of adverse events that are different from those occurring with conventional cytotoxic anticancer agents or molecularly targeted agents, defined as "immune-related adverse events," are available. Thrombosis has also been reported as an adverse event[6], but it is not specific to immune checkpoint inhibitors and occurs at a certain rate with cytotoxic anticancer agents, and its frequency is not significantly different from that of immune checkpoint inhibitors[6]. However, thrombus formation in the left atrium due to concomitant treatment with curative thoracic radiotherapy and cytotoxic anticancer agents and subsequent administration of multiple immune checkpoint inhibitors, as in this case, is considered to be an extremely rare event. So far, there have been no previous reports of thrombosis in the same region after radiotherapy or chemotherapy. To date, based on the successful results of concurrent treatment with curative thoracic radiotherapy and chemotherapy and subsequent treatment with immune checkpoint inhibitors[7], immune checkpoint inhibitors and radiotherapy are expected to be administered more frequently as treatment options for advanced lung cancer. As a result, it is possible that the frequency of adverse events, which are now considered to be rare, may increase, as in this case. It is important to accumulate similar cases in the future to clarify the mechanism of thrombosis and to establish preventive methods.

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Conflicts of interest

The authors declare no competing interests.

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