Acute Arterial Thrombosis during Postoperative Adjuvant Cisplatin-based Chemotherapy for Completely Resected Lung Adenocarcinoma

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Abstract:
A malignant tumor can cause hypercoagulation and it also often coexists with thrombosis. Cisplatin-based chemotherapy can also induce adverse vascular effects, including arterial thrombosis. We herein report a case of acute arterial thrombosis in a patient undergoing postoperative adjuvant cisplatin-based chemotherapy for completely resected lung cancer. The patient complained of acute leg pain after chemotherapy, and computed tomography revealed multiple thrombi from the thoracic to popliteal arteries. Arterial thrombosis during adjuvant chemotherapy is extremely rare; however, careful clinical observation of patients receiving cisplatin-based chemotherapy is important, because arterial thrombosis, even in the absence of the primary malignant tumor, is possible.

Key words: arterial thrombosis, cisplatin, lung cancer, resected

Introduction
A malignant tumor can cause hypercoagulation and it also often coexists with thrombosis (a phenomenon known as Trousseau’s syndrome) (1). Chemotherapy for malignant diseases can also promote thrombogenicity; cisplatin-based chemotherapy, for example, has been shown to elicit thromboembolic events (TEEs), such as aortic thrombosis, myocardial and cerebral infarction, and deep vein thrombosis (2). Although arterial thrombosis during cancer chemotherapy has been described (3–6), chemotherapy-induced arterial thrombosis in patients with a completely resected cancer has been rarely seen.

We herein report a case of acute arterial thrombosis that occurred during adjuvant cisplatin-based chemotherapy administered after complete resection of lung cancer.

Case Report
A 68-year-old man was referred to our hospital because of abnormal chest computed tomography (CT) findings (Fig. 1). He had undergone appendectomy at 26 years of age and colon polypectomy (adenoma) at 62 years of age, but had no medical history of TEEs and was in good condition, with an Eastern Cooperative Oncology Group performance status of 0. He had a smoking history of 45 pack-years but no other risk factors for atherosclerosis, such as hypertension, diabetes, dyslipidemia, chronic kidney disease, or a history of cerebral infarction or peripheral artery disease. He had a family history of lung cancer in his sister but was negative for thromboembolic disease. No abnormal findings

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were observed on a physical examination or electrocardiogram. A blood test showed no abnormalities, including his lipid profiles, plasma glucose, serum creatinine, levels of carcinoembryonic antigen (4.7 ng/mL), and coagulation markers. A contrast-enhanced CT body scan and gadolinium-enhanced magnetic resonance imaging brain scan revealed an abnormal shadow in the right lung and calcification of the abdominal aorta and common iliac artery but no metastatic lesions or thrombi. Lung cancer was suspected, and the patient underwent right lower lobectomy.

Histology revealed lung adenocarcinoma (pT2aN1M0, stage IIA) with negative surgical margins. The patient had an uneventful postoperative course and was discharged from the hospital nine days after admission. One month after surgery, the patient received the first cycle of an adjuvant chemotherapy regimen consisting of cisplatin (80 mg/m², intravenously on day 1) and vinorelbine (25 mg/m², intravenously on days 1 and 8). On day 13 of cycle 1, he complained of acute pain in his right leg and intermittent claudication, which diminished within 1 h. The next day, he again experienced sudden pain and coldness in his right leg while walking. A physical examination showed the absence of pulsation in the right popliteal and dorsalis pedis artery and coldness in the peripheral part of the right lower leg.

Contrast-enhanced CT revealed an intramural thrombus extending from the thoracic artery to the abdominal aorta, 90% narrowing of the right common iliac artery, and complete occlusion of the right popliteal artery (Fig. 2). The ankle brachial pressure index (ABI) was 0.33 on the right side and 1.14 on the left. The laboratory findings concerning coagulation were as follows (normal range): fibrin/fibrinogen degradation, 12.7 μg/mL (0.0-4.9); D-dimer, 5.7 μg/mL (0.0-0.9); protein C, 109% (75.0-128.0); protein S, 51.2% (74.0-132.0); von Willebrand factor (vWF) antigen, 280% (50.0-155.0); anti-β2-glycoprotein I antibodies, 1.2 U/mL (0.0-3.5); anticardiolipin IgG antibody, 8 U/mL (0.0-10.0); and lupus anticoagulant, 1.01 (normalized ratio, 0.0-1.3). Echocardiography showed no thrombi in the heart.

We consulted vascular surgeons concerning the treatment of the patient and decided to carry out medication prior to operative treatment since his symptoms were relieved. He was managed conservatively via the administration of unfractionated heparin followed by warfarin, and his symptoms subsided completely after two weeks. Chemotherapy was permanently stopped, and he was discharged from the hospital with warfarin therapy. Positron emission tomography performed 1 month after the first day of chemotherapy showed no evidence of lung cancer relapse. The right-side ABI returned to 1.10 after 2 months. Contrast-enhanced CT performed 115 days after the onset of thrombotic event showed resolution of all arterial thrombi (Fig. 3). The vWF antigen level peaked (576%) 2 weeks and declined to 182% 4 months after the onset of TEEs.

**Discussion**

The relationship between malignancy and venous thrombosis described by Trousseau suggests that malignancy is associated with an increased risk of venous and arterial TEEs (1). Among the factors that influence the incidence of TEs in cancer patients (e.g. an increase in the expression of proteins that facilitate coagulation, including tissue factor and plasminogen activator inhibitor type 1), chemotherapy imparts a significant risk. The chemotherapeutic agent cisplatin in particular has been associated with a wide range of TEEs in tongue carcinomas (7), esophageal adenocarcinomas (8), gastric cancers (9), rectosigmoid adenocarcinomas (3, 6), lung cancers (3, 6), cervical cancers (10), and germ cell tumors (11). Cool et al. reported recurrent arterial
thrombosis during cisplatin and etoposide chemotherapy (12), and in a large retrospective analysis, Moore et al. found that 169 of 932 (18.1%) patients experienced a TEE during cisplatin-based chemotherapy for any type of malignancy (2). In the Moore et al. study, most TEEs (88%) occurred within the first 100 days after the initiation of cisplatin treatment, and although deep venous thrombosis and pulmonary embolus were the predominant events, arterial TEEs occurred in 19 of the 169 (11.3%) patients (2). Several cases of arterial TEEs during cisplatin-based chemotherapy for lung cancer have been reported; however, all patients in these cases were cancer-bearing (3-5). To our knowledge, we are the first to report a case of arterial thrombosis that occurred during postoperative adjuvant cisplatin-based chemotherapy in a patient with completely resected lung cancer (i.e., a non-cancer-bearing patient). Our case strongly suggests an association between cisplatin-based chemotherapy and the development of arterial TEEs. The exact mechanism of action by which cisplatin-based chemotherapy causes TEEs has not been clarified. Licciardello et al. correlated vWF levels with arterial thrombosis in cisplatin-treated patients; in their study, the median vWF level increased significantly after cisplatin-based chemotherapy (13). Others reported elevated plasma vWF levels in patients with germ cell tumors receiving cisplatin-based chemotherapy (14). In our case, the level of vWF antigen substantially increased after the occurrence of TEEs, perhaps due to drug-induced endothelial cell damage. Cisplatin may promote vascular endothelial injury, such as vacuolation, subendothelial edema, and the destruction of the internal elastic membrane, via free radical-induced lipid peroxidation (15), platelet phospholipase A2-mediated platelet aggregation (16), or the upregulation of intercellular adhesion molecule-1, tissue-type plasminogen activator, and plasminogen activator inhibitor type 1 (17, 18), all of which can induce arterial thrombosis.

Cisplatin-induced hypomagnesemia is also a possible risk factor for TEEs; in the study by Vogelzang et al., hypomagnesemia caused thrombosis by eliciting arterial spasms (19). Although we did not measure the magnesium level before the onset of TEEs, we routinely administer magnesium sulfate to prevent hypomagnesemia due to cisplatin. Therefore, it is unlikely that hypomagnesemia contributed to the thrombosis in our case. Furthermore, hypomagnesemia has not been shown to cause large vessel thrombotic effects.

Protein S deficiency predisposes subjects to develop venous thromboembolism (20). Engesser et al. found that venous thrombotic events occurred in 55% of protein S-
deficient patients, and the age at the first thrombotic event ranged from 15 to 68 years (mean, 28 years) (21). Borgel et al. reported protein S activity ranging from 5% to 30% in patients who developed thrombotic events (22).

In our patient, the protein S activity (51.2%) was below the lower limit of normal (74.0-132.0%), however, he did not have a history of any TEEs in the past. In addition, protein S deficiency was not regarded as a risk factor for arterial thromboembolism in a familial protein S deficiency cohort (23, 24). Therefore, we suspect that the low protein S activity was not related to the arterial thrombosis in our case.

Male gender, smoking, and age ≥45 years for men are known risk factors for atherosclerotic cardiovascular diseases (25), all of which applied to this case. Furthermore, calcification of the abdominal aorta and common iliac artery was detected in our patient. We therefore speculate that patients with multiple risk factors for cardiovascular diseases and aortic calcification may tend to develop arterial thrombosis when receiving cisplatin-based chemotherapy, even in the absence of the primary malignant tumor. Prophylactic anticoagulation should be considered for cancer patients in high-risk settings. Indeed, prophylactic antithrombotic agents have been shown to reduce the incidence of TEEs in patients with solid cancer who are receiving chemotherapy (26, 27). However, the patients included in these trials had metastatic or locally advanced cancers, and most of the TEEs were venous thrombosis. Therefore, the benefit of prophylactic anticoagulation for arterial thrombosis in postoperative adjuvant chemotherapy for completely resected cancer needs to be validated.

In conclusion, careful clinical observations of patients receiving cisplatin-based chemotherapy is important because of the possible risk of arterial TEEs, even when the primary malignant tumor has been completely resected.

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

Written informed consent was obtained from the patient for publication of this case report.

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