INTERNAL MEDICINE

□ CASE REPORT □

Acute Bilateral Renal and Splenic Infarctions Occurring during Chemotherapy for Lung Cancer

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Abstract

We herein report a rare case of acute bilateral renal and splenic infarctions occurring during chemotherapy for lung cancer. A 60-year-old man presented with acute and intensive upper abdominal and back pain during chemotherapy with cisplatin and etoposide for lung cancer. Contrast-enhanced computed tomography (CT) revealed bilateral renal and splenic infarctions. After the administration of unfractionated heparin his pain was relieved with a clearance of the infarctions in the CT findings and a recovery of renal dysfunction. Enhanced coagulation by lung cancer and arterial ischemia by chemotherapy may therefore contribute to the development of these infarctions.

Key words: chemotherapy, lung cancer, renal and splenic infarction

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Introduction

Renal infarction occurs due to embolic infarction in either the main or branched renal arteries. The main causes of such infarction are injury, aortic aneurysm, thrombosis with arrhythmias, systemic inflammatory disease, renal transplantation, and arterial angiography. The most frequent cause is embolic occlusion due to thrombus from atrial fibrillation. However, it is often difficult to diagnose because of its nonspecific symptoms (1).

In malignant diseases, coagulation is enhanced and the incidence of thrombosis is known to increase. The thrombosis accompanied with malignant disease is known as Trousseau's syndrome (2). Lung cancer most often causes thrombosis among all malignant diseases, followed by pancreatic cancer and gastric cancer (3). However, renal thrombosis accompanied with malignant diseases is very rare. Such renal infarction often results in renal dysfunction, which thus makes it impossible to continue to administer platinum based combination chemotherapy. It is therefore important to make an early diagnosis and perform timely treatment for such renal infarction in malignant diseases. We herein report a case of acute bilateral renal and splenic infarctions occurring during chemotherapy for lung cancer, which improved with a recovery of renal dysfunction owing to an early diagnosis and the performance of timely treatment with heparin.

Case Report

A 60-year-old man came to our hospital because of hoarseness. He had a medical history of hypertension and had smoked one pack of cigarettes per day for 42 years. Chest X-ray revealed a 5 cm-sized tumor in left hilar with lympho-adenopathy. He was diagnosed to have small cell lung cancer (cT2bN3M1b: stage IV brain metastasis) and thus was admitted to undergo chemotherapy. Before starting the chemotherapy there was no perfusion defect in the bilateral kidney or spleen on contrast-enhanced computed tomography (CT). Cisplatin (80 mg/m^2) was infused on the first day and etoposide (100 mg/m^2) was infused on the second and third day. On the seventh day, he experienced abdominal pain, which resolved spontaneously. On the ninth day, he again suffered acute upper abdominal pain. The pain was intensive and accompanied with back pain. There was no rebound tenderness on the physical examination or any abnormal findings on abdominal X-rays. Urinalysis did not show hematuria. An electrocardiogram showed no signs of

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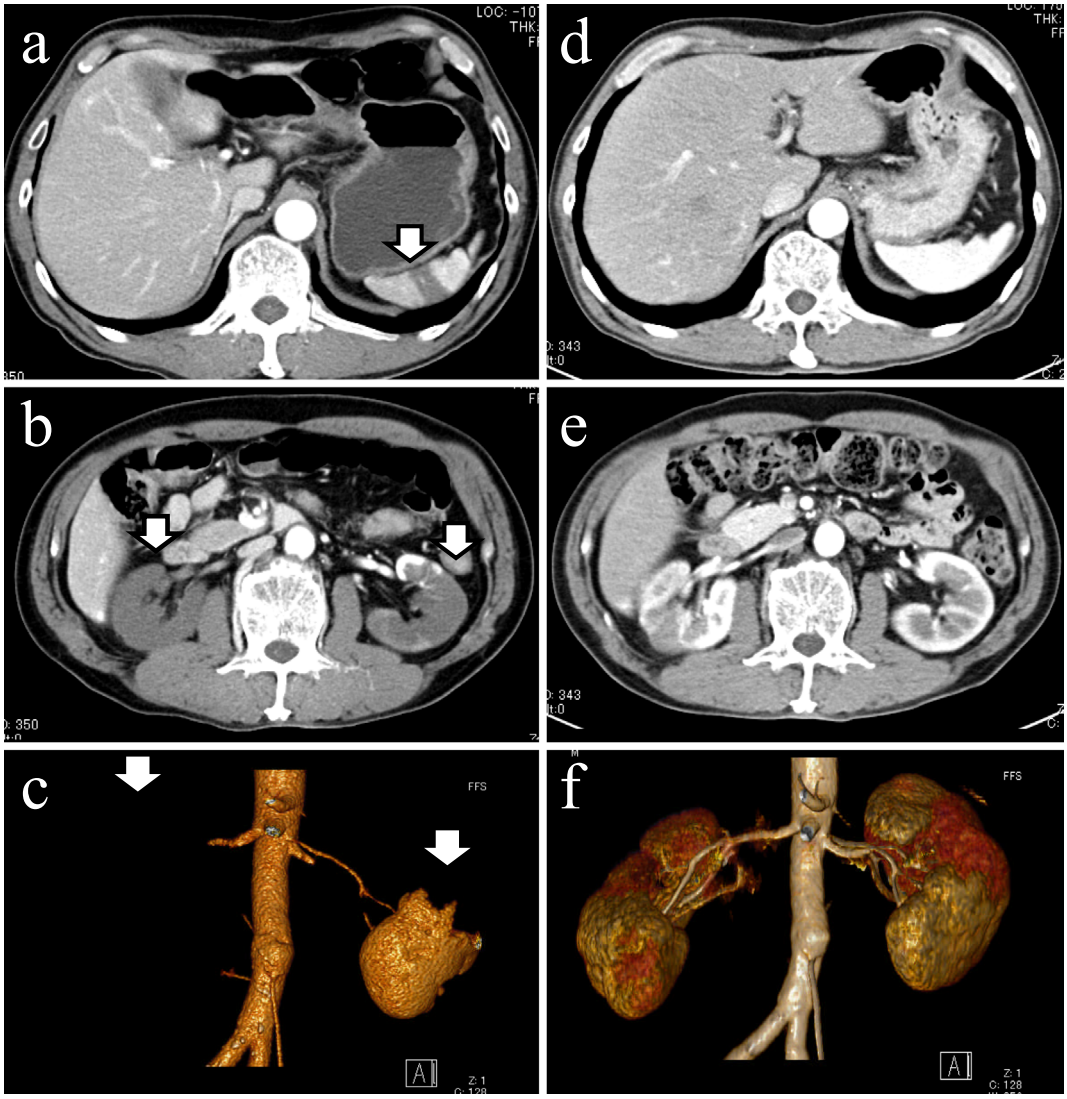

Figure 1. **A contrast-enhanced CT scan revealing perfusion defects (arrows) in the spleen (a), kidney (b, c) on the ninth day. The perfusion defects decreased significantly on the 29th day after treatment with unfractionated heparin (d-f).**

arrhythmia or myocardial infarction. Abdominal contrast-enhanced CT demonstrated perfusion defects in the bilateral kidneys and spleen (Fig. 1). Ultrasonic cardiography demonstrated neither intramural thrombus nor valvar heart disease. We diagnosed acute bilateral renal and splenic infarctions associated with lung cancer. No abnormal findings related to collagen diseases or congenital diseases were detected as shown in Table 1. Two days after starting the administration of unfractionated heparin and a calcium channel antagonist, the abdominal and back pain attenuated and then subsided with the clearance of perfusion defects in bilateral kidneys and spleen on abdominal CT (Fig. 1). The serum creatinine level was elevated to 2.97 mg/dL two days after the onset, while the D-dimer was elevated to 5.9 μg/mL and LDH to 3,138 IU/L. After administering anti-coagulant therapy these data all declined to the normal ranges on the 26th day (Fig. 2). A transient decrease in the platelet count by myelosuppression induced by chemotherapy was observed. The bimodal change pattern in D-dimer, which paralleled the changes in the platelet count, may be partially related to the myelosuppression induced by chemotherapy. From the 22nd day, whole brain radiation and next chemotherapy with etoposide (100 mg/m^2) and carboplatin (AUC5) instead of cisplatin was restarted. Finally, he was discharged after three more serial cycles of this chemotherapy without any recurrence of renal infarction.

Discussion

The main cause of renal infarction is thrombosis. Two major types of thrombosis related to renal infarction are known to exist. One is thromboemboli, which originates from a thrombus in the heart or aorta while another is in-situ thrombosis, which may cause the complete occlusion of the main renal artery or a segmental branch artery (4, 5). In the present case, in-situ thrombosis is thought to have mainly contributed to the onset of renal infarction because no thrombus in the heart or aorta was detected.

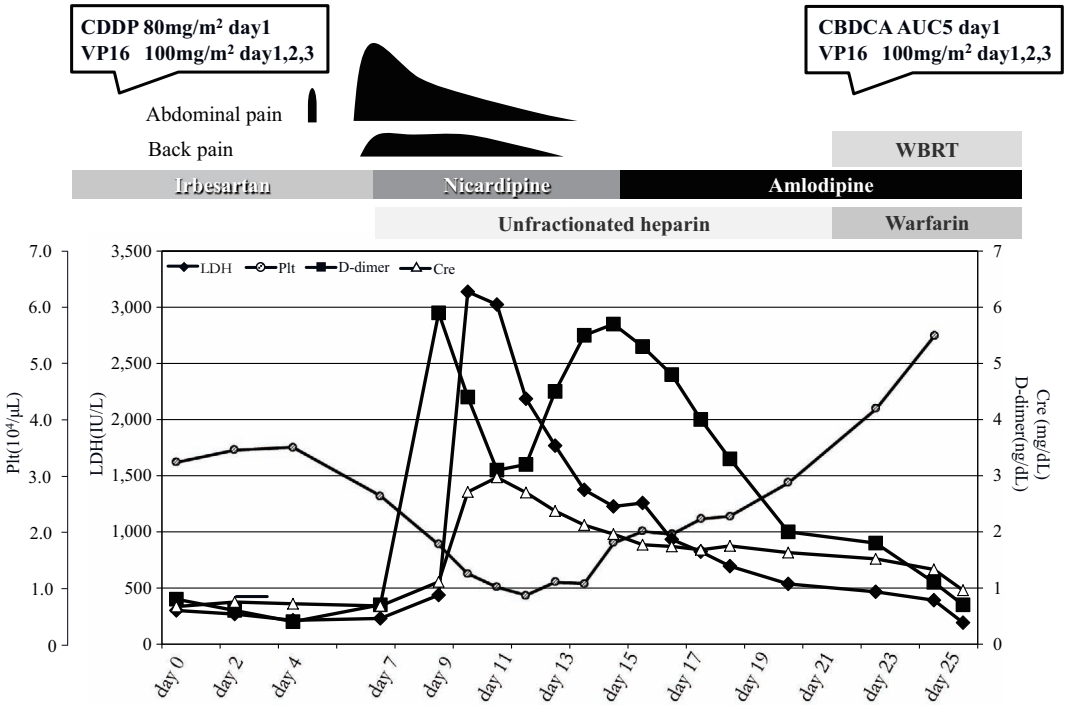

Figure 2. **Clinical course. CDDP: cisplatin, VP16: etoposide, CBDCA: carboplatin, WBRT: whole brain radiation therapy, LDH: lactate dehydrogenase, Plt: platelet counts, Cre: serum creatinine**

Table 1. **Laboratory Findings at the Onset.**

Parameters		normal range
WBC	7,900/μL	(3,900-,9800/μL)
Hb	15.1 g/dL	(13.5-17.6g/dL)
Plt	17.8×10⁴/μL	(13.1-36.2×10⁴/μL)
PT	10.0 sec	(10.0-15.0sec)
APTT	25.6 sec	(25.0-50.0sec)
Fibrinogen	535 mg/dL	(200-400mg/dL)
D-Dimer	2.7 μg/mL	(0.0-1.0μg/mL)
Antithombine III	120%	(80-120%)
Protein C activity	110%	(64-146%)
Protein S antigen (free)	91%	(60-150%)
Lupus anticoagulant	(-)	(-)
Anti-cardiolipin antibody	(-)	(-)
Glucose	109 mg/dL	(60-100mg/dL)
ALT	45 IU/L	(12-32IU/L)
AST	40 IU/L	(5-36IU/L)
LDH	437 IU/L	(116-230IU/L)
Mg	1.7 mg/dL	(1.7-2.7mg/dL)
CRP	3.8 mg/dL	(0.0-0.2mg/dL)
Urinary test		
Protein	30 mg/dL	(-)
Glucose	100 mg/dL	(-)
Occult blood	(-)	(-)

The development of thrombosis in this case was thought to be related to enhanced coagulation caused by cancer and arterial ischemia induced by chemotherapy. At first, we were concerned about the possibility of enhanced coagulation induced by cancer. Since Trousseau et al. have demonstrated that patients with malignant disease have potential risks for thrombosis. A case of excessive coagulation associated with cancer is known as Trousseau's syndrome (2, 6). There are multiple overlapping and interacting mechanisms of Trousseau's syndrome, such as mucin, tissue factor, cysteine proteinase and inflammatory cytokines that serve to activate endothelial and platelet adhesion molecules.

Secondly, arterial ischemia is known to be induced by chemotherapy, including cisplatin. Doll et al. reported that acute arterial ischemic events occurred most frequently after cisplatin based combination chemotherapy (7). Among such arterial ischemic events, myocardial infarction, stenosis in the cerebral artery and thrombus in the peripheral arteries has been reported (7, 8). The mechanisms of arterial ischemic events caused by cisplatin have been explained by drug-induced endothelial cell damage (9), arterial vasospasm due to hypomagnesemia (10) and enhanced alpha-adrenergic tone (11), perturbation of the clotting system (12), activation of platelets (13) or an abnormality of thromboxane-prostacyclin homeostasis (7). Dehydration due to nausea induced by chemotherapy may also possibly accelerate the arterial ischemia through an impaired blood flow as described in Virchow's triad (14).

In the present case, after the induction of chemotherapy renal infarction occurred with an acute onset because there was no embolus in CT scans before the start of chemotherapy. The acute onset was caused by the acute arterial ischemia induced by chemotherapy based on the enhanced coagulation caused by malignant disease.

Table 2. Renal Infarction in Lung Cancer Patients.

Case	Age /sex	Histology	Previous treatment	Risk factors	Location or type of thrombi	Management	Reference
1	54 /Female	Adeno	None	Undescribed	Multiple brain infarction Renal infarction Nonbacterial thrombotic endcarditis	Undescribed	15
2	70 /Male	Large cell	Left lower Lobectomy	DM HT	Renal infarction	Observation	16
3	50 /Male	Adeno	None	APS	Brain infarction Pulmonary thromboembolism	Warfarin Ticlopidine	17
4	46 /Female	Non-small cell	Cisplatin GEM	Undescribed	Bilateral renal infarction	Aspirin ACEI	18
5	67 /Male	Squamous cell	CRT Pneumonectomy	HT Smoking	Bilateral renal infarction Splenic infarction Brain infarction	Embolectomy Dialysis	19
6	52 /Female	Adeno	Left upper lobectomy	None	Renal infarction	Dipyridamole	20
7	60 /Male	Small cell	Cisplatin VP16	Smoking HT	Bilateral renal infarction Splenic infarction	Anticoagulation Ca antagonist	Present case

DM: diabetes mellitus, HT: hypertsension, APS: antiphospholipid antibodies syndrome

Six previously reported cases of renal infarction with lung cancer were reviewed at Table 2 (15-20). Only two of these cases had undergone chemotherapy with CDDP. Renal infarction itself is a rare disease compared with cerebral and pulmonary infarction. There may be more such cases because this infarction is difficult to diagnose because of nonspecific symptoms. The distribution, size and blood flow in renal artery may also be associated with the low incidence of this problem.

In the present case, an early diagnosis and the administration of timely treatment for acute renal infarction made it possible to continue the administration of combination chemotherapy for lung cancer. The therapeutic management of renal infarction usually involves the administration of intravenous heparin followed by oral anticoagulants. When a thrombotic risk remains after the treatment, then the anticoagulant therapy should be continued. Despite the use of such treatments, nevertheless approximately 5% of such patients with renal infarction require hemodialysis due to severe renal dysfunction (5). In addition to this anticoagulant therapy, it is also important to administer magnesium to prevent the onset of vasospasm due to hypomagnesemia induced by cisplatin-based combination chemotherapy. Finally, it is very important to make an early diagnosis and provide timely treatment for renal infarction because renal dysfunction induced by the infarction often makes it impossible to continue administering chemotherapy for lung cancer.

In conclusion, a case of acute bilateral renal and splenic infarctions occurred during chemotherapy for lung cancer was herein reported. This case improved with a recovery of renal dysfunction owing to an early diagnosis and timely treatment with heparin.

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

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