

Case Report

Acute ischaemic stroke and myocardial infarction after chemotherapy with vinorelbine for non-small cell lung cancer: a case report

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Vinorelbine is an important chemotherapeutic agent which is used in metastatic non-small cell lung cancer. Case reports have described the occurrence of acute cardiac ischaemic events as a side effect. It has not been established whether the suspected mechanisms for cardiac ischaemia might also cause other vascular events. We report about a 70-year-old male with metastatic non-small cell lung cancer who received vinorelbine as an outpatient. The patient presents with a cardiovascular risk profile. He was admitted to the hospital 3 days later with acute left-sided hemiplegia and hemianopia. Brain computed tomography (CT) demonstrated acute right hemispheric ischaemic stroke. Nine days after admission, the patient additionally suffered ST elevation myocardial infarction. A coronary angiogram demonstrated high grade stenosis of the right coronary artery treated with two bare-metal stents. Caution should be noted in patients who present with a cardiovascular risk profile as they might be vulnerable experiencing acute ischaemic events.

Keywords: Stroke, Myocardial infarction, Cardiovascular risk profile, Vinorelbine, Metastatic non-small cell lung cancer

Background

Bronchial carcinomas have an incidence of 70 patients per 100 000 people in industrialized countries.¹ This tumour entity has the highest mortality in men and the third highest mortality in women.² Based on the tumour findings, it is possible to establish a tumour stage classification for each patient according to the Union of International Cancer Control (UICC) criteria.³ Recommendations for UICC stage II and IIIA tumours are a curative resection and lymph node dissection followed by an adjuvant scheme of platinum-based chemotherapeutics and vinorelbine. Appropriate patients in UICC stages IIIB and IV with poor general medical condition or contraindications against platinum-based chemotherapeutics receive vinorelbine as a monotherapy.⁴

Vinorelbine is a semi-synthetic derivate of the vinca alkaloid vinoblastine and can be administered orally or intravenously. It suppresses the formation of the tubulin cytoskeleton and thus mitosis. Common side effects of vinorelbine are neutropenia (80%), febrile

neutropenia (9%), thrombocytopenia (3%), nausea and/or vomiting (20%), obstipation (4%), nephrotoxicity (1%), and neuropathy (3%).⁵ There have been several patients described in the literature who had experienced acute cardiac ischaemic events up to seven days after vinorelbine administration and were previously treated for or had known coronary heart disease and cardiovascular risk factors.⁶ The timely correspondence between vinorelbine administration and acute cardiac ischaemia suggests causality.

It has not been established whether vinorelbine might also be associated with the occurrence of different vascular events other than coronary artery disease. In this article, we report a patient who suffered an acute ischaemic stroke and subsequent myocardial infarction within 10 days after vinorelbine administration.

Case Presentation

This 70-year-old man was first diagnosed with non-small cell lung cancer in 2001. The tumour was initially staged as pT4 N0 M0 when the left lower lobe was surgically resected and radical lymphadenectomy performed. The patient subsequently remained tumour-free for 9 years. He was then diagnosed with non-small cell lung cancer of the

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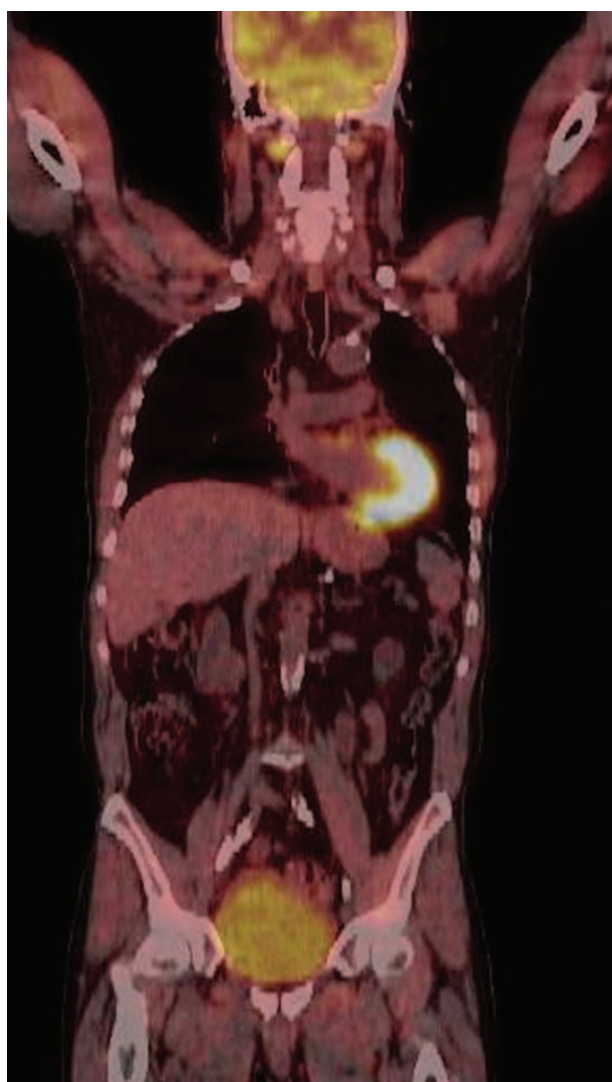


Figure 1 Positron emission tomography scan demonstrating relapse of bronchial carcinoma. Accumulation of fluorodesoxyglucose (FDG) in a tumour without sharply defined edges in segments 1 and 2 of the left lung, compatible with a bronchial carcinoma.

right upper lobe (cT4 N0 M0) in 2010 and received 3 months of chemotherapy with carboplatin and paclitaxel and additional radiotherapy of 60 grey. Palpable subcutaneous nodes in the right upper abdominal quadrant brought the patient to seek medical care again in 2014. The node was biopsied and found to be an adenocarcinoma. Glucose positron emission tomography in April 2014 revealed relapse of tumour tissue in the upper lobe of the patient's left lung as well as cutaneous metastases (cT0 rcN2 rcM1b) (Fig. 1). The patient's situation was deemed palliative and he received the first application of a chemotherapy cycle with intravenous vinorelbine in May 2014.

The patient had an additional past medical history of smoking, arterial hypertension, hypercholesterolemia, and peripheral artery disease, and was treated with clopidogrel and naftidrofuryl. Three days after the administration of vinorelbine, the patient noticed



Figure 2 Cerebral CT scan showing right-hemispheric stroke. Hypoattenuating brain tissue in the right middle cerebral artery territory with focal swelling consistent with acute ischaemic stroke.

mild left facial palsy. Later on, he was then found with a left-sided hemiparesis by his wife who called emergency. By the time of hospital arrival, the patient presented with left-sided hemiplegia and hypoesthesia, left homonymous hemianopia, gaze deviation to the right, and multimodal left-sided hemineglect. A cerebral computed tomography (CT) scan displayed subtotal ischaemic infarction of the right middle cerebral artery territory (Fig. 2). Intravenous thrombolysis was not performed due to the extent of early ischaemic changes. Etiologic work-up for ischaemic stroke demonstrated generalized atherosclerosis as well as multiple plaques without haemodynamically significant stenoses or vasospasms on Duplex ultrasound. The initial electrocardiogram (ECG) as well as the 24-hour monitoring did not detect atrial fibrillation and transthoracic echocardiography did not show other sources for cardioembolism.

Baseline laboratory on admission revealed elevated levels for the cardiac markers creatine kinase, creatine kinase muscle type, myoglobin, and troponin (1.13 $\mu\text{mol}/(\text{s}^*1)$, 6.60 $\mu\text{g}/\text{l}$, 279.90 $\mu\text{g}/\text{l}$, and 350.00 ng/l, respectively). Other than that the laboratory examinations including blood count, C-reactive protein, coagulation panel, electrolytes, creatinine, and liver enzymes were normal. As the patient's baseline ECG showed no ST-segment elevation (Fig. 3) but T-wave inversions, we diagnosed non-ST segment elevation

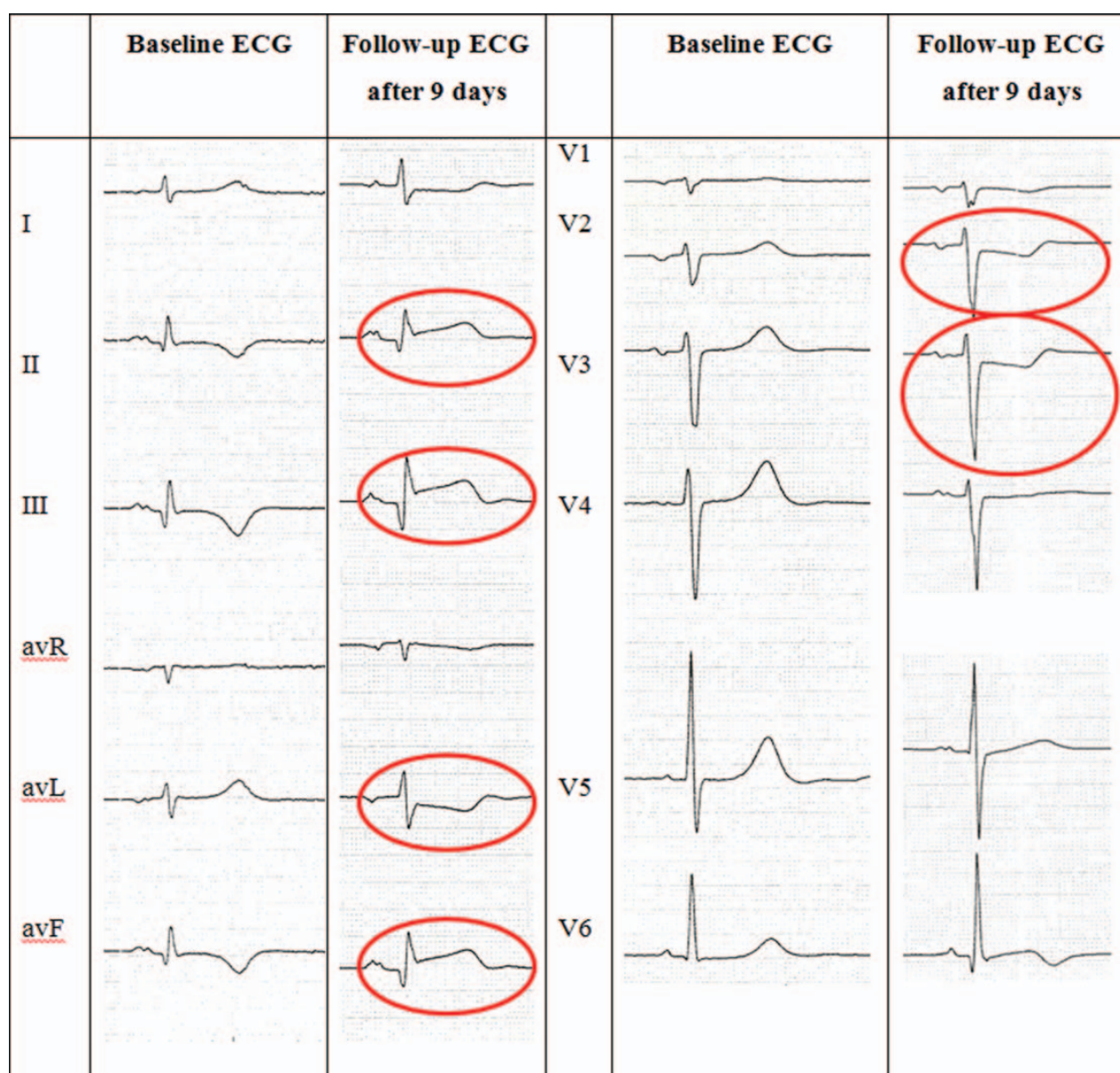


Figure 3 ST-segment changes in the patient's ECG throughout the hospital course. Normal baseline ECG compared with ST-segment elevations in leads II, III (Einthoven), and avF (Goldberger), as well as ST-segment depressions in leads V₂ and V₃ (Wilson) of the follow-up ECG after 7 days is highlighted with red circles. Findings are compatible with an acute ST-segment elevation posterior wall.

myocardial infarction. After discussion with our cardiologists, coronary angiography was withheld in risk-benefit assessment because of the concomitant acute ischaemic stroke and metastatic cancer. The patient was treated with dual antiplatelet medication (aspirin and clopidogrel), simvastatin, bisoprolol, and ramipril.

Nine days after hospital admission, the patient complained of substernal pain. Repeated ECG now demonstrated ST-segment elevations in leads II, III (Einthoven), and avF (Goldberger), as well as anterior wall ST-segment depressions in leads V₂ and V₃ (Wilson; Fig. 3). In view of the clinical progression and newly diagnosed ST-segment elevation infarction, we performed acute coronary angiography which established high-grade stenosis and thrombotic material in

segment 2 of the right coronary artery (Fig. 4A). Two bare metal stents were implanted without periprocedural complications (Fig. 4B) and thrombolysis in myocardial infarction III flow in the right coronary artery. Hereinafter, the patient's chest pain subsided and he was clinically stable. After 17 days in hospital, the patient was discharged for rehabilitation with a residual left-sided hemiparesis and hemianopia with continued dual antiplatelet therapy.

Discussion

The patient we present in our report suffered two acute vascular events — ischaemic stroke and myocardial infarction — within 10 days after intravenous vinorelbine administration as a palliative chemotherapy for non-small cell lung cancer.

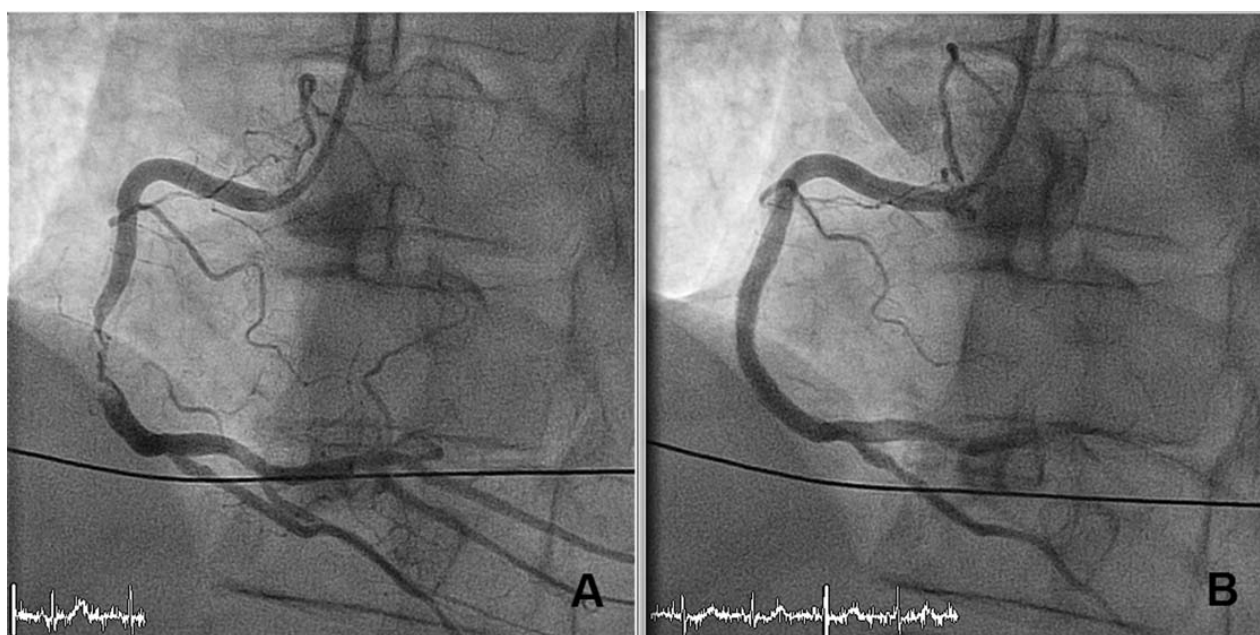


Figure 4 Coronary angiogram demonstrating high-grade stenosis of right coronary artery. Acute coronary angiogram 9 days after admission demonstrates high-grade stenosis of the right coronary artery (A) that was successfully treated with two bare-metal stents (B).

Previously reported cardiac ischaemic events suggested different potential cardiotoxic effects of vinca alkaloids, i.e. the release of vasoactive agents or direct vasospastic effects,⁷ toxic effects on the myocardial cells themselves,⁸ destruction of the parasympathetic nervous system,⁹ or activation of the *in vitro* extrinsic coagulation pathway¹⁰ have been hypothesized. We had no evidence of intracerebral vasospasm (transcranial Doppler sonography) or coronary vasospasm (coronary angiogram) in the patient in our report. There was no definite proof of an activated *in vitro* extrinsic coagulation pathway caused by vinorelbine based on the patient's laboratory examinations since international normalized ratio, partial thromboplastin time, and thrombocytes were normal. As no specific tests were performed in the acute situation, we cannot comment on possible direct toxic effects or damaging of the parasympathetic nervous system in this patient.

About 20% of patients older than 70 years of age with newly diagnosed cancer have coexisting cardiovascular disease.¹¹ As all the previously described cases of ischaemic cardiac events after vinorelbine administration, our patient presented with a pronounced cardiovascular risk profile. Baseline laboratory tests and ECG confirmed non-ST segment elevation myocardial infarction. The risk of suffering a stroke after a myocardial infarction is increased.¹² Cardiac ischaemia leads to regional contraction disorders and endocardial irritations enabling microthrombosis. Global contraction disorders result in decreased ejection fraction with haemodynamic changes to cerebral perfusion. This as well as the pre-existing vascular damage aggravated by direct

toxic effects of vinorelbine and thrombophilia due to his cancer could have led to the cerebral ischaemia in our patient.

Conclusion

Although vinorelbine is an important chemotherapeutic agent especially in metastatic lung and breast cancer, caution should be exercised in patients who present with a cardiovascular risk profile, as they might be vulnerable to experience acute vascular events. Patients should be rigorously monitored during and after vinorelbine administration. The frequency of the above-mentioned vascular events as vinorelbine side effects is currently unclear.^{13,14} The impact of the route of administration (orally or intravenously) of vinorelbine on those unexpected side effects needs to be evaluated.

Disclaimer Statements

Contributors CZ acquired clinical data, prepared the figures, and wrote the manuscript. MG prepared the figures and revised the manuscript for intellectual content. GF revised the manuscript for intellectual content. VP revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Conflicts of interest The authors declare that they have no competing interests.

Ethics approval Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the

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