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CASE REPORT
Coronary heart disease

Multiple spontaneous coronary artery dissections associated with intravenous daunorubicin treatment for acute myelocytic leukaemia: a case report

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Background Multiple spontaneous coronary artery dissection (SCAD) is a rare condition which may lead to serious consequences such as sudden cardiac death, acute myocardial infarction (AMI), and acute heart failure.

Case summary In this paper, we report the case of a 57-year-old woman with acute myelocytic leukaemia who was undergoing her second phase of chemotherapy. After the first induction cycle of intravenous infusion of daunorubicin, the patient experienced chest pain, shortness of breath, and low blood pressure. The electrocardiograms revealed significant ST-elevation in the D1, aVL, and V2–V6 leads, which indicated AMI. Coronary catheterization showed spontaneous coronary dissection in the mid-left descending coronary artery and first obtuse marginal artery of the circumflex. The patient died immediately.

Discussion This is the first reported case of multiple SCAD associated with intravenous (IV) daunorubicin infusion. We also reviewed the literature and proposed the mechanism of this complication.

Keywords Case report • Myocardial infarction • Daunorubicin • Acute myeloid leukaemia • Electrocardiography • Coronary artery dissection

Learning points

- Multiple spontaneous coronary artery dissection is a rare condition. It can cause fatal consequences such as sudden cardiac death, acute myocardial infarction, and acute heart failure.
- Acute myeloid leukaemia (AML) is the most prevalent malignancy of the bone marrow in adults. Its conventional treatment regimen includes intravenous infusion of daunorubicin for 3 days and cytarabine for 7 days.
- It is essential to recognize the cardiac complications following daunorubicin intravenous administration for AML, such as multiple coronary dissections.

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Introduction

Acute myeloid leukaemia (AML) is the most prevalent malignancy of the bone marrow in adults. Its conventional treatment regimen includes intravenous infusion of 45 mg/m^2 daunorubicin for 3 days with 100–200 mg/m^2 cytarabine infusion for 7 days.[1] Löwenberg *et al.*[2] reported an early mortality rate of 12% after the first two cycles of conventional dose of daunorubicin. However, sudden cardiac death following spontaneous dissection has not been reported yet.

Spontaneous coronary artery dissection (SCAD) is defined as a non-iatrogenic, non-atherosclerotic, and non-traumatic spontaneous separation of the coronary artery wall.[3] More than 90% of SCAD cases occurs in women with negligible cardiovascular risk factors.[4] Moreover, SCAD is highly associated with fibromuscular dysplasia (FMD)[5] and caused by other risk factors such as hormonal therapy, Marfan syndrome, vascular Ehlers–Danlos, Loyes–Dietz syndrome, and polycystic kidney.[6] However, no study has indicated that daunorubicin could be associated with SCAD.

Herein, we report a case of multiple SCAD in a patient with AML type M3. During the second phase of chemotherapy with daunorubicin and cytarabine, she experienced acute myocardial infarction (AMI) with ST-elevation and died suddenly.

Timeline

Day 0	A 57-year-old woman presented with left lower arm purpura and several weeks old of left thigh intra-muscle haemorrhage in the left thigh.
Day 1	She was diagnosed with acute myeloid leukaemia type M3. Chemotherapy with cytarabine and tretinoin was administered.
Day 3	The first chemotherapy cycle with cytarabine and tretinoin was successful without complications and the patient was discharged in stable condition.
Day 30 (1 month after discharge)	The patient was re-hospitalized with cough, exertional dyspnoea, and tooth bleeding. Physical examination revealed scattered subcutaneous purpura.
Day 31	The second cycle of chemotherapy with daunorubicin 45 mg/m^2 of body mass diluted by 200 mL of 0.9% sodium chloride followed by cytarabine 100 mg/m^2 was administered.
Day 31	Immediately after the intravenous infusion of daunorubicin and cytarabine infusion, the patient suddenly complained of fatigue, acute dyspnoea, and heavy chest pain.
Day 31	The patient was intubated and transferred to the intensive care unit for mechanical ventilation.
Day 31	The patient was transferred to the catheterization laboratory. Diagnostic angiograms showed multiple coronary dissections. Suddenly, she collapsed and after unsuccessful resuscitation, she died.

Case presentation

A 57-year-old woman presented with left lower arm purpura and several weeks of left thigh intra-muscle haemorrhage (IMH) in the left thigh. She was diagnosed with AML type M3. Chemotherapy with cytarabine and tretinoin was administered. The first chemotherapy cycle with cytarabine and tretinoin was successful without complications and the patient was discharged in stable condition.

One month later, she was re-hospitalized with cough, exertional dyspnoea, and tooth bleeding. Physical examination revealed scattered subcutaneous purpura. She had no history of hypertension, diabetes, smoking, heart failure, or other risk factors for coronary diseases. She had no complaint of fever, weight loss, or chest pain. She denied any occurrence of lung diseases in the past. On admission, a chest X-ray showed the lung was clear without any evidence of pulmonary infiltration or pleuro-pericardial effusion (*Figure 1*).

The complete blood count showed anaemia with Hb of 7.5 g/dL, significant leucocytosis with leucocyte count of 67.7 $\times$ 10^9/L, neutrophil concentration of 86.1%, and thrombocytopenia (42 G/L). The second cycle of chemotherapy with daunorubicin 45 mg/m^2 of body mass diluted by 200 mL of 0.9% sodium chloride followed by cytarabine 100 mg/m^2 was administered.

Immediately after the intravenous infusion of daunorubicin and cytarabine infusion, the patient suddenly complained of fatigue, acute dyspnoea, and heavy chest pain. Physical examination showed wheezing, respiratory coarse crackles, and a 100-150 b.p.m. heart rate. Blood pressure dropped from 130/70 to 100/60 mmHg. The SpO_2 decreased from 95% to 73% with 15 L O_2/min. D-dimer, prothrombin, and fibrinogen were 65.230 ng/mL, 61%, and 1.04 g/L, respectively.

Arterial blood gas analysis revealed a developed respiratory failure with 7.23 pH, $PaCO_2$ of 52 mmHg, and a PaO_2 of 54 mmHg. Therefore, she was intubated and transferred to the intensive care unit for mechanical ventilation. The chest radiograph revealed

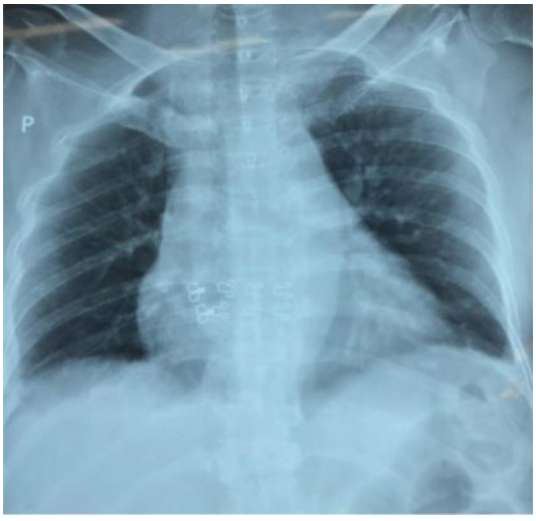

Figure 1 Chest X-ray on admission showed lung clear, no pulmonary infiltration or pleuro-pericardial effusion.

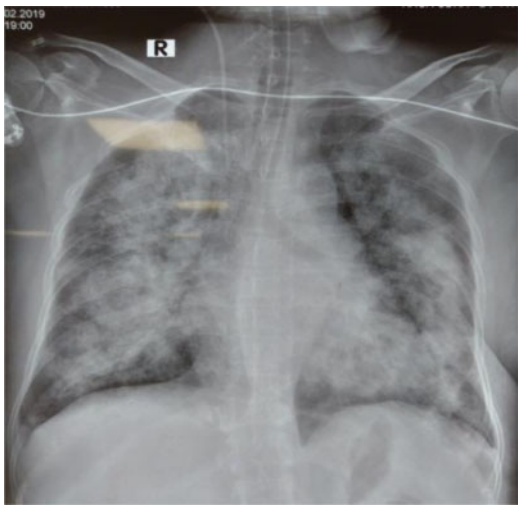

Figure 2 Chest radiograph revealing bilateral ground-glass opacity reflecting fluid filling of the alveolar spaces.

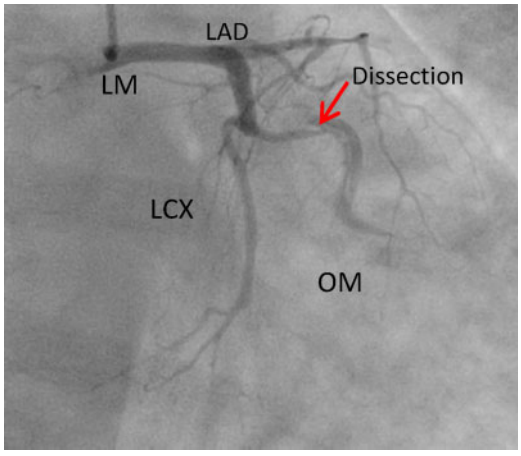

Figure 4 Left caudal angiographic view showing mid-circumflex dissection (LAD, left anterior descending; LCX, left circumflex; LM, left main; OM, obtuse marginal, place of dissection indicated by an arrow).

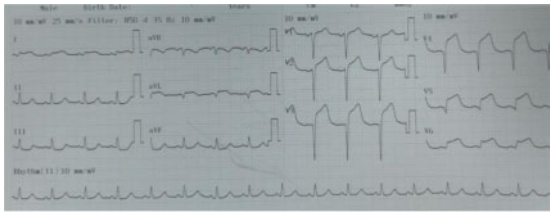

Figure 3 A 12-lead electrocardiogram showed a normal axis, 2–4 mm elevated ST-segment at V2–V6, and DI, aVL.

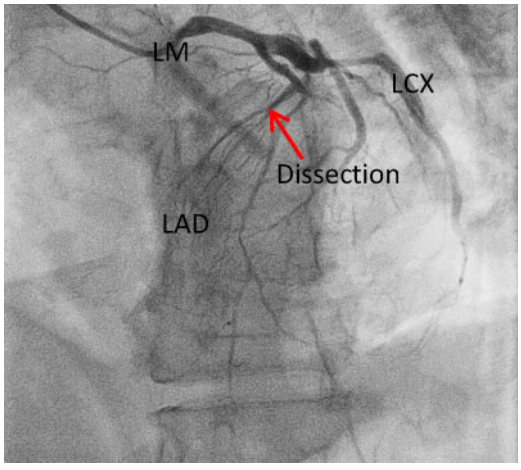

Figure 5 Left cranial angiographic view showing mid-descending artery dissection (LAD, left anterior descending; LCX, left circumflex; LM, left main; OM, obtuse marginal, place of dissection indicated by an arrow).

bilateral ground-glass opacity reflecting fluid filling of the alveolar spaces (*Figure 2*). And the 12-lead electrocardiogram showed a normal axis, 2–4 mm elevated ST-segment at V2 to V6, and DI, aVL, which suggested a typical AMI (*Figure 3*).

Transthoracic echocardiography showed the left ventricular ejection fraction of 50%, apical and septal hypokinaesia, with systolic pulmonary arterial pressure of 48 mmHg.

Due to suspected AMI, the patient was transferred to the catheterization laboratory. Diagnostic angiograms showed multiple coronary dissections (*Figures 4–6*). Suddenly, she collapsed and after unsuccessful resuscitation, she died.

Discussion

To the best of our knowledge, this is first report on multiple SCAD associated with daunorubicin intravenous infusion for AML. According to the American Heart Association scientific statement on SCAD, predisposing conditions for SCAD include FMD, pregnancy, multiparity, hereditary arteriopathy, connective tissue disorders, exogenous hormonal therapy, systemic inflammatory diseases, migraine headaches, and coronary spasms.[7] However, a paucity of case reports exists regarding the usage of intravenous daunorubicin in AML treatment.

Spontaneous coronary artery dissection is characterized by spontaneous IMH within the coronary artery wall, which is confirmed by intravascular ultrasound,[8] histopathology, case reports, and case series.[9–11] Clinical symptoms of SCAD are usually chest pain, typically consistent with acute coronary syndrome, while 26–87% and 13–69% patients present with ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), respectively.[12] Our case presented with typical chest pain and ST-

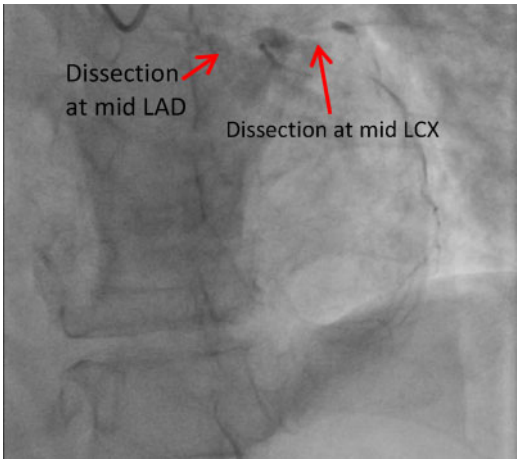

Figure 6 Contrast remained at the positions of dissections (arrows).

elevation on electrocardiogram (ECG). Thereafter, the patient immediately experienced a cardiogenic shock, which primarily caused the collapse.

We performed an in-depth literature searches to uncover the pathological mechanism underlying this episode of cardiovascular complication of daunorubicin. However, we could not find any published literature pertaining to this condition. Daunorubicin is an anthracycline, antineoplastic, antibiotic drug. It exhibits cytotoxic activity through topoisomerase-mediated interaction with DNA, thereby inhibiting DNA replication; DNA repair; and RNA and protein synthesis.[13] Lawrence *et al.* reported a case of AML involving acute heart failure as a complication after intensified treatment with daunorubicin, with decrease in ejection fraction (EF) from 60% to 10%, which is recovered after few months of medical treatment. Additionally, Takotsubo cardiomyopathy was associated with the use of daunorubicin.[14] Thus, these cases indicate the acute cardiotoxicity of daunorubicin.

Disseminated intravascular coagulation (DIC) or 'late' differentiate syndrome may contribute to the severity of the patient's condition. According to the diagnostic scoring system for DIC, this patient had platelet count <50 (2 points) and D-dimer was five times above the upper limit of normal (3 points).[15] Consequently, she got an overt DIC. However, changes in ECG tracing and coronary dissections cannot be explained by DIC. Disseminated intravascular coagulation maybe a contributory factor but not a cause of the patient's collapse. Regarding 'late' differentiate syndrome, a chest X-ray at admission was clear without any evidence of pulmonary infiltration or pleuropericardial effusion. Moreover, clinical symptoms/signs that lead to high suspicion of DS include dyspnoea, oedema, unexplained fever, hypotension, weight gain more than 5 kg, and/or vascular leakage syndrome, were absent. Therefore, it was less likely that the patient had a 'late' differentiate syndrome.

We treated the patient according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for AML.[16] However, the risk of cardiotoxicity, specifically that of spontaneous coronary dissection, has not yet been established. We believe that our report can create awareness regarding the adverse effects of daunorubicin among physicians who prescribe daunorubicin for the treatment of AML regardless of the drug's dosage and timing.

We could not ascertain whether the treatment of the complication in our case was adequate. Initially, we intended to perform diagnostic angiography followed by coronary stenting or coronary artery bypass grafting (CABG) surgery. However, as the patient collapsed sooner, we were unable to perform percutaneous coronary intervention (PCI). We believe that PCI may not be a suitable treatment of SCAD because guidewires may enter the false lumen and occlude the true lumen. In our patient, there were multiple dissections of the mid-left descending coronary artery and left circumflex (LCX) that led to more complications. Meanwhile, we also found a paucity of evidence to support CABG in SCAD. Only one small study showed the initial success of CABG for treatment of SCAD.[17]

Conclusion

It is essential to recognize the cardiac complications following daunorubicin intravenous administration for AML, such as multiple coronary dissections as illustrated in this case. Following the evaluation of the patient, immediate medical decision-making and accurate treatment are warranted in such cases as the risks of mortality is quite high.

Lead author biography

Dr Do Van Chien, MD, PhD, graduated from Volgograd Medical School, Russia with distinction in 2006 and currently works as Deputy Head, Department of Cardiology, 108 Central Military Hospital, Hanoi, Vietnam. He was also a fellow of interventional cardiology at Sydney Concord Repatriation, Australia in 2011 and National Heart Centre Singapore in 2014. His clinical and research interests include interventional cardiology, echocardiography, and cardiomyopathy.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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