

Anthracycline-induced delayed-onset cardiac toxicity: A case report and literature review

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Abstract. Anthracycline (ANT) drugs are widely used for patients with malignant tumors and can markedly prolong the disease-free survival rate of patients. As its clinical application becomes more common, information regarding serious cardiotoxicity as a result of ANT treatment is becoming understood. However, to the best of our knowledge, delayed-onset cardiotoxicity due to ANT use has not been studied sufficiently. The present report describes a 36-year-old male patient who presented to Guiqian International General Hospital (Guiyang, China) with a complaint of dyspnea in the last 10 days. Substantially elevated B-type natriuretic peptide levels and echocardiography showing enlargement of the entire heart, of the patient suggested that severe heart failure was the cause of his symptoms. However, the cause of this potential heart failure was not apparent until the patient was questioned about his cancer treatment history. Following consultation to evaluate the assessment of end-stage heart failure, currently only anti-heart failure treatment and symptomatic treatment can be provided. The present report describes this case and reviews the existing literature to provide a basis for the diagnosis and treatment of patients with delayed-onset heart failure following ANT treatment.

Introduction

Anthracycline (ANT) is a first-line chemotherapy drug with high clinical efficacy and a broad antitumor spectrum (1). Adriamycin, daunorubicin, epirubicin, mitoxantrone and nortodoxorubicin all belong to the ANT family of agents that are

commonly used in clinical practice and widely used for treating hematological and solid tumors (2). As the clinical application of ANTs has become more common, clinical side effects on the heart following ANT treatment are also becoming gradually understood. Since Lefrak *et al* (3) first reported cardiotoxicity induced by ANT in 1973, various reports have pointed out that its cardiotoxicity is potentially more harmful to the prognosis of patients with cancer compared with the cancer recurrence itself (4,5). In particular, information regarding delayed-onset cardiotoxicity as a result of ANT treatment remains lacking. Recent studies have found that subclinical cardiotoxicity caused by low total cumulative doxorubicin doses can manifest into cardiomyopathy in long-term cancer survivors (6,7). Chronic cardiotoxicity of chemotherapy drugs in cancer patients is clinically common, and typically occurs within 1 year of treatment (6). It manifests as congestive heart failure and/or cardiomyopathy that can induce irreversible changes such as Enlargement of the atria and ventricles or decreased myocardial activity (6). In addition, its clinical onset is frequently hidden and the mortality rate can reach as high as 30-60% (6). The occurrence of chronic cardiotoxicity has been documented to be closely associated with the cumulative dose of ANTs (7).

The present case report describes a 36-year-old patient with heart failure due to new adjuvant chemotherapy and osteosarcoma resection based on a combination of Doxorubicin, Cisplatin, and high-dose Methotrexate (MAP regimen). The expert group of the hospital held a consultation to assess the situation of the patient in detail and formulated a diagnosis and treatment plan. In addition, the existing literature was reviewed to provide a basis for the diagnosis and treatment of the patient.

Case report

A 36-year-old young male patient presented to the Cardiology Department of Guiqian International General Hospital (Guiyang, China) in October 2022 due to 'difficulty breathing for >10 days. The patient felt shortness of breath after a little exercise, following which the symptoms progressively worsened, accompanied by paroxysmal nocturnal dyspnea and orthopnea. The electrocardiogram (ECG) (ECG-2306, Shanghai Optoelectronic Medical Electronic Instrument Co., Ltd) revealed 'ST-segment elevation in leads V1-V4,

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ST-segment depression in multiple leads, and flat and inverted T waves (Fig. 1). Comprehensive evaluation of the chest CT and cardiac ultrasonography results revealed no anomalous findings.

The patient was diagnosed with osteosarcoma of the lower left extremity 14 years before presenting to the hospital, and underwent MAP regimen at Guangzhou Cancer Hospital (Guangzhou, China). During the following 5 years of regular follow-up, there was no recurrence of osteosarcoma and no abnormalities were detected in the cardiac-related examinations. Auxiliary examination at the time of visit revealed that serum B-type natriuretic peptide (BNP) level in the patient was 2,146 pg/ml (normal, 0-100 pg/ml) (7). Echocardiography (EPIQ 7C, Royal Dutch Philips Electronics Ltd.) indicated that the whole heart was enlarged, and the left ventricular systolic function was markedly reduced (Fig. 2), suggesting heart failure. Coronary angiography (Azurion 7 M20; Royal Dutch Philips Electronics Ltd; contrast agent dosage, 60 ml, Contrast catheter: TIG 5F, contrast guidewire: 150 cm) revealed coronary atherosclerotic heart disease, and the most severe stenosis was observed in the proximal segment of the anterior descending artery. Specifically, 80% stenosis was found in the proximal segment of the anterior descending artery; there was 90% stenosis in the opening of the first diagonal branch and 70% stenosis in the distal segment of the circumflex artery (Fig. 3). Cardiac MRI indicated no obvious myocardial diffuse fibrosis, myocardial inflammation, myocardial infarction or specific cardiomyopathy manifestations. In addition, urine light chain, serum antibody light chain (κ/λ), immunoglobulin electrophoresis, antinuclear antibody spectrum were also found to be normal.

In the present case, it was first considered whether the clinical symptoms were caused by acute myocardial infarction. Although the admission ECG yielded multiple leads, such as ST-segment depression and T wave low flatness, there was no change in their localizations or any marked increases in troponin levels after two reexaminations 1 day apart (October 2022). In addition, the patient had no recent history of sudden chest tightness or chest pain, which was not consistent with acute myocardial infarction. In addition, ultrasound showed enlargement of the whole heart, thickening of the posterior left ventricular wall and ventricular septum not reaching 15 mm, but the ratio of ventricular septum to left ventricular posterior wall did not reach 1.3-1.5 (1.18) and was not classed as hypertrophic cardiomyopathy (5,7). Patients with hypertension with blood pressure $\leq 160/100$ mmHg may develop hypertensive heart disease without antihypertensive therapy (4) This may explain the thickening of ventricular septum in the present case. However, this was not sufficient to explain the concentric enlargement observed. Therefore, it was considered whether the coronary multivessel lesion in the patient could be due to ischemic cardiomyopathy. However, if such a severe type of heart failure has recently been reached, then the clinical history of coronary heart disease should be long with the relevant symptoms such as changes in myocardial enzymes and previous exertion-associated chest pain and tightness (7). Therefore, the occurrence of sudden illness in the present patient was inconsistent with the diagnosis of 'coronary heart disease'. The patient was diagnosed with chronic heart failure, cardiac function class IV (New York Heart Association class) (8). However,

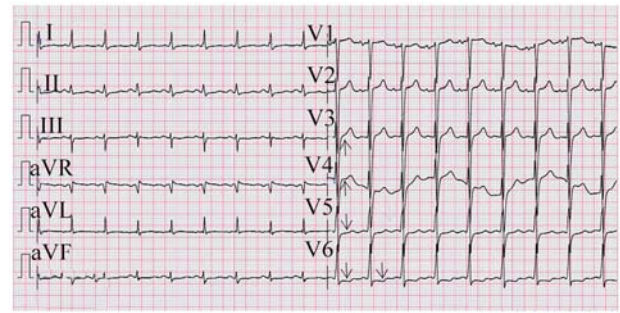


Figure 1. Electrocardiogram (October 2022) showing ST-segment elevation in leads V1-V4, ST-segment depression in multiple leads, and flat and inverted T waves. Arrows indicate the elevation and depression of the ST segment. aVR, augmented Vector Right; aVL, Augmented Vector Left; aVF, Augmented Vector Foot.

it was considered uncommon that a patient of such young age was not found with any predisposing factors for severe heart failure. After assessing the medical history, it was revealed that the patient underwent chemotherapy 14 cycles of treatment 5 years ago, specifically with ifosfamide (108 g), cisplatin (200 mg) and paclitaxel (1,400 mg), where the total usage of pirarubicin hydrochloride reached 1,031 mg, exceeding the recommendation (National Comprehensive Cancer Network. Bone Cancer, Version 2.2021). Finally, following discussion with the panel, antineoplastic drug-induced heart failure was considered. Chemotherapy for osteosarcoma typically consists of three or more chemotherapy drugs. Cisplatin is the basic chemotherapeutic agent for osteosarcoma and can also cause cardiotoxicity (6). However, since there was no evidence of cisplatin overdose in the treatment history of the patient, cardiac toxicity due to cisplatin appeared unlikely. Furthermore, since no other drugs reported to cause marked cardiotoxicity (such as Hydrochloride Tolvaptan, Vitamin C) (7) were found in the treatment history of the patient, the symptoms observed in the present report were proposed to be attributed to delayed cardiotoxicity caused by ANT. Therefore, subsequent reviews focused on this. Follow-up patients by phone every six months after discharge to track their health. The patient reported during the latest phone follow-up in December 2022, that clinical symptoms had not significantly worsened over the past months.

Discussion

The present patient was young and onset of cardiotoxicity was sudden. Acute myocardial infarction was first considered; however, the admission ECG had multiple leads of ST-segment depression and T-wave flattening, coupled with no localization changes or significant increases in troponin levels. There was also no history of sudden chest tightness, chest pain or elevated cardiac enzymes. None of these aforementioned observations conformed to the manifestations of acute myocardial infarction (9). Subsequent echocardiography revealed enlargement of the whole heart and thickening of the posterior wall of the left ventricle. However, the ventricular septum did not reach 15 mm and the ratio of ventricular septum to posterior wall of the left ventricle did not reach 1.3-1.5, which was not in line with hypertrophy cardiomyopathy (10). Therefore, the overall

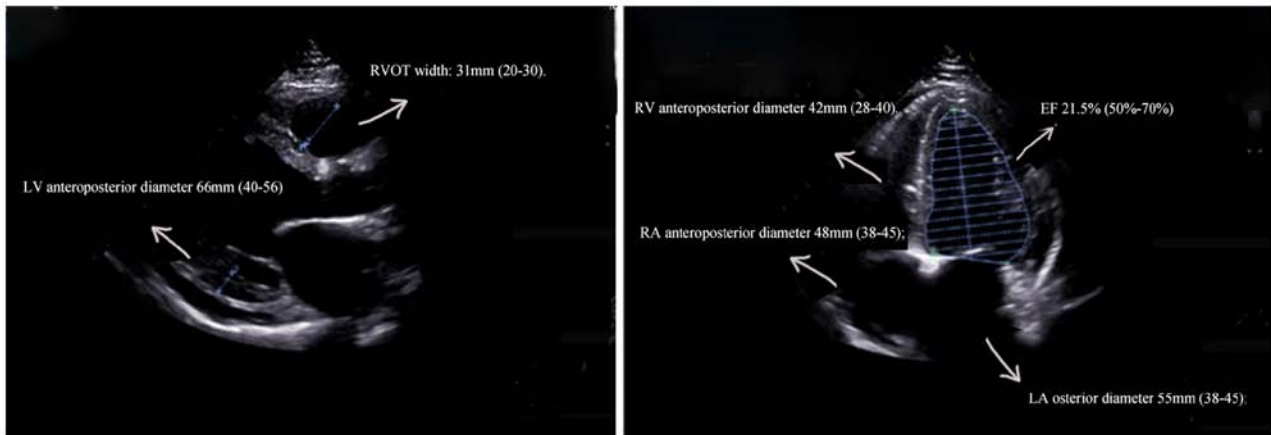


Figure 2. Echocardiography showing that the whole heart was enlarged. LVEF, left ventricular ejection fraction; LA, left atrial; RA, right atrial; RVOT, right ventricular outflow tract.

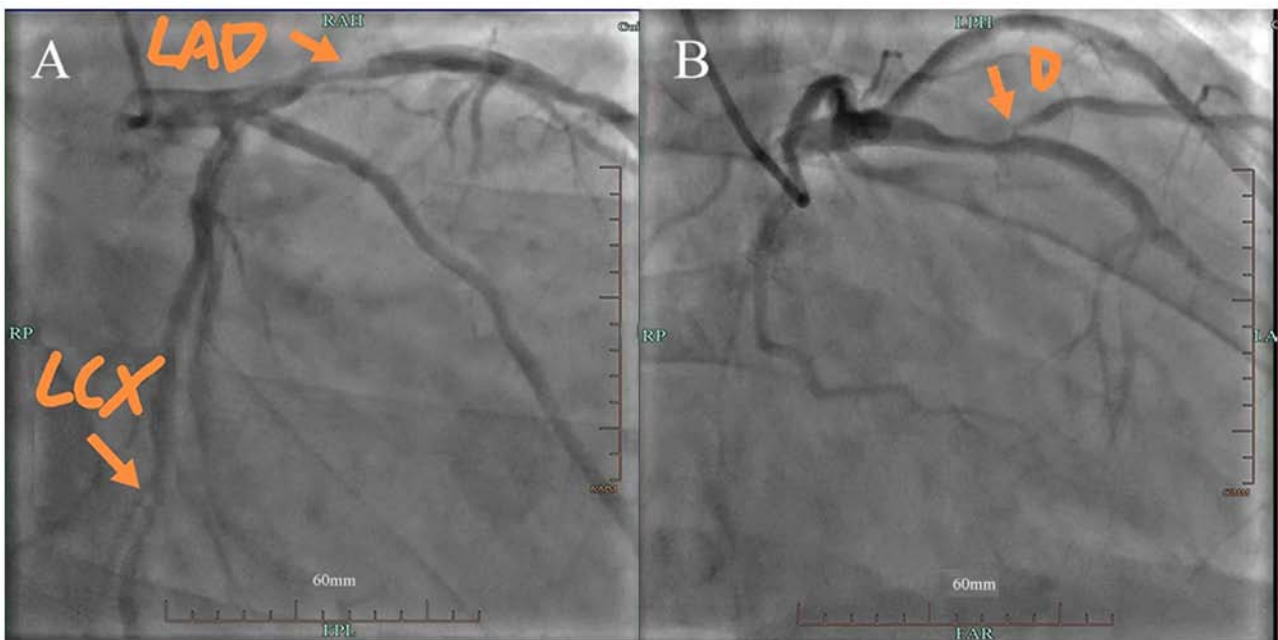


Figure 3. Coronary angiography images. (A) An 80% severe stenosis of the proximal segment of the anterior descending artery and a 70% stenosis of the distal segment of the circumflex artery were found. (B) A 90% stenosis of the opening of the first diagonal branch was found. LAD, descending artery; D, first diagonal branch; LCX, circumflex artery; RAH, right Coronary Artery; FPL, Frontal Descending Diagonal Branch of Left Anterior Descending Coronary Artery; RP, Right Posterior Descending.

ECG was more consistent with that of a coronary ischemia ECG. To achieve such a severe form of heart failure, the medical history should have been long (11,12).

The patient had an enlarged heart and a history of chemotherapy. Among the chemotherapy drugs, ANTs have potent cardiotoxic effects. Cardiotoxicity caused by ANTs can be divided into three categories, namely acute, chronic and delayed cardiotoxicity (13). A recent report estimated that subclinical but pathological echocardiographic findings of left ventricular tissue and function, such as increased afterload or decreased systolic function, typically occur in >50% of patients in 1 years after ANT administration (14). For the maximum cumulative injected dose of pirarubicin hydrochloride, the total limit is recommended to be 700-950 mg/m² based on the body surface area (8). However, the total dose

received by the present patient was 1,030 mg. Therefore, global heart enlargement may be considered to be a characteristic of delayed cardiotoxicity caused by ANT. Although the notion that such a delayed effect can continue for ~10 years is difficult to understand, similar case of this have been reported previously. Tran *et al* (15) reported a case of delayed and sudden doxorubicin-associated cardiotoxicity that occurred 7 years after MAP regimen chemotherapy completion, which provides evidence that this type of long-term effect is possible.

The present case can be summarized with the following:
i) The patient had a foundation of heart disease and the left ventricular ejection fraction (LVEF) was low, suggesting that this patient had a long history of heart disease; ii) although the coronary artery had lesions and the anterior descending artery had borderline lesions, it was not sufficient to explain

the size of the heart and the low ejection fraction; iii) based on the recent heart failure and, combined with the low ejection fraction results, it can be inferred that cardiac function has been severely compromised.; and iv) damage of chemotherapy drugs to the heart can include direct damage to cardiomyocytes, influence on cell signaling and systemic changes during chemotherapy. The condition of the present patient was attributable to the destruction of cardiomyocytes, but it is unclear to what extent the damage caused by the chemotherapeutic drugs contributed to the symptoms of this patient. According to these hypotheses, a review of the relevant literature was conducted.

For the literature search, the following databases were searched: i) PubMed (ncbi.nlm.nih.gov/); ii) Embase (https://www.embase.com); and iii) Cochrane Library (https://www.cochranelibrary.com). The search terms used were: i) 'heart failure'; ii) 'chemotherapy'; iii) 'cancer'; iv) 'treatment'; v) 'side effects'; vi) 'adverse events'; vii) 'management'; viii) 'prevention'; and ix) 'interventions'. Subsequently, 2 doctors independently screened the relevant literature. Searches were limited to studies published in English and conducted on human individuals. The inclusion criteria were: i) Studies investigating chemotherapy treatment for cancer; ii) studies reporting on the side effects or adverse events of chemotherapy; iii) studies investigating interventions or management strategies for chemotherapy side effects; and iv) studies published in English and conducted on human subjects. The exclusion criteria were: i) Studies conducted on animals or *in vitro*; ii) studies not reporting on chemotherapy treatment, side effects or management strategies; iii) studies published in non-English languages; and iv) studies published as abstracts or conference proceedings without full-text articles available.

ANT is one of the most common clinically used drugs for chemotherapy (16). However, cumulative low-dose cardiac toxicity has hindered its further clinical applications. As early as 1979, a clinical study confirmed the relationship between heart damage caused by ANT and its cumulative dosage (16).

The Guidelines for the Prevention and Treatment of Cardiotoxicity of ANT Chemotherapy Drugs (2013 Edition) (17) define cardiotoxicity as having one or more of the following manifestations, but do not include subclinical cardiovascular damage occurring early following the use of chemotherapeutic drugs/targeted drugs: i) Cardiomyopathy with reduced LVEF, manifested by decreased global function or markedly diminished interventricular septal motion; ii) symptoms related to congestive heart failure appear; iii) appearance of signs related to congestive heart failure, such as S3 gallop rhythm and/or tachycardia; and iv) If LVEF decreased by $\geq 5\%$ compared to the baseline value, and the absolute value is $< 55\%$, it should be accompanied by symptoms or signs of congestive heart failure. Alternatively, if there is a $\geq 10\%$ reduction in LVEF with an absolute value $< 55\%$, it can be considered without associated symptoms or signs.

Depending on the occurrence of heart damage, heart damage caused by ANT can be divided into acute, chronic and delayed heart damage (17). Acute heart damage refers to heart damage occurring within a few hours or days after medication, which is manifested as internal conduction disorders and arrhythmia. A proportion of patients can experience pericarditis and acute left heart failure. Chronic heart damage refers

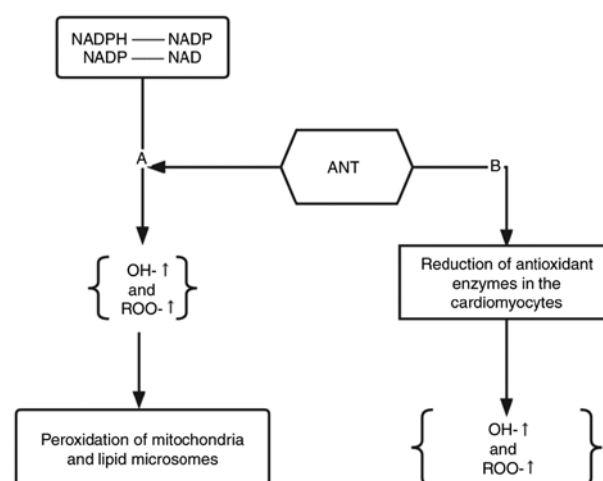


Figure 4. Proposed ANT-induced oxidative stress in cardiomyocytes. (A) ANTs can induce the generation of free radicals via enzymatic mechanisms. (B) ANTs can reduce the antioxidant enzymes expression in the cardiomyocytes, so free radicals and superoxides accumulate in the cardiomyocytes. ANT, anthracycline.

to heart damage that occurs within 1 year after chemotherapy, which can be manifested as a left ventricular dysfunction, and there is a risk of congestive heart failure. Delayed heart damage refers to cardiac damage that occurs > 1 or several years after treatment ends, which may present in various forms (17).

There are various proposed mechanisms of cardiotoxicity caused by ANT use. ANT-generated free radicals are produced through enzymatic mechanisms, with NADPH oxidase as an important mediator (18). NADH dehydrogenase and other reductases react with oxygen to generate superoxide anion radicals and hydroxyl radicals, resulting in mitochondria damage and lipid microsome peroxidation, which damages cardiomyocytes (18). In addition, the ANT family of chemotherapeutic drugs can enter the myocardium, which decreases antioxidant enzymes expression in the cardiomyocytes and leads to the accumulation of free radicals and superoxides, which can aggravate the damage to the cardiomyocytes (Fig. 4) (19).

Disruption of iron homeostasis is another key mechanism that can cause ANT cardiotoxicity. ANT drugs can disrupt the accumulation of iron ions in cells through iron regulatory proteins and transferrin receptors (20). They can achieve this by interacting with iron regulatory proteins, resulting in the promotion of transferrin receptor expression and inhibition of ferritin expression. As a result, iron uptake is increased but iron storage is decreased, leading to free iron overload, especially in mitochondria (20). In addition, ANTs are capable of binding to iron to form complexes, which can then combine with cardiac phospholipids to damage organelle membranes to induce myocardial cell necrosis (Fig. 5) (21). In addition, calcium overload, apoptosis, DNA damage response, cardiac inflammation, cardiac energy stress and the adenylate-activated protein kinase signaling pathway have also been reported to be associated with progressive cardiac damage (22,23). However, these mechanisms require further research.

ECG is the most economical and convenient monitoring method in clinical application. Cardiotoxicity caused by ANT chemotherapy can manifest as abnormalities in the cardiac conduction system, such as non-specific ST or T wave

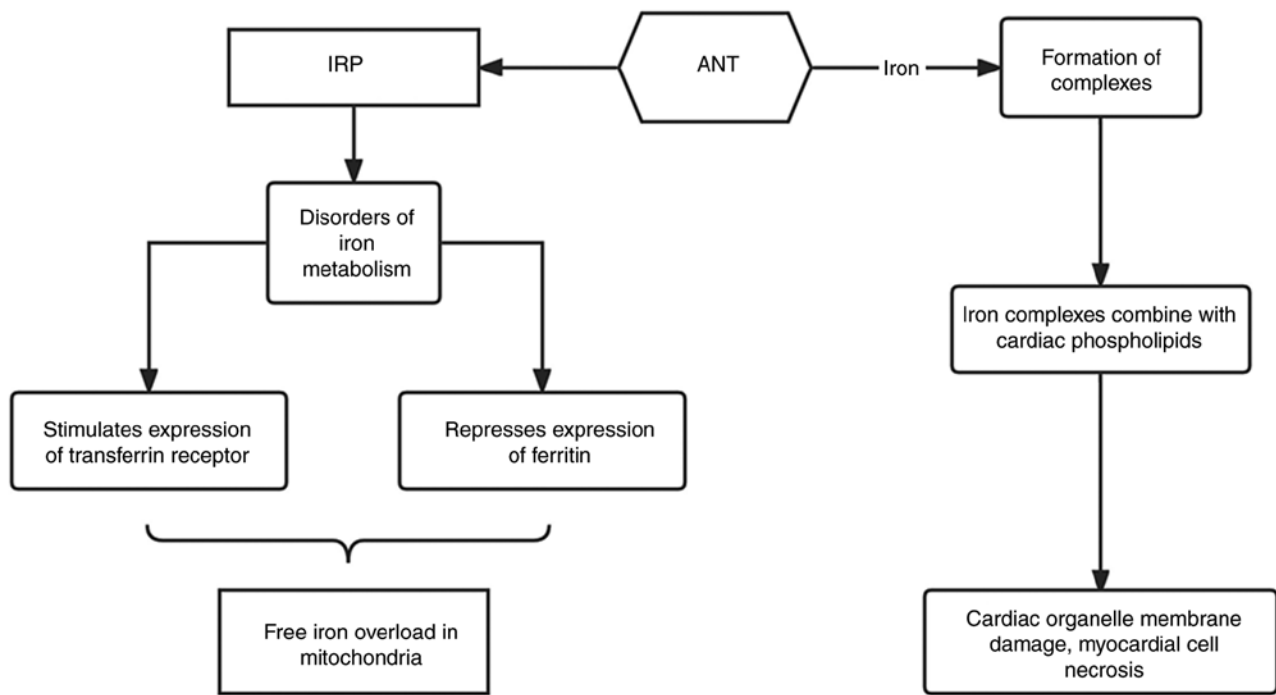


Figure 5. ANT causes myocardial damage by disrupting the iron metabolism balance. A schematic is shown. ANT, anthracycline; IRP, iron regulatory protein.

abnormalities, decreased QRS complex voltage, prolonged QT interval in the cardiac conduction system (24). In particular, the QT interval dispersion of patients with breast cancer after 4 cycles of ANT chemotherapy was markedly increased according to a previous study, and cardiac damage may occur in the early stage of ANT chemotherapy (24). This underlines the necessity of ECG as an inspection method. However, the ECG examines the heart condition of a patient within a specific time period, but its specificity and accuracy for diagnosing cardiotoxicity are poor. This is compounded by the lack of clear guiding significance for clinical practice.

Cardiac color Doppler ultrasound is another monitoring method that is commonly used for diagnosing cardiotoxicity, where LVEF is the most commonly used parameter (25). Markedly lower LVEF frequently occurs in the latter stages of chemotherapy-induced cardiotoxicity, indicating abnormalities in the cardiac structure and function of the patient (26). However, in the early stages of chemotherapy, patients typically present with subclinical cardiotoxicity without any changes in the cardiac structure and function (13,15). Therefore, LVEF cannot be used as a parameter to observe whether early cardiac damage has occurred in patients with tumors during chemotherapy. Velocity vector imaging technology is an ultrasound technology used to study the overall and local tissue movement of the heart, which is based on dimensional gray-scale imaging (26). It avoids the angle dependence of Doppler technology and can accurately perform automatic eye tracking of myocardial movement, which provides a novel method for evaluating ANT myocardial damage (26).

Serum biological indicators of myocardial injury, including the myocardial enzyme cardiac troponin T (CTnT), are used as detection indicators for the early diagnosis of cardiac damage before any permanent and irreversible cardiac damage occurs (14,21). The clinical significance of CTnT and

N-terminal precursor BNP (NT-pro-BNP) in the diagnosis of cardiotoxicity after chemotherapy is controversial. Elevated CTnT indicates myocardial cell damage, whereas elevated NT-pro-BNP reflects increased myocardial stress. Previous studies have confirmed its feasibility in predicting cardiotoxicity (21,27). However, other previous studies have also found that CTnT and NT-pro-BNP lacked specificity for monitoring early myocardial damage for diagnosing ANT-induced cardiotoxicity (28,29). Therefore, the clinical value of CTnT and NT-pro-BNP for monitoring early cardiac damage remains questionable.

Strategies for preventing cardiotoxicity due to ANT chemotherapy include limiting the cumulative dose of the drug, changing the mode of administration and using cardioprotective drugs. Von Hoff *et al* (16) previously found that the effects of ANT chemotherapy drugs on the heart mainly depend on the cumulative dose of ANT chemotherapy drugs. Although the development and application of drugs such as propofol, β -blockers have reduced the occurrence of cardiac damage, dose-related cardiotoxicity is inevitable. Therefore, the cumulative dose of the drug should be limited during treatment to reduce the risk of cardiotoxicity. Changing the method of administration can also effectively decrease the cardiac toxicity of ANT. Previous meta-analysis have demonstrated that the intravenous ANT injection method can reduce the incidence of heart damage in adults compared with oral administration (30). In addition, lipid ANT drugs are packed in lipids to protect the drugs from being degraded and lost in plasma, thereby preventing cardiotoxicity by decreasing drug uptake (31).

During treatment, cardiotoxicity can be reduced by using cardioprotective drugs. At present, studies have demonstrated that the addition of ANT for patients with breast cancer using the iron ion chelator dextropropamine can reduce the cardiac

adverse reactions caused by chemotherapy drugs. However, the exact mechanism remains unclear (32-34). Janbabai *et al* (33) previously found that for breast cancer patients receiving chemotherapy with ANTs, oral administration of enalapril 7 days to 6 months before treatment could effectively preserve the systolic and diastolic functions of the heart. In addition, Chotenimitkhun *et al* (34) found that chronic statin administration may attenuate early anthracycline-associated declines in left ventricular ejection function by studying clinical data of 51 patients with breast cancer. These aforementioned studies therefore provide a basis for clinical medication.

In conclusion, the treatment plan provided in the present case was compared with the latest research. The judgment for the present case was accurate. However, for the condition, only symptomatic treatment could be provided, which cannot improve the poor prognosis of the patient due to the significant enlargement of the heart, it is difficult to completely reverse with drug treatment. Furthermore, due to loss to follow-up, we are still unable to ascertain whether the patient is currently alive.

Compared with delayed-onset cardiac toxicity, it is rarer for patients with cancer to relapse after ~10 years of long-term disease-free survival. Therefore, discussion remains valuable for such a rare case. The present case is a reminder that even if the heart injured by ANT toxicity does not develop clinical symptoms immediately, they can manifest in the long-term. Therefore, early monitoring is of great significance for the diagnosis and treatment of cardiotoxicity. It is hoped that the diagnosis and treatment of the present case may provide references for the treatment of such patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XC and JL conceived and participated in the design of the study. XC and JL confirm the authenticity of all the raw data. MK wrote the manuscript and made significant contributions to the conceptualization and design of the work. QP made substantial contributions to analysis and interpretation of data, participated in the clinical diagnosis and treatment of the patient and reviewed the manuscript. YG and XT reviewed the manuscript and interpreted data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Guiqian International General Hospital (GIGH) Research Ethics Committee (Guiyang, China) confirmed that no ethical approval was required.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of their data in the present study.

Competing interests

The authors declare that they have no competing interests.

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