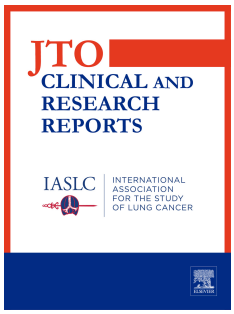

Unexpected cardiotoxicity in *HER2*-mutant non-small cell lung cancer patients treated with trastuzumab deruxtecan

Mariona Riudavets, MD, PhD, Arshid Azarine, MD, MSc, Sondes Smaali, MD, Young-Wouk Kim, MD, Vincent Thomas de Montpréville, MD, Alina Miruna Grecea, MD, Charles Naltet, MD, Annas Gazzah, MD, David Planchard, MD, PhD

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CARDIOTOXICITY CLINICAL CASES / CASE REPORT

TITLE: Unexpected cardiotoxicity in *HER2*-mutant non-small cell lung cancer patients treated with trastuzumab deruxtecan

AUTHORS AND AFFILIATIONS

Mariona Riudavets MD, PhD[1]; Arshid Azarine, MD, MSc[2]; Sondes Smaali, MD[3]; Young-Wouk Kim, MD[2]; Vincent Thomas de Montpréville, MD[4]; Alina Miruna Grecea, MD[1]; Charles Naltet, MD[1]; Annas Gazzah, MD[1]; David Planchard MD, PhD[1]

[1]Cancer Medicine Department, Gustave Roussy Cancer Campus, Villejuif, France
[2]Radiology Department, Groupe Hospitalier Paris Saint-Joseph, Paris, France
[3]Cardiology Department, Gustave Roussy Cancer Campus, Villejuif, France
[4]Pathology Department, Hôpital Marie-Lannelongue, Le Plessis-Robinson, France

Corresponding author and address:
David Planchard MD, PhD
Department of Cancer Medicine
Gustave Roussy Cancer Campus
114 Edouard Vaillant street
F-94800, Villejuif, France
E-mail: David.PLANCHARD@gustaveroussy.fr

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ABSTRACT

Antibody-drug conjugates (ADC) targeting receptor tyrosine-protein kinase erbB-2 (*ERBB2, HER2*) have emerged as promising targeted options for *HER2*-mutant non-small cell lung cancer (NSCLC). Among ADCs targeting HER2, trastuzumab deruxtecan has shown the most impressive efficacy and is a potential new standard of care. Drug-related interstitial lung disease remains a serious unpredictable identified risk for patients treated with trastuzumab deruxtecan, requiring careful monitoring and multidisciplinary management. We report the first two cases of drug-related cardiotoxicity with acute myocarditis that developed after the first trastuzumab deruxtecan cycle. Routine cardiovascular risk screening is advisable, with close collaboration between cardiology specialists and oncologists.

KEYWORDS

non-small-cell lung cancer; *HER2* mutation; antibody drug conjugates; trastuzumab deruxtecan; cardiotoxicity

KEYPOINTS

- ADC targeting *HER2* are a promising targeted therapy for *HER2*-mutant NSCLC
- First two cases of trastuzumab deruxtecan-induced cardiotoxicity in the form of acute myocarditis in lung cancer patients
- Routine cardiovascular risk screening and troponin monitoring is advisable, with close collaboration between cardiology specialists and oncologists.

INTRODUCTION

Human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) mutations are found in approximately 1-4% of non-squamous lung cancer cases.[1,2] Today, non-small cell lung cancer (NSCLC) harboring *HER2* alterations is considered a distinct subgroup of NSCLC with a driver molecular alteration. Targeted therapies against *HER2* have significantly improved the prognosis of patients with breast and gastric cancers, however they are yet to be approved in *HER2*-mutant NSCLC.[3] Antibody drug conjugates (ADC) are novel antitumor agents that combine the particular binding capacities of monoclonal antibodies with the cytotoxic activity of chemotherapy to specifically target and damage tumor cells.[3] Trastuzumab deruxtecan (T-Dxd or DS-8201a) is an emerging *HER2*-targeting ADC composed of trastuzumab, an enzymatically cleavable peptide-linker, and a novel topoisomerase I inhibitor called MAAA-1181. Its mechanism of action differs from other ADCs, since it binds to topoisomerase I-DNA complexes inducing DNA double-strand breaks and apoptosis.[4]

Results from the multicenter single-arm phase II trial DESTINY-Lung01, evaluating the efficacy of trastuzumab deruxtecan in refractory NSCLC harboring *HER2* molecular alterations, were recently published. Unprecedented efficacy data were reported, notably in the *HER2*-mutant cohort, with an overall response rate (ORR) of 55% (95% confidence interval [CI], 44-65%) and median duration of response (DoR) of 9.3 months (95% CI, 5.7-14.7). Median progression-free survival (PFS) and overall survival (OS) were 8.2 months (95% CI, 6.0-11.9) and 17.8 months (95% CI, 13.8-22.1), respectively.[5,6]

The most common adverse events (AEs) associated with ADCs are gastrointestinal and hematologic of any grade. In the DESTINY-Lung01 trial, 26% of patients in the *HER2*-mutant cohort presented drug-related interstitial lung disease (ILD), which resulted in death in two cases.[6] So far, no other serious AEs have been reported with trastuzumab deruxtecan. Here, we present two cases of cardiac toxicity in patients with *HER2*-mutant NSCLC treated with trastuzumab deruxtecan.

CASE PRESENTATIONS

Case 1:

A 69-year-old non-smoker woman was diagnosed in December 2019 with a lung adenocarcinoma with bilateral lung metastases harboring an *HER2* exon 20 insertion (p.Tyr772_Ala775Dup) detected by next-generation sequencing (NGS). She suffered of type 2 diabetes, hypertension, cholesterol and obesity grade I. She received first-line treatment with four cycles of carboplatin (AUC 5), pemetrexed (500 mg/m^2), and pembrolizumab (200 mg), every 3 weeks (Q3W) achieving a partial response, followed then

by maintenance with pemetrexed and pembrolizumab until early August 2021 (total of 4 + 20 cycles). Stereotaxic lung radiotherapy was delivered to the left lung lobe in November 2020 (no further information available). A computed tomography (CT) scan in August 2021 showed progression in the lung, and the patient was included in the phase II randomized DESTINY-Lung02 study with trastuzumab deruxtecan as second-line therapy. After screening, including a cardiac evaluation showing no morphological or functional alterations, treatment was started at 6.4 mg/kg Q3W in October 2021.

Twenty-one days after the first trastuzumab deruxtecan infusion (November 2021), elevated troponin I levels were reported (1910 pg/ml) without symptoms, during a per-protocol visit. The patient was referred to the cardiology department where an electrocardiogram (ECG) was normal and no repercussions on the left ventricular ejection fraction (LVEF) were observed in a trans-thoracic echocardiography (TTE). A coronary angiography was performed as the patient was considered to be high-risk, however no significant lesions were identified. Cardiac magnetic resonance imaging (MRI) demonstrated signs of acute myocarditis according to Lake Louise Criteria (LLC), with apico-lateral subepicardial late gadolinium enhancement (LGE) associated with local increase of native T1 (1200 ms; LLC-T1 >1000 ms; normal 950-1000 ms) and T2 (72 ms; LLC-T2 >55.9 ms; normal 40-50 ms) (**Figure 1**).[7,8] As myocarditis has never been reported with trastuzumab deruxtecan, a right ventricular endomyocardial biopsy was performed, which found no lymphocytic infiltrates and any other alteration. Serology and auto-immunity parameters were negative, with no epidemiological context or symptoms of viral infection. Treatment with trastuzumab deruxtecan was discontinued after the first cycle due to this abnormality. The patient presented spontaneous favorable clinical evolution and her troponin I levels rapidly lowered, allowing hospital discharge 4 days after the event started. The first CT scan (December 2021) showed a partial response according to RECIST 1.1.

A cardiac evaluation in January 2022 showed complete normalization of troponin I with normal and stable ECG and TTE parameters. Following disease progression in February 2022, the patient started third-line therapy with weekly paclitaxel 80 mg/m^2 and trastuzumab 6 mg/kg Q3W, with no significant toxicities and stable cardiac function at the last follow-up in June 2022.

Case 2:

A 57-year-old non-smoker male was diagnosed in August 2020 with an extensive lymphangitic lung adenocarcinoma carrying a duplication in *HER2* exon 20 (p.Y772_A775dup). As other medical conditions, he presented a medically controlled hypertension, as well as a pulmonary embolism and a deep vein thrombosis of the right upper extremity treated with a new oral anticoagulant.

He received first-line therapy with cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 Q3W achieving a partial response after three cycles, and continued with maintenance pemetrexed monotherapy. Progression in

the lung was documented by CT scan in May 2021, and second-line treatment with nivolumab 2 mg/kg Q2W was started in June 2021. However, new bone and infra-diaphragmatic lymph node lesions were detected 4 months later, in October 2021.

The patient was pre-screened for inclusion in the phase II DESTINY-Lung02 study. Baseline troponin I was 141 pg/ml (upper limit: 45 pg/ml), related to a mild pericardial effusion identified by TTE during a recent visit with the patient's cardiologist. The case was discussed with cardiology experts, who concluded that tumoral pericardial infiltration was more likely than an immune-related cardiac complication since nivolumab was discontinued in September 2021, after 5 injections. Thus, in the absence of any contraindication, treatment with trastuzumab deruxtecan 6.4 mg/kg Q3W was initiated in November 2021, after 2 months of immunotherapy discontinuation.

Increased troponin I (to 1368 pg/mL) was reported during a per-protocol visit 7 days after treatment initiation. The patient reported recent recurrent chest pain episodes starting 48 hours after trastuzumab deruxtecan administration. Repolarization alterations with T biphasic waves in V3-V6 and DII-DIII / avF, seen at baseline were present in a repeat ECG. TTE found a moderate to severe pericardial effusion with no clinical signs of hemodynamic compression. A cardiac MRI confirmed a circumferential pericardial effusion of 35 mm width; there was no evidence of LGE, and mild local elevation of T2 and native T1 was noted on the basal anteroseptal wall (T2=62 ms; T1=1050 ms), suggestive of possible early-stage myocarditis (**Figure 2**). The patient was admitted to the cardiac intensive care unit for pericardial drainage (650 mL). Cytological analyses found evidence of tumoral cells. Serology and autoimmunity parameters were negative. A coronary angiography did not find any endovascular lesion. Endomyocardial biopsy was not performed after recent pericardial drainage. A control cardiac MRI performed 10 days later showed no recurrence of pericardial effusion and appearance of a mid-septal LGE lesion suggestive of myocarditis. As in case 1, no specific treatment was administered, and after a slow and progressive decrease in troponin I levels and no evidence of cardiac complications, the patient was discharged (13 days after the initial event). No further treatment with trastuzumab deruxtecan was administered.

A CT scan at the end of December 2021 showed stable disease per RECIST v1.1. In early February 2022, the patient started a new line of treatment with weekly carboplatin AUC 2 and paclitaxel 80 mg/m^2 after a positron emission computed (PET)-CT scan revealing lung and diffuse bone progression. An echocardiography in March 2022 showed a mild pericardial effusion with a conserved LVEF. A subsequent 3-month control cardiac MRI demonstrated a more obvious septal medio-mural

myocarditis scar with normal T1 and T2 values (Figure 2C). At last follow-up (July 2022) the patient was well and still receiving the same chemotherapy regimen.

DISCUSSION

New therapeutic opportunities are being explored with the emergence of HER2-targeted therapies in *HER2*-driven advanced NSCLC. Novel selective HER2-tyrosine kinase inhibitors (TKIs) such as poziotinib and pyrotinib have shown promising activity in *HER2*-mutant previously-treated NSCLC, with ORRs up to 38% and 44%, respectively.[3] However the most encouraging data come from phase II studies evaluating the ADCs ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan in patients with *HER2*-mutant NSCLC, with response rates of 50% and 55%, respectively.[3] In August 2022, the Food and Drug Administration (FDA) granted accelerated approval to trastuzumab deruxtecan in refractory *HER2*-mutant NSCLC.

The phase II DESTINY-Lung02 (NCT04644237), was designed to evaluate the safety and efficacy of trastuzumab deruxtecan in *HER2*-mutated metastatic NSCLC patients with disease recurrence or progression during or after at least one platinum-based chemotherapy regimen. To date, no treatment-related cardiac AEs have been declared with trastuzumab deruxtecan in lung cancer. Among the phase II studies evaluating ado-trastuzumab emtansine, only Peters *et al*. reported two cases of grade 1-2 cardiac dysfunction in HER2-overexpressing NSCLC patients, without specifying further.[9]

Cardiotoxicity with anti-HER2 TKIs in lung cancer has been objectivated, although at low rates, with pyrotinib (grade 3 hypertension and prolonged QTc, both in 1.7% of cases) and with tarloxotinib (all grade and grade 3 prolonged QTc observed in 61% and 39% of cases, respectively).[3] As expected, in studies evaluating the combination of the monoclonal antibody trastuzumab with chemotherapy in HER2-positive NSCLC, 6-7% of patients in the combination arm presented decreased LVEF, and caused treatment discontinuation in one patient treated with cisplatin-gemcitabine plus trastuzumab.[3]

In the phase II DESTINY-Breast01 trial evaluating trastuzumab deruxtecan in metastatic HER2-positive breast cancer after prior ado-trastuzumab emtansine, grade 3 or higher cardiotoxicity occurred in only 1.6% of patients (two prolonged QT intervals and one case of decreased LVEF), whereas ILD was the main safety signal of concern leading four deaths (2.2%).[10] LVEF decline was also observed with ado-trastuzumab emtansine, at a comparable or even lower rate (<2%) than with other treatments including trastuzumab, lapatinib, and/or chemotherapy.[11–15] In the gastric cancer setting, any case of decrease in LVEF or heart failure was described in DESTINY-Gastric01; results in the phase 2 are awaiting.[16]

Thus, to date, anti-HER2-related cardiotoxicity has been only reported in the form of electric or functional alterations. Only Wadhwa *et al.* found that during a 6-month-follow-up, 34 of 36 breast cancer patients with trastuzumab-induced cardiomyopathy, demonstrated subepicardial linear delayed enhancement of the lateral wall of the left ventricle on cardiac MRI, suggesting trastuzumab-induced myocarditis.[17]

Our two patients both presented acute myocarditis, developed early at 7 and 21 days after initiating treatment. Both presented with cardiovascular risk factors, which were more evident for the first case (**Figure 3**). The second patient presented a pericardial effusion at baseline, and although the first and early cardiac MRI was not consistent with inflammatory myopericarditis, the large and rapid elevation of troponin I and the apparition of chest pain 48 hours after trastuzumab deruxtecan initiation, suggest the coexistence of two different entities, as demonstrated by imaging findings, with acute myocarditis induced by trastuzumab deruxtecan. Cardiac MRI parameters qualifying for myocarditis were initially incomplete, occurring slightly later, as demonstrated in patients with immunotherapy-induced myocarditis.[18]

Interestingly, both two cases were previously treated with immune-checkpoint inhibitors (ICI) before trastuzumab deruxtecan administration. ICI can induce acute myocarditis, and they could be considered one of the risk factors for cardiac toxicity development. The phase 2 study with trastuzumab emtansine plus atezolizumab in HER2-positive refractory breast cancer did not report any increase in cardiac toxicity;[19] the phase 1b study combining trastuzumab deruxtecan and pembrolizumab in *HER2*-positive refractory breast and lung cancers (NCT04042701), still ongoing, will probably add some relevant information in the near future.

In preclinical models focused in breast cancer, pembrolizumab plus trastuzumab lead to strong cardiac pro-inflammatory effects mediated by overexpression of NF-kB and Leukotriene B4 related pathways;[20] and although this combination therapy was not associated with an increase in cardiac toxicity in breast cancer, 4 cases of decreased LEVF were described in the field of oesophageal and gastric cancers.[20,21] If radiotherapy in the upper left lobe in case 1 may have also contributed to myocarditis development remains an open and interesting question.

The *ERBB*-neuregulin (NRG1) signaling axis is a critical component of the stress response of the heart. Neuregulin is secreted by coronary endothelial cells, required for normal cardiac growth and maintenance, with a putative role in myofilament architecture, cell survival, glucose metabolism, contractility, angiogenesis and conduction system.[22,23]

NRG1 binds to *HER2-ERBB4* receptor dimers on the cardiac myocyte plasma membrane, activating downstream effectors critical for protection against oxidative stress and induced cell death, including the phosphatidylinositol 3-kinase (PI3K)-AKT, mitogen-activated protein kinase (MAPK) and JAK/STAT3 pathways. Therefore, trastuzumab blocks NRG1 function, promoting the damaging effects of oxidative stress, leading to DNA breakage and mitochondrial apoptosis.[22,23] In cardiac myocyte-specific *ERBB2*- and *ERBB4*-conditional knockout mice, cardiomyopathy developed by 8 to 12 weeks of life. [24]

Consensus documents and guidelines on cardiotoxicity with cancer therapy generally agree that before starting any potentially cardiotoxic therapy, all patients should undergo a baseline assessment of cardiac function, including a complete screening of any potential cardiovascular diseases and risk factors, as well as the realisation of an ECG, an ETT plus baseline troponin measurement.[25] Imaging by cardiac MRI is recommended as an alternative to ETT once LVEF falls, or when poor image quality prevents accurate measurements.[25,26] In breast cancer, elevation in troponin I predicts LVEF reduction and cardiac AEs in patients treated with trastuzumab, particularly in those who have previously received anthracyclines, and measurements should be taken before and/or 24 hours after each cycle of cancer therapy.[22]

HER2 mutations are a targetable driver for HER2-directed therapies in NSCLC. Strategies for preventing, monitoring, and detecting cardiac AEs associated with anti-HER2 agents are needed. Although pre-existing risk factors can identify many high-risk patients, a significant number present no known predisposing factors. Additional criteria, including imaging data and blood-based biomarkers such as troponin, may be required to improve the accuracy of future risk models. Given the present two consecutive cases of cardiotoxicity with trastuzumab deruxtecan, we strongly encourage to systematically monitor troponin I levels before each injection of anti-HER2 ADCs.

So far, any specific protocol exist for the management of cardiac toxicity related to trastuzumab deruxtecan and other anti-HER2 ADCs; however, most recent guidelines on cardio-oncology recommend to start cardioprotective therapy with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and/or beta-blockers when cardiac dysfunction related to HER2-targeted therapy occurs.[26]

The mechanisms of action of ADCs remain poorly understood and require additional studies to elucidate unanswered speculations about these molecules and to better define the target population and mechanisms of toxicity, especially pulmonary and cardiac, as in our two patients.

CONCLUSIONS

In conclusion, to our knowledge, we report here the first two cases of trastuzumab deruxtecan-induced cardiotoxicity in the form of acute myocarditis, appearing early after the first treatment injection. These two cases reinforce the importance routine troponin monitoring from initiation of trastuzumab deruxtecan and the role of cardiac MRI to depict myocarditis in these patients, and suggest that repeat cardiac MRI may be useful in the event of an initial "negative" outcome. Further investigation into screening, understanding, and management is required to limit cardiotoxicity related to trastuzumab deruxtecan.

FIGURES

Figure 1. Case 1: Myocarditis as demonstrated by cardiac magnetic resonance imaging.

Cardiac magnetic resonance imaging of patient 1 demonstrating subepicardial late gadolinium enhancement (arrow) of the inferior lateral apical wall, suggestive of myocarditis, seen on the short-axis view (left panel), and the three chambers long-axis view (right panel). RV, right ventricle; LV,left ventricle; LA, left atrium.

Figure 2. Case 2: Trans-thoracic echocardiography and cardiac magnetic resonance imaging showing a large pericardial effusion and late appearance of myocarditis.

2A. Transthoracic echocardiography, 4-chamber view at baseline, 8 days after the first trastuzumab deruxtecan administration, demonstrating a severe circumferential pericardial effusion (*), inducing septal flattening.

2B. Cardiac magnetic resonance imaging: short-axis views showing delayed enhanced images 10 minutes after gadolinium administration at baseline (left panel), 7 days later after pericardial drainage (middle panel), and at 3 months (right panel).

The initial cardiac MRI (left panel) confirmed a severe circumferential pericardial effusion without any obvious sign of myopericarditis (*), as demonstrated by the absence of pericardial and myocardial late gadolinium enhancement (LGE). One week later (middle panel), after pericardial effusion was removed, a control cardiac MRI revealed intramural septal LGE (arrow) suggestive of myocarditis, confirmed at the 3-month cardiac MRI control (right panel). Pericardial enhancement seen at the second cardiac MRI is probably reactional to pericardial drainage. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium.

Figure 3. Management of acute cardiotoxicity in 2 cases developed after one infusion of trastuzumab deruxtecan

Abbreviations: BMI, body mass index; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; bpm, beats per minute; MRI, magnetic resonance imaging; TTE, trans-thoracic echocardiography.

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Authors contribution

MR: Conceptualization, Data curation, Writing - original draft.

AA, SS, YK: Data curation, Validation, Writing - review and editing.

VTM, MAG, CN, AG: Validation, Writing - review and editing.

DP: Project administration, Conceptualization, Data curation, Supervision, Validation, Writing - review and editing.

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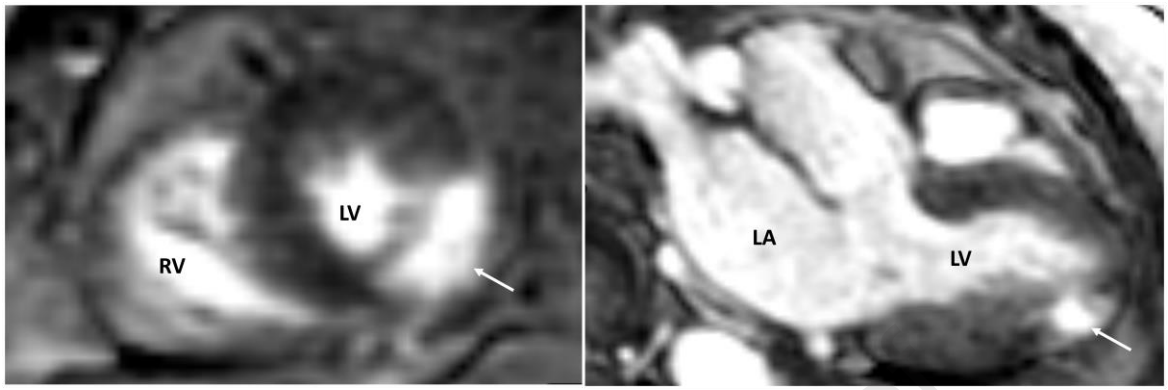
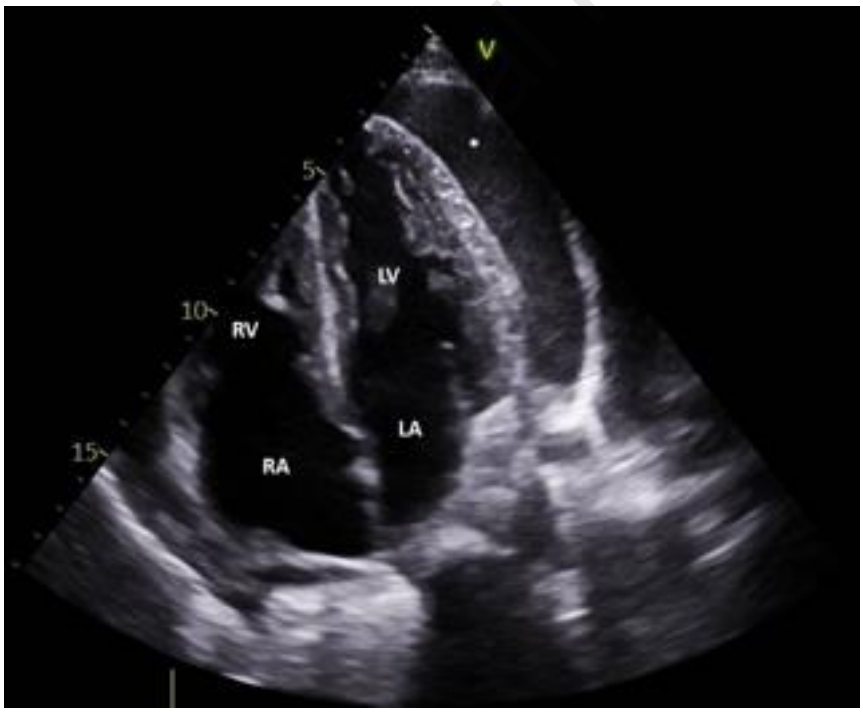
FIGURES

Figure 1. Case 1: Myocarditis as demonstrated by cardiac magnetic resonance imaging.



Cardiac magnetic resonance imaging of patient 1 demonstrating subepicardial late gadolinium enhancement (arrow) of the inferior lateral apical wall, suggestive of myocarditis, seen on the short-axis view (left panel), and the three chambers long-axis view (right panel). RV, right ventricle; LV,left ventricle; LA, left atrium.

Figure 2. Case 2: Trans-thoracic echocardiography and cardiac magnetic resonance imaging showing a large pericardial effusion and late appearance of myocarditis.



2A. Transthoracic echocardiography, 4-chamber view at baseline, 8 days after the first trastuzumab deruxtecan administration, demonstrating a severe circumferential pericardial effusion (*), inducing septal flattening.

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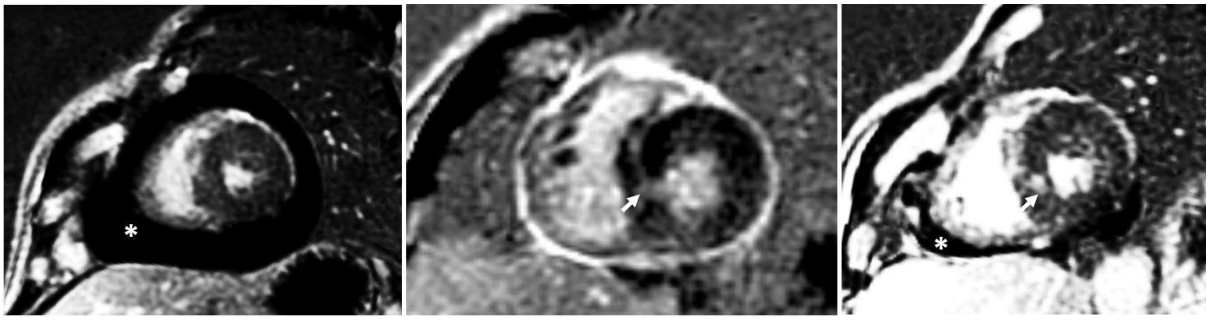
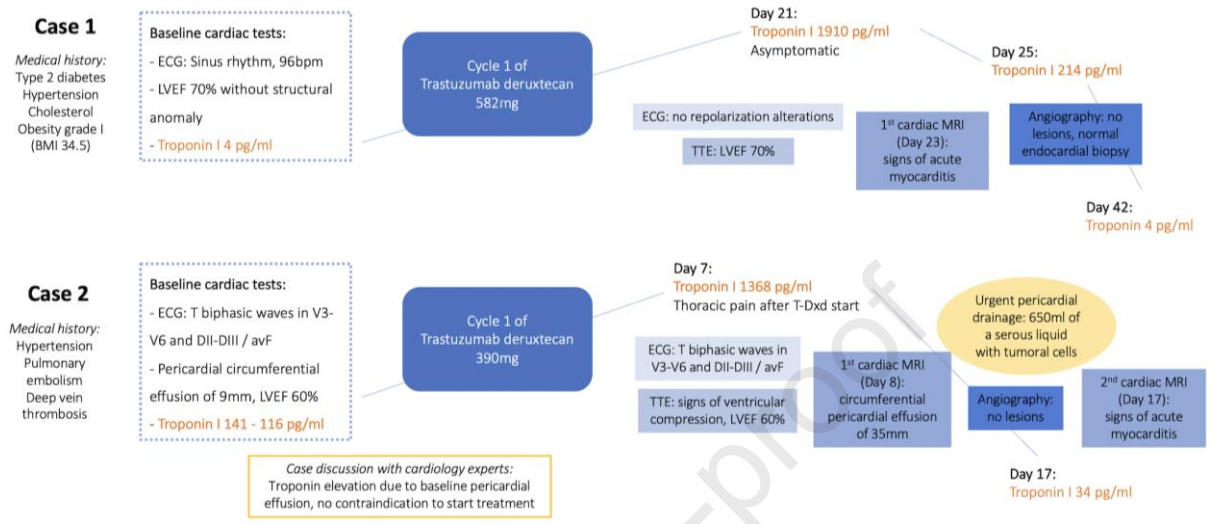


2B. Cardiac magnetic resonance imaging: short-axis views showing delayed enhanced images 10 minutes after gadolinium administration at baseline (left panel), 7 days later after pericardial drainage (middle panel), and at 3 months (right panel).

The initial cardiac MRI (left panel) confirmed a severe circumferential pericardial effusion without any obvious sign of myopericarditis (*), as demonstrated by the absence of pericardial and myocardial late gadolinium enhancement (LGE). One week later (middle panel), after pericardial effusion was removed, a control cardiac MRI revealed intramural septal LGE (arrow) suggestive of myocarditis, confirmed at the 3-month cardiac MRI control (right panel). Pericardial enhancement seen at the second cardiac MRI is probably reactional to pericardial drainage. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium.

FIGURES

Figure 3. Management of acute cardiotoxicity in 2 cases developed after one infusion of trastuzumab deruxtecan



Abbreviations: BMI, body mass index; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; bpm, beats per minute; MRI, magnetic resonance imaging; TTE, trans-thoracic echocardiography.