Anthracycline-induced myocarditis following Ewing/PNET sarcoma treatment: A case report

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Case Report

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Abstract

Background

Extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) is a rare neoplasm that typically affects children. The treatment of choice for this neoplasm is the VAC/IE regimen, which includes doxorubicin. Cardiotoxicity is the prominent side effect of anthracyclines, and myocarditis is an uncommon adverse effect, usually occurring idiosyncratically and being reversible.

Case Presentation

In the current study, we report the case of a 19-year-old female with a mass on the abdominal wall diagnosed with ES/PNET. She was treated with the VAC/IE regimen. A month after the last session of chemotherapy, she experienced dyspnea. Upon evaluation, a high level of troponin and a low left ventricular ejection fraction (LVEF) were detected on transthoracic echocardiography. She was treated with anti-heart failure drugs, but the response was not satisfactory. The possibility of anthracycline-induced myocarditis was suspected, and cardiac magnetic resonance imaging (CMR) confirmed acute myocarditis. This patient exhibited a significant response to intravenous immunoglobulin (IVIG), with her LVEF improving from 20–25–45% within three months.

Conclusion

In this case, anthracycline-induced myocarditis was reversible with accurate diagnosis and treatment, showing a remarkable response to IVIG, which is a favorable treatment for myocarditis in younger patients.

Background

Anthracyclines are commonly used and highly effective chemotherapies for treating hematological malignancies and solid tumors, including Ewing sarcoma. The use of anthracyclines can lead to cardiotoxicity, which is primarily dose-dependent but may also occur early during treatment. Anthracycline-induced cardiotoxicity primarily results from topoisomerase-II inhibition and oxidative stress induced by reactive oxygen species (1–3).

While the cardiotoxic effects of anthracyclines are well-known, myocarditis is considered a rare manifestation (4). This study presents a case of anthracycline-induced myocarditis following the treatment of PNET-Ewing sarcoma.

Case Presentation

A 19-year-old female presented to the hospital with a complaint of dyspnea categorized as mMRC grade III. This dyspnea initially began one month ago at mMRC grade I but has worsened over the last week. At presentation, her pulse rate was 110 beats per minute, blood pressure measured at 90/70 mmHg, and her

oxygen saturation was 90% on room air. Additionally, she exhibited tachypnea. During the cardiovascular examination, S3 sound was auscultated, and crackles were noted during lung auscultation.

Last year, she noticed a small, painless, and non-mobile mass on her left lower abdominal wall that initially resembled a lipoma but gradually increased in size over two months, prompting further evaluation. Following surgery in July 2022, her biopsy showed a malignant tumor composed of atypical round cells with positive CD99 and positive Vimentin cytoplasmic reactions, while Desmin, LCA, WT-1, and Myogenin tests returned negative results. (Figure-1) (Microscopic examination with H&E staining reveals sheets of small to medium-sized round neoplastic cells with hyperchromatic nuclei, scant clear to eosinophilic cytoplasm, and small nucleoli (A-C). Areas of necrosis with a peritheliomatous pattern of tumor cells around vessels are also observed (A&B). Immunohistochemistry shows strong, diffuse membranous staining for CD99 (D) and a positive cytoplasmic reaction for Vimentin (E). Tumor cells do not react to Desmin (F), LCA (G), Myogenin (H), or WT1 (I).)

she was diagnosed with Extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET). Subsequently, she underwent eight courses of chemotherapy, which included Vincristine (2 mg/m^2 D1), Doxorubicin (37.5 mg/m^2 D1-D2), and Cyclophosphamide(1200 mg/m^2 D1), alternating with Ifosfamide (1800 mg/m^2 D1-D5)and Etoposide(100 mg/m^2 D1-D5) (VAC/IE). This treatment regimen began in the following month after her diagnosis.

Her ECG showed sinus tachycardia without significant ST-T changes. Transthoracic echocardiography in the emergency room revealed an ejection fraction (EF) of 20–25%, without pericardial effusion.

With the diagnosis of doxorubicin-induced cardiomyopathy, standard anti-heart failure treatment was initiated based on GDMT (guideline-directed medical therapy). This treatment consisted of Spironolactone (25mg daily), Empagliflozin (5mg daily), Sacubitril-Valsartan (24/26 mg ½ tab twice a day), and Lasix (100 mg infusion in 24 hours). However, her troponin level was reported as 130 ng/L. Given this elevated troponin level and the absence of the expected response to the anti-HF treatment, a cardiac MRI (CMR) was performed to investigate the possibility of myocarditis.

The patient had no recent history of viral infections, exhibited no current symptoms of one, and the probability of viral myocarditis was very low. Additionally, viral tests were negative.

The CMR revealed active myocarditis (Figure-2)(A: The short-axis view of LGE image reveals subepicardial to mid-myocardial enhancement in the mid-inferior LV wall. B: In the three-chamber view of the LGE image, mid-myocardial enhancement is observed in the ineferolateral LV wall. C: The T2 mapping image in the short-axis view shows a globally increased T2 value of 56ms D: The T1mapping image displays diffusely increased T1 values (noting an incresed T1 at value at the ROI:1118ms).), and a treatment plan was initiated, which included Prednisolone at a dose of 1 mg/kg, as well as four sessions of Intravenous Immunoglobulin (IVIG) at 5 mg every day. Following the second session of IVIG, the patient's condition began to improve, and her symptoms gradually subsided. After completing the four sessions of IVIG, the patient's left ventricular ejection fraction (LVEF) had increased to 30%. One month

later, during the follow-up, the EF had further improved to 40%, and in the last echocardiography in last month it was 45%. She is currently receiving Sacubitril-Valsartan (24/26 mg half a tablet twice a day), empagliflozin 12.5 mg daily, carvedilol 3.125 mg twice daily, and prednisolone 15 mg daily.

Discussion and conclusion

In this article, we present a case of a rare neoplasm with an uncommon therapy side effect, along with its timely management and treatment. Extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET), which belongs to the Ewing sarcoma family of tumors (ESFTs), is a rare small round cell carcinoma. PNETs are most common in children and adolescents, with no significant gender predisposition. The incidence rates range from 0.15 per 100,000 in those younger than 5 years old, decreasing to 0.03 per 100,000 in young adolescents up to 19 years old (5–7).

The first-line treatment regimen for Ewing sarcoma is VAC/IE (8), which includes Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide.

The assessment of cardiac toxicity caused by anthracyclines commonly involves monitoring the reduction in left ventricular ejection fraction (LVEF). Anthracycline-related cardiomyopathies can vary from subclinical and asymptomatic myocyte damage, resulting in a gradual decline in LVEF, to potentially leading to irreversible myocardial infarction if left untreated. Acute myocarditis, although rare, may occur as a result of anthracycline-induced cardiotoxicity and is independent of the dose, with reversibility seen in the majority of cases (3, 4, 9).

The primary known causes of anthracycline-induced cardiotoxicity include interference with topoisomerase-II and the presence of reactive oxygen species. Cardiac toxicity primarily results from impaired myocardial function and can manifest as a wide range of cardiomyopathy disorders that may deteriorate into heart failure (3, 10, 11).

The treatment for myocarditis typically involves diuretics, vasodilators, and remodeling therapy, such as ACE inhibitors or angiotensin II receptor blockers, beta-blockers, and aldosterone antagonists. Regular follow-up using echocardiography and cardiac magnetic resonance imaging (CMR) is also essential. In this patient's case, these treatments were administered. However, the absence of a positive response led us to consider intravenous immunoglobulin (IVIG), which has shown favorable results in pediatric cases (12).

Contrary to the common belief that anthracycline-induced cardiotoxicity is irreversible and dose-dependent, this case of myocarditis was idiosyncratic and reversible, as demonstrated.

Abbreviations

mMRC scale: Modified Medical Research Council scale

Declarations

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Author's contributions

AA, FS, PF and ND: critical revision and major contributor in writing the manuscript. AE and KR: acquisition of data by performing the oncologic treatment. MH and MS: acquisition of data by performing the histological examinations. SM: acquisition of data by performing the radiologic examinations. MS: acquisition of data by performing the echocardiographic examinations. The author(s) read and approved the final manuscript.

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The authors can confirm that all relevant data are included in the article.

Ethics approval and consent to participate

This study protocol was approved by Rajaie Cardiovascular, Medical and Research Center ethics committee.

Consent for publication

Consent for publication obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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Figures

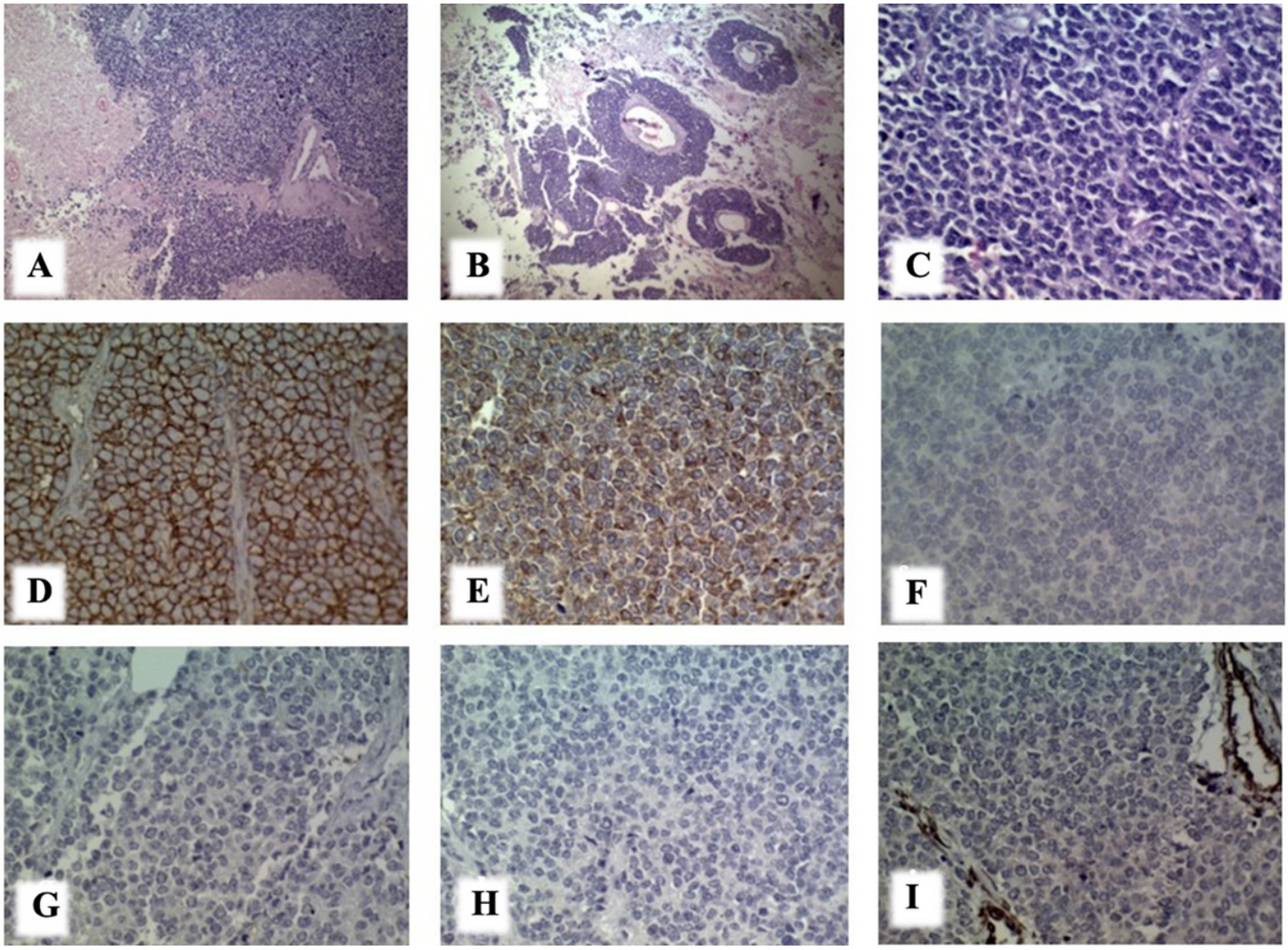

Figure 1

The histopathology and immunohistochemistry of the mass.

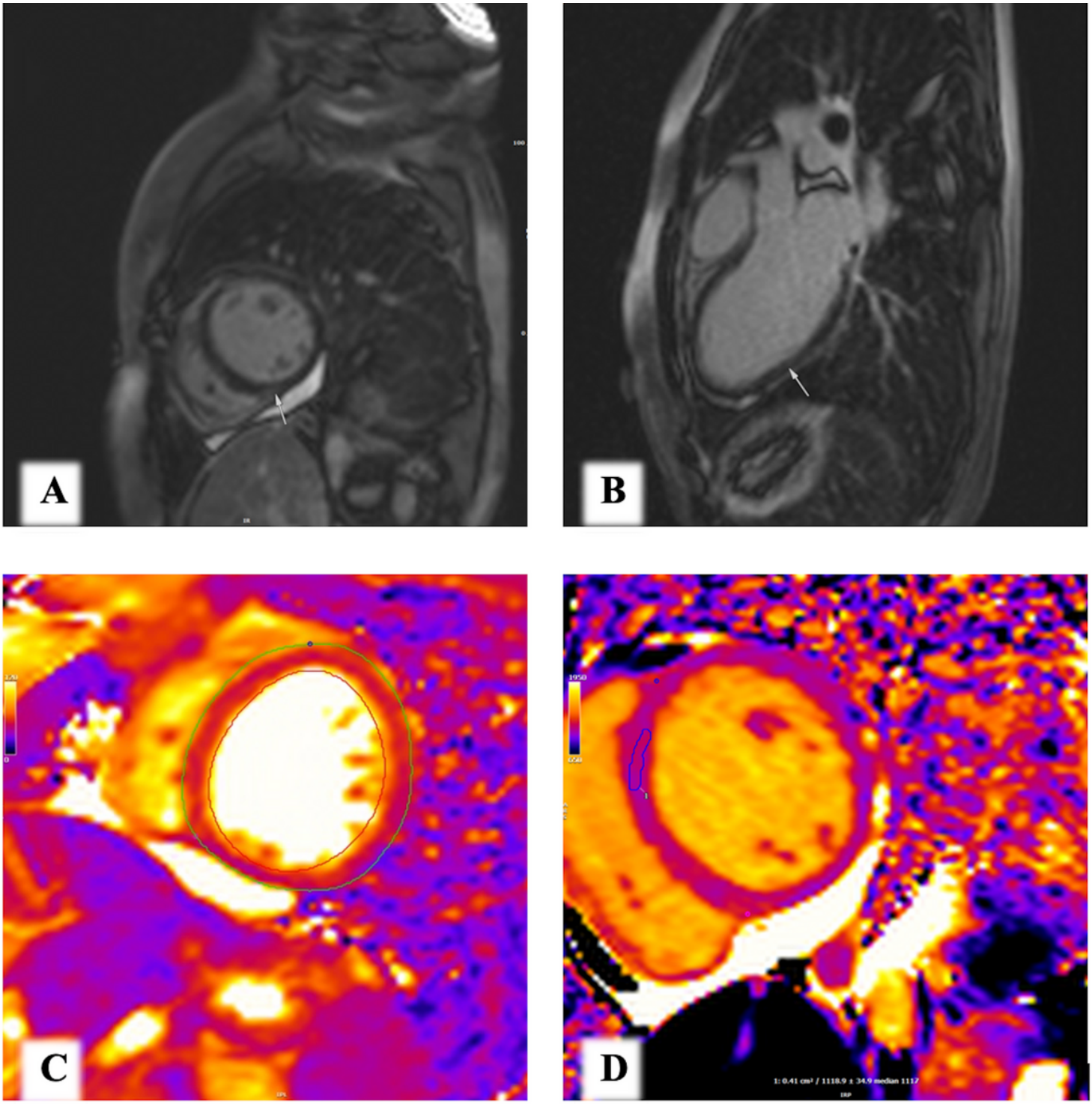

Figure 2

cardiac magnetic resonance