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CASE REPORT

Takotsubo syndrome after treatment with non-cardiotoxic chemotherapy agents

Kardiyotoksik olmayan kemoterapötik sonrası Takotsubo sendromu

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Summary– Takotsubo syndrome (TTS), acute stress-induced cardiomyopathy, is known to have a dramatic clinical presentation mimicking acute myocardial infarction. Recently developed chemotherapeutic drugs have resulted in improvements in morbidity and mortality in many forms of cancer. However, some chemotherapeutic drugs are cardiotoxic and may cause heart failure. Gemcitabine and vinorelbine are commonly used drugs for various solid organ neoplasms. While neither of these chemotherapeutic drugs has been directly associated with cardiotoxicity, there are a few case reports in the literature related to gemcitabine treatment-induced cardiomyopathy. This case report describes a case of TTS developing within hours of gemcitabine and vinorelbine chemotherapy.

Özet– Akut stres ile tetiklenen Takotsubo sendromu (TTS), akut miyokart enfarktsü ile sıklıkla karıştırılan, dramatik klinik seyri olan bir kardiyomiyopatidir. Son yıllarda kanser tedavisi alanındaki gelişmeler ile kansere bağlı morbidite ve mortalitede olumlu gelişmeler yaşanmıştır. Ancak, bazı kemoterapötik ilaçlara bağlı kardiyotoksisite gelişmekte ve kalp yetersizliği ve ölümcül ritim bozukluğuna yol açabilmektedir. Gemsitabin ve vinorelbin solid organ kanserlerinde tercih edilen kempoterapi ilaçlarıdır. Her iki kemoterapi ajanın doğrudan kardiyotoksisitesi ile ilgili literatürde veri bulunmamaktadır. Gemsitabine bağlı kardiyomiyopati gelişebileceğine dair sadece birkaç olgu sunumu mevcuttur. Burada, gemsitabin ve vinorebin sonrası ani gelişen TTS sendromu olgusu bildirilmiştir.

Takotsubo syndrome (TTS) is a weakening of the left ventricle (LV) often brought on by acute stress. The symptoms and clinical presentation can be very similar to acute myocardial infarction. It is typically a temporary condition, but heart failure and other complications can occur. The mechanisms of TTS remain unclear and the precise cause has not yet been established. Chemotherapeutic drugs have successfully reduced mortality and morbidity in many forms of cancer; however, some of these drugs are cardiotoxic and may have severe cardiovascular consequences, including heart failure. The interaction between cancer, drugs used in treatment, and the cardiovascular system is complex and not yet fully understood. Gemcitabine and vinorelbine are drugs frequently used to treat various solid organ neoplasms. While neither is directly associated with cardiotoxicity, there are some case reports of gemcitabine-induced cardiomyopathy in the literature. Presently described is a case where TTS occurred shortly after a patient received gemcitabine and vinorelbine chemotherapy.

Abbreviations:

ECG	*Electrocardiography*
Echo	*Echocardiography*
LV	*Left ventricle*
LVEF	*Left ventricular ejection fraction*
TnT	*Troponin T*
TTS	*Takotsubo syndrome*

CASE REPORT

A 65-year-old female presented at the emergency department with epigastric pain 3 hours after receiving a chemotherapy infusion (second cycle of gemcitabine and vinorelbine). She had been diagnosed

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with urothelial renal carcinoma 8 months previously. Carboplatin and gemcitabine had been used as first-line chemotherapy. Due to a lack of response to the treatment after 4 months, docetaxel was administered as second-line treatment. A gemcitabine and vinorelbine regimen was given after 3 cycles of docetaxel as a result of progression of the disease observed with positron emission tomography-computed tomography imaging. At admission, the patient was normotensive and tachycardic without any findings of dyspnea, such as crepitation. The cardiology department was consulted due to progressive high troponin T (TnT) levels and electrocardiography (ECG) findings. Blood test results indicated a TnT level of 111 ng/dL (reference value <14 ng/dL) and a creatinine level of 0.81 mg/dL (reference value: 0.6–1.1 mg/dL). She had no relevant medical history other than the urothelial carcinoma of 8 months and hypertension for 7 years. She was taking valsartan 160 mg daily for the hypertension. The ECG findings at admission illustrated a symmetrical T wave inversion on the precordial derivations (Fig. 1a). Echocardiography (echo) showed typical apical ballooning of the LV (Fig. 2a, b) and the LV ejection fraction (LVEF) was 25% to 30%. The patient's prior cardiac performance was unknown; however, she described prior functional capacity of New York Heart Association Class I and reported no cardiovascular disease history. Thus, TTS was the pre-

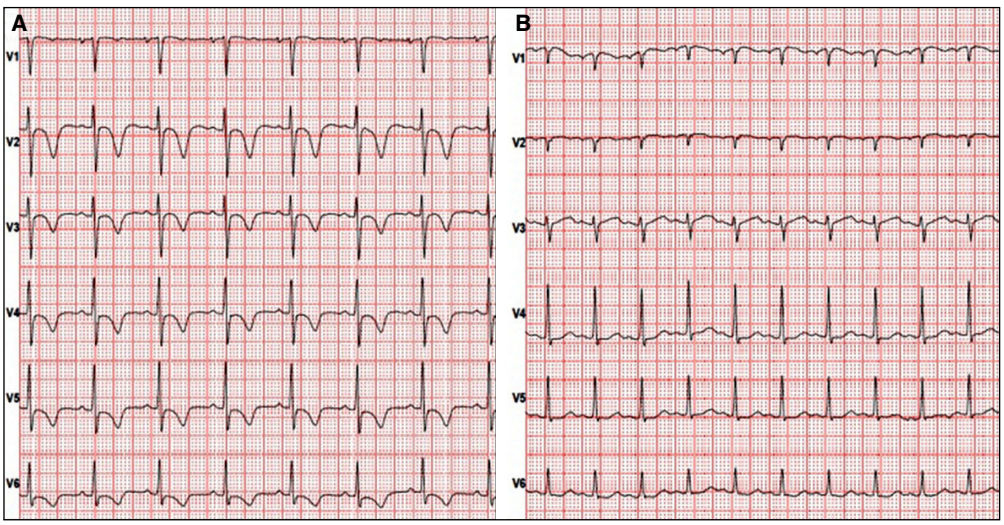

Figure 1. **(A)** Electrocardiogram (ECG) at admission with symmetrical T wave inversion; **(B)** ECG resolution after 3 days.

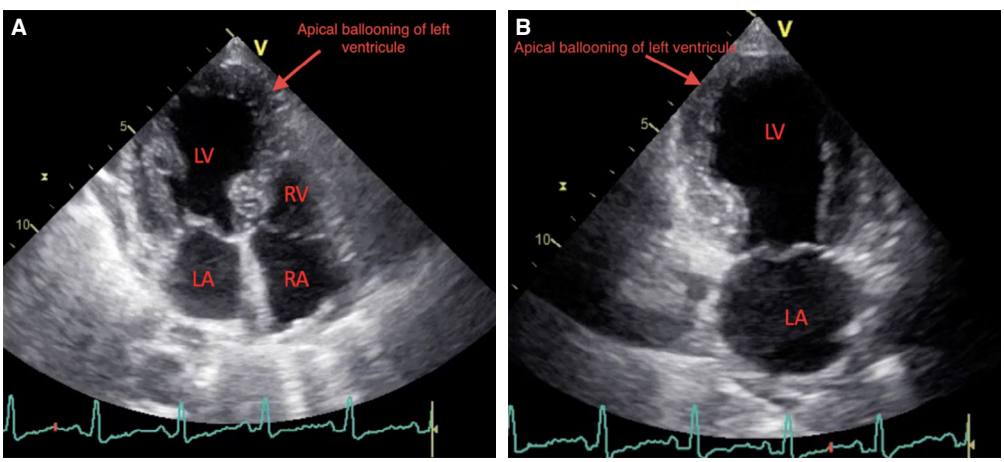

Figure 2. **(A)** Typical apical ballooning of the left ventricle. **(B)** Typical apical ballooning of the left ventricle. LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle.

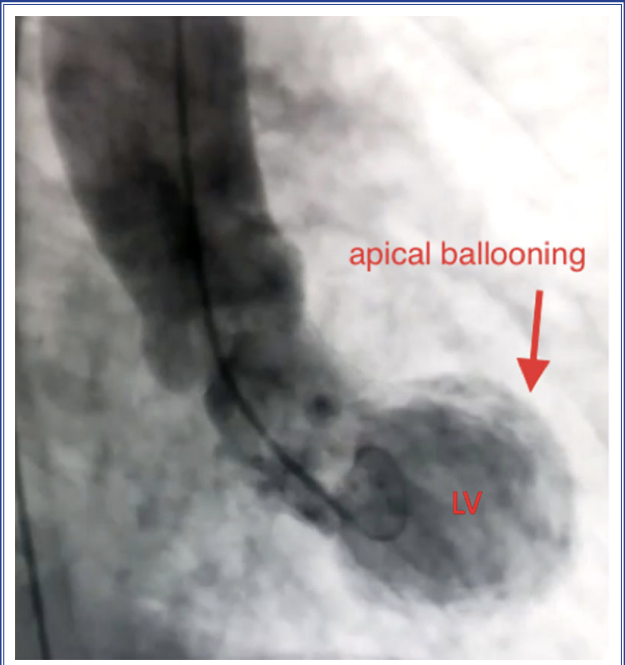

Figure 3. Apical ballooning movement of the left ventricle (LV) seen on ventriculography.

liminary diagnosis. Normal coronary arteries were seen on coronary angiography, and ventriculography revealed apical ballooning movement of the LV (Fig. 3), which supported the TTS diagnosis. Metoprolol 50 mg daily and enoxoparin 6000 IU subcutaneous twice a day was added to the valsartan 160 mg daily. A deep, symmetrical T wave inversion persisted on the ECG for 3 days before resolving (Fig. 1b). Echo images also demonstrated recovery and the LVEF improved to 50% to 55%. The TnT level decreased to 36 ng/dL. She was discharged uneventfully and continues follow-up. The patient provided written, informed consent for publication.

DISCUSSION

To best of our knowledge this is the first case report in the literature of TTS occurring immediately after vinorelbine and gemcitabine chemotherapy treatment. These antineoplastic drugs are not classified as cardiotoxic agents. Gemcitabine and vinorelbine are recommended in the European Association of Urology guidance as adjuvant chemotherapy to treat metastatic urothelial carcinoma.[1] Vinorelbine is not considered to be cardiotoxic; however, cases of heart failure associated with gemcitabine have been reported in the literature.[2] The underlying mechanism of cardiotoxicity and the cumulative dose of gemcitabine required to induce myocardial toxicity are unknown. Most of the patients who developed gemcitabine-induced cardiomyopathy in Phase I and II clinical trials had underlying coronary arterial disease.[3]

Recently, TTS has increasingly been diagnosed in cancer patients. Physical and emotional stressors have been associated as triggers for TTS, especially surgical operations.[4] With any cancer patient with TTS it is always difficult to determine whether the TTS is due to the underlying malignancy, a direct negative effect of chemotherapy, emotional or physical stressors, catecholamine fluctuation, or a combination of all of these. In this case, our patient had been treated with a different chemotherapy protocol 8 months prior upon receiving a cancer diagnosis, the cardiac event occurred very soon (within 3 hours) after a gemcitabine and vinorelbine infusion, and LV systolic dysfunction resolved after medical treatment. All of these factors support our hypothesis that the triggering factor for TTS was most likely the gemcitabine and vinorelbine therapy. The mechanisms and causes of TTS remain unclear. An excessive release of catecholamines seems to have a pivotal role in the development of stress cardiomyopathy. Although the patient in this case did not report that she was under stress, cancer itself can be considered a physiological and emotional stressor. We don't know if there was a different underlying mechanism in this case other than the typical cardiotoxicity pathogenesis.

Vinorelbine is a derivative of vinca alcoloids. The underlying mechanism of cardiotoxicity is thought to be the direct effect of the alkaloids on cellular microtubuli and an impairment of myocardial cell metabolism and contractility or an indirect effect on coagulation leading to arterial occlusion or paralytic effects on the autonomic nervous system. Autonomic cardioneuropathy has been associated with other vinca alcoloid derivatives. Vinorelbine may also trigger autonomic cardioneuropathy and cause TTS.[5]

The exact reasons for gemcitabine-induced acute cardiotoxic events, such as acute coronary syndrome, are not clear; however, authors have speculated that a direct endothelial injury resulting in coronary thrombosis or gemcitabine-induced vascular spasm may be possible mechanisms.[2] Nonetheless, at present, we do not know the exact mechanism of gemcitabine-induced TTS.

Chemotherapeutic drugs that are not associated with typical cardiotoxicity are not as innocent as once thought. Acute cardiotoxicity may have a different pathogenesis than ordinary paths of toxicity. Currently, the literature provides no statement as to whether the physician should choose the same regimen for next therapy. This case report was submitted to highlight these points.

Conclusion

Acute cardiotoxicity due to chemotherapeutic drugs may be a result of a different pathogenesis than an ordinary toxicity mechanism. Physicians must be careful even when choosing antineoplastic drugs that are not associated with typical cardiotoxicity. Gemcitabine-induced cardiotoxicity should be considered a potential cause of acute heart failure or TTS in patients receiving chemotherapy with this drug.

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Anahtar sözcükler: Kardiyomiyopati; kardiyotoksisite; kemoterapi; Takotsubo sendromu.