Bradycardia associated with pegylated liposomal doxorubicin administration: a case report

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SUMMARY

The cardiotoxicity of doxorubicin is dose dependent and progressive, but its mechanisms remain unclear. Measures to prevent the cardiotoxicity of doxorubicin have had limited success. We report here on a patient who had received intravenous infusion of pegylated liposomal doxorubicin and developed sinus bradycardia despite the prior administration of the iron-chelating agent, dexrazoxane. The adverse effect of pegylated liposomal doxorubicin might be due to the difference in metabolic related genes for anthracyclines. Therefore, monitoring the cardiac condition of patients who receive doxorubicin treatment, even at low doses, is highly recommended.

BACKGROUND

Doxorubicin is a commonly used chemotherapeutic drug with well-known clinical effectiveness in the treatment of various haematopoietic and solid tumors,¹ but which has dose-dependent adverse cardiac effects.² Attempts to prevent the cardiac damage by limiting the accumulation of the drug, choosing the liposome-encapsulated form and applying antioxidants and iron-chelating agents have had limited success.³ Although the adverse cardiac effect of conventional doxorubicin commonly occurs, the cardiotoxicity associated with pegylated liposomal doxorubicin treatment in a patient who has previously received an iron-chelating agent has not yet been reported. Here we report a case of sinus bradycardia in a patient with mesenchymal chondrosarcoma who received liposome-encapsulated doxorubicin after treatment with dexrazoxane.

CASE PRESENTATION

A 26-year-old woman with mesenchymal chondrosarcoma was admitted to the oncology department for chemotherapy after palliative radiotherapy in January 2015. Six years earlier, a left maxillary mass resection had been carried out after she was diagnosed with left maxillary mesenchymal chondrosarcoma. In December 2013, the left maxillary mass recurred while the patient was pregnant. She terminated the pregnancy and 3 months later, progressive enlargement of the tumour was seen during her second pregnancy. Seven months after termination of the second pregnancy, she was admitted to hospital in October 2014 with bilateral nasal obstruction and blindness in both eyes. The patient received radiotherapy of 40 Gy and the tumour mass shrank.

A pre-chemotherapy cardiac examination disclosed a normal heart rate of 78 bpm, with no

murmurs. No symmetrical crural oedema was seen and chest X-ray imaging showed no anomaly (figure 1). On the fifth day of hospitalisation, systemic chemotherapy with liposomal doxorubicin and nedaplatin was started (doxorubicin hydrochloride liposome 20 mg/day, every other day for 5 days; nedaplatin 60 mg/day for 2 consecutive days). The patient received the infusion of dexrazoxane to reduce the cardiotoxicity before the administration of doxorubicin. Only 3–5 min after initiation of the intravenous infusion of doxorubicin, the patient experienced chest distress and palpitation, and a decreased heart rate (45–55 bpm) was recorded.

INVESTIGATIONS

Arrhythmia is one of the adverse cardiac effects of doxorubicin, which might be reflected as tachycardia or bradycardia. The heart rate is essential in the diagnosis and evaluation of arrhythmia. The pre-chemotherapy investigations showed that the patient had a normal heart rate (78 bpm), and did not complain about distress in the heart. She developed chest pain and palpitation immediately after the first exposure to the doxorubicin and her heart rate was then only 48 bpm.

TREATMENT

In view of the probability of drug-induced bradycardia, the infusion of doxorubicin was suspended immediately and 1 mg of atropine was injected intravenously.

OUTCOME AND FOLLOW-UP

The heart rate of the patient returned to a range of 51–58 bpm after intravenous injection of 1 mg atropine. Sinus bradycardia (heart rate 46 bpm) reappeared (figure 2) on the next day without evidence of cardiac damage. The patient's heart rate recovered to 60–70 bpm during the next 2 days without atropine injection, and no sinus bradycardia reappeared. The patient received continuous ECG monitoring and no further doxorubicin was administered.

DISCUSSION

Since the first case of cardiac toxicity of doxorubicin in chemotherapy was reported in 1970,⁴ the mechanisms of cardiac toxicity due to anthracyclines have been extensively studied, but remain unclear. A recent study demonstrated that doxorubicin-induced cardiotoxicity may be due to specific accumulation of iron inside the mitochondria,⁵ and topoisomerase-2 β was shown to mediate the doxorubicin-induced cardiotoxicity.⁶ It is also speculated that lipid peroxidation and reduced

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Figure 1 Chest X-ray image before doxorubicin treatment.

levels of antioxidants and sulfhydryl groups might also contribute to the cardiotoxicity of doxorubicin.⁷

In this reported case, anthracycline was given for the first time to this patient as a chemotherapy agent. The accumulated dose of doxorubicin was much lower than the estimated high-risk dose, as only a small amount of drug was infused before its prompt termination. Moreover, doxorubicin the patient received was pegylated liposomal doxorubicin, which has been shown to be less cardiotoxic than conventional doxorubicin as it has a lower accumulation in cardiomyocytes.⁸ However, the occurrence of cardiotoxicity at the first use of anthracyclines and low-dose drug treatment has been reported previously.^{9–10} Therefore, no dose range for anthracyclines is completely safe. Variations in the metabolic related genes of anthracyclines in patients may lead to different sensitivity to the drug.¹¹ As the patient was given no other drugs with the potential to cause

cardiac damage, and dexrazoxane was infused before administration of the doxorubicin to prevent cardiotoxicity, it is likely that the adverse effect in this case can be ascribed to individual patient difference.

The cardiac damage caused by the doxorubicin is progressive, irreversible and sometimes life-threatening. To prevent doxorubicin-mediated cardiac damage, patients receiving doxorubicin should be monitored, risk factors assessed and excessive accumulation of the drug in the heart avoided. It is worth noting that the monitoring of patients receiving doxorubicin must include the assessment of cardiac performance before, during and after the drug administration because even with the protection of an iron-chelating agent the patient reported here exhibited cardiotoxicity after treatment with a low dose of doxorubicin.

Learning points

- ▶ We present here a case of sinus bradycardia in a patient with mesenchymal chondrosarcoma who received liposome-encapsulated doxorubicin after treatment with an iron-chelating agent.
- ▶ The adverse effect occurring in this case can probably be ascribed to individual patient difference.
- ▶ Monitoring of patients should be carried out even with low-dose doxorubicin treatment.

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Competing interests None declared.

Figure 2 ECG showing sinus bradycardia.

Female 26 year		Vent. rate	46	bpm
		PR interval	144	ms
		QRS duration	82	ms
		QT/QTc	420/380	ms
		P-R-T axes	35/80/38

Patient consent Obtained.

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