Cardiac Transplantation for Doxorubicin-induced Heart Failure after Chemotherapy of Ewing's Sarcoma

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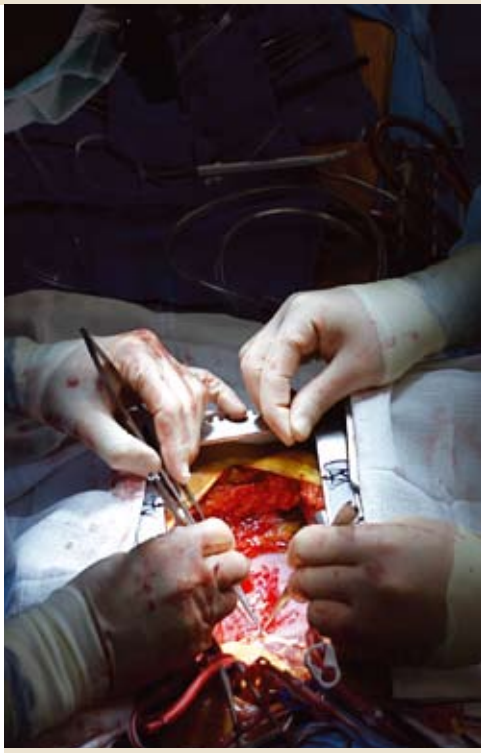

Abstract:
A 30-year-old woman presented with doxorubicin-induced heart failure. She had been treated due to Ewing's sarcoma five years ago. Traditional heart failure treatment has been performed but its effect was mostly very limits. We, therefore, decided to perform heart transplantation for her.

Keywords: doxorubicin-induced heart failure, Heart transplantation, Ewing's sarcoma

Background:
Doxorubicin (Adriamycin) is an anthracycline antibiotic. It is one of the most important anticancer drugs. Major toxicity of doxorubicin is include a potentially irreversible cumulative, dose-related cardiac toxicity. The mechanism of cardiac toxicity is still under study but appears to involve excessive intracellular production of free radicals within the myocardium by doxorubicin. This is rarely seen at doxorubicin dosages below 500mg/m2. Use of lower weekly doses or continuous infusions of doxorubicin that avoid high peak plasma concentration appear to reduce the frequency of cardiac toxicity as compared with intermittent (every 3-4 weeks) higher doses schedules. In this paper, we present a case of doxorubicin-induced heart failure.

Case report:
We present the case of a 30 year-old woman with a history of Ewing's sarcoma in right tibia since 5 years ago. She had been treated with Doxorubicin, Cyclophosphamide, Vincristine, Etoposide, and Ifosfamide with 21 days period. Six months after the onset of treatment, she developed progressive dyspnea. Echocardiography showed ejection fraction 25%. Doxorubicin-induced heart failure had been suggested for her. She was in remission during 5 years. She wasn't cachectic. She had function class IV and echocardiography revealed mild-to-moderate TR, Global hypokinesia, PAP 35 mmHg, RA & RV enlargement and ejection fraction 20%. Chest radiography showed moderate cardiomegaly. Computed tomography of her chest revealed cardiomegaly. Hematological tests were normal. Liver and renal function tests were normal. Because the medical treatment did not improve her clinical condition, she underwent a successful orthotopic cardiac transplantation. She had a slow but progressive recovery before being discharged 3 weeks postoperatively. Histological examination of harvested heart revealed vacuolization and loss of myofibrils, interstitial fibrosis, and focal myocyte necrosis (figure 1, 2).

Discussion:
Doxorubicin-induced heart failure is rare but associated with a poor prognosis. Doxorubicin is one of the most important anticancer drugs, with major clinical application in carcinomas of the breast, endometrium, ovary, testicle, thyroid, and lung and in treatment of many sarcomas, including neuroblastoma, Ewing's sarcoma, osteosarcoma and rhabdomyosarcoma. It is useful also in hematologic cancers including acute leukemia, multiple myeloma, Hodgkin's disease, and

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diffuse non- Hodgkin's lymphoma.1 Doxorubicin may produce cardiac toxicity, both as an acute, usually transient disturbance of cardiac function marked by ECG abnormalities and, sometimes, arrhythmias, and as a delayed, sometimes fatal, chronic heart failure. Severe cardiotoxicity is more likely in adults receiving total cumulative doses of doxorubicin greater than 550 mg/m2 body-surface area, and may occur months or even years after administration.2

Beside the cumulative dose, older or very young age, a combination therapy, hypertension, liver disease, radiation of the left chest or mediastinum as well as preexisting cardiac disease seem to be added risk factors for doxorubicin-induced heart failure. Females may be at greater risk than males. Concomitant administration of cyclophosphamide may increase the likelihood of cardiomyopathy. In those given relatively-high doses on an infrequent schedule (presumably resulting in higher peak concentrations) rather than lower, weekly doses, or continuous infusion.1,2

The exact causal mechanism of doxorubicin-induced cardiomyopathy remains unclear, but most of the evidence indicates that free radicals accompanied by a decrease of endogenous antioxidants and the subsequent increase in oxidants results in enhanced oxidative stress leading to a slow loss of myofibrils and vacuolization of myocardial cells which are the typical changes in the doxorubicin-induced heart failure. Additional myocardial damage may be caused by an increase in tissue calcium, the inhibition of nucleic acid protein synthesis, lipid peroxidation, the release of vasoactive amines, TNF-α and interleukin-2, liberation of cytokine from the tumor, changes in adrenergic function, lysosomal alterations and the inhibition of the coenzyme Q10 and the sodium-potassium-activated ATPase.3 Each patient treated with doxorubicin should undergo an assessment of base-line cardiac function before chemotherapy, a regular monitoring during treatment and a close lifelong follow-up. Neither the physical examination nor the electrocardiography changes are specific for the doxorubicin-induced cardiomyopathy. Therefore, a transthoracic echocardiography evaluating particularly the ejection fraction should be the basis of the lifelong screening examinations. The diagnostic test with the greatest specificity and sensitivity for doxorubicin-induced cardiomyopathy is endomyocardial biopsy (EMB). But beside its invasive nature it remains possible that patient with low grade myocardial damage may develop severe congestive heart failure. Therefore, the endomyocardial biopsy should only be used with great caution as a guide for the continuation or termination of doxorubicin therapy or in patients with advanced heart failure.1

Prevention is virtually important in reducing chronic anthracycline cardiac toxicity. Current approaches to risk reduction include change in dose and schedule, and use of analogs, new delivery systems, and specific blocking agents. Dose adjustment may be achieved by limiting anthracycline doses in-patients at increased risk for toxicity or by empiric limitation of cumulative doses of doxorubicin to 400 mg/m2 to 450 mg/m2. Weekly schedule resulted in decreased clinical toxicity, and improved endomyocardial biopsy scores.

Liposomal drugs are a new class of agents that may permit more specific organ targeting of anthracyclines, thereby producing less systemic and cardiac toxicity. Several free radical generation including alpha tocopherol (vitamin E), n-acetyl cysteine, coenzyme Q10, and prenylamine, have been tested as selective cardiac protectors with negative or inconclusive results. Dexrazoxane has been approved for use in the United States and is clearly cardioprotective. The putative mechanism of cardioprotection is that dexrazoxane strips Fe2+ from the iron-doxorubicin complex, thereby preventing free radical generation. It is generally recommended to stop the doxorubicin treatment when the first sign of heart failure are detected and to start a conventional heart failure therapy. If this fails, surgical therapeutic options should be taken into consideration. Currently, the only treatment option that has been recognized as successful in doxorubicin-induced end stage heart failure is cardiac transplantation.4 But usually the proof that neoplasm has been cured or a 5-year (some authors also accept shorter intervals in specific cases) cancer-free period is requested before transplantation.5,6 The long waiting time following chemotherapy results in a considerable number of patients are die of cardiac failure mortality rate up to 70% have been reported.7 Based on these considerations, other treatment strategies need to be developed. Implantation of ventricular assist devices has been proven to be effective in patients with end-stage heart failure.8 Results of long term support in LVAD patients have improved over time, but the rate of complications as well as costs remain considerable.8 Dynamic and passive cardiomyoplasty, partial left ventriculectomy, and cell transplantation have not been proven effective in clinical therapies until now.

Conclusion :

Anthracycline drugs have been widely used as chemotherapeutic agents against a range of cancers, including sarcomas, carcinomas, leukaemias, and lymphomas. However, cardiotoxic effects, in particular the development of cardiomyopathy, have limited their clinical use. Among the mechanisms responsible for anthracycline-mediated cardiac toxicity are formation of free reactive oxygen radicals and immunologic reactions. Identification of mechanisms of doxorubicin-induced cardiotoxicity has been important for the development of strategies to prevent the cardiotoxic effects of doxorubicin without interfering with its anti-tumor effects. For instance, the antioxidant, chelating agent dexrazoxane is used clinically as a cardioprotective drug in cancer patients receiving doxorubicin. If a doxorubicin-induced cardiomyopathy is diagnosed a conservative treatment should be tried. In therapy-refractory patients who suffer from an advanced heart failure, surgical treatment options such as cardiac transplantation and ventricular assist device implantation should be taken into consideration. So as in presented case, the rare occurrence is reported in our country, it is better to prevent doxorubicin-induced heart failure in the first step. In the next step, it is important to diagnosis it in the early phase of the disease; because delay can lead to irreversible consequences. Therefore, the medical treatment procedure must be begun as soon as possible and if this treatment is failed, the heart transplantation is suggested after a 5-year (some also accept shorter intervals in specific cases) cancer-free period.

Figure 1. *Histologically, doxorubicin-induced cardiomyopathy is characterized by extensive fibrosis (Masson's trichrome stain, ×10).*

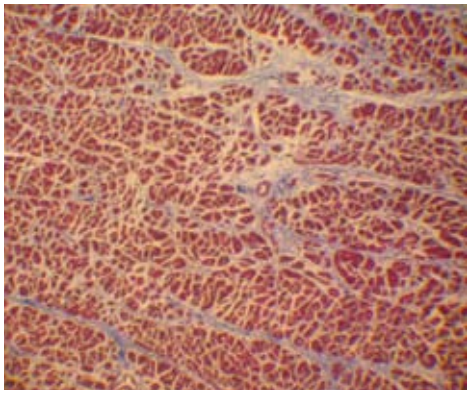
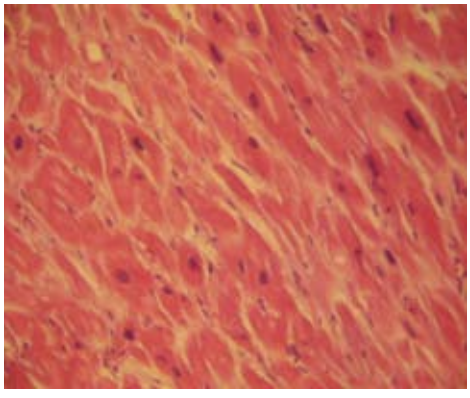


Figure 2. *Scattered cardiomyocytes with vacuolar degeneration (H&E stain, ×10)*



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