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Case report

Late doxorubicin cardiotoxicity

Michael Lishner,[CA] Avishay Elis and Mordchai Ravid

The authors are at the Department of Medicine, Sackler Faculty of Medicine, Tel Aviv University and Meir hospital, Kfar Saba 44281, Israel.
Tel: 52-900516. Fax: 52-910596.

The occurrence of late congestive heart failure (CHF) as the first clinical manifestation of doxorubicin-induced cardiac toxicity is unusual in children and very rare in adults. However, subclinical cardiac dysfunction is commonly detected in children years after treatment with doxorubicin containing regimens. We report a 58 year old woman who developed stage IV CHF 7 years after completion of doxorubicin treatment for carcinoma of the ovary. Occult cardiac dysfunction was first demonstrated by radionuclide angiography 6 years prior to the occurrence of the clinical manifestations. This unique course of the disease and the management of the CHF are discussed.

Key words: Congestive heart failure, dobutamine, doxorubicin.

Introduction

The major adverse effect of the antracyclines is the dose-related cardiotoxicity. A high incidence of late subclinical cardiac dysfunction was recently demonstrated by non-invasive methods in doxorubicin-treated children.[1,2] However, late onset of clinically manifest congestive heart failure (CHF) is infrequent in children[3–5] and very rare in adults.[6,7]

We report a 58 year old patient in whom occult left ventricular dysfunction was detected by radionuclide angiography 1 year after completion of doxorubicin treatment while she was completely asymptomatic. Class IV CHF developed 6 years later. Major symptomatic improvement was achieved with intermittent dobutamine treatment.

[CA] Corresponding Author

Case report

A 58 year old woman was admitted in September 1989 because of progressive dyspnea, orthopnea and paroxysal nocturnal dyspnea of several weeks duration.

In 1980 she had undergone panhysterectomy, and bilateral salpingo-oophorectomy with adjuvant radiotherapy of 40 cGy to the whole abdominal field for adenocarcinoma of the ovary. In 1982 she had an intra-abdominal relapse and received eight monthly courses of CAP (cyclophosphamide, doxorubicin and cisplatinum). The total dose of doxorubicin was 500 mg/m^2. Complete remission was achieved and she has remained disease-free without further treatment. In 1983 a resting gated pool radionuclide angiography with technetium 99 m was performed.[8] The resting left ventricular ejection fraction was 30%. Until her recent admission she was physically active and enjoyed good health.

Physical examination revealed tachycardia, tachypnea, a third heart sound and rales over the lower lung fields. The jugular venous pressure was normal and there was no leg edema. The electrocardiograph showed sinus tachycardia with poor progression of R waves in V_1 to V_3. Chest X-ray showed cardiomegaly, marked interstital infiltrates and bilateral pleural effusion. On echocardiography there was a global reduction of the left ventricular function, consistent with dilated cardiomyopathy. A repeated radionuclide angiography showed a left ventricular ejection fraction of 21%. Some relief was obtained with diuretics and converting enzyme inhibitors. However, converting enzyme inhibitors had to be discontinued due to severe orthostatic hypotension. A steady and significant improvement

took place upon administration of eight courses of dobutamine (2.5 μg/min/kg for 24 h every 4 weeks). Today, 22 months after the beginning of her CHF symptoms and a year after the last dobutamine treatment, she is in functional class II and is treated with only diuretics.

Discussion

The main dose-limiting factor of doxorubicin is the cardiotoxic effect of this very effective anticancer medication.[9–11] Cardiotoxicity is usually observed during the first months after the last dose of doxorubicin (mean 33 days).[12] Later onset of CHF, years after doxorubicin treatment, is very rare in adults,[6,7] though it was recently reported in children.[3–5] Although a myocardial biopsy was not performed in our patient we believe that her cardiac derangement is indeed a late manifestation of doxorubicin toxicity. She had no risk factors, no history of coronary heart disease and no recent exposure to infectious agents. Her electrocardiographic and echocardiographic findings were also compatible with doxorubicin cardiomyopathy.[5–7]

Von Hoff *et al.*[13] reviewed studies addressing the problematics of early detection of doxorubicin-induced cardiac dysfunction. They concluded that although a wide range of non-invasive (and one invasive) tests have been used, no method has a reliable predictive value for the development of doxorubicin-induced CHF.

Recently, cardiac dysfunction was demonstrated by echocardiography in children years after doxorubicin treatment. Yeung *et al.*[2] showed a lower increase in fractional shortening by post-exercise echocardiography. Lipshultz *et al.*[1] reported a high rate (57%) of abnormalities in left ventricular afterload and contractility in children with acute lymphatic leukemia 1–15 years after doxorubicin treatment. They hypothesized that loss of myocytes during such treatment and failure of growth of the cardiac mass to match the somatic growth may result in cardiac dysfunction in later years.[1,3] This hypothesis, however, fails to explain the occurrence of late CHF in adults. It is possible that different pathophysiological mechanisms are involved or additional factors are important in adults.

Patients who had a transient CHF within the first year after completion of doxorubicin therapy are probably at risk of devloping late CHF.[1,4] Additionally, it is possible, as demonstrated by our patient, that in some patients subclinical deterioration of cardiac function develops gradually over a long period until it manifests as late CHF. Controlled studies with longer follow up are needed to verify this theory. If confirmed, measures such as early administration of converting enzyme inhibitors (which are effective in asymptomatic patients with left ventricular dysfunction after anterior wall myocardial infarction)[14] should be evaluated in asymptomatic patients with reduced cardiac function and in those with early doxorubicin-induced cardiotoxicity.

Stage IV, doxorubicin-induced, CHF is often difficult to manage. Intermittent dobutamine infusion was successfully administered to some patients with congestive cardiomyopathy (among them one patient with doxorubicin cardiomyopathy) by a weekly, 48 h infusion.[15] In our patient, though initially very difficult to manage, a marked alleviation of the congestive failure was obtained with a monthly infusion of only 24 h duration. We believe that dobutamine should be tried in all class III or IV patients with doxorubicin cardiomyopathy. Future studies will hopefully confirm that doxorubicin cardiotoxicity can indeed be prevented by either the administration of the drug by a prolonged infusion[16] or by the use of bispiperazinedione ICRF-187 which binds iron in the heart muscle and prevents the generation of free radicals which are toxic to the myocytes.[17]

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