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Transient congenital dilated cardiomyopathy after maternal R-CHOP chemotherapy during pregnancy

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ABSTRACT

Pregnancy-associated diffuse large B-cell lymphoma (DLBCL) is a rare event. Experience regarding fetal effects of maternal treatment during pregnancy is limited. Cardiotoxicity is a known adverse effect of some antineoplastic agents especially of doxorubicin. We report a case of pregnancy-associated DLBCL, which was treated between gestational week 26 and 33 with three cycles of R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone combined with rituximab). At gestational age 34 2/7 she delivered a male infant who was admitted to neonatal care due to cardiomyopathy. In the absence of other explanations it was interpreted as a direct toxic effect of maternal chemotherapy. At age 6 months the boy's cardiac output had normalized. This case report is the first presenting congenital cardiomyopathy after maternal R-CHOP during pregnancy. Since especially anthracyclines are known to cause acute and chronic cardiotoxicity in treated patients, the most probable explanation for neonatal cardiomyopathy in this case is doxorubicin.

Introduction

Diffuse large B-cell lymphoma during pregnancy is a rare event requiring multidisciplinary support. Experience regarding the fetal safety of maternal treatment is limited to case reports and small retrospective studies [1]. In order to provide patients with the best chance of survival often chemotherapy is required. Approximately 1:1000 pregnancies is complicated by a malignant disease; of those lymphoma occurs in approximately 1:6000 deliveries [2]. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), constituting more than 30% of lymphomas [3]. Without appropriate treatment the prognosis is very poor. Currently, most patients with DLBCL are treated with cyclophosphamide, doxorubicin, vincristine and prednisone or prednisolone respectively (CHOP) combined with rituximab (R-CHOP) [4]. Cardiotoxic side effects have been described in patients treated with R-CHOP regimen. Anthracycline exposure is particularly associated with acute and chronic cardiotoxicity [5], and the dose- and time-dependent cardiotoxicity of doxorubicin is well described for infants and adults [6–8]. Although the exact mechanism of doxorubicin cardiotoxicity is still not fully understood, the most accepted hypothesis involves increased oxidative stress due to free radicals and iron accumulation in the mitochondria of the myocytes [9].

Experience with the R-CHOP regime during pregnancy is limited. There are a few case reports [10–13]. Chemotherapy after first trimester of pregnancy has not been shown to elevate the risk of malformations, but is associated with an increased rate of stillbirth, intrauterine growth restriction, and fetotoxicity [14]. Although management of DLBCL during pregnancy is controversial, most oncologists recommend standard treatment independently of pregnancy to ensure high rates of survival [2,14,15].

Abbreviations: CHOP, cyclophosphamide doxorubicin vincristine, prednisolone chemotherapy-regimen; DLBCL, diffuse large B-cell lymphoma; GA, gestational age; NHL, non-Hodgkin lymphoma; NTP, National Toxicology Program; pBNP, probrain natriuretic peptide; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy-regimen; TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus and herpes simplex virus serology.

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Table 1
Mother's clinical history timeline.

Time in weeks after LMP	Clinical condition/therapeutic intervention
23	Vaginal bleeding and diagnosis of DLBCL Tumor size 55 × 15 × 27 mm
25	Rituximab
26	1st R-CHOP cycle
29	2nd R-CHOP cycle
32	3rd R-CHOP cycle
34	**Delivery** of a son
Time in weeks after delivery	
1	4th R-CHOP cycle
4	5th R-CHOP cycle
7	6th R-CHOP cycle
10	Tumor size 16 × 7 x 14 mm
13	Hysterectomy
16	1st consolidation cycle
19	2nd consolidation cycle
52	Complete remission

Abbreviations: LMP: last menstrual period; DLBCL: diffuse large B-cell lymphoma; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy-regimen.

2. Case report

The German Embryotox pharmacovigilance institute in Berlin offers risk assessment on drug use in pregnancy. The oncology department of the university clinic in Salzburg, Austria, contacted Embryotox regarding a 36-year-old pregnant patient. She presented at gestational age (GA) 23 6/7 weeks with vaginal bleeding of a 55 × 15 × 27 mm tumor of the cervix uteri. It was her second pregnancy which had been uneventful prior to presentation. A biopsy revealed a diffuse large B-cell lymphoma. Rituximab treatment (700 mg) was started at GA 25 6/7 weeks. 4 days later, R-CHOP chemotherapy was initiated with three cycles during pregnancy (GA 26 3/7 weeks, GA 29 3/7 weeks and GA 32 3/7 weeks). In each cycle rituximab 700 mg, cyclophosphamide 1400 mg, doxorubicin 95 mg, and vincristine 2 mg were given as single doses; prednisolone 100 mg was given on 5 consecutive days. At GA 34 2/7 weeks she delivered a male infant by planned caesarean section. After delivery the mother received another three cycles of R-CHOP, had hysterectomy and two post-op cycles of chemotherapy for consolidation. One year after delivery the mother had experienced complete remission (Table 1).

The infant's birth weight and length were 2074 g and 46 cm, respectively. Head circumference was 31.5 cm; Apgar scores assessed at 1, 5 and 10 min were 7/6/7 and umbilical cord pH was 7.2. Directly after delivery the neonate presented with normal respiration, strong first cry and his heart rate was above 100/min. A few minutes postnatal the newborn developed respiratory insufficiency with acidosis and required mechanical ventilation. After surfactant application the respiratory situation improved for a short time only. He also presented with symptoms of cardio-circulatory insufficiency including slow time to capillary refill, low mean arterial pressure (28 mmHg), and grey skin color. Echocardiography and chest x-ray suggested a cardiomyopathy with insufficient cardiac output (Fig. 1). Complete blood count was in accordance with age. On the second day of life echocardiography revealed an ejection fraction of 49% and a fractional shortening of 23%.

Treatment with dobutamine was initiated. In order to improve the infant's cardiac situation furosemide was given and fluids were restricted. The patient's cardiac function improved shortly following the beginning of this treatment, and he was subsequently weaned from assisted ventilation on the second day of life followed by another day with nasal high-flow support. Dobutamine treatment was required to be maintained for seven days. Blood pressure values thereafter remained within a normal range. From postnatal day 4 the newborn's renal function was impaired due to the reduced cardiac output until acute renal failure occurred with a short period of anuria at the age of 10 days. Under supportive clinical management (volume loading, diuretics, supplementation of electrolytes) renal function improved rapidly. During the first days of life the infant's main problem was the reduced cardiac output which improved within a few days under dobutamine treatment. Cardiac improvement was confirmed by decreasing cardiac markers (Table 2).

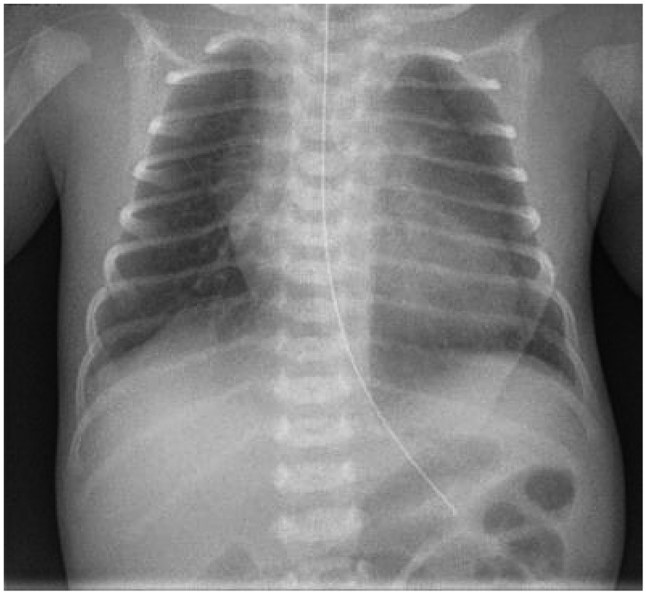

Fig. 1. Chest x-ray on second day of life: slight cardiac enlargement.

Table 2
Time course of cardiac markers.

Cardiac marker	Age:	3 days	31 days
pBNP		>70 000 pg/ml	6 555 pg/ml
hs-cTnT		13 331 ng/l	107 ng/l
Total CK		1 710 U/l	132 U/l
CK-MB mass		18.7 μg/l	7.6 μg/l

pBNP: pro-brain natriuretic peptide; hs-cTnT: high sensitive cardiac Troponin T; CK: creatine kinase; CK-MB mass: creatine kinase-muscle brain mass concentration.

Although cardiac function was impaired no dilatation could be seen on echocardiography directly after birth. In the further course an increasing dilatation of the left ventricle was observed whereas the cardiac function was only slightly reduced; although the left ventricle was still conspicuously spherical with an increased volume load (Fig. 2). The maximum cardiac dilatation was seen at the age of 4 weeks and therefore enalapril was started.

Etiology of the infant's cardiomyopathy remained unclear. The family history was unremarkable for cardiac disorders. There was no evidence of an anomalous left coronary artery arising from the pulmonary artery. Laboratory investigations including complete blood count, electrolytes, liver function tests, screening for TORCH and viral infections, metabolic newborn screening, anti-cardiolipin antibodies, anti-beta 2-glycoprotein antibodies and lupus antibodies were all negative. There were no suspicious clinical or laboratory signs for an underlying syndromatic disease. No genetic analysis was performed because of the newborn's rapid improvement.

At the age of 33 days, weighing 2690 g, the boy, was discharged on enalapril 0.2 mg twice a day in stable condition. During the following months weight gain was regular according to his age and