Early Ultrasound Screening for Fetal Malformations in the Second Pregnancy after Combined Modality Treatment for Hodgkin's Disease: A Case Report

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ABSTRACT

Introduction: Therapeutic progress in HD has led to a high rate of cure, but at the expense of some side effects. Abnormalities reported so far are: cardiac toxicity, pulmonary toxicity, endocrinal failure, second cancers and congenital malformations. Although several studies reported in the literature showed no or slightly increased risk of congenital abnormalities among newborns of women previously treated for Hodgkin’s disease compared with the general population, abnormalities do occur and sometimes they are very odd and difficult. This is the first report of delayed appearance of specific malformations found in the literature.

Case Report: We report a case of female patient, 25 years old, macedonian, presented with Hodgkin’s disease, subtype nodular sclerosis, stage IIIA. The patient received chemotherapy according to ABVD protocol – 6 cycles. Thereafter she received mantle field radiation with 3600 cGy. The first and normal pregnancy occurred after 36 months. Second pregnancy occurred 87 months after completion of treatment. At 13th gestational week ultrasound assessment revealed malformations and induced abortion was performed. A male fetus with malformations on the head such as proboscis, cyclopia and omphalocele on the front abdominal wall containing liver and small bowels was found.

Conclusion: I consider this case important in bringing the potential late side-effect to the attention of both patients and doctors. They should be alert for the risk of congenital abnormalities in newborns of women previously treated for Hodgkin’s disease, especially with combined modality treatment, and should check for them during pregnancy, at birth, in early childhood, or in adulthood. Thus, odd and difficult malformations could be avoided.

Keywords
Hodgkin’s disease, Pregnancy, Abortion, Malformations.

Abbreviations
HD: Hodgkin’s disease; LBW: Low Birth Weight; TLI: Total Lymphoid Irradiation.

Introduction
Hodgkin's disease (HD) is one of the most frequent neoplastic diseases in patients of procreation age. Treatment of HD has been improving over the past few decades. Gold standard for treatment of HD is ABVD protocol with eventual adjuvant radiotherapy. Recent trials have indicated higher survival rates than have previously been seen. In one recent European trial, the 5-year survival rate for those patients with a favorable prognosis was 98%, while that for patients with worse outlooks was at least 85% [1]. Therapeutic progress in HD has led to a high rate of cure, but at the expense of some side effects. Usually, they are cardiac toxicity, pulmonary toxicity (especially when radiation therapy to the chest is given as part of the treatment), endocrinal failure such as hypothyroidism.
(usually after mantle radiation), second cancers (caused by radiation, chemotherapy or both) and congenital malformations (lacrimal duct blockage, hydrocele, ventricular septal defect etc.). Treatment with chemotherapy, radiation therapy or both may have adverse effects on germ cell survival, fertility and health of offspring. Congenital abnormalities occur in 3-5% of all live-births [2]. However, each individual type of congenital abnormality is rare with the most common occurring in about 1/1000 live births [2]. Although several studies reported in the literature showed no or slightly increased risk of congenital abnormalities among newborns of women previously treated for HD compared with the general population, abnormalities do occur and sometimes they are very odd and difficult. This is the first report of delayed appearance of specific malformations found in the literature.

Case Report
Female patient, 25 years old, macedonian, presented with HD, subtype nodular sclerosis, stage IIIA (lymph nodes in the neck, mediastinal, paratracheal, paraaortal). The patient received chemotherapy according to ABVD protocol – 6 cycles. Thereafter, she underwent reevaluation. The chest CT scan revealed paratracheal and mediastinal lymph nodes. It was recommended to receive mantle radiation therapy (this includes neck, mediastinum and axillae). She received 3600 cGy from a 6-mV linear accelerator in 20 treatment exposures (fractions) over 4 weeks. On the next evaluation she was free of disease. She was followed for the next 36 months and then she became pregnant. Ultrasound confirmed a normal fetus of appropriate gestational age. A normal female baby was born with Caesarian section at term. Clinical assessment in the follow-up period showed normal development. Also the mother was assessed regularly and was free of disease. The next pregnancy occurred 87 months after completion of treatment. At 13th gestational week ultrasound assessment revealed malformations and induced abortion was suggested. After provoked, spontaneous expulsion of the fetus occurred. Obstetrical records from the delivering hospital: missed abortion at 13th gestational week, induced abortion. The autopsy report from the Institute of Pathology: male fetus with malformations on the head such as proboscis and cyclopia (one eye beneath proboscis), and omphalocele on the frontal abdominal wall containing liver and small bowels. Other findings were normal. The patient has been followed-up regularly until now. She is disease free, with no more pregnancies. Subsequent follow-up of the female child showed no delayed appearance of malformations.

Discussion
The probability of maintaining ovarian function, becoming pregnant, and delivering a normal child is important to young women anticipating successful therapy for HD. Overall results are reassuring regarding the risks of adverse birth outcome for women previously treated for HD, although the possibility of an increased risk of congenital abnormalities in newborns cannot be ignored.

More studies have examined birth outcome in women with previous HD. Janov et al. did not find any substantial increased risk of low birth weight (LBW) and no congenital abnormalities among newborns of 15 women with pre-pregnancy HD compared with the general population [3]. Likewise, Swerdlov et al. reported no increased risk of preterm birth, LBW, stillbirth, or congenital abnormalities among 49 children of 16 women and 11 men who had previously been treated for HD compared with the general population [4]. Another study, which compared 52 births by 29 women previously treated for HD with births by the women’s siblings, found no overall increased risk of congenital abnormalities and stillbirths combined among children of HD patients. The study also found no association of birth outcome with radiotherapy alone (supra- or infra-diaphragmatic), whereas women treated with both chemotherapy and radiation were more likely to give birth to an abnormal child [5]. The 3 studies, however, were all based on small study populations and did not control for potential confounders. A recent Danish cohort study of birth outcome in women with previous HD found no increased risk of preterm birth and only 1 stillbirth among 192 women, of whom more than 75% had been diagnosed with HD in adulthood (about 20 years of age at diagnosis) [6]. The results from the Danish study, however, indicated a slightly increased risk of congenital abnormalities among newborns of women with previous HD. Aisner et al. reported that among the 84 pregnancies, there were one premature birth at 29 weeks, three spontaneous abortions, 11 elective abortions, and two stillborn: one at 32 weeks and one set of twins. There was no apparent increase in complications of pregnancy, spontaneous abortions, or congenital abnormalities after treatment compared with pregnancies in this patient group before treatment or with pregnancies in the general population [7]. Horning et al. reported a study of 103 women 40 years old or younger who had undergone treatment for HD with total-lymphoid irradiation (TLI) alone, combination chemotherapy, or combined TLI and chemotherapy. Even after intensive treatment programs, women successfully treated for Hodgkin's disease have become pregnant and delivered phenotypically normal children (no fetal wastage occurred and no birth defects were seen) [8]. Most studies observed favorable pregnancy outcome in long-term survivors after therapy for HD. Brusamolino et al. did not observe congenital malformations in the offspring [9] and this supports prior data on favorable pregnancy outcome in long-term survivors after therapy for HD [8].

Limitations
Only those major malformations that were diagnosed during the perinatal period were considered, whereas minor malformations probably have remained undiagnosed.

Conclusion
I consider that this case is important in bringing the potential late side-effect to the attention of both patients and doctors. Also, this case reveals odd and difficult malformations as potential birth outcome. Doctors and patients should be alert for the increased risk of congenital abnormalities in newborns of women previously treated for Hodgkin’s disease, especially those with combined modality treatment. So, they should check for eventual abnormalities during pregnancy, at birth, in early childhood, or in adulthood. Thus, odd and difficult malformations could be avoided.
References