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Case Report

Alobar Holoprosencephaly Following Treatment of Breast Cancer (Case Report)

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Abstract

An unexpected pregnancy during the treatment of a neoplastic pathology is an increasingly frequent situation, amplifying the complexity of therapeutic management. Due to the impact of pregnancy on the oncological prognosis, and the potential teratogenic effects of anti-cancer agents.

Many birth defects have been reported in oncological patients undergoing chemotherapy. In order to improve the management of pregnancy-associated cancers, additional studies on the safety of the administration of anticancer agents during pregnancy should be conducted.

With the intention of bringing additional data to the scientific community, especially in this field where human study is difficult, mostly because of ethical issues, we present to readers a case of alobar holoprosencephaly (HPE) occurring following treatment for HER2+ breast cancer.

Keywords: *Holoprosencephaly; Malformation; HER2+ Breast Cancer; Pregnancy; Trastuzumab; Case Report*

Abbreviations

HPE: Alobar Holoprosencephaly; HER2+: Human Epidermal Growth Factor Receptor 2; Ig: Immunoglobulin

Introduction

Over the last few decades, the prevalence of pregnancy associated cancers has risen steadily. This situation represents a real medical challenge in terms of the impact of treatments on maternal and foetal health.

The literature currently available on the safety of administration of traditional anti-cancer agents is rich and satisfying, unlike that on new treatments such as targeted agents.

Trastuzumab is one of these agents, which has proven its worth in the therapy of breast cancers with HER2 overexpression, significantly reducing the risk of recurrence and improving overall survival [1].

According to ESMO (European Society of Medical Oncology) and NCCN (National Comprehensive Cancer Network) guidelines, the use of trastuzumab is forbidden during pregnancy, given the apparent risk of oligo- and/or anamnios as well as the yet unknown long-term effects for the foetus [2,3].

Unlike chemotherapy, trastuzumab does not cause amenorrhoea. In the absence of effective contraception, patients are exposed to unplanned pregnancies [4]. The main complications generally described in the literature are oligo-anamnios. Trastuzumab has never been shown to be associated with any increased risk of congenital malformations.

Holoprosencephaly (HPE) is a congenital malformation secondary to a neural tube diverticulation disorder occurring during the first weeks of intra uterine life.

The causes vary and are dominated by genetic factors and environmental agents (diabetes, alcohol, retinoids, CMV infection, etc.).

Holoprosencephaly has been reported following exposure to chemotherapeutic agents (Doxorubicin- Cyclophosphamide-Docetaxel), but has never been associated with Trastuzumab.

Observation

Patient aged 36, married with no history of consanguinity, mother of 2 healthy children (aged 7 and 11), followed up since February 2019 for right breast cancer: invasive breast carcinoma, Scarff-Bloom-Richardson (SBR) grade III, hormone receptor negative, HER2+++, Ki 67 at 40%, classified T2N0M0. The patient underwent neoadjuvant chemotherapy (anthracyclines followed by docetaxel and trastuzumab), conservative surgery, adjuvant chemotherapy with trastuzumab and radiotherapy, and then continued with trastuzumab for a total of one year (18 cycles with a 21-day interval).

The patient, who had been on mechanical contraception (condom), presented 8 weeks after her last course of Trastuzumab for the insertion of an intrauterine device. The pelvic ultrasound performed that day revealed a 5-week pregnancy, that to say, a pregnancy conceived 3 weeks after herceptin.

The pregnancy was poorly monitored, in a dispensary, where all she received was a normal prenatal check-up, screening for gestational diabetes and viral serologies (toxoplasmosis, rubella). No morphological ultrasound was performed. The patient presented at 33 weeks of gestation with a decrease in active foetal movements. The ultrasound confirmed fetal death in utero with a biometry corresponding to 28 weeks, along with visualization of a single ventricle. Labour was induced with misoprostol. The stillborn foetus was female, weighing 1140g, with a dysmorphic face with cyclopia, nasal agenesis, proboscis and a single umbilical artery. The performed karyotype was normal.

In terms of oncology, the clinical and radiological assessment showed no signs of relapse.

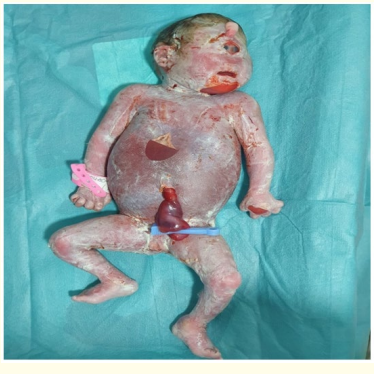

Figure 1: *Image showing holoprosencephaly in its alobar form with a dysmorphic face including cyclopy, nasal agenesis and proboscis.*

Discussion

Holoprosencephalies result from a cleavage anomaly of the median line of the prosencephalon which occurs early in pregnancy (around the 33rd day) [5] and presents with craniofacial malformations of varying severity, proportional to the degree of failure of hemispheric separation, ranging from cyclopia to minor dysmorphia (hyper or hypotelorism, cleft lip or palate, trigonocephaly).

Its prevalence is 1 in 15,000 births, but the most severe forms lead to spontaneous abortion (holoprosencephaly is noted in one in 250 spontaneous abortions) [6,7].

Four types of holoprosencephaly have been described: alobar, semi-lobar, lobar and central inter-hemispheric [8]. The alobar form is the most serious: there is only one cerebral ventricle without a median line, and the choroid plexuses are fused at the front. This anomaly is accompanied by malformation of the face with, in the most complete form, cyclopia, a median and maxillary facial cleft, the absence of a nose and the presence of a proboscis above the single orbit.

Diagnosis is usually made in the first trimester of pregnancy. In the second trimester, the fusion of the thalamus is visible on ultrasound [9]. The diagnosis is confirmed by CT scan or magnetic resonance imaging [10].

The etiologies of holoprosencephaly are heterogeneous and can be classified into two categories:

1. Genetic causes: Non-syndromic monogenic causes: four genes have been identified Sonic hedgehog (Shh), SIX3, ZIC2 and TGIF [11]. Syndromic causes: in 32% to 42% of cases HPE is due to chromosomal abnormalities dominated by those of chromosome 13, followed by chromosome 18 and triploidy. And specific syndromes: identical to Kallman's syndrome and Steinfeld's syndrome.
2. Non-genetic causes: Maternal factors, especially diabetes [12]. Animal studies have shown that HPE can be linked to exposure to certain substances such as alcohol, salicylates, retinoids and statins [13] environmental factors, including polycyclic aromatic hydrocarbons in cigarette smoke, charred meat and Δ9-tetrahydrocannabinol (THC) [14].

The link between HPE and other risk factors, including infections during pregnancy (e.g. cytomegalovirus infection), drugs (e.g. anti-epileptics, salicylates and antibiotics), remains fragile and is based mainly on case reports or animal studies [15].

Taxanes and anthracyclines act on DNA damaging mechanisms in cancer cells, the first class disrupt microtubular networks [16], the second proceed by divers operations such as inhibition of both DNA replication and RNA transcription [17], free radical generation, leading to DNA damage or lipid peroxidation [18], DNA alkylation [19], DNA cross-linking [20], interference with DNA unwinding of DNA strand separation and helicase activity [21], direct membrane damage due to lipid oxidation [22], inhibition of topoisomerase II.

Their transplacental transfer has been confirmed in many eminent studies on baboon models [23] and holoprosencephaly has already been reported after their administration during pregnancy [24].

Trastuzumab is a recombinant humanised IgG1 class monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2). HER2 overexpression is observed in 20-30% of primary breast cancers [25].

It is a drug that is contraindicated during pregnancy, and its transplacental passage has been demonstrated in baboons by a study conducted by Kristel Van Calsteren, which showed similar maternal and foetal plasma concentrations 2 hours after an infusion of Trastuzumab (foetal/maternal plasma concentration = 0.85) [26].

In the case of breast cancer with overexpression of the HER2 gene, the learned societies recommend waiting two years after the last chemotherapy (and therefore one year after the end of trastuzumab) before considering pregnancy [27].

The data available in the literature on the complications of trastuzumab administration during pregnancy were pooled in a meta-analysis by Lin-Yu Xia of 22 studies involving 22 pregnant women and 23 foetuses. The results were as follows:

- Complications occurred in 77.27% of patients during pregnancy and 56.52% of newborns: One of the main complications was oligo/anamnios (68.18%) with all its complexities (renal insufficiency, pulmonary hypoplasia, etc.), while for their newborns at birth was respiratory distress or tachypnea (30%).
- After an average of 25 to 28 months follow-up, 17.39% (4/23) of the children died. No complications were observed during pregnancy or delivery in patients treated with Trastuzumab in early pregnancy [28].
- Within the limits of the available literature, no congenital malformations have been reported with the use of Trastuzumab [29].

Conclusion

The declaration of a pregnancy during the course of treatment for a neoplastic pathology requires specific and meticulous multidisciplinary monitoring. It would be preferable to avoid combining them by introducing effective contraception before starting the treatment protocol, while respecting the recommended time between the end of treatment and conception.

The observation we have presented was drawn up with the intention of reinforcing the available data on the safety of chemotherapeutic agents during pregnancy.

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