Case Report

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Breast Cancer with Trastuzumab Treatment in Mid-Gestation Complicated with Placental Defects and Fetal Growth Restriction: A Case Report

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Breast cancer is the most common invasive cancer in women which affects 14% of women worldwide. HER-2 (c-erbB-2 or HER-2/neu) is overexpressed in 25% – 30% of breast cancer. HER-2 overexpression in breast cancer is associated with increased recurrence and poorer prognosis. Trastuzumab is well-known to be effective in treating HER2-positive breast cancer, but the use during pregnancy remains inconclusive due to its potential side effects to the fetus. Herein, the histopathological examinations of the placenta of a pregnancy complicated by HER-2 (+) breast cancer with non-reassuring fetal status is reported. Immunostaining of vimentin, cytokeratin-7, 8-Hydroxy-2'-deoxyguanosine (8-OHdG), proliferating cell nuclear antigen (PCNA), and caspase 3 as well as Masson's trichrome stain demonstrated that Trastuzumab might induce adverse effects on placenta via suppressing trophoblast proliferation, oxidative deoxyribonucleic acid (DNA) damage and inducing apoptosis that ultimately resulted in placental dysfunction and fetal growth restriction.

Key words: Fetal growth restriction, pregnancy-associated breast cancer, trastuzumab, placenta

Introduction

Pregnancy-associated breast cancer (PABC) is defined as breast cancer that is diagnosed during pregnancy. Breast cancer affects approximately 1 in 3,000 pregnancies and is the second most common malignancy during pregnancy.[1] Surgery, particularly modified radical mastectomy, is the first-line of treatment for operable breast cancer in pregnancy.[2] Adjuvant chemotherapy seems to be safe for the baby if it is administered in second or third trimester, but it is not recommended in the first trimester. Trastuzumab, a monoclonal antibody for HER-2 (c-erbB-2 or HER-2/neu), was

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approved in 2006 as a first-line chemotherapy or (neo-) adjuvant treatment following surgery in HER-2-overexpressing metastatic breast cancer.[3] However, such adverse pregnancy outcomes as fetal growth restriction (FGR), oligohydramnios and anhydramnios were occasionally reported in Trastuzumab-treated PABC patients.[4] The side effects of chemotherapy during pregnancy on the placenta remains understudied. Abellar et al. reported that placental underdevelopment was a side effect in patients exposed to chemotherapy in second and third trimesters.[5] In the current report, histological abnormalities and immunohistochemical changes were demonstrated in the placenta obtained from a woman with Trastuzumab treatment for metastatic breast cancer in second and third trimesters. These abnormalities are thought to be responsible for adverse pregnancy outcomes manifested by fetal growth restriction with severe oligohydramnios. Placentae obtained from gestational age-matched idiopathic preterm delivery idiopathic preterm (IPT, 32 weeks) and preterm delivery complicated by FGR were used as controls.

Case Report

A 32-year-old primigravida visited our clinic at 20 weeks of gestation. Breast cancer (grade 3 invasive carcinoma of right breast with the involvement of axillary lymph nodes) was diagnosed at 18 weeks of gestation. Immunohistochemistry (IHC) revealed negative staining for estrogen receptor (ER) and progesterone receptor (PR), whereas HER-2 was positive (3+). Trastuzumab (6 mg/kg) intravenous infusion every 3 weeks was started from 22 weeks of gestation. After three courses of Trastuzumab therapy, additional chemotherapeutic agents, including paclitaxel and cisplatin, were administered weekly from 28 weeks of gestation throughout pregnancy. After the completion of the first course of Trastuzumab, a late-for-growth fetus approximately 2 weeks behind gestational age with oligohydramnios (amniotic fluid index < 5 cm) was noticed. The conditions deteriorated as the gestation proceeded. At 18+ weeks of gestation before chemotherapy, the biochemical tests revealed elevated glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels at 169 U/L and 168 U/L, respectively. Before delivery, the GOT and GPT levels were 151 U/L and 223 U/L, respectively. Neither renal dysfunction nor proteinuria was detected throughout pregnancy. No significant abnormality in blood sugar levels was noted. With the concern of chronic fetal distress, a 967-gm female infant was delivered by cesarean section at 32 + 1 weeks of gestation with Apgar scores 1 and 5 at 1- and 5-minute, respectively. Figure 1 outlined the pregnancy course with chemotherapy and the development of FGR with oligohydramnios was observed after the initiation of Trastuzumab treatment. The neonate received cardiopulmonary resuscitation at birth and was discharged three months later with mild left occipital intracranial hemorrhage and retinopathy attributed to prematurity.

Compared with gestational age (GA)-matched placentae derived from idiopathic preterm (IPT) birth (Fig. 2A & D) and term pregnancy with FGR (Fig. 2B & E), the placenta obtained from this patient showed widespread destruction of villous structure with necrotic changes and profuse intervillous fibrin deposition as well as reduced numbers of villi (Fig. 2C, F & G). Moreover, thickening of intravillous vessel wall was also observed in placentae derived from FGR-complicated pregnancy and this patient, while the thickening was more profound in this patient than that of FGR-complicated term pregnancy (Fig. 2E, F & H). Masson's trichrome staining revealed that intravillous collagen expression was significantly increased in term pregnancy with FGR and even higher in this patient (Fig. 3A – E). In addition, compared with IPT and FGR-

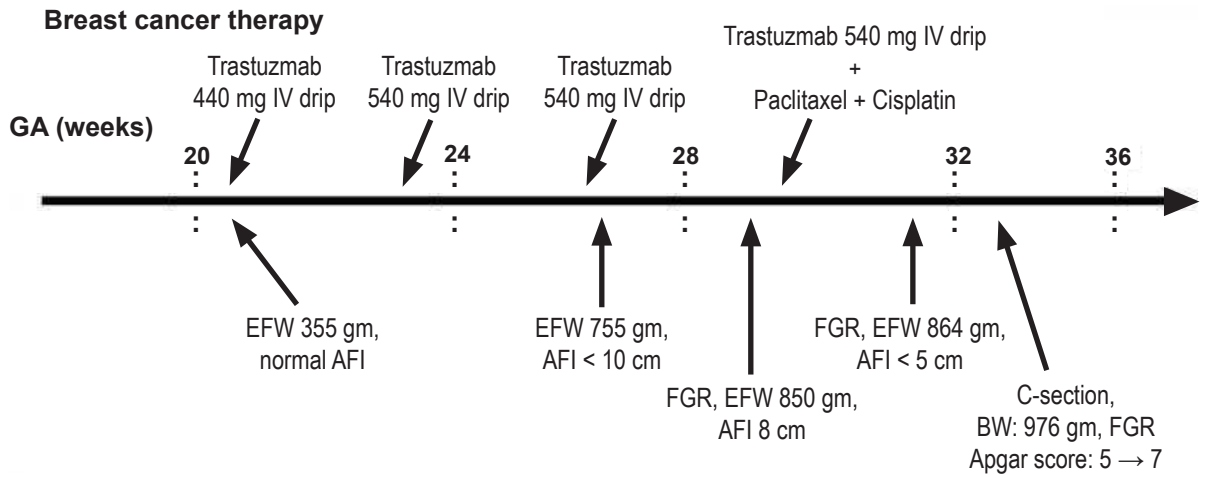

Fig. 1 The timeline of pregnancy events after treatment with target therapy for breast cancer during pregnancy. EFW: estimated fetal weight, AFI: amniotic fluid index, FGR: fetal growth restriction.

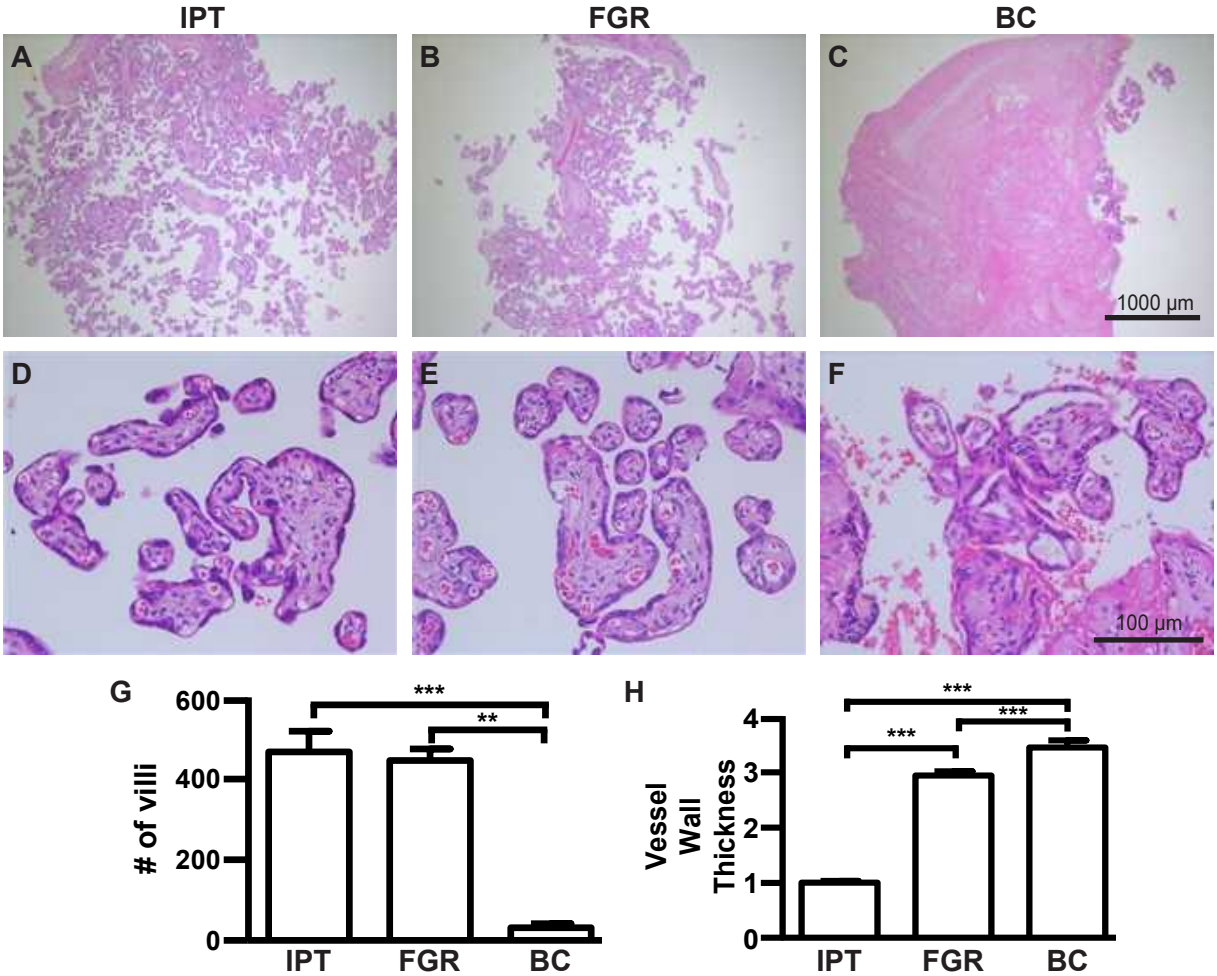

Fig. 2 Villi presentation in the IPT (A), pregnancy with FGR (B), and breast cancer (BC) cases (C) (H&E stain). Villi are well vascularized with numerous vasculosyncytial membranes on the terminal villi (IPT [D], FGR [E]). Villi in the BC case (F) revealed prominent edematous change, perivillous fibrin deposition and villous dysmaturity which presented as loss of distance between the villi and missing of vasculosyncytial membranes. Dilated veins scattering was also noted. Small area of mature villi with fetal capillaries inside still can be seen focally. (G) Widespread destruction of villous structure with necrotic changes and profuse intervillous fibrin deposition as well as reduced numbers of villi. (H) The thickening was more profound in this patient than that of FGR-complicated term pregnancy. Magnification for A – C: 40X Magnification for D – F: 400X.

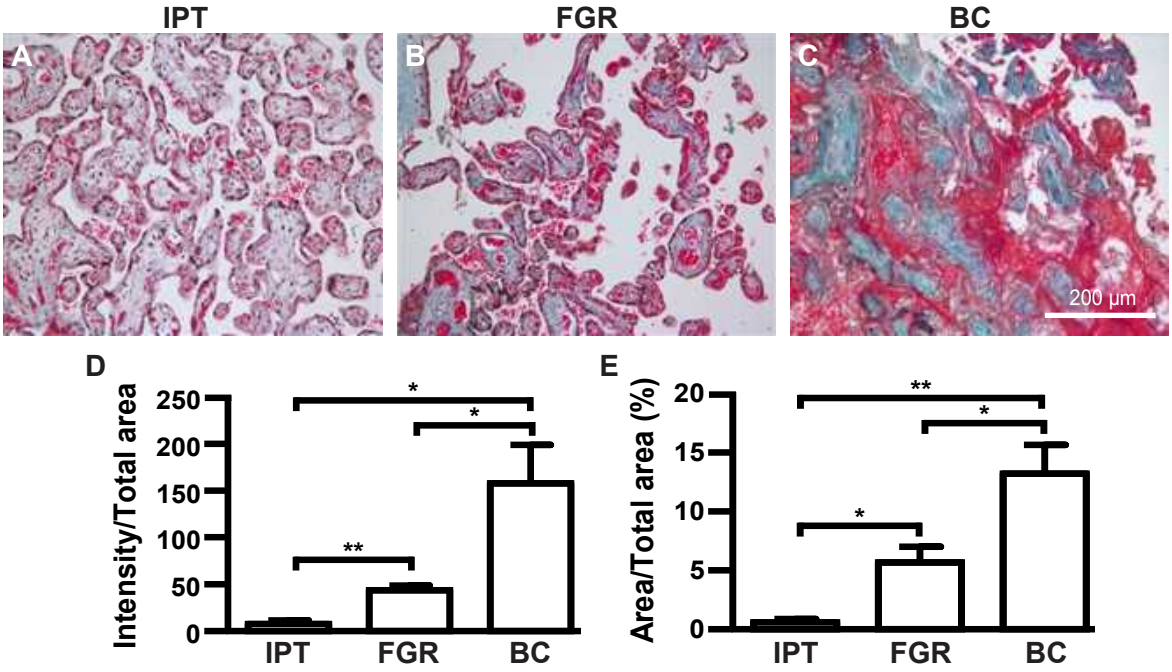

Fig. 3 In the Masson's trichrome method of staining of the IPT (A), pregnancy with FGR (B), and breast cancer (BC) cases (C) profuse green and red color staining can be found in the BC case in comparison with other cases which means massive collagen deposition and muscle or keratin like tissue occupying this placenta. Masson's trichrome staining revealed that the intensity (D) and area (E) significantly increased in term pregnancy with FGR and were even higher in this patient. Magnification: 200X.

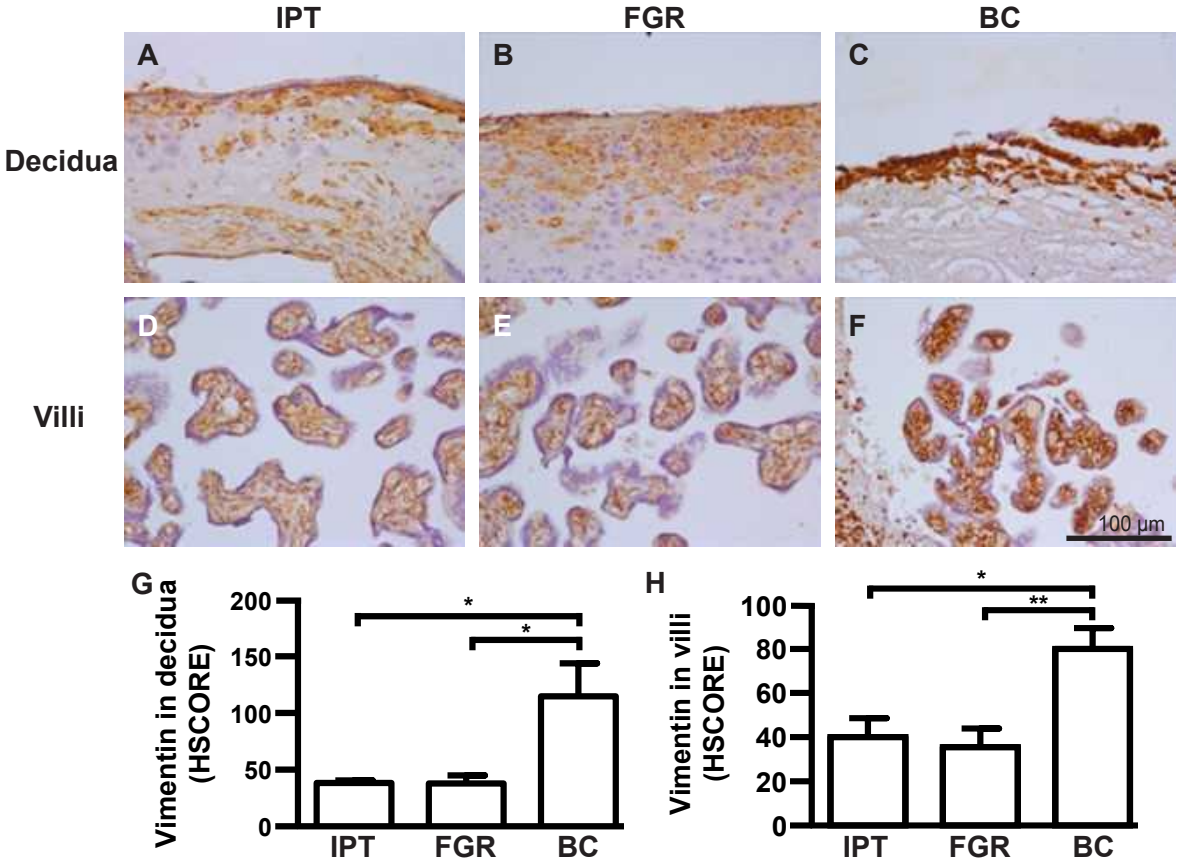

Fig. 4 Expressions of vimentin indicate intracellular markers of mesenchymal cells in placental tissue with the IPT (A for decidua)(D for villi), pregnancy with FGR (B for decidua)(E for villi), and BC cases (C for decidua)(F for villi). Markedly increased vimentin staining was found in decidual (G) and villous trophoblasts (H) in the BC case. Magnification: 400X.

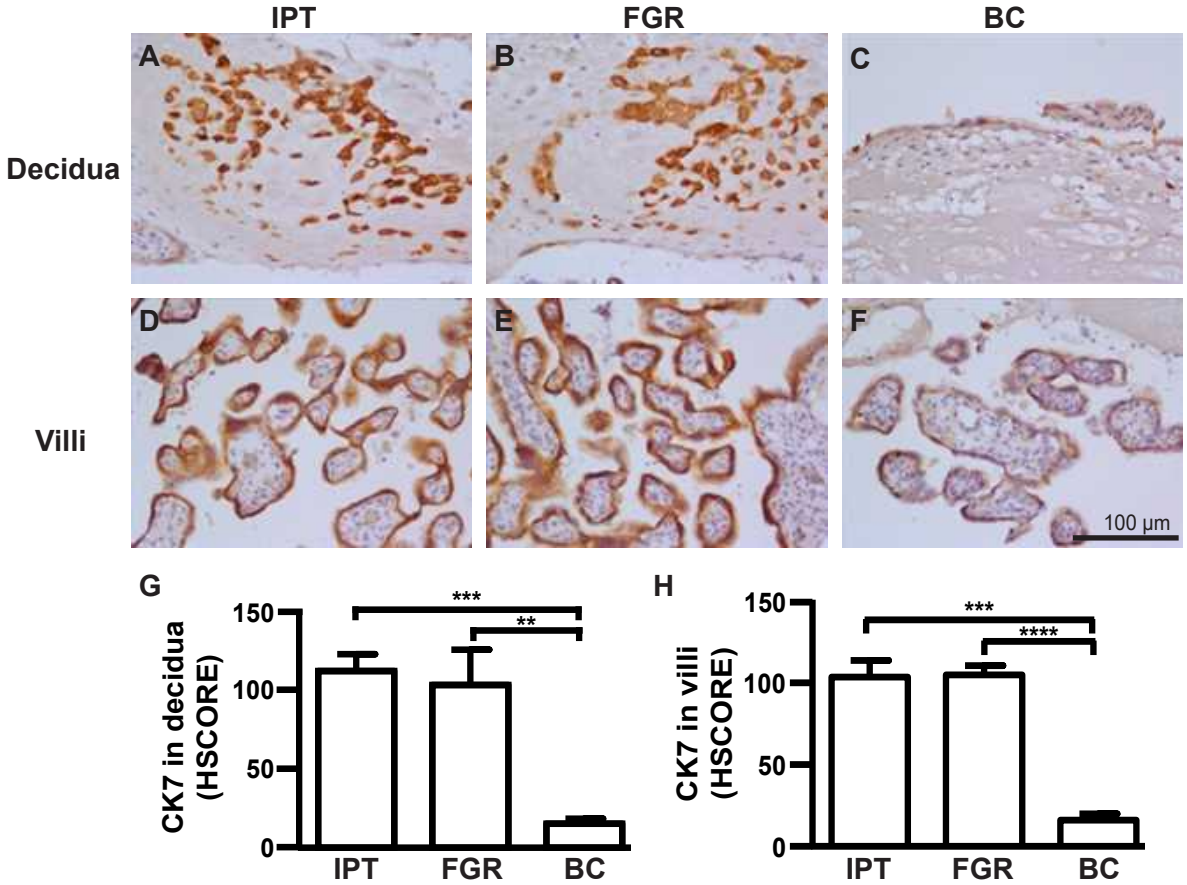

Fig. 5 Expressions of CK-7 indicate intracellular markers of trophoblasts in placental tissue with the IPT (A for decidua)(D for villi), pregnancy with FGR (B for decidua)(E for villi), and BC cases (C for decidua)(F for villi). Markedly decreased CK-7 staining was found in decidual (G) and villous trophoblasts (H) in the BC case. Magnification 400X.

complicated term pregnancy, a corresponding increase in vimentin (Fig. 4A – H) expression in decidua and villous trophoblasts of placenta from Trastuzumab-treated patient was demonstrated by IHC, whereas cytokeratin 7 (CK7) expression in the same areas of placenta (Fig. 5A – H) was decreased. These findings implied a profound devastating effect of Trastuzumab on the trophoblasts extending from the maternal side to the villi. Taken together, these results indicated that increased fibrosis with a reduction in normal trophoblasts was found in the placenta of Trastuzumab-treated patient, compared with control cases. To investigate the relationship between the severity of hypoxic changes and oxidative deoxyribonucleic acid (DNA) damage in the placenta, IHC demonstrated that compared with IPT placenta, 8-OHdG expression was up-regulated in the decidua and villous cytotrophoblasts as well as syncytiotrophoblasts of FGR-complicated placenta. In the current case, the expression of 8-Hydroxy-2'-deoxyguanosine (8-OHdG) was even higher in the areas where the placental destruction existed in H & E staining. (Fig. 6A – H). Compared with the placentae from IPT and term pregnancy with FGR, proliferating cell nuclear antigen (PCNA) expression in this patient was lower in the similar regions of placenta as those shown in 8-OHdG staining (Fig. 7A – H). In addition, cytoplasmic and nuclear caspase-3 immunoreactivity was lower either in the decidual or villous trophoblasts of IPT placentae than those from FGR-complicated term pregnancy and this patient (Fig. 8A – H).

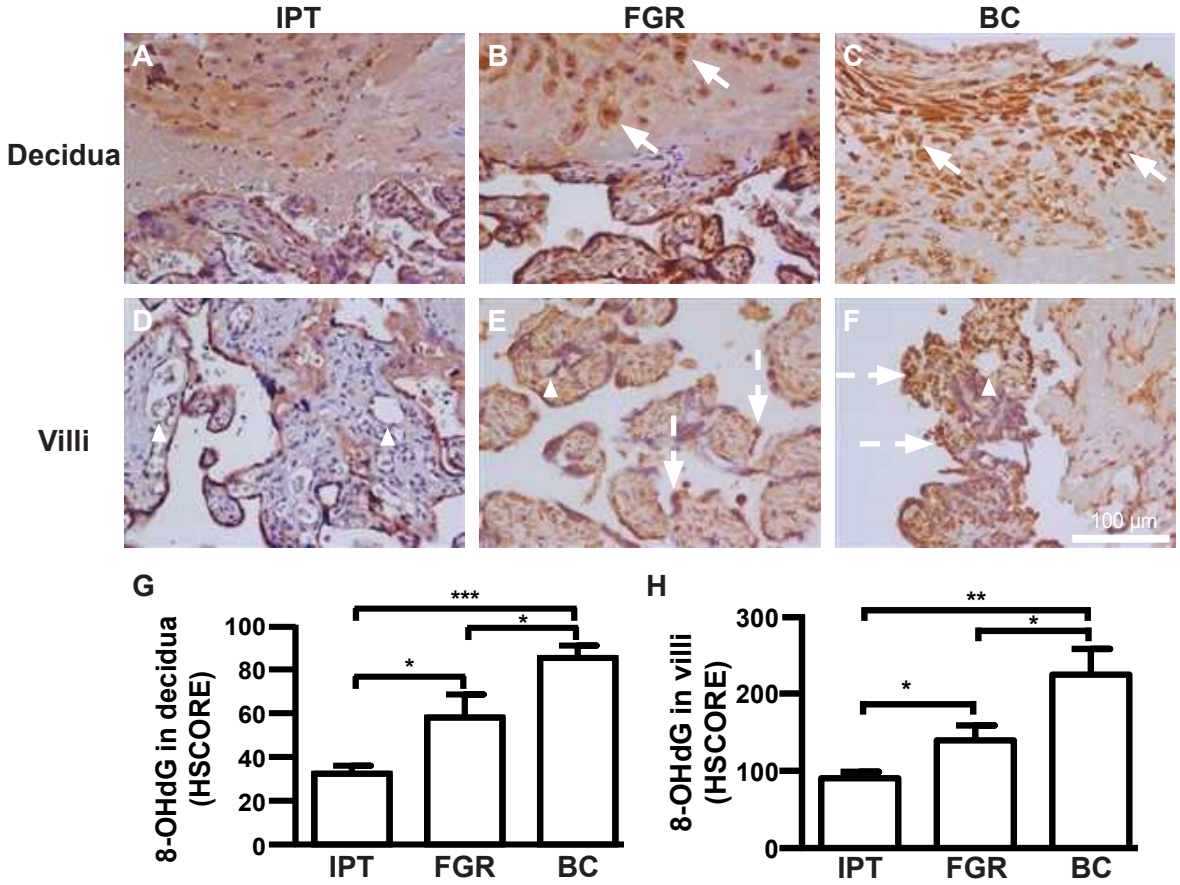

Fig. 6 Expressions of 8-OHdG in placental tissue indicate hypoxic changes and oxidative DNA damage of the IPT(A for decidua)(D for villi), pregnancy with FGR (B for decidua)(E for villi), and BC cases (C for decidua)(F for villi). Lesser extent of 8-OHdG reactions were found in the decidual layer of BC case (G). Markedly decreased density on the cytotrophoblasts surrounding the villi in the FGR and BC case in comparison with IPT (H). Arrows are the decidual layers. Arrowheads are cytotrophoblasts. Big arrows are syncytiotrophoblasts. Magnification 400X.

Discussion

In the US, breast cancer is the most common cancer in women. The majority of invasive breast cancer patients are women older than 50 year-old. In contrast, only 19% of the cases are between 20 to 50 year-old. The incidence of invasive breast cancer during pregnancy is low. The mortality rate of invasive breast cancer has declined because of the advance of diagnostic tools and treatments. Systemic chemotherapy for PABC after 14 weeks of gestation appears to be harmless to the fetus. However, radiation and anti-hormonal therapies are strictly prohibited during pregnancy, while anti-HER-2 therapy are recommended after delivery.[3] In the current patient, oligohydramnios and FGR were detected following Trastuzumab treatment after 20 weeks of gestation. The adjuvant chemotherapy with paclitaxel and cisplatin was given after 28 weeks of gestation (Fig. 1) when FGR had already been observed. Hence, FGR is more likely to be induced by Trastuzumab.

HER-2 protein is a membrane glycoprotein growth factor receptor homologous to epidermal growth factor receptor (EGFR). HER-2 can be identified on the cell membrane of epithelial cells in the placenta, skin as well as gastrointestinal, respiratory, reproductive, and urinary tracts.[4] Specific subtypes of breast, esophageal and stomach cancers express high levels of HER-2 which promote the growth

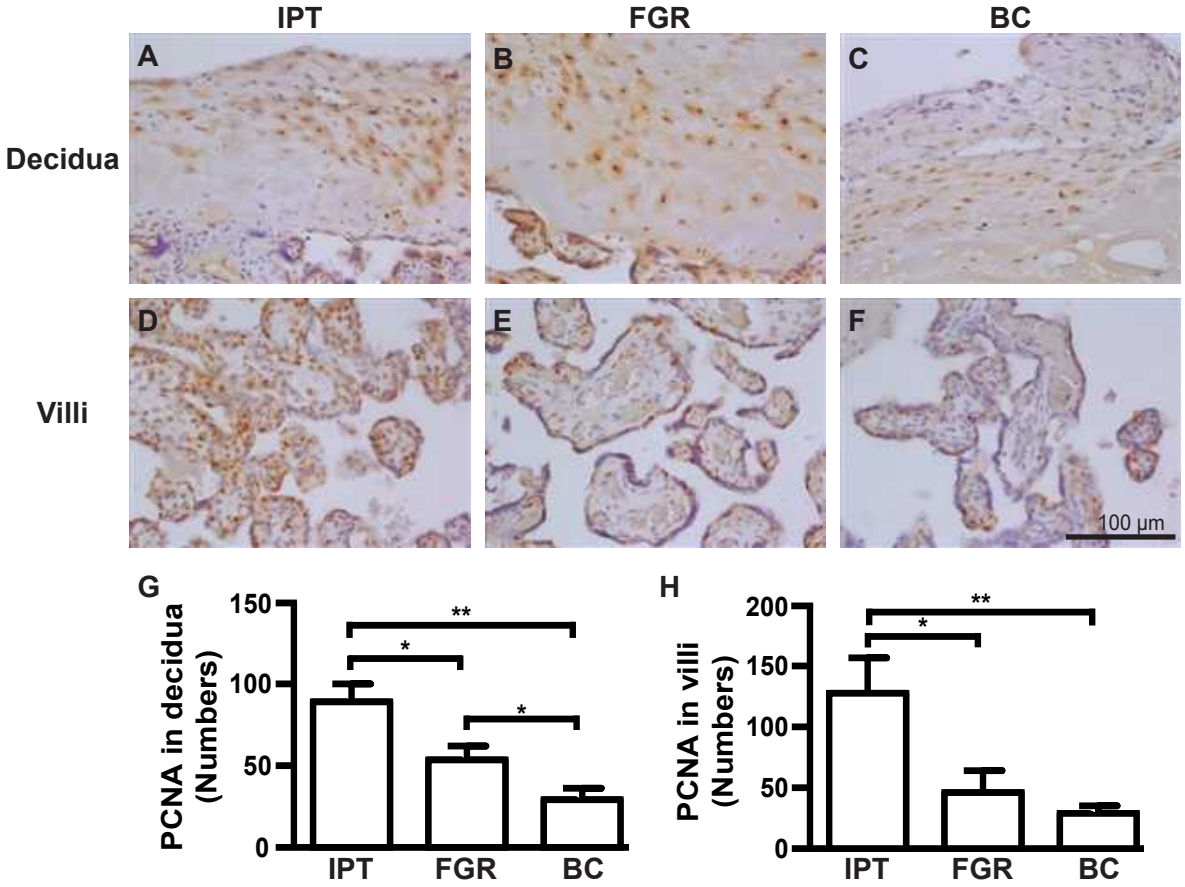

Fig. 7 Expressions of PCNA in placental tissue indicate nuclear DNA replication of the IPT(A for decidua)(D for villi), pregnancy with FGR (B for decidua)(E for villi), and BC cases (C for decidua)(F for villi). Lesser extent of PCNA reactions were found in the decidual layer of BC case (G). Markedly decreased density on the cytotrophoblasts surrounding the villi in the FGR and BC case in comparison with IPT (H). Magnification 400X.

and survival of cancer cells. HER-2-positive tumors consist of 14% of patients with invasive breast cancer. These tumors are more resistant to chemotherapies. Trastuzumab is commonly used as a targeted chemotherapeutic agent in treating HER-2-overexpressing tumors in non-pregnant women. It acts through inhibiting HER-2 function and augmenting patient's immune response to cancer cells. In pregnant women having HER-2-positive breast cancer, such regimens as fluorouracil, doxorubicin, and cyclophosphamide (FAC) as well as cyclophosphamide, methotrexate, and fluorouracil (CMF) are usually recommended. Docetaxel was reported to be safe in second and third trimesters. Hormonal therapy, such as tamoxifen, is not recommended during pregnancy.

The incidence of oligohydramnios or anhydramnios is increased in pregnancies treated with Trastuzumab for PABC. Damage to the fetal renal cells was thought to cause the reduction of amniotic fluid. Moreover, neonatal respiratory failure and transient renal failure were also shown in these patients. Trastuzumab is known to act through promoting internalization and degradation of HER-2, G1 arrest-induced reduction of proliferation, apoptosis, suppression of angiogenesis, antibody-dependent cellular cytotoxicity as well as inhibition of HER-2 extracellular domain cleavage and DNA repair to treat breast cancers.[7] Although several reports have shown the Trastuzumab-associated complications, such as oligohydromnios, FGR, and fetal renal failure, the current report further

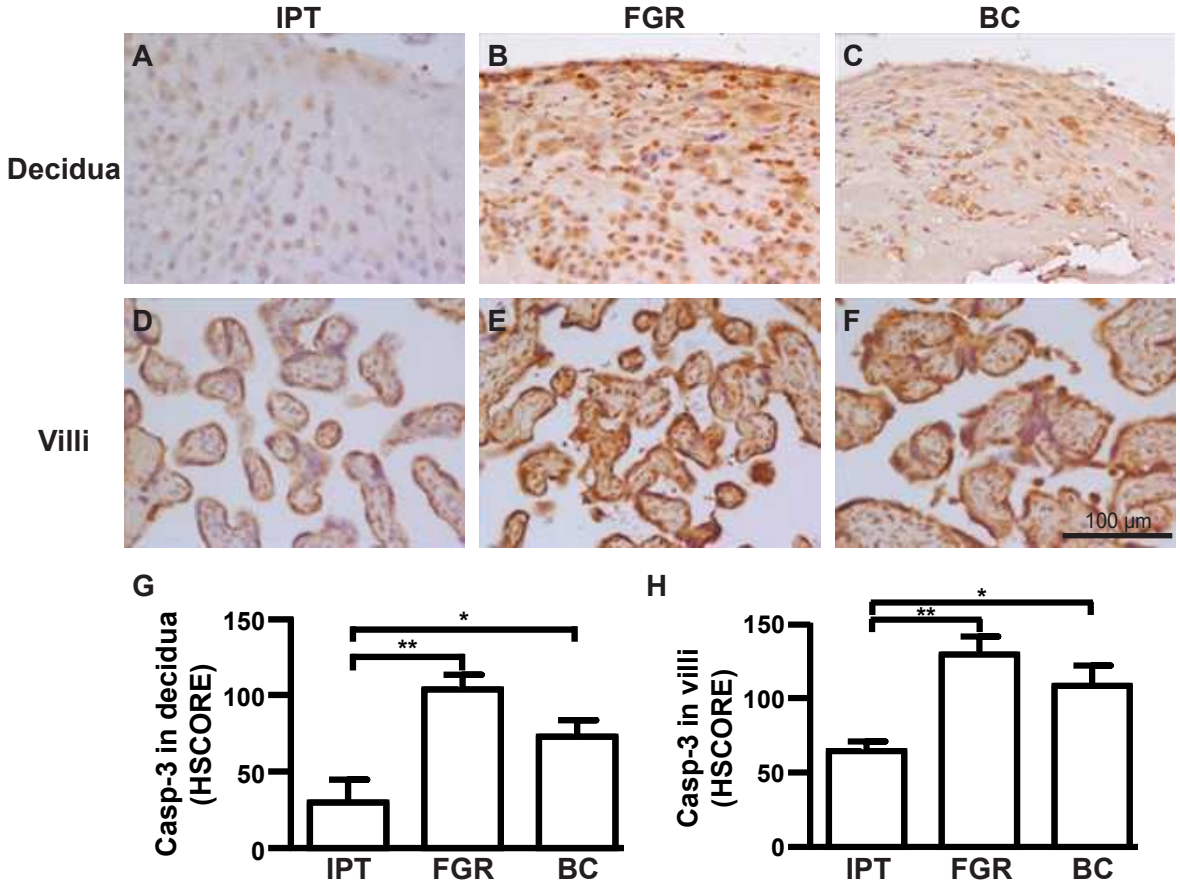

Fig. 8 Expression of Caspase-3 in placental tissue indicates the apoptotic reactions in the IPT(A for decidua)(D for villi), pregnancy with FGR (B for decidua)(E for villi), and BC cases (C for decidua)(F for villi). Comparing with IPT, stronger apoptotic reactions can be found in the decidual layer (G) and villous cytotrophoblast (H) as well as syncytiotrophoblasts in both FGR and BC cases. Magnification 400X.

demonstrated the placental changes induced by Trastuzumab in a breast cancer-complicated pregnancy.

Placenta is responsible for the exchange of nutrients, gases and wastes between a mother and her fetus. The resulting suboptimal and inadequate placental function due to the destruction of placenta will lead to such pregnancy complications as preterm birth, preeclampsia, and FGR.[8] The current case started Trastuzumab treatment from 22 weeks and delivered at 32 + 1 weeks of gestation with FGR and oligohydramnios. The placental histopathology revealed severe deformity with markedly decreased number of villi, fusion of collapsed villi, loss of complete vasculosyncytial membrane, and profuse intervillous fibrin deposition that is compatible with fibrinoid necrotic and fibrotic changes of the placenta. An FGR-complicated pregnancy is often accompanied with a smaller placenta, increased thickness of tertiary-stem villi vessel wall, decreased lumen circumference, and an increased resistance index of the umbilical artery Doppler flow velocimetry. In the current case, markedly increased thickness of vessel wall was observed in FGR-complicated placenta without breast cancer, compared with IPT. The thickness of decidual vessel wall in breast cancer-complicated pregnancies treated with Trastuzumab was further increased, compared with FGR-complicated placenta. Fibrotic changes were observed in FGR-complicated placenta, whereas Trastuzumab exposure further increased the placental fibrosis. Moreover, the numbers of chorionic villi and trophoblasts were significantly reduced

by Trastuzumab treatment. Increased placental 8-OHdG expression in both early and late onset preeclampsia indicated severe hypoxic changes and oxidative DNA damage that ultimately caused FGR. Verheecke et al. demonstrated a significant increase in 8-OHdG expression as well as a decrease in endothelial nitric oxide synthase (eNOS) and PCNA expression in syncytiotrophoblasts of cancer patients receiving chemotherapy. These changes were proposed to play potential roles in the development of FGR.

The consistent changes from decidua to villous trophoblasts demonstrate the detrimental effects of Trastuzumab on placenta in the patient with breast cancer. Nevertheless, these results can only implicate the potential association of oxidative stress-induced trophoblast apoptosis and proliferation inhibition with FGR in breast cancer patient receiving Trastuzumab treatment during pregnancy. Further studies are required to confirm whether Trastuzumab can induce apoptosis and inhibit proliferation in trophoblasts.

Conclusions

In summary, our results indicate that Trastuzumab treatment results in the induction of oxidative DNA damage which may activate apoptosis and suppress the proliferation of trophoblasts. Placental function is therefore hampered. Consequently, FGR develops. However, a cohort study is required to confirm these findings. Currently, the use of Trastuzumab during pregnancy remains controversial.[4] The amniotic fluid volume and fetal growth should be closely monitored throughout the pregnancy in patients receiving Trastuzumab treatment. Moreover, the toxicity of Trastuzumab on neonatal kidney and heart needs to be carefully assessed.

Author Contributions

Study Design, Yun-Hsiang Hung, Chun-Yen Huang, and S. Joseph Huang; Data Collection, Chun-Yen Huang, Ya-Chun Yu, and Chan-Yen Kuo; Statistical Analysis, Chun-Yen Huang; Data Interpretation, Yun-Hsiang Hung and S. Joseph Huang; Manuscript Preparation, Yun-Hsiang Hung, Chun-Yen Huang, and S. Joseph Huang; Literature Search, Yu-Chieh Fang and Chan-Yen Kuo; Funding Acquisition, Yun-Hsiang Hung, and S. Joseph Huang.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the E-Da Hospital (protocol code EMRP65107N and 2021/05/06 of approval).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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