Critical Reviews in Oncology/Hematology 114 (2017) 77–90

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Oncology reviews

Insights into dovetailing GTD and Cancers

Revathy Nadhan[a], Jayashree V. Vaman[b], Nirmala C[c], Satheesh Kumar Sengodan[a], Sreelatha Krishnakumar Hemalatha[a], Arathi Rajan[a], Geetu Rose Varghese[a], Neetha RL[a], Amritha Krishna BV[a], Ratheeshkumar Thankappan[a], Priya Srinivas[a,*]

[a] Cancer Research Program 5, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala, India
[b] Department of Obstetrics and Gynecology, SAT Hospital, Government Medical College, Thiruvananthapuram, Kerala, India
[c] Department of Obstetrics and Gynecology, T D Medical College, Alappuzha, Kerala, India

Contents

1. Introduction 78
2. Trophoblasts: pregnancy to GTD 78
3. Trophoblastic tumors: GTT and GTN 78
   3.1. Hydatidiform moles 78
   3.2. Invasive moles 78
   3.3. Choriocarcinoma 78
   3.4. Placental site trophoblastic tumor 81
   3.5. Epithelioid trophoblastic tumor 81
4. GTD: incidence and risk factors 81
   4.1. Age 82
   4.2. Prior history of GTD 82
   4.3. Prior abortions 82
   4.4. Familial history of GTD 82
   4.5. Other factors 82
5. Molecular alterations in GTD 82
6. Is there a link between Breast Cancer and GTD? 85
   6.1. hCG and cancers 85
   6.2. Integrating hCG – GTD and Breast Cancer 85
   6.3. Integrating the incidence and risk factors of Breast Cancer and GTD; Cohort studies correlating GTD and Breast Cancer risk 86
   6.4. Hormone receptors: ER/PR/Her-2 in GTD 86
   6.5. Does molar hCG affect distant tissues? 86
   6.6. Lack of studies linking Breast Cancer and GTD 86
7. Conclusion 87
   Conflict of interest 87
   Acknowledgements 87
   References 88
   Biographies 90

ARTICLE INFO

Article history:
Received 6 May 2016
Received in revised form 15 March 2017
Accepted 3 April 2017

Keywords:
GTD
Cancers
Trophoblast
β-hCG
Breast cancer

ABSTRACT

Gestational trophoblastic diseases (GTD) encompass a group of placental tumors which mostly arise due to certain fertilization defects, resulting in the over-proliferation of trophoblasts. The major characteristic of this diseased state is that β-hCG rises up manifold than that is observed during pregnancy. The incidence of GTD when analyzed on a global scale, figures out that there is a greater risk in South-East Asia, the reason of which remains unclear. An insight into any possible correlation of GTD incidence with cancers, other than choriocarcinoma, is being attempted here. Also, we review the recent developments in research on the molecular etiopathology of GTD. This review would render a wider eye towards a new paradigm of thoughts to connect GTD and breast cancer, which has not been into the picture till date.

* Corresponding author at: Cancer Research, Rajiv Gandhi Centre for Biotechnology, Thycaud PO, Thiruvananthapuram 695 014, Kerala, India.
E-mail address: priyasrinivas@rgcb.res.in (P. Srinivas).

http://dx.doi.org/10.1016/j.critrevonc.2017.04.001
1040-8428/

1. Introduction

Gestational trophoblastic diseases (GTD) includes a group of pregnancy associated tumors (trophoblastic tumors), ranging from benign to malignant forms. The benign forms include the complete hydatidiform moles (CHM), partial hydatidiform moles (PHM) and the invasive moles (IM), while the malignant forms include choriocarcinoma (CCA), placental site trophoblastic tumors (PSTT) and the epithelioid trophoblastic tumors (ETT) (Fig. 1). After the fertilization process, the fertilized ovum develops into a single celled zygote. Further divisions and proliferations within the zygote would give rise to the fetus, which is surrounded by a placental layer which supplies the fetus with nutrition and nourishment. This placental layer, morphologically, is composed of the epithelial cells termed as the 'trophoblasts'. It is the abnormal proliferation of these trophoblastic cells, due to certain fertilization defects, that give rise to the trophoblastic tumors.

2. Trophoblasts: pregnancy to GTD

Once the single celled zygote reaches the blastocyst stage, the outer layers of the structure becomes the specialized cells termed as trophoblasts. These cells can be of four types namely the villous cytotrophoblasts (v-CTBs), syncytiotrophoblasts (STBs), extra-villous cytotrophoblasts (ev-CTBs) and the intermediate trophoblasts. The v-CTBs are the cells covering the inner layer of the outer part of the blastocyst structure, especially in the villous projections. These cytotrophoblasts (CTBs) are mononuclear in nature, which gradually fuses with each other to form the multinucleated STBs, which constitutes the outer layer of the blastocyst structure. At certain villous endings, the CTBs proliferate deeper inside the maternal decidua and forms the ev-CTBs, which help in the interaction between maternal and fetal structures. There is also another class of trophoblasts termed as the intermediate trophoblasts, which are the prominent cells at the site of implantation helping in the invasion into the myometrium. In short, trophoblast cells help in the exchange of nutrients and waste between the fetus and the mother.

The trophoblast cells gain significance in the context of pregnancy, as they are the only cells secreting the human chorionic gonadotrophin (hCG), which is known as the pregnancy hormone. hCG is essential for the successful implantation and maintenance of the pregnancy. During the initial days of pregnancy, the root CTB cells are formed which secretes the hyperglycosylated hCG (H-hCG). H-hCG plays a role in promoting invasion, successful implantation and also the fusion of the mononuclear CTBs for the formation of multinucleated STBs. These STBs then secrete the regular hCG which maintains the pregnancy. Hence, the total fraction of hCG contributing to the events of pregnancy after fertilization, composes both the regular and the hyperglycosylated ones, all of which are secreted by the trophoblast cells (Cole, 2011, 2012).

3. Trophoblastic tumors: GTT and GTN

The benign forms of GTD are classified under Gestational Trophoblastic Tumors (GTT) and the malignant forms are termed as Gestational Trophoblastic Neoplasia (GTN) (Table 1).

3.1. Hydatidiform moles

They are the benign trophoblastic tumors arising due to the abnormal proliferation and swelling of the vesicular villi composed of the trophoblasts. It can be accompanied with or without a fetus. The swollen villous resembles hydatid morphology, hence the name hydatidiform moles (Savage, 2008; Ngan and Seckl, 2007; Agboola, 1979; Igwegbe and Eleje, 2013; Lawler et al., 2016).

CHM occurs when an anucleated ovum (chromosome either inactive or absent) fuses with a single sperm and followed by duplication or fuses with a diploid sperm, both resulting in a diploid androgenetic karyotype. In the former case, the genotype would be 46 XX, while in the latter, it can be either 46 XX or 46 XY. About 90% CHMs are 46 XX, while the rest 10% constitute the 46 XY group (Kovacs et al., 1991; Szulman and Surti, 1978). An incidence of CHM, as compared with PHM, contributes to an increased susceptibility for a CCA or an IM in the subsequent pregnancies by 15–20%. There will be a uniform and early vesicular enlargement of the trophoblastic villi, mostly with the absence of a fetus or an embryo. Pathological features exhibit diffuse hydropic villi with extensive or diffused circumferential trophoblastic hyperplasia, mostly accompanied with nuclear pleomorphisms, presence of few or no blood vessels, presence of pseudo-inclusions in trophoblast and presence of clumps of extra villous trophoblasts. The common symptoms associated with CHM include vaginal bleeding, uterine enlargement, hyperemesis, pregnancy-induced hypertension and bilateral theca lutein cyst enlargement of the ovaries. GTD presents hCG levels which are often greater than 1,00,000 mIU/mL (Szulman and Surti, 1978; Berkowitz et al., 1991; Mosher et al., 1998; Lage et al., 1992; Paradinas et al., 1996; Sebire et al., 2003a,b; Lurain, 2016).

PHM occurs when a normal ovum fertilizes with two sperms mostly or with a diploid sperm, both of which results in a triploid karyotype namely 69 XXX, 69XXY or 69XYY. PHM rarely develops into post molar GTN with a frequency of less than 5%. The cases of metastasis associated with PHM are also very low. It is characterized by focal trophoblastic hyperplasia but patchy in nature and less extensive unlike CHM, abnormal distributions of the highly vacuolated trophoblasts, prominent fibrosis of the villi which is focal in nature rather than the hydrops, presence of blood vessels with few nucleated fetal red cells, rounded inclusions in the villi and fibrotic stroma. Embryonic tissue may be present in the cases of PHM, but the fetal tissue is identified only in less than 20% cases. The symptoms seen in cases of PHM include incomplete or missed abortion, vaginal bleeding, excessive uterine enlargement, hyperemesis, pregnancy-induced hypertension, hyperthyroidism and theca lutein cysts development. Pre-evacuation hCG levels are generally less than 1,00,000 mIU/mL (Kovacs et al., 1991; Szulman and Surti, 1978; Berkowitz et al., 1991; Mosher et al., 1998; Lage et al., 1992; Paradinas et al., 1996; Sebire et al., 2003a,b; Lurain, 2016).

3.2. Invasive moles

Also termed as *Chorioadenomadestruens*, IM represents the cases of hydatidiform moles (HM), especially CHM, involving deep villous invasion of the trophoblasts into the myometrium, either directly into the tissues or through the blood vessels, owing to the uterine perforation and in certain cases it is associated with extension into adjacent organs accompanied with high levels of β-hCG (Lurain and Brewer, 1982; Ilancheran, 1998; Hertz, 1976). PHM rarely results into IM. It is clinically diagnosed by the persistence of the elevated levels of β-hCG even after the evacuation of vesicular moles. About 10–17% of the HM results into IM and of these, 15% metastasize to lungs or vagina. It presents the symptoms of abnormal penetration, excessive trophoblastic proliferation, extensive local invasion and swollen villi with well-preserved villi pattern similar to that of CHM (Lurain et al., 1983; Alazzam et al., 2016; Palmer, 1994).

3.3. Choriocarcinoma

CCA is a malignant disease characterized by the abnormal trophoblastic hyperplasia and anaplasia of both CTBs and STBs, extensive hemorrhage, absence of chorionic villi and necrosis