Genetic Characterization of Choriocarcinoma and Potential Clinical Implications

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Abstract

Choriocarcinoma is a unique neoplasm that can occur after a pregnancy, as a component of germ cell tumors, or follow the trophoblastic differentiation of neoplastic somatic cells that completely lose their normal phenotype and produce hCG. Gestational Choriocarcinoma (GC) and Nongestational Choriocarcinoma (NGC) are pathologically and morphologically similar, but differ in genetic origin, immunogenicity, sensitivity to chemotherapy, and prognosis (with GC having a better prognosis than NGC). GC can follow any type of pregnancy, while NGC usually arises from ovarian germ cell tumors, or from any epithelial cancer.

Approximately equal numbers of GC cases follow molar or non-molar pregnancies. The genetic make up of the tumor is determined by the nature of the antecedent pregnancy. Tumors resulting from term pregnancies, nonmolar abortions, or partial hydatidiform moles will have both maternal and paternal chromosomes, while those derived from complete hydatidiform moles will be androgenetic in origin. Although choriocarcinoma karyotypic analyses have shown no consistent chromosomal abnormalities, chromosomal gains, losses, and rearrangements have been identified. Distinguishing between GC and NC is clinically important in determining the prognosis and optimum management approach. The treatment of choice for GC is chemotherapy. Patients with NGC frequently respond well to initial chemotherapy, but will not be ultimately cured and should be managed more aggressively with surgical removal and multiagent chemotherapy. Although the overall survival of patients with choriocarcinoma receiving chemotherapy is high, some women still die due to chemoresistance. Identifying tumor origin by genetic parental analyses is essential to determine the prognosis and most appropriate treatment.

Introduction

Choriocarcinoma is a unique neoplasm composed of cytotrophoblast and syncytiotrophoblast that secrete Human Chorionic Gonadotrophin (hCG). It can occur after a pregnancy, as a component of germ cell tumors, [1,2] or follow the trophoblastic differentiation of neoplastic somatic cells that completely lose their normal phenotype and produce hCG [2,3].

Choriocarcinoma represents the most immature form of trophoblastic diseases. It resembles the most primitive trophoblast at the first stage of placentation development, and is characterized by sheets of trophoblastic cells invading and permeating vessels and tissues [4,5]. Except in the rare case of choriocarcinoma with a term pregnancy, villi are absent. It shows considerable cellular atypia with large pleomorphic nuclei, abnormal mitotic figures and bizarre cellular configuration. Central hemorrhage and necrosis are present, with a rim of normal tissue around the interface of viable tumor cells. In addition, diffuse and strong immunoreactivity for hCG is observed [5].

Most commonly, choriocarcinoma derives from term or preterm pregnancies, non-molar abortions, and molar pregnancies. On rare occasions, choriocarcinoma occurs independent of pregnancy, and is therefore called nongestational choriocarcinoma. Gestational choriocarcinoma cannot be morphologically distinguished from nongestational choriocarcinoma [6,7].
Gestational Choriocarcinoma (GC) can follow any type of pregnancy: 50% arise after hydatidiform mole, 25% after spontaneous abortion, 22.5% after a normal pregnancy, and 2.5% following ectopic pregnancy [1].

Nongestational Choriocarcinoma (NGC) most commonly arises from ovarian germ cell tumors, but can originate from any epithelial cancer, including those from lung, gastric and bowel [8]. In some instances, there are mixed tumors comprising epithelial elements and choriocarcinoma, but in others they may have completely lost their epithelial phenotype [9]. The incidence of NGC is still unknown, being reported as a very rare tumor.

**Genetic Origin**

Although gestational and nongestational choriocarcinoma are pathologically and morphologically similar, they differ in genetic origin, immunogenicity, sensitivity to chemotherapy, and prognosis, with Gestational Choriocarcinoma (GC) having a better prognosis than Nongestational Choriocarcinoma (NGC).

Genetically, NGC is similar to other tumors. It originates entirely from the patient and, consequently, has poor immunogenicity that results in lower sensitivity to chemotherapy. GC contains material from the paternal genome that induces a vigorous reaction of the maternal immune system, and is considered to be a semiallograft [4,10]. The remarkable curability of GC with chemotherapy reflects the underlying immune response of the mother to paternal antigens expressed on the surface of the tumor [10].

Approximately equal numbers of GC cases follow molar or non-molar pregnancies. The genetic make up of the tumor is determined by the nature of the antecedent pregnancy [11]. Tumors that result from term pregnancies, nonmolar abortions, or partial hydatidiform moles will have both maternal and paternal chromosomes, while those derived from complete hydatidiform moles will be androgenic in origin [6,11]. Trophoblastic neoplasms are rare and often treated with chemotherapy without the surgical removal of their active focus. As a result, tissue specimens, especially those from fresh tumors, are rarely available for study [12]. Where performed, cytogenetic analyses of choriocarcinoma cell lines and tumor tissue usually reveal an aneuploid karyotype with modes in the hyperdiploid and hypotetraploid range and chromosomal alterations involving almost every chromosome. Choriocarcinoma karyotypic analyses show no consistent chromosomal abnormalities. However, a range of abnormalities, including chromosomal gains, losses, and rearrangements have been identified [6,11]. Molecular genetic studies have identified frequent loss of specific regions of the genome. The most significant of these are loss of 7p12-q11.2, [13] amplification of 7q21-q31, [14] and loss of 8p12-p21 [12,14]. More recently, genetic profiles have been demonstrated to be more heterogeneous (losses of 9q33.1, 17q21.3 and 18q22.1; and gains of 1p36.33-p36.32 and 17q25.3), whereas NGC shows only a few abnormalities with a homogeneous profile [7]. However, the specific genes involved remain not identified.

NECC1, located on chromosome 4q11-q12 is one of the most widely studied tumor suppressor gene in choriocarcinoma [15]. It is abundantly expressed in normal placental vili and absent in choriocarcinoma. NECC1 transfection into choriocarcinoma cell lines alters cell morphology and suppresses tumorigenesis, suggesting that loss of NECC1 expression is involved in the malignant transformation of normal trophoblast to choriocarcinoma [2,11].

The role of onecogenes in the development of choriocarcinoma is less known. However, the amplification of 7q21-q31 observed in a series of choriocarcinoma suggests a role for onecogenes located in this region [6,11].

**Clinical Implications**

Given that choriocarcinomas tend to be fast-growing and the risk of developing chemoresistant metastatic disease is high, establishing the pathogenesis of these neoplasias is of substantial interest [4,16].

Distinguishing between GC and NC has a very important impact on the clinical course and management of the patient. The type of pregnancy in which a tumor arises and the time interval between that pregnancy and the diagnosis of the tumor cannot be determined morphologically but are clinically relevant in determining the appropriate chemotherapeutic regimen. Studies have demonstrated that the causative pregnancy of gestational choriocarcinoma is not always the antecedent pregnancy [3,17-21]. In some cases, it may be a much earlier pregnancy.

Comparing the microsatellite polymorphisms in the tumor with the previous pregnancies can identify the causative pregnancy and reveal the time interval in a woman who has had multiple pregnancies. It can also inform whether the origin of a particular tumor is gestational or nongestational [22].

The treatment of choice for GC is chemotherapy, [16,23] which is tailored to each patient’s risk score (score 0-6 = low-risk, ≥7 = high-risk) and response to treatment [24]. Among GC patients treated with chemotherapy, the overall worldwide survival rate, even for metastatic choriocarcinoma, is 80-90% [23]. Patients with low-risk GC can normally be cured with single agent chemotherapy (methotrexate or actinomycin D) [25]. Still, a minority of women will have chemotherapy resistance or high-risk disease. Those with high-risk GC require a multiagent chemotherapy regimen such as EMA/CO (etoposide, methotrexate, actinomycin-D alternating with cyclophosphamide and vincristine), [26] EP/EMA (Etoposide and cisplatin / EMA) [27] or EP/EMA modified [28,29]. Studies have shown that interferon alpha may be a useful biomarker for predicting methotrexate resistance in gestational trophoblastic neoplasia. This finding may provide a target for potential novel therapies for the treatment of methotrexate resistance in the future [30].

On the other hand, patients with NGC frequently respond well to initial chemotherapy, but will not be ultimately cured of their illness and should be managed more aggressively with surgical removal and multiagent chemotherapy. Unlike GC cases, NGCs are not categorized according to a risk score system. Cases of NGC are usually treated with surgical resection followed by chemotherapy [31]. However, the prognosis of NGC is much less favorable despite advances in surgery and chemotherapy regimens [32,33]. Indeed, molecular studies have demonstrated that most patients with tumors containing no definite paternal genes die of their disease (84% of the cases) [32].

NGC should be suspected in the presence of unusual features such as metastases from unknown primary tumor, long interval since a recognized pregnancy, uterine tumors with unusual pathology, and primary ovarian choriocarcinoma [3,8].

**Primary ovarian tumour**

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Although the overall survival of patients with choriocarcinoma receiving chemotherapy is high, some women still die due to chemoresistance. Characterization of the molecular changes in choriocarcinoma would allow the target-based treatment of metastatic forms of this disease that are refractory to conventional therapy. The use of molecular genetic techniques to identify genomic imbalances in the tumor by array-based comparative genomic hybridization (aCGH) together with microarray analysis should facilitate these investigations. Identifying tumor origin by genetic parental analyses, (aCGH) together with microarray analysis should facilitate these investigations. Identifying tumor origin by genetic parental analyses, such as polymorphic microsatellite markers, is essential to determine the prognosis and most appropriate treatment. Further genetic studies on choriocarcinomas are necessary to elucidate the pathogenesis of this peculiar form of tumor.

References

