Clinics in Oncology

Mini Review
Published: 07 Apr, 2017

Genetic Characterization of Choriocarcinoma and Potential Clinical Implications

Izildinha Maestá[1,2], Luz Angela Correa Ramírez[3], Julia Bette Homem de Mello[4], Marilza Vieira Cunha Rudge[1], Silvia R Rogatto[5]*

[1]Department of Gynecology and Obstetrics, Botucatu Medical School, UNESP-Sao Paulo State University, Botucatu, SP, Brazil

[2]Trophoblastic Diseases Center of the Botucatu Medical School, UNESP-Sao Paulo State University, Botucatu, SP, Brazil

[3]Clinical Department, Caldas University, Manizales, Caldas, Colombia

[4]International Research Center - AC Camargo Cancer Center, Sao Paulo, SP, Brazil

[5]Department of Clinical Genetics, Vejle Sygehus and Institute of Regional Health, University of Southern Denmark, Vejle, Denmark

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 removaland 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 analysesis essential to determine the prognosis and most appropriate treatment.

OPEN ACCESS

Correspondence:
Izildinha Maestá, Department of Gynecology and Obstetrics, Botucatu Medical School, UNESP-Sao Paulo State University, Botucatu, SP, Brazil, Tel: +55 14 3880-1401; Fax: +55 14 3882-1933;
E-mail: imaesta@fmb.unesp.br

Received Date: *19 Dec 2016*
Accepted Date: *04 Apr 2017*
Published Date: *07 Apr 2017*

Citation:
Maestá I, Ramírez LAC, de Mello JBH, Rudge MVC, Rogatto SR. Genetic Characterization of Choriocarcinoma and Potential Clinical Implications. Clin Oncol. 2017; 2: 1261.

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 placental 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 derivedfrom complete hydatidiform moles will be androgenetic 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 chromosal 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, GC genetic profile has been demonstrated to be more heterogeneous (losses of 9q33.1, 17q21.3 and 18q22.1; and gains of 1p36.33-p363.32 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 villi 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 oncogenes in the development of choriocarcinoma is less known. However, the amplification of 7q21-q31 observed in a series of choriocarcinoma suggests a role for oncogenes 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 relevantin 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, score ≥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 removaland 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

A Oladipo,

a

J Mathew,

b

A Oriolowo,

c

I Lindsay,

d

R

Conclusion

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, such as polymorphic microsatellite markers, is essential to determine the prognosis and most appropriate treatment. Further genetic studies on choriocarcinomas are necessary to elucidatethe pathogenesis of this peculiar form of tumor.

References

1. Smith HO, Kohorn E, Cole LA. Choriocarcinoma and gestational trophoblastic disease. Obstet Gynecol Clin North Am. 2005;32(4):661-84.
2. Cheung AN, Zhang HJ, Xue WC, Siu MK. Pathogenesis of choriocarcinoma: clinical, genetic and stem cell perspectives. Future Oncol. 2009;5(2):217-31.
3. Fisher RA, Savage PM, MacDermott C, Hook J, Sebire NJ, Lindsay I, et al. The impact of molecular genetic diagnosis on the management of women with hCG-producing malignancies. Gynecol Oncol. 2007;107(3):413-9.
4. Shih IeM. Gestational trophoblastic neoplasia--pathogenesis and potential therapeutic targets. Lancet Oncol. 2007;8(7):642-50.
5. Shih Ie-M, Mazur MT, Kurman RJ. Gestational trophoblastic disease and related lesions. In: Kurman Robert J, editor. Blaustein' s Pathology of the Female Genital Tract, 5th ed. New York: Springer-Verlag, Inc.; 2002. p. 1193-1247.
6. Hoffner L, Surti U. The genetics of gestational trophoblastic disease: a rare complication of pregnancy. Cancer Genet. 2012;205(3):63-77.
7. Mello JB, Ramos Cirilo PD, Michelin OC, Custódio Domingues MA, Cunha Rudge MV, Rogatto SR, et al. Genomic profile in gestational and non-gestational choriocarcinomas. Placenta. 2017;50:8-15.
8. Oladipo A, Mathew J, Oriolowo A, Lindsay I, Fisher R, Seckl M, et al. Nongestational choriocarcinoma arising from a primary ovarian tumour. BJOG. 2007; 114(10):1298-300.
9. Talerman A. Germ cell tumors of the ovary. In: Blaustein's pathology of the female genital tract. Editor Robert J. Kurman 5ª edition. Springer-Verlag New York, Inc. 2002; p. 967-1033.
10. Wang X, Fu S, Freedman RS, Liu J, Kavanagh JJ. Immunobiology of gestational trophoblastic diseases. Int J Gynecol Cancer. 2006;16(4):1500-15.
11. Dearden H, FisherRA. Genetics. In Gestational trophoblastic disease. Edited by Hancock BW, Seckl MJ, Berkowitz RS. Fourth edition. Connecticut, ISSTD, 2015, p.1-45.
12. Burke B, Sebire NJ, Moss J, et al. Evaluation of deletions in 7q11.2 and 8p12-p21 as prognostic indicators of tumour development following molar pregnancy. Gynecol Oncol. 2006;103(2):642-8.
13. Matsuda T, Sasaki M, Kato H, Yamada H, Cohen M, Barrett JC, et al. Human chromosome 7 carries a putative tumor suppressor gene(s) involved in choriocarcinoma. Oncogene. 1997;15(23):2773-81.
14. Ahmed MN, Kim K, Haddad B, Berchuck A, Qumsiyeh MB. Comparative genomic hybridization studies in hydatidiform moles and choriocarcinoma: amplification of 7q21-q31 and loss of 8p12-p21 in choriocarcinoma. Cancer Genet Cytogenet. 2000;116(1):10-15.
15. Asanoma K, Kato H, Inoue T, Matsuda T, Wake N. Analysis of a candidate gene associated with growth suppression of choriocarcinoma and differentiation of trophoblasts. J Reprod Med 2004;49:617-26.
16. Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. Curr Opin Oncol. 2007;19(5):486-91.
17. Shahib N, Martaadisoebrata D, Kondo H, Zhou Y, ShinkaiN, Nishimura C, et al. Genetic origin of malignanttrophoblastic neoplasms analyzed by sequence tag sitepolymorphic markers. Gynecol Oncol. 2001;81(2):247-53.
18. Fisher RA, Newlands ES, Jeffreys AJ, Boxer GM, BegentRH, Rustin GJ, et al. Gestational and nongestationaltrophoblastic tumors distinguished by DNA analysis. Cancer. 1992;69(3):839-45.
19. Arima T, Imamura T, Sakuragi N, Higashi M, Kamura T,Fujimoto S, et al. Malignant trophoblastic neoplasms withdifferent modes of origin. Cancer Genet Cytogenet. 1995;85(1):5-15.
20. Suzuki T, Goto S, Nawa A, Kurauchi O, Saito M, TomodaY. Identification of the pregnancy responsible for gestationaltrophoblastic disease by DNA analysis. Obstet Gynecol. 1993;82(4 Pt 1):629-34.
21. Roberts DJ, Mutter GL. Advances in the molecular biologyof gestational trophoblastic disease. J Reprod Med. 1994;39(3):201-8.
22. Alifrangis C, Seckl MJ. Genetics of gestational trophoblastic neoplasia: an update for the clinician. Future Oncol. 2010;6(12):1915-23.
23. Hoekstra AV, Lurain JR, Rademaker AW, Schink JC. Gestational trophoblastic neoplasia: treatment outcomes. Obstet Gynecol. 2008;112(2 Pt 1):251-258.
24. Ngan HYS, Benedet JL, Jones III HW, et al. FIGO Staging and risk factor scoring for trophoblastic neoplasia. Int J Gynecol Obstet. 2002;77: 285-287.
25. McNeish IA, Strickland S, Holden L, Rustin GJ, Foskett M, Seckl MJ, et al. Low-risk persistent gestational trophoblastic disease: outcome after initial treatment with low-dose methotrexate and folinic acid from 1992 to 2000. J Clin Oncol. 2002;20(7):1838-44.
26. Bower M, Newlands ES, Holden L, Short D, Brock C, Rustin GJ, et al. EMA/CO for high-risk gestational trophoblastic tumors: results from a cohort of 272 patients. J Clin Oncol. 1997;15:2636-43.
27. Newlands ES, Mulholland PJ, Holden L, Seckl MJ, Rustin GJ. Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors. J Clin Oncol. 2000;18(4):854-859.
28. Michelin OC, Maestá I, Braga AR, et al. Tratamento da neoplasia trofoblástica gestacional resistente ao metotrexate. Femina. 2007; 35(1):35-40.
29. Maestá I, Michelin OC, Traiman P. Conduta na neoplasia trofoblástica gestacional de alto risco resistente ao regime poliquimioterápico. In: Belfort P, Madi JM, Grillo BM, Viggiano M, editores. Neoplasia trofoblástica gestacional-controvérsias. Rio de Janeiro: Editora Rubio. 2007. p.193-202.
30. Elias KM, Harvey RA, Hasselblatt KT, Seckl MJ, Berkowitz RS. Type I

interferons modulate methotrexate resistance in gestational trophoblastic neoplasia. Am J Reprod Immunol. 2017.

31. Jiao LZ, Xiang Y, Feng FZ, Wan XR, Zhao J, Cui QC, et al. Clinical analysis of 21 cases of nongestational ovarian choriocarcinoma. Int J Gynecol Cancer. 2010; 20(2):299-302.

32. Newlands ES. The management of recurrent and drug-resistant gestational trophoblastic neoplasia (GTN). Best Pract Res Clin Obstet Gynaecol. 2003;17(6):905-23.

33. Maestá I, Michelin OC, Traiman P, Hokama P, Rudge MV. Primary non-gestational choriocarcinoma of the uterine cervix: a case report. Gynecol Oncol. 2005;98(1):146-150.