Commentary

Circulating Tumor DNA: A Potential Novel Diagnostic Approach in Gestational Trophoblastic Neoplasia

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Gestational trophoblastic diseases (GTD) are a group of disorders that originate from the trophoblast, which is the outer layer of the blastocyst that normally gives rise to the placenta and is the first tissue to differentiate from the developing embryos after implantation. The human chorionic gonadotropin (hCG) is one of the pregnancy hormones and is secreted by trophoblastic cells. hCG is detected in maternal blood seven days after fertilization (Cole, 2009) and is an excellent marker to detect chemical, normal and abnormal pregnancies.

GTD include pre-malignant stages, partial and complete hydatidiform moles, and gestational trophoblastic neoplasia (GTN), which encompass invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor, and are all characterized by excessive proliferation of the trophoblast and therefore excessive production of hCG. Among GTD, hydatidiform mole is the most common. After initial diagnosis by ultrasound and serum hCG quantitation, hydatidiform moles are removed by dilatation and curettage suction and the patients are followed-up with serial hCG measurements until negativity or non-pregnant levels. Abnormal decrease of hCG after curettage indicates risk of persistent trophoblastic disease and malignant transformation into GTN (Fig. 1) that are classified and treated according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines (FIGO Oncology Committee, 2002; Scelld et al., 2010). The implementation of these guidelines has contributed to a better management of GTD and changed their outcomes from nearly 100% fatality 60 years ago (Goldstein, 2012) to nearly 100% cure rates in current clinical practice (Bolze et al., 2015). However, some patients still present with advanced or chemoresistant GTN. In addition, hCG is a common tumor marker that is expressed by germ cell tumors of the testis and the ovary and by 20–40% of common epithelial carcinomas such as bladder, cervix, lung, and naso-pharynx (Iles, 2007). Many of these tumors are not 100% curable and those that express hCG have the lowest survival rate.

In this issue of EBioMedicine, Openshaw et al. (2016) looked for circulating free DNA (cfDNA) in the plasma of 18 women with post-molar GTN, two with metastatic gestational choriocarcinoma, and five with hCG-secreting tumors of unknown origin. They isolated cfDNA and used it in a multiplex assay that amplifies 15 short tandem repeat (STR) loci and the Amelogenin gender-determining marker to identify whether the cfDNA contains circulating tumor DNA (ctDNA). By comparing the genotypes of cellular DNA of the patients and their partners with those amplified from available preceding molar pregnancies and cfDNA, they show the presence of paternal alleles in cfDNA in 13 patients, 12 with GTN and one with a tumor of unknown origin. The amount of non-maternal ctDNA ranged from 9% to 55% of total cfDNA. Multiplex STR genotyping on the tumor DNA is commonly used to determine the parental contribution to molar pregnancies. It is also used on choriocarcinoma tumor DNA to determine whether these tumors have germ cell (e.g. ovarian origin) or gestational origin. The identification of paternal alleles is therefore a reliable and robust criterion to confirm the gestational origin of these tumors. This is particularly important for the patients because the management and prognosis of gestational and non-gestational hCG-secreting tumors are totally different (Alifrangis et al., 2013).

The study by Openshaw and his colleagues demonstrated the presence of circulating tumor DNA (ctDNA) in many patients with GTN (60%) and will most likely open new testing opportunities aimed at determining the origin of hCG-secreting tumors by genotyping cfDNA. In post-molar GTN, the gestational origin of the tumor is usually less questionable and such test may not be needed. However, genotyping cfDNA is important in patients when tumor sampling exposes the patients to the risk of bleeding and tumor dissemination. Similarly, when the preceding pregnancy is not a hydatidiform mole or/and occurred several years ago, genotyping cfDNA offers a unique source for determining the origin of the tumor and therefore adjust the FIGO score to choose the best chemotherapy regimen. An illustration of the importance of genotyping cfDNA is the case of patient CFD-023 whose latest pregnancy was terminated 11 years ago.

In the study by Openshaw et al. (2016), a significant correlation between the amount of ctDNA and serum hCG was found in patients with GTN and detectable ctDNA by genotyping. However, the exact relationship between circulating tumor DNA and serum hCG remains to be elucidated in future studies. Such studies may need to consider some confounding factors such as the gestational stage of the pregnancy, the time interval between the curettage and the diagnosis of GTN and collection of blood to search for ctDNA; if accounted for, may help reaching a better correlation. It would be also interesting to look for
correlation between the amounts of ctDNA and the risk of developing post-molar GTN on blood samples drawn at the time of the curettage of the moles and during the follow-up and treatments (Fig. 1). Furthermore, to better understand the diagnostic value of ctDNA, it is important to know the cellular origin of the DNA that is shed in the maternal circulation. In pre-eclampsia and intra-uterine growth restriction, the amounts of circulating fetal DNA correlate with placental apoptosis and necrosis rather than with placental volume (Taglauer et al., 2014). In GTDs, apoptotic cells are found at higher amounts in hydatidiform moles that regress spontaneously than in moles that give rise to GTNs (Chiu et al., 2001). Therefore, even if all confounding factors are taken into consideration, it is possible that the amounts of ctDNA may not correlate positively with the amounts of serum hCG in all patients.

In conclusion, the present study opens interesting new perspectives to better understand the pathophysiology of GTN and provides hope for a reliable diagnostic approach from a simple blood sample to improve the management of patients with hCG-secreting tumors of unknown origin.

Disclosure

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Fig. 1. Clinical management timeline of a patient with post-molar gestational trophoblastic neoplasia. A standard presentation of a patient with a clinical suspicion of hydatidiform mole based high serum hCG and suggestive pelvic ultrasound. The patient underwent dilatation curettage and the diagnosis of hydatidiform mole was histologically confirmed few days after curettage. Serum hCG was monitored weekly. According to FIGO guidelines, rising hCG indicated a post-molar malignant transformation into GTN. After imaging and establishment of the FIGO score, the patient was placed under single agent chemotherapy. Rising hCG despite 4 courses of single agent chemotherapy indicated monochemo resistance and the patient was cured after 9 courses of polychemotherapy. hCG, stands for human chorionic gonadotropin; IU/L, international units per liter; HM, hydatidiform mole; GTN, gestational trophoblastic neoplasia; FIGO, International Federation of Gynecology and Obstetrics.

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