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No Evidence of Cancer or Cancer Markers 3 Years After Receiving a Non-Reportable Cell-Free DNA Sequence Analysis During Pregnancy

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Abstract

The blood test performed in pregnant women who are at least 10 weeks from conception that measures cell free DNA from the placenta that can detect fetal aneuploidy that could lead to live deliveries (especially for aneuploidies e.g., trisomy 13,18, and 21) is known as non-invasive prenatal testing (NIPT). When this test is not able to be interpreted, if there are no fetal anomalies present or benign tumors e.g., fibroids, researchers have found a high percentage of various cancers in these women. Even in the low percentage of women found who do not have obvious cancer at the present time, or a known non-malignant etiology for the uninterpretable NIPT, thereafter is the possibility that an occult cancer is present and will manifest shortly. Presented is a case where there is still no evidence of cancer 2 years post-partum despite an unreportable NIPT (x2).

Keywords: Cell free DNA; Non-invasive prenatal testing; Cancer; Fibroid tumors; Fetal anomalies.

Introduction

The source during pregnancy of circulating cell free (cf) DNA is predominately from the hemopoietic system of the woman carrying the pregnancy with a minor contribution from the placenta (about 10%) [1, 2]. This test known as the non-invasive prenatal test (NIPT), has become a very popular test used routinely as a screen especially for trisomies 13,18, and 21 [1-3]. Tumors (benign or malignant) can also shed cfDNA in the maternal blood [4]. The presence of cfDNA from tumor distorts the expected ratios for a euploid or aneuploid fetuses, and thus the lab states that the aneuploidy results cannot be determined [4]. Though some fetal abnormalities e.g., multiple trisomies or autosomal monosomy may lead to nonreportable cfDNA sequencies, the presence of an unreportable NIPT with a normal fetus can be associated with an increased risk of benign tumors (e.g., fibroids) or malignant tumors in the mother [4-10]. A recent study found that women who had an unreportable cfDNA sequencing test had within 2 years of the unreported test, a variety of difference cancers: 59.6% with lymphoma, 17.3% with colorectal cancer, and 7.7% with breast cancers [4]. Other cancers found were cholangiocarcinoma, adrenocortical carcinoma, non-small cell lung cancer, pancreatic cancer, Ewing's sarcoma, and renal carcinoma [4]. Benign fibroid tumors can also cause uninterpretable cfDNA sequencing [11]. In the study by Turriff et al, they found by performing total body MRI as a screen with subsequent pathologic confirmation that 52 of 107 participants (48.6%), after excluding fetal or placental causes of a nonreportable NIPT, there were only 10 (9.3%) where the non-reportable NIPT was unexplained [4]. These 10 participants were to be followed by the group headed by Amy Turriff for the next five years [4].

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Reported here in a case where the NIPT was not reportable by 2 different laboratories in which the pregnant woman not only had a healthy baby, but so far there is no evidence of cancer 3 years from the unreportable NIPT and 2 years post-partum.

Case Report

The patient conceived at age 31 initially without any fertility treatment. At 10 weeks the NIPT was not interpretable. It was repeated 4 weeks later at a different laboratory and was still unable to be interpreted. She had within 2 months of becoming pregnant, a normal PAP smear. All ultrasounds during her pregnancy showed no suspicious ovarian lesions. General health studies, e.g., complete blood count and, comprehensive metabolic profile were all negative.

The following serum tumor markers were evaluated during her pregnancy and 1 and 2 years after delivery. CA-125, CA 15-3, CA-19.9, CA-27.29, and carcinoembryonic antigen (CEA).

Her latest mammography 2 years post-partum and transvaginal sonography were negative. A colonoscopy 1-year post-partum was negative. She also had a negative colonoscopy and a negative esophagogastroduodenoscopy 2 years post-partum which were negative. She has had yearly skin exams by a dermatologist, also with negative findings. A pelvic ultrasound 2 years post-partum showed no ovarian lesions or fibroid tumors and normal endometrial thickness for mid follicular phase. Her latest pap smear was normal.

The patient had a family history of breast, prostate, brain (glioblastoma multiforme) and leukemia. The only family member with cancer at an early age was a sister with breast cancer in her mid-thirties. Nevertheless, two years post-partum the patient was approved by her insurance carrier to have the 48 gene My Risk gene panel. There were no mutations detected. The genes evaluated were: APC, ATM, AXIN2, BAP1, BARDI, BRCA1, BRCA2, BMPRIA, BRIPI, CDH1, CDK4, CDKN2A, CHEK2, CTNNAI, EGFR, EPCAM, FH, FLCN, GREMI, HOXB13, MENI, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTIH, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TERT, TP53, TSC1, TSC2, VHL

She has not had a total body MRI as performed in the aforementioned study by Turriff et al because her insurance carrier denied financial coverage, and it was too expensive for the patient to pay out of pocket for the procedure. Repeat tumor markers 2 years post-partum are still negative.

Discussion

In the study by Turriff et al 34 of 52 patients with cancer had at least one tumor marker present. Fourteen of the 55 patients without detectable cancer had a tumor marker present. This means the possibility that cancer was present but was not able to be detected as yet [4]. They did not state if any of the 14 patients with cancer markers present without detectable cancer (at least as yet) were in the group of 10 who had the NIPT that could not be analyzed where there was no other explanation, e.g. benign tumors, (e.g., fibroids) or fetal/placental abnormalities. The patient that we described would be similar to the 10 patients that did not have a known cause of the cell free DNA sequencing that could not be interpreted. These 10 represented less than 10% of the participants. We do not know, as yet, if any of these 10 patients were found to have a type of cancer 2 years post-partum. It is not clear what percent, if any, of these 10 patients, where cancer could not be found, were positive for a tumor marker. Thus, our case may be the first reported case of a woman whose NIPT was not able to be interpreted, who did not have a cancer, or some other factor known to cause inability to interpret the NIPT, who still does not show evidence of cancer 2 years post-partum. She may be the first to also demonstrate no cancer predisposition by evaluating 48 genes that are associated with a higher risk of developing cancer in the future. Perhaps there are still some factors unknown at this time that can interfere with the interpretation of the NIPT in pregnant women.

Conflict of Interest: None

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