Comparing maternal malignancies and multiple aneuploidies on prenatal cell-free DNA (cfDNA)

I. Introduction

Maternal malignancies are a rare cause of prenatal cfDNA screening results that are non-reportable or discordant for fetal status. Although prenatal cfDNA screening is not currently designed nor validated to detect neoplasms, cases associated with maternal malignancies do rarely occur (~1 in 10,000 samples in our laboratory), creating challenges for both the clinician and laboratory. With the advent of prenatal genome-wide cfDNA screening, a handful of cases have identified an increased risk for multiple aneuploidies in a pregnancy, which may raise concomitant concern for a neoplasm. However, data from these samples is often distinct from cases of known maternal malignancy.

II. Methods

Maternal blood samples submitted MaterniT® GENOME genome-wide cfDNA analysis at Sequenom Laboratories® were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing. Sequencing data were analyzed using an algorithm to detect trisomies and sub-chromosomal, genome-wide events 7 Mb and larger.

IV. Discussion

Results suggestive of multiple aneuploidies in cfDNA screening are rare but challenging. Such results in an ongoing pregnancy are most likely associated with placental mosaicism which is reflected in the laboratory reports. While malignancy cannot be ruled out with any result, cases in which maternal neoplasm is present often look distinctly different. As shown in cases 3, 4, and 5, the data is globally abnormal with aberrations throughout the genome. The raw data appears chaotic with multiple areas that are grossly over or underrepresented. Such a pattern is highly unusual in the context of cfDNA screening for fetal chromosome abnormalities. Currently, cfDNA screening during pregnancy is not validated to detect or rule out cancer; however, this understanding of differences in laboratory data may help clinicians navigate these complex results. The availability of raw data from the entire genome, such as is available in cfDNA screening technologies that utilize genome-wide sequencing, can provide both the laboratory and clinician valuable insight that may not be available with a targeted approach. The laboratory should consider malignancy as a possible etiology for non-reportable results with unusual data and discuss this consideration with the ordering provider. While such results are rare, cfDNA screening for fetal chromosome abnormalities may reveal unexpected information, much like other genetic tests and providers may wish to include this information in their pre-test counseling.

III. Results

In data suggestive of multiple aneuploidy, events are generally confined to specific chromosomes, appear as full trisomies, and are consistent with the sample’s expected fetal representation. These have been reported out by the laboratory as positive for multiple aneuploidy. Conversely, the case examples shown here with malignancy known or later confirmed were reported out as non-reportable (NR) due to their chaotic appearance and genome-wide aberrant sequencing data. Usually, cases with such unusual data that receive a non-reportable result prompt a phone call from the laboratory to the ordering provider to discuss these concerns about the data and any additional clinical information that may not have been provided on the test requisition form.

Figure 1: An example of a normal 50 kb trace from a “negative” MaterniT GENOME result. Note the relatively flat horizontal orange line throughout the trace.

Case 1:

Reason for referral: Maternal age
MaterniT GENOME result: Positive for trisomy 13, 15, and 20 (see Figure 2)
Amniocentesis: Normal karyotype
Maternal blood chromosomes: Normal
Nuchal translucency: Normal
First trimester serum analytes: Normal
Fetal anatomy survey: Normal at 20 weeks
Follow-up ultrasound: Severe oligohydramnios, cardiomegaly, inferior vena cava (IVC) dilatation, growth at 50th percentile at 51 weeks
Outcome: Delivered outside of practice and additional outcome information is unavailable.

Case 2:

Reason for referral: Maternal age
MaterniT GENOME result: Positive for trisomy 8 and 22
Amniocentesis: Normal karyotype and mosaicism
Nuchal translucency: Normal
Outcome: Uneventful delivery at term, no further testing.

Case 3:

Reason for referral: Personal/family history of a chromosome abnormality
MaterniT GENOME result: Non-reportable; globally aberrant sequencing data discussed with clinician.

Case 4:

Reason for referral: Recent breast cancer diagnosis
MaterniT GENOME result: Non-reportable; discussed with provider that known maternal malignancy precluded fetal assessment.

Case 5:

Reason for referral: Maternal age
MaterniT GENOME result: Non-reportable; globally aberrant sequencing data discussed with clinician.

V. References