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Hyperglycosylated hCG in the management of quiescent and chemorefractory gestational trophoblastic diseases

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ABSTRACT

Introduction. The literature shows that hyperglycosylated hCG is the invasion stimulus in malignant gestational trophoblastic diseases. The USA hCG Reference Service has characterized 2 gestational trophoblastic disease conditions marked by low proportion of hyperglycosylated hCG. These are quiescent gestational trophoblastic disease, defined as inactive or benign invasive disease, and minimally invasive gestational trophoblastic disease, defined as slow growing or chemorefractory disease with hCG increasing very slowly (doubling rate 2–6 weeks). Here we examine the USA hCG Reference Service experience with both diseases.

Methods. Patient were referred to the USA hCG Reference Service, 133 cases shown to have quiescent gestational trophoblastic disease, 35 cases with aggressive and 30 with minimally invasive gestational trophoblastic disease.

Results. Quiescent or inactive gestational trophoblastic disease was demonstrated in 133 women. In 127 of these cases, no hyperglycosylated hCG was detected, and in 6 cases 4–27% hyperglycosylated hCG was detected. This is quiescent or inactive disease.

Only 1 of 35 cases with aggressive gestational trophoblastic disease (>40% hyperglycosylated hCG) was chemorefractory. In contrast, 30 of 30 minimally invasive cases (<40% hyperglycosylated hCG) were chemorefractory. In chemorefractory cases hyperglycosylated hCG ranged from <1% to 39% of total hCG. The USA hCG Reference Service showed that proportions hyperglycosylated hCG significantly increases as total hCG rises. They recommended in minimally invasive cases to wait to hCG was >3000 IU/L before commencing chemotherapy. This was successful in 10 of 10 minimally invasive cases.

Discussion. Measurement of hyperglycosylated hCG or invasiveness is a critical step in management of invasive gestational trophoblastic disease. Quiescent of inactive gestational trophoblastic disease requires no therapy. Minimally invasive disease in chemorefractory. The USA hCG Reference Service experience suggests waiting until hCG exceeds 3000 IU/L before commencing any chemotherapy.

Introduction

Low level hCG (human chorionic gonadotropin) plateaus outside of pregnancy can pose a difficult management dilemma for health care providers. As ELISA (Enzyme-linked immuno-spectrometric assay) assays evolved in the late 1990s, false positive hCG test results due to interfering heterophile antibodies were described and became a common cause for referral to the USA hCG Reference Service. Between 1999 and 2003 we consulted and subsequently reported many false positive hCG cases [1–4]. As this phenomenon became better recognized, assays were corrected and practitioners became more confident in making the diagnosis. Today, we will consult on only 4 to 5 false positive cases each year. However, our group continues to receive many requests per year to evaluate persistent low level hCG cases. Between 2002 and 2003 we dealt with many cases of assumed false positive hCG tests by physicians. The problem with these cases was that they were truly positive for hCG, their only oddity was the absence of hyperglycosylated hCG [5,6]. This led to the discovery of quiescent gestational trophoblastic disease in 2003. Today we look carefully at the cases with very low hyperglycosylated hCG and observe two disorders, quiescent gestational trophoblastic disease and minimally invasive gestational trophoblastic disease [7]. The USA hCG Reference Service experience with these two disorders is presented here.

Quiescent GTD (gestational trophoblastic disease) and minimally invasive GTD represent biologic phases of GTD diagnosed by clinical behavior and a biomarker signature. Critical to both disorders is the presence of minimal or absent hyperglycosylated hCG. As published by multiple authors, hyperglycosylated hCG is a variant of regular hCG with double size O-linked sugar units and larger triantennary N-linked sugar units boosting the size of hCG from 36,700 to

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>40,000 molecular weight. It acts as an autocrine growth factor or cytokine to promote cytotrophoblast cell invasion and malignancy as occurs in implantation of pregnancy and in all invasion cases by trophoblast cells [8–13]. Quiescent disease arises from highly differentiated trophoblast cells. Because of the minimal presence or absence of cytotrophoblast cells it does not produce hyperglycosylated hCG and is a stable non-malignant non-invasive condition.

We have noticed though the years that choriocarcinoma, GTN (gestational trophoblastic neoplasm, choriocarcinoma without pathology) and invasive mole can all be conditions that present with low proportions of hyperglycosylated hCG and commonly slow growing chemorefractory conditions. Based on follow-up data, we have discovered that avoiding therapy in these cases and allowing patients to advance to an hCG levels of approximately 3000 IU/L permits the advancement of the cytotrophoblast proportions of trophoblasts which elevate the percent of hyperglycosylated hCG [7]. Patients then have a better likelihood of complete response from chemotherapy [7]. We call this group of conditions minimally invasive gestational trophoblastic diseases. As the spectrum of GTD expands, the biomarker evaluation becomes more difficult to interpret. The problem now is that low concentrations of hyperglycosylated hCG overlap in quiescent and minimally invasive conditions. We present both disorders and their overlapping hyperglycosylated hCG results here.

Methods

The USA hCG Reference Service is a unique one-of-a-kind referral service specializing in gestational trophoblastic diseases and cases of positive hCG outside of pregnancy. They examine patients records and serum and urine samples, measuring specifically total hCG, hyperglycosylated hCG, free β-subunit, β-core fragment, nicked hCG, intact hCG with the β-subunit C-terminal peptide and intact hCG without the C-terminal peptide, luteinizing hormone and follicle stimulating hormone. From the patient records and the test results a formal clinical report with suggested diagnoses and management is prepared. The USA hCG Reference Service is certified by the CLIA (32D0972561) and constancy is monitored by the College of American Pathologists (7176750-01).

We measure total hCG in serum and urine using the Siemens Immulite 1000 automated platform immunometric assay. This assay detects regular hCG, hyperglycosylated hCG, free β-subunit and nicked hCG equally on an equimolar basis. Most laboratory assays used by different laboratories throughout the world measure these three forms of hCG. The Siemens Immulite 1000 also detects β-core fragment at one quarter of the molar concentration than it detects regular hCG [14]. As demonstrated, this assay detects serum and urine hCG equally, with similar sensitivity (1.0–2000 mIU/ml), with no requirement for making any adjustments in the assay [15].

We measure hyperglycosylated hCG using a microtiter plate assay. Plates are coated with monoclonal antibody B152 for capturing hyperglycosylated hCG only. After a 4-h incubation at room temperature, the plate is washed and the tracer antibody monoclonal antibody 2009 labeled with peroxidase (Medix Inc., Division of Genzyme Inc., Norwalk CT) is added. After a further 2 h incubation, enzyme is reacted with the substrate and the concentrations of hCG are measured from a quadruplicate standard curve. We use the C5 standard for hyperglycosylated hCG [14]. An internal control is added to the hyperglycosylated hCG assay which is assessed daily and recorded according to CLIA regulations. The Service has consulted on 584 cases over 10 years. The Service has followed the guidelines from the University of New Mexico Human Research Review Committee the Internal Review Board (protocols 99-349, 02-548 and 04-132), concerning obtainment of data, patient confidentiality and reporting data.

All USA hCG Reference Service data are stored in a Microsoft Excel 2007 spreadsheet where it analyzed for mean, median, standard deviation and t test. This spreadsheet, as it is updated, is shared with the review board each year.

Results

From 1999 to the present, the USA hCG Reference Service has observed 133 cases diagnosed as quiescent or benign/inactive gestational trophoblastic disease (Fig. 1). All cases seemingly had low levels of hCG persisting for 3 months or longer and a history of documented gestational trophoblastic disease, 7 cases followed chemotherapy for choriocarcinoma, 62 cases followed evacuation or chemotherapy for complete hydatidiform mole, 9 cases followed the disappearance of hCG after treatment for ectopic pregnancy (assumed hydatidiform mole), 11 cases followed chemotherapy for GTN, 31 cases followed disappearance of hCG after miscarriage or spontaneous abortion (assumed hydatidiform mole), 8 cases followed evacuation or chemotherapy for partial mole, and 5 cases followed termination of pregnancy (assumed hydatidiform mole) (Fig. 1). In all cases of quiescent gestational trophoblastic disease diagnosed by the USA hCG Reference Service, all therapy was subsequently halted. Up until the referral to the USA hCG Reference Service, 55 of the 133 cases (41%) received ineffective chemotherapy with some patients receiving multiple regimens, including methotrexate ($n=44$), actinomycin D ($n=13$), EMA-CO (etoposide, methotrexate, actinomycinD, cycled with cylophoshamide and onvocin) ($n=8$), EMA-EP (etoposide, methotrexate, actinomycinD, cycled with etoposide and platinin) ($n=2$) or carboplatin, taxol and BEP combination therapy ($n=1$). No chemotherapy proved effective for this slow growing inactive disease.

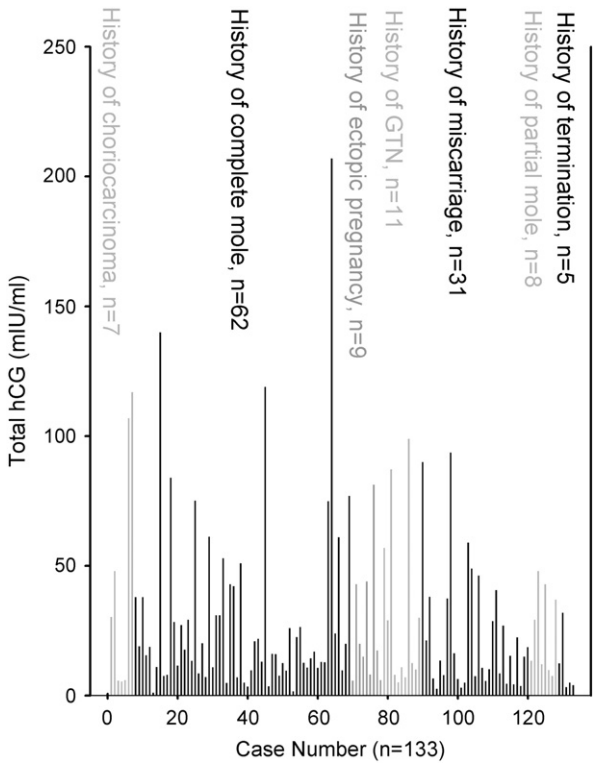

Fig. 1. Quiescent gestational trophoblastic disease as diagnosed by the USA hCG Reference Service, 133 cases. All cases seemingly had low levels of hCG persisting for 3 months or longer and a history of documented or presumed gestational trophoblastic disease, 7 cases followed chemotherapy for choriocarcinoma, 62 cases followed evacuation or chemotherapy for complete hydatidiform mole, 9 cases followed the disappearance of hCG after treatment for ectopic pregnancy (assumed hydatidiform mole), 11 cases followed chemotherapy for GTN, 31 cases followed disappearance of hCG after miscarriage or spontaneous abortion (assumed hydatidiform mole), 8 cases followed evacuation or chemotherapy for partial mole, and 5 cases followed termination of pregnancy (assumed hydatidiform mole).