Gynecologic Oncology Reports 10 (2014) 47–48

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case Report

# Familial HCG syndrome: A diagnostic challenge

Alvin Tan [a,*], Anna-Marie Van der Merwe [b], Xunjun Low [c], Kathryn Chrystal [a]

[a] Department of Medical Oncology, Auckland City Hospital, New Zealand
[b] Department of Gynaecology and Obstetrics, Middlemore Hospital, New Zealand
[c] Department of Pathology, Middlemore Hospital, New Zealand

ARTICLE INFO

*Article history:*
Received 16 April 2014
Accepted 21 May 2014
Available online 2 June 2014

*Keywords:*
Familial HCG syndrome
Gestational trophoblastic disease
Chemotherapy
Ectopic pregnancy

## Introduction

Familial hCG syndrome is a rare condition and was first described in 2009.(Cole, 2012) Affected family members produce a mutated form of hCG with multiple alterations in the C-Terminal Peptide region of the hCG molecule, resulting in persistently elevated Human Chorionic Gonadotropin (hCG) levels. The site of origin of the mutated hCG is still unknown but does not appear to arise from trophoblastic tissue or the pituitary. The syndrome does not have clinical sequelae; in particular, it does not appear to affect fertility.

We present a case of a 34-year-old woman diagnosed with familial hCG syndrome which we believe is the first to be reported in New Zealand.

## Case report

A 34-year-old Polynesian woman, presented to the Gynaecology services with intermittent vaginal bleeding and a raised total serum hCG of 96 IU/L (Abbott Architect, Abbott Laboratories. Reference Range <5 IU/L) which was confirmed on weekly serial hCG levels over the preceding month. She did not have a significant past medical history or family history and was not on regular medications. Her reproductive history included four live births (the most recent was a term pregnancy six months prior to presentation), a spontaneous miscarriage and a termination of pregnancy. Histological analyses of the products of conception for the latter were not available.

Clinical examination was unremarkable apart from a palpable right breast lump, shown to be consistent with lactational change on mammogram and ultrasound investigation. Pelvic ultrasound did not reveal an obvious ectopic pregnancy or underlying mass. She underwent a laparoscopy and dilation and curettage to exclude an ectopic pregnancy or malignancy. The histology from endometrial curettings was normal. The patient elected to have bilateral salpingectomies performed at the same time as her family was complete.

The initial working diagnosis was of an occult ectopic pregnancy and the patient received two doses of intramuscular methotrexate. The total hCG levels did not change and she was referred to the Gynaecologic Oncology Multi-disciplinary Meeting (MDM). The outcome of the MDM review was a referral to the Medical Oncology services with a presumed diagnosis of gestational trophoblastic neoplasia (GTN) — persistently raised total hCG for more than six months following an antecedent term pregnancy. Repeat imaging with a transvaginal ultrasound, CT body and MRI head did not reveal any abnormal findings apart from an incidental finding of an enlarged right axillary node which was shown to be a reactive node on biopsy.

Treatment options for gestational trophoblastic neoplasia were discussed, including systemic chemotherapy with methotrexate or total hysterectomy. The rarer diagnosis of placental site trophoblastic tumour (PSTT) was considered, for which primary treatment is a radical hysterectomy. The patient was reluctant to undergo chemotherapy and because of the possibility of occult PSTT, she was referred for a total hysterectomy.

During the diagnostic work-up, serum and urine samples were sent to the USA hCG Reference Service based in the United States for further analysis. This revealed a raised total hCG in both serum and urine (206 IU/L and of 215 IU/L respectively, Siemens Immulite, Siemens Healthcare Global. Reference Range <5 IU/L), excluding a false positive hCG test. Additionally, the follicle stimulating hormone level of 4.6 IU/L (Siemens Immulite, Siemens Healthcare Global) was within normal range for a woman with normal menstrual cycle and excluded a pituitary source for hCG. She had a low hyperglycosylated hCG level of <5.5 IU/L (microtiter plate assay, USA hCG Reference Service. Reference Range <5.5 IU/L) or <2.7% of total hCG which excluded active gestational trophoblastic disease (GTD) although quiescent GTD remained a differential (Cole et al., 2006).

In the absence of radiological and histological evidence for occult malignancy and given the initial laboratory findings, a rarer differential

* Corresponding author at: Level 1 Offices, Building 7, Auckland City Hospital, Auckland, New Zealand. Fax: +64 93074984.
*E-mail address:* aatbt@hotmail.com (A. Tan).

http://dx.doi.org/10.1016/j.gynor.2014.05.005
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**Table 1**
Plasma total hCG results for index case and her four children.

| | Sex | Age | Abbott Architect Total hCG IU/L | Roche Cobas Total hCG IU/L |
|---|---|---|---|---|
| Patient | F | 34 years | 82 | 120 |
| Child 1 | M | 12 years | 119 | 180 |
| Child 2 | F | 6 years | 101 | 140 |
| Child 3 | M | 4 years | 115 | 160 |
| Child 4 | F | 8 mths | 133 | 190 |

of familial hCG syndrome was thus considered. The Siemens Immulite assay detects hCG missing the ß-subunit C-terminal peptide segment (CTP), nicked hCG and hyperglycosylated hCG equally. Her total hCG measured with the Siemens Immulite assay was 206 IU/L. The Siemens Dimension assay which utilises carbohydrate-sensitive detection antibodies directed towards the ß-subunit CTP alone gave a lower total hCG level of 87 IU/L. A subtraction of the two values (206 IU/L − 87 IU/L), representing the amount of total hCG molecules missing the CTP, gave a raised value of 119 IU/L. The Johnson and Johnson non-CTP based hCG assay, which detects hCG free ß-subunit levels, returned a level of 175 IU/L, equivalent to 85% of the total hCG (206 IU/L). The predominance of free ß-subunit is a hallmark for the familial hCG syndrome. (Cole, 2012).

We were then able to obtain heparin plasma samples from her four children and tested them with the Abbott Architect and Roche Cobas total hCG assays (Table 1). All four children had raised total hCG levels. The free ß-subunit predominance, the raised total of hCG molecules missing the C-terminal peptide, the elevated hCG levels in all her children and the absence of hyperglycosylated hCG were in keeping with the diagnosis of familial hCG syndrome.(Cole, 2012) The patient was counselled that she did not require a hysterectomy nor further oncological treatment.

## Discussion

We believe this to be the first case of familial hCG syndrome reported in New Zealand. It is important to note that familial hCG syndrome is rare, with only 10 cases reported in published literature.(Cole, 2012) To date, The USA hCG Reference Service has observed only 25 cases worldwide (L. Cole, Personal communication, August 20th 2013).

More common causes of a raised hCG such as pregnancy, gestational trophoblastic disease, germ cell malignancies and drug doping must be excluded before considering a diagnosis of familial hCG syndrome. However, it is important to consider this diagnosis, in order to prevent unnecessary oncological treatment in the setting of presumed gestational trophoblastic neoplasia or germ cell tumours without radiological or histological evidence of malignancy, as well as to avoid social stigma in the setting of presumed drug doping in sports. In particular, systemic chemotherapy causes acute toxicity and is associated with long-term sequelae including secondary malignancies, fertility issues and increased risk for metabolic syndrome. Of the ten cases reported, four patients received methotrexate, two patients received other systemic chemotherapy and one patient underwent a total hysterectomy before a diagnosis of familial hCG syndrome was made. (Cole, 2012) Children of affected families would also be spared unnecessary investigations in the setting of persistently raised but low levels of total HCG following a pregnancy or on incidental finding.

The differential diagnosis for this patient on presentation to Medical Oncology included GTN, PSTT or occult malignancy. PSTT, a rare variant of gestational trophoblastic disease, may present with a persistent mild elevation in hCG, often lower than that seen in typical gestational trophoblastic neoplasia. It can have a latent onset after gestation but has the potential for distant metastases which are usually not responsive to systemic chemotherapy at advanced stages (Shih and Kurman, 2001; Kim, 2003). If PSTT is confined to the uterus, standard treatment is with total hysterectomy with a curative intent. Although uncommon, malignancies other than germ cell tumours can also present with elevated hCG levels such as with upper gastrointestinal, lung and breast cancer. (Kenny and McAleer, 2004; Szturmowicz et al., 1995; Reisenbichler et al., 2009).

The USA hCG Reference Service and their different hCG assays played a key role in the discovery of her high proportion of hCG molecules either missing the CTP or having a mutated form of CTP. Although the free ß-subunit predominance is a hallmark of the familial hCG syndrome, this can also be present in PSTT and does not exclude PSTT as a differential. However, the hyperglycosylated hCG level, usually raised in active gestational trophoblastic disease, (Cole et al., 2006) was low in our index case, reflecting the absence or reduced number of invasive cytotrophoblast cells.

The testing and confirmatory results of raised total hCG in all four children then led to our diagnosis of familial hCG syndrome. The inheritance pattern for familial hCG syndrome is suggestive of a dominant gene with high penetrance; all four children of our index patient were affected. The syndrome did not impact upon this patient's fertility, consistent with published literature. (Cole, 2012) There is active research into the specific gene mutations which drive the production of the mutated hCG molecules internationally (Ulf-Hakan and Henrik, 2013) and further serum and urine samples will be obtained from our patient's immediate and extended family to contribute to this work.

In summary, a multidisciplinary approach and additional hCG assays conducted by the USA hCG reference service were pivotal in making the diagnosis of this rare syndrome, without which our patient may have had unnecessary oncological treatment.

### Conflict of interest

The authors declare that they have no conflict of interests.

## References

Cole, L.A., 2012. Familial HCG, syndrome. J. Reprod. Immunol. 93, 52–57.
Cole, L.A., Butler, S.A., Khanlian, S.A., Giddings, A., Muller, C.Y., Seckl, M.J., Kohorn, E., 2006. Gestational trophoblastic disease: 2. Hyperglycosylated hCG as a reliable marker of active neoplasia. Gynaecol. Oncol. 102, 151–159.
Kenny, L., McAleer, J., 2004. Elevated serum beta-hCG due to a tumour of unknown origin. Ulster Med. J. 73 (1), 47–49.
Kim, S.J., 2003. Placental site trophoblastic tumour. Best Pract. Res. Clin. Obstet. Gynaecol. 17 (6), 969–984.
Reisenbichler, E.S., Krontiras, H., Hameed, O., 2009. Beta-human chorionic gonadotropin production associated with phyllodes tumour of the breast: an unusual paraneoplastic phenomenon. Breast J. 15 (5), 527–530.
Shih, I.M., Kurman, R.J., 2001. The pathology of intermediate trophoblastic tumours and tumor-like lesions. Int. J. Gynaecol. Pathol. 20 (1), 31–47.
Szturmowicz, M., Wiatr, E., Sakowicz, A., Slodkowska, J., Roszkowski, K., et al., 1995. The role of human chorionic gonadotroprin beta subunit elevation in small-cell lung cancer patients. J. Cancer Res. Clin. Oncol. 121 (5), 309–312.
Ulf-Hakan, Stenman, Henrik, Alfthan, 2013. Determination of human chorionic gonadotropin. Clin. Endocrinol. Metab. 27 (6), 783–793.