CASE REPORT

When cancer patients suddenly have a positive pregnancy test

Daniela Groza,^{1,2} Donat Duerr,³ Mathias Schmid,⁴ Beatrix Boesch⁴

¹Internal Medicine, Stadtspital Triemli, Zurich, Switzerland
²Oncology, Stadtspital Triemli, Zurich, Switzerland

³Department of Oncology, Stadtspital Triemli, Zurich, Switzerland

⁴Stadtspital Triemli, Zurich, Switzerland

Correspondence to

Dr. Daniela Groza, dr.daniela.groza@gmail.com

Accepted 29 May 2017

SUMMARY

We present the case of non-small cell lung cancer (NSCLC) in a 48-year-old woman with an active history of smoking. The patient initially presented to her general practitioner with a progressive swelling on the neck. Further investigations diagnosed a metastatic lung tumour, and palliative chemotherapy was started. After 5 months of treatment, by newly reported amenorrhoea, cautiously before a restaging CT scan of the abdomen, a pregnancy test was performed and was positive. Both the gynaecological examination and the hormonal panel yielded no signs of pregnancy. Immunohistochemically, staining of the tumour was strongly positive for β -subunit of human chorionic gonadotropin (β -hCG) suggesting that the tumour was responsible for high β -hCG levels.

Paraneoplastic β -hCG secretion from adenocarcinomas is rare. In the literature, only a few such cases have been reported. Previous studies suggested that the ability to secrete β -hCG in tumours may correlate to some extent to chemoresistance and thus, to a worse prognosis.

BACKGROUND

Human chorionic gonadotropin (hCG) is a 38 kDa glycoprotein hormone comprising two subunits, α and β joined non-covalently, which physiologically is produced by syncytiotrophoblasts in the placenta during pregnancy. Its most well-known function is at the beginning of the pregnancy, in promoting the conservation of the corpus luteum and thus, the secretion of the hormone progesterone. The latter, due to its role in converting the endometrium to its secretory stage, plays an essential role in the growing of the fetus.¹ hCG can also be secreted by tumours, mainly by germ cell tumours and gestational trophoblastic neoplasias, but also by a number of tumours of non-endocrine origin and thus can be used as a tumour marker.^{1,2} hCG has several variants among which regular hCG, hyperglycosylated hCG and the free β -subunit of hyperglycosylated hCG are the most researched. Each of these variants has different physiological functions.¹

Extravillous invasive cytotrophoblast cells secrete the variant hyperglycosylated hCG, which has shown to promote cell growth and malignancy;^{1,2} therefore, hyperglycosylated hCG can be a marker for gestational trophoblastic neoplasia and testicular germ cell malignancies.^{1,3} hCG can be measured in blood and urine. In order to reduce false positives results (mistaking hCG with LH and FSH), most tests use a monoclonal antibody, which is specific to

the β -subunit of hCG (β -hCG).^{4,5} However, this test cannot distinguish between normal hCG, hyperglycosylated hCG and the free β -subunit of hyperglycosylated hCG.

Other non-trophoblastic malignancies such as non-small cell cancer of the lung,^{6,7} gastric carcinoma,⁸ renal cell carcinoma,⁹ squamous cell carcinoma of the head and neck,¹⁰ ovarian cancer¹¹ and leiomyosarcoma¹² can produce a hyperglycosylated free β -hCG, which has a role in facilitating cancer cell survival and proliferation by acting as an auto-crine factor antagonising apoptosis.¹

Only a few reports of paraneoplastic β -hCG secretion can be found in the literature for several different cancers. However, as far as we researched, paraneoplastic β -hCG secretion accompanied by onset of amenorrhoea after months of chemotherapy has never been reported.

CASE PRESENTATION

A 49-year-old woman with an active tobacco addiction presented to her general practitioner (GP) with a progressive swelling on her neck bilaterally, which she first noted several months ago. Chest examination revealed dullness to percussion of the right upper zone with associated decreased breath sound.

Her medical history included an abortion on request in 2004, a diagnosis of leiomyoma uteri in 2007 for which she underwent a hysteroscopic myomectomy. She was mother of one child, born in 2001 through caesarean section. The last gynaecological examination 1 month prior to the GP consultation revealed no abnormal findings and no pregnancy. The patient had regular menses. She had smoked 20 cigarettes daily for a period of 32 years. She did not drink alcohol and had no allergy.

A sonography, which revealed a bilateral cervical and supraclavicular adenopathy, was followed by a fine needle punctation/biopsy of the right supraclavicular lymph node. An adenocarcinoma was diagnosed. Molecular tests were negative for ALK, KRAS, BRAF, Her-2 and EGFR-mutations. Consequently, the patient was referred to our hospital for further diagnosis and treatment. The computer tomography revealed a mass in the right upper lobe (30×25 mm) (figure 1A,B) with extensive bilateral lymphadenopathy as well as right-sided pleural metastases and a pericardial effusion (approximately 1.3 cm). Palliative chemotherapy with carboplatin and pemetrexed was started and a pericardial puncture was performed. After four cycles of

CrossMark

To cite: Groza D, Duerr D, Schmid M, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220493

Figure 1 CT of the thorax showing the tumour in the right upper pulmonary lobe. (A) Longitudinal section; (B) transverse section.

chemotherapy, the second line chemotherapy with docetaxel had to be initiated due to tumour progression.

After three cycles of docetaxel, the patient presented to the emergency room with a tonic-clonic seizure. She also reported amenorrhoea for 2 months. Cautiously before the restaging CT of the abdomen, a pregnancy test was performed and was positive. The quantitative β -hCG level in blood was 1161 mIU/mL (in our laboratory normal upper limit 1 mIU/mL in non-pregnant woman). Subsequently, the FSH, oestradiol and LH were measured and followed by a gynaecological examination, all of which ruled out a pregnancy. An immunohistochemically staining of the malignant recurrent pericardial effusion was strongly positive for β -hCG (figure 2A,B), supporting the hypothesis of the paraneoplastic β -hCG secretion.

A CT of the head showed brain metastases as morphological correlate for the tonic-clonic seizure; the CT of the chest and abdomen demonstrated a general tumour progression. Palliative radiotherapy of the brain and of the primary tumour as well as a therapy with dexamethasone were started. The levels of β -hCG decreased; 2 months later, we registered 25 mIU/mL. Nevertheless, the patient deceased at home several weeks later.

DISCUSSION

Lung cancer is the most common cause of worldwide cancer mortality in men and women, causing approximately 1.7 million deaths per year. Tobacco use is, by far, the most important risk factor for lung cancer, being responsible for 70% of global lung cancer deaths.¹³

hCG is a hormone secreted by the syncytiotrophoblast cells in the placenta after implantation of the fetus.⁵ Physiologically, it stimulates the progesterone secretion and inhibits the menstruation. In the absence of pregnancy, hCG can also be produced by germ cell tumours, gestational trophoblastic neoplasias and, rarely, in non-endocrine tumours.

Figure 2 (A,B) Cytological examination from pericardial effusion with plenty of cell clusters from adenocarcinoma. Carcinoma cells positive for β -subunit of human chorionic gonadotropin

In our described case, gynaecological examination as well as luteinising hormone and follicle stimulating hormone measurements excluded pregnancy. The immunochemistry staining for β -hCG of the tumour tissue was positive suggesting all the β -hCG in the blood and urine was produced by the pulmonary adenocarcinoma itself. This is a rarely seen phenomenon. To our best knowledge, there are less than 100 cases reports of paraneoplastic β -hCG secretion in the English literature, out of which only a handful being linked to pulmonary carcinomas.^{14–17} In a study done over a period of 5 years by pathologist Lee *et al* from the University School of Medicine in Seoul, Korea, it was stated that the prevalence of β -hCG producing pulmonary carcinoma is 0.002% (6/2790 of the cases).¹⁵ According to another study done by Szturmowicz *et al*, elevated β -hCG levels seem to be more frequent in adenocarcinoma than in other non-small cell lung cancer (NSCLC) (although the differences are not relevant) and in patients with advanced lung cancers.¹⁸ Except for one postmenopausal patient, in all reported cases of β -hCG secretions by lung tumours, the patients *initially* presented with gynaecological symptoms (amenorrhoea, uterine bleeding). Levels of β -hCG were always very high (ranges between 128 and 11,211 mIU/mL, normal values in the study <0.5 mIU/mL).^{14 15 17 18}

The pathophysiological role of β -hCG is not investigated very well. Some studies indicated that ectopic expression of β -hCG in tumours may act as a growth factor by blocking apoptosis.^{18 19} This could at least partly elucidate why ectopic β -hCG secretion from tumour tissue is connected with resistance to chemotherapy and poor prognosis.

In our case, the patient had regular menses and normal gynaecological findings at the time of the tumour diagnosis. The start of amenorrhoea occurred with the start of second line of chemotherapy with docetaxel. In the general context, we suspect that the onset of amenorrhoea was linked to the chemotherapy itself as well as to the reduced performance status of our patient at that time point. However, we cannot exclude that the β -hCG produced by the tumour had an impact on the amenorrhoea. As already mentioned, most cases described in the literature presented gynaecological symptoms such as amenorrhoea or uterine bleeding. We suspect that these symptoms were probably the reason a pregnancy test has been ordered. However, this should be further investigated.

The fact that our patient died 3 months after measurement of elevated β -hCG supports the general observation that paraneoplastic β -hCG production is accompanied by an unfavourable prognosis. Interestingly, in our case, the level of β -hCG decreased after radiation; however, the medical condition of our patient did not improve. This suggests that the lower β -hCG level did not correlate with a lower tumour load. More likely, a further dedifferentiation of the tumour and therefore a ceasing of β -hCG production occurred.

Some authors suggest introducing β -hCG measurements as a standardised tumour marker in all epithelial carcinoma. This would allow a better understanding of the exact role of β -hCG secretion in tumour prognosis and thus its therapeutic consequences.

Contributors All the authors were involved in the diagnosis and treatment of the patient. DG, under the supervision of MS, was responsible for treating the patient in the hospital setting. DD was the oncologist treating the patient in an ambulant setting. BB was the pathologist who diagnosed the cancer and the β -hCG tumour secretion.

Competing interests None declared.

Patient consent Obtained from next of kin.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Paraneoplastic β -subunit of human chorionic gonadotropin (β -hCG) secretion can occur in any cancer and in any phase of the evolution of the disease.
- ▶ β -hCG in tumours may correlate to chemoresistance and thus to an unfavourable prognosis.
- ▶ Decrease of β -hCG levels due to therapy does not seem to correlate with a lower tumour load or influence the bad prognosis.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Cole LA. New discoveries on the biology and detection of human chorionic gonadotropin. *Reprod Biol Endocrinol* 2009;7:8.
- 2 Handschuh K, Guibourdenche J, Tsatsaris V, et al. Human chorionic gonadotropin produced by the invasive trophoblast but not the villous trophoblast promotes cell invasion and is down-regulated by peroxisome proliferator-activated receptor-gamma. *Endocrinology* 2007;148:5011–9.
- 3 Cole LA, Khanlian SA, Riley JM, et al. Hyperglycosylated hCG in gestational implantation and in choriocarcinoma and testicular germ cell malignancy tumorigenesis. *J Reprod Med* 2006;51:919–25.
- 4 en.wikipedia.org/wiki/Human_chorionic_gonadotropin
- 5 "Tumor Markers Found in Blood or Urine". *American Cancer Society* (Retrieved 21 January 2014).
- 6 Yoshida J, Nagai K, Nishimura M, et al. Secretion of hCG/BhCG by squamous cell carcinoma of the lung in a 31-year-old female smoker. *Jpn J Clin Oncol* 2000;11:163–6.
- 7 Szturmowicz M, Slodkowska J, Zych J, et al. Frequency and clinical significance of beta-subunit human chorionic gonadotropin expression in non-small cell lung cancer patients. *Tumour Biol* 1999;20:99–104.
- 8 Rau B, Below C, Haensch W, et al. [Significance of serum beta-hCG as a tumor marker for stomach carcinoma]. *Langenbecks Arch Chir* 1995;380:359–64.
- 9 Mohammed Ilyas MI, Turner GD, Cranston D. Human chorionic gonadotropin-secreting clear cell renal cell carcinoma with paraneoplastic gynaecomastia. *Scand J Urol Nephrol* 2008;42:555–7.
- 10 Turner JH, Ross H, Richmon J. Secretion of beta-HCG from squamous cell carcinomas of the head and neck. *Otolaryngol Head Neck Surg* 2010;143:169–70.
- 11 Goldstein J, Pandey P, Fleming N, et al. A non-pregnant woman with elevated beta-HCG: A case of para-neoplastic syndrome in ovarian cancer. *Gynecol Oncol Rep* 2016;17:49–52.
- 12 Mansi IA, Ashley I, Glezerov V. Retroperitoneal leiomyosarcoma and enlarged epididymis associated with a positive pregnancy test. *Am J Med Sci* 2002;324:104–5.
- 13 Eriksen M, Mackay J, Ross H. *The tobacco atlas*. USA: American Cancer Society, 2012. Fourth Edition.
- 14 Wong YP, Tan GC, Aziz S, et al. Beta-human Chorionic Gonadotropin-secreting Lung Adenocarcinoma. *Malays J Med Sci* 2015;22:76–80.
- 15 Lee S, Jeong JY, Han J, et al. Pulmonary carcinoma with β -Human Chorionic Gonadotropin expression: further understanding and suggestions for this entity from six cases experience in a single Institution. *J Lung Cancer* 2011;10:44–8.
- 16 Mehta H, Bahuva R, Sadikot RT. Lung Cancer mimicking as pregnancy with pneumonia. *Lung Cancer* 2008;61:416–9.
- 17 Vicier C, Tabouret E, Tallet A, et al. BetaHCG secretion by a pulmonary adenocarcinoma. *World J Surg Oncol* 2013;11:228.
- 18 Szturmowicz M, Slodkowska J, Zych J, et al. Frequency and clinical significance of beta-subunit human chorionic gonadotropin expression in non-small cell lung cancer patients. *Tumour Biol* 1999;20:99–104.
- 19 Iles RK. Ectopic hCGbeta expression by epithelial Cancer: malignant behaviour, metastasis and inhibition of tumor cell apoptosis. *Mol Cell Endocrinol* 2007;260-262:260–2.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow