CASE REPORT

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hCG-secreting malignancies — diagnostic pitfalls

We present a case of a 34-year-old male patient referred to our Uro-oncology Department with a suspicion of a metastatic germ cell tumour, owing to enlarged left testicle and elevated \( \beta \)-hCG concentration (39 mIU/mL). Impaired performance status caused by extensive pulmonary and liver metastases, accompanied by significant lymphadenopathy, necessitated prompt management. However, a testicular tumour was excluded on ultrasound imaging; a hydrocele only was found. The \( \beta \)-hCG concentration was not increasing (37 mIU/mL). We found a diagnosis of an extragonadal germ cell tumour doubtful, and a liver biopsy was performed. Due to the patient’s quick deterioration, we decided to commence pre-phase chemotherapy with cisplatin and etoposide, which resulted in a significant clinical improvement. The pathological examination, along with immunoassays, revealed undifferentiated cholangiocarcinoma, and the patient continued chemotherapy with a biliary tract cancer regimen, i.e. cisplatin and gemcitabine. Unfortunately, the clinical response was short-lived; the disease progressed, the patient was offered best supportive care and died two months after the diagnosis.

The case underpins the literature review with respect to differential diagnosis of an elevated hCG concentration. In particular, we discuss ectopic secretion in non-trophoblastic and non-germinal malignancies and the causes of false positive assays.

**Key words:** human chorionic gonadotropin (hCG), germ cell tumour, paraneoplastic syndrome

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**ABSTRACT**

We present a case of a 34-year-old male patient referred to our Uro-oncology Department with a suspicion of a metastatic germ cell tumour, owing to enlarged left testicle and elevated \( \beta \)-hCG concentration (39 mIU/mL). Impaired performance status caused by extensive pulmonary and liver metastases, accompanied by significant lymphadenopathy, necessitated prompt management. However, a testicular tumour was excluded on ultrasound imaging; a hydrocele only was found. The \( \beta \)-hCG concentration was not increasing (37 mIU/mL). We found a diagnosis of an extragonadal germ cell tumour doubtful, and a liver biopsy was performed. Due to the patient’s quick deterioration, we decided to commence pre-phase chemotherapy with cisplatin and etoposide, which resulted in a significant clinical improvement. The pathological examination, along with immunoassays, revealed undifferentiated cholangiocarcinoma, and the patient continued chemotherapy with a biliary tract cancer regimen, i.e. cisplatin and gemcitabine. Unfortunately, the clinical response was short-lived; the disease progressed, the patient was offered best supportive care and died two months after the diagnosis.

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Introduction

Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced by trophoblast during pregnancy. In oncology, it serves as a marker of gestational trophoblastic disease (GTD) and germ cell tumours (GCT). Additionally, hCG in its various forms has been found in tissues of non-trophoblastic and non-germinal malignancies [1], where it promotes tumour growth and invasion. Serum hCG reactivity may therefore pose diagnostic difficulties.

GCTs account for the majority of malignancies in young men. Usually testicular in origin, they may also develop in the retroperitoneum, mediastinum, or cerebrum, along the body’s midline. Because the cure rate and prognosis are excellent even in the metastatic cases, the issues of prompt diagnosis and adequate treatment are of utmost importance [2, 3]. In selected patients, the diagnosis of GCT can be solely established on the basis of elevated tumour marker concentrations, i.e. \( \alpha \)-foetoprotein (AFP) and/or \( \beta \)-hCG [3]. Therefore, it is crucial to be aware of and avoid pitfalls that may mislead a physician and postpone the correct diagnosis.

We present a case of hCG-secreting cholangiocarcinoma, referred to our centre with a suspicion of GCT. Possible scenarios of paraneoplastic secretion and false positive hCG assays are also reviewed.
Case report

A 34-year-old male patient was admitted to a respiratory medicine centre with a four-month history of persistent, unproductive cough and dyspnoea, first on exertion and then at rest. A chest computed tomography (CT) scan revealed disseminated bilateral lung nodules, thickened bronchial walls, ground-glass opacity, enlarged heart, pericardial effusion (14 mm), as well as fractured sternum and 2nd left rib. Abdominal and pelvic CT scans showed abdominal and retroperitoneal lymphadenopathy (38 mm and 17 mm, respectively), multiple liver metastases (max. 40 mm), and agenesis of the left kidney. No abnormalities apart from a maxillary sinus polyp were found on CT scan of the head. Moreover, the patient gave a six-month history of left testicle enlargement; on ultrasound (US) the picture was characteristic of a testicular hydrocele, but the presence of a tumour could not be ruled out. Serum hCG concentration of 39 mIU/mL (normal < 5 mIU/mL) gave rise to a suspicion of a germ cell tumour. At this stage, in February 2019, the patient was referred to our centre.

On admission, he presented with cough and dyspnoea, ECOG performance status 2, and pulse oximetry of 88% (94% on O2). hCG concentration was 37 mIU/mL (normal < 5 mIU/mL), and α-fetoprotein (AFP) and lactate dehydrogenase (LDH) concentrations were within normal limits. Blood count and chemistry as well as coagulation parameters showed no important abnormalities. Scrotal US revealed a left testicular hydrocele (15 mL) and no suspicious tumours. Haemodynamically insignificant pericardial effusion and normal contractility of cardiac muscle (left ventricle ejection fraction of 65%) were found on echocardiography.

The case was presented at a multi-disciplinary clinical meeting. Due to a relatively low increase in hCG concentration together with massive metastases, the diagnosis of an extragonadal germ cell tumour was dubious. We agreed that a pathological diagnosis should be established; one of the liver metastases was chosen for a core biopsy.

Once the biopsy had been performed, we decided to commence pre-phase chemotherapy due to the patient’s steady clinical deterioration. Cisplatin (20 mg/m²) and etoposide (100 mg/m²) were administered on days 1–2, with prophylaxis of the acute tumour lysis syndrome (ATLS) and thromboprophylaxis. The pre-phase resulted in a rapid improvement with respect to dyspnoea and pulse oximetry (94–98% with no O2 supply).

The pathology report revealed an undifferentiated (G3) adenocarcinoma with high mitotic activity. Immunostaining was as follows: CKAE 1/3 (+), CK19 (+), CK7 (−), CK20 (−), SALL4 (−), PLAP (−), β-hCG (−), CD 30 (−), CDX2 (−). It was characteristic of cholangiocarcinoma (highly-aggressive type? — untypical lack of CK7 expression) or gastric carcinoma (Figures 1–3). Germ cell tumours were ultimately excluded. On gas-
troscopy, gastric and duodenal inflammatory lesions were biopsied; chronic gastritis/duodenitis was diagnosed pathologically.

This led to the final diagnosis of cholangiocarcinoma (TNM 8th edition: cT1cN1pM1; clinical stage IV). The chemotherapy regimen was changed to GP (gemcitabine 800–1000 mg/m² days 1, 8 and cisplatin 30 mg/m² days 1, 8; to be repeated every three weeks). Only two cycles were administered. Although substantial, the clinical improvement was short-lived. Dyspnoea recurrence and performance status decline (ECOG 4) was observed. With best supportive care, the patient died two months after the diagnosis.

Discussion

Germ cell tumours (GCT), however rare, account for the most common malignancies in males aged 15–40 years [2]. The highest incidence rates are observed in developed countries (11.8 per 100,000 in Norway) [3]. Therefore, given the patient’s age, clinical presentation, and an elevated hCG concentration, the suspicion of GCT in the patient described was justified. However, once a testicular tumour was ruled out on US, the probability of GCT decreased, because only 5% of GCT are extragonadal (EGGCT) [2]. Importantly, EGGCTs typically arise in the body’s mid-line, e.g. retroperitoneum, mediastinum, or cerebrum [2]. This, in turn, was not the case in our patient. Massive pulmonary and liver metastases were accompanied by relatively small retroperitoneal lymphadenopathy (17 mm) and no mediastinal lymphadenopathy. Still, such a presentation could have resulted from an aggressive non-seminomatous GCT, e.g. choriocarcinoma, a histological component more likely to give visceral metastases with a small or even burned-out primary testicular tumour. In this case, however, the hCG concentration would have been much higher, corresponding with the tumour burden. Overall, we considered the possible diagnosis of GCT doubtful and decided on the liver biopsy.

Some GCT patients are not fit enough to start treatment with full doses of combination chemotherapy. This usually stems from a massive tumour volume with significantly elevated marker concentrations and a high risk of bleeding (e.g. choriocarcinoma) as well as impaired performance status and organ dysfunction. To avoid fatal complications, a pre-phase chemotherapy should be administered, for instance 2–3 days of cisplatin and etoposide or single-agent low-AUC carboplatin. Once the patient has improved, full-dose chemotherapy must be started [3]. Understandably, there are scarce data available on this topic. We decided to administer such induction treatment to our patient, without liver biopsy results, given his rapidly deteriorating status. In case of GCT diagnosis, we would have continued with four cycles of standard BEP or VIP chemotherapy. Even with another tumour histology, which finally proved the case, cisplatin and etoposide would have been likely to decrease the tumour volume before adapting further treatment to the pathology outcome.

hCG is a protein composed of two subunits: α, common to all glycoprotein hormones; and β, responsible for its specific structure and activity [1]. Different forms of the hormone are encountered in vivo, e.g. the native hCG, hyperglycosylated hCG (hyp-hCG), nicked-hCG, or the free β-subunit. Apart from the role played in pregnancy, hCG is capable of promoting angiogenesis, suppressing macrophage activity, blocking apoptosis (hyp-hCG), promoting choriocarcinoma invasion, as well as enhancing malignant transformation, growth, and invasion of non-trophoblastic malignancies (β-subunit and hyp-hCG) [1]. The hormone variants may be detected both in serum and cancer tissue.

Elevated in all cases of gestational trophoblastic disease, hCG serves as an ideal marker, contributing to diagnosis, treatment monitoring, and follow-up. hCG-secreting germ cell tumours account for 40–50% of non-seminomas and 15–20% of seminomas tumours [1]. In non-seminomas tumours, the hCG concentration is one of the prognosis factors.

Other malignancies very often express and secret hCG [4–21]; the protein is synthesised either by the whole tumour cell population or by a subclone of undifferentiated cells. Most frequently, the β-subunit is produced [1]. Many authors point out that hCG synthesis is a factor of poor prognosis. Examples of non-gestational and non-germinal neoplasms secreting hCG are shown in Table 1. Many others, however, have been reported in the literature.

Truly elevated serum hCG concentrations may be observed in hypogonadal men [22] and postmenopausal women [23]. The pituitary gland, normally secreting small amounts of the hormone, is stimulated to hCG production in the event of a marked decrease in sex hormones concentrations. A two-week hormone replacement therapy should suffice to assess whether this is the case in our patient [23, 24]. Another reason, sometimes difficult to elicit from the patient, is self-administering of hCG. Male athletes who abuse anabolic steroids withdraw them at intervals and switch to hCG in order to stimulate endogenous testosterone production and prevent testicular atrophy [25].

In oncological daily practice, it is worth remembering that markers may be secreted from the tumour mass after chemotherapy initiation, i.e. during the first cycle, or even from necrotic tissues after the completion of treatment [26]. Germ cell tumour patients with persistent elevated markers after first-line chemotherapy should be closely followed up and scheduled for prompt residual
tumour resection unless there is an unequivocal increase in marker concentration, which justifies second-line chemotherapy. Another possibility of a rapid serum hCG (or any marker) increase is re-infusion with autologous peripheral blood stem cell (PBSC) transplant [27] in patients undergoing high-dose chemotherapy. PBSCs are harvested at the beginning of induction chemotherapy, [27] in patients undergoing high-dose chemotherapy. PBSCs are harvested at the beginning of induction chemotherapy, serum markers are elevated. Their concentrations, decreased or normalised in responders, may increase again after the transplant, but such a phenomenon is transient and concordant with a marker’s half-life [27].

The results of hCG assays may also be false positive for various reasons. Heterophilic antibodies (HA), frequently found in sera, may appear as a result of infections or contact with foreign (e.g. animal) tissues [24]. They are capable of interfering with two-sided (‘sandwich’) assays, hence giving false positive outcomes. A similar mechanism is related to additives or preservatives in blood collection tubes [24]. Commercial kits of heterophilic blocking reagents (HBR) are available to bind HA in the sample and prevent this effect; such kits are used at our centre. HA molecules are too big to be filtered in kidney glomeruli; therefore, a negative hCG assay in the urine sample may explain the false positivity of the serum [28]. However, even in case of true positive serum, the hCG concentration in urine may be too low to be detected [24].

Reports of false positive hCG assays due to cannabinoid use can also be found in the literature [29], although not confirmed by some authors [30]. Nevertheless, history taking should cover this aspect as well.

In our patient, hCG immunostain in the liver biopsy specimen was notably negative despite serum positivity. This may have been due to a small sample or the fact that only a subclone of cancer cells produced β-hCG. Another explanation may be rapid secretion of hCG outside the cancer cells and into circulating blood, hence leaving an undetectable amount in the cytoplasm. Low sensitivity of the assays used may have added to the outcome [15].

The differential diagnosis of GCT, other malignancies, and false-positive hCG assays is of utmost importance. In selected cases of substantial tumour burden, extensive visceral metastases, and impending organ failure, the diagnosis of GCT may be established on the basis of unequivocally elevated serum markers (hCG, AFP). This may pose serious difficulties because there is no objective concentration cut-off value. In the literature reviewed, the highest paraneoplastic hCG result was 7660 mIU/mL [4]. On the other hand, a typical clinical presentation, along with very high GCT marker concentrations and a need for immediate chemotherapy, sanctions treatment initiation without histological confirmation.

In conclusion, the subtleties of GCT marker interpretation, given the expected radical treatment outcome, support referring such patients to high-volume centres of excellence [2, 3].

Table 1. Examples of non-gestational, non-germinal hCG-secreting neoplasms with the reported hCG concentrations

| Primary site, histology | Serum hCG [mIU/mL] |
|-------------------------|---------------------|
| Lung adenocarcinoma [4] | 7660                |
| Non-small cell lung cancer [5] | 4261              |
| Solitary fibrous tumour of the pleura [6] | 2174             |
| Gastric signet-ring cell carcinoma [7] | 458              |
| Gallbladder adenocarcinoma [8] | 558              |
| Colorectal Cancer [9] | 903.7               |
| Phyllodes tumour of the breast [10] | 58             |
| Cervical squamous carcinoma [11] | 50.05           |
| Mucinous adenocarcinoma of the ovary [12] | 227             |
| Endometrial carcinoma [13] | 201              |
| Urinary bladder high-grade transitional cell carcinoma [14] | 95             |
| Nephroblastoma (Wilms tumour) [15] | 469              |
| Columnar cell variant of papillary thyroid carcinoma [16] | 2800            |
| Cribiform-morular variant of thyroid papillary carcinoma [17] | 139            |
| High-grade osteosarcoma [18] | 2177             |
| Liposarcoma with rhabdomyosarcomatous differentiation [19] | 843            |
| Osteoblastoma [20] | 24.7                |
| Giant cell tumour of the bone [21] | 263            |

hCG — human chorionic gonadotropin

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