Prevalence of paraneoplastic hyperthyroidism in patients with metastatic non-seminomatous germ-cell tumors


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Background: Patients with elevated human chorionic gonadotrophin (HCG) can have hyperthyroidism. We assessed the prevalence of hyperthyroidism in patients presenting with disseminated non-seminomatous germ-cell tumors (NSGCT).

Patients and methods: In all patients with metastatic NSGCT who started chemotherapy at our center from April 2001 to April 2007, thyroid function was analyzed. The association between thyroid function and HCG level was examined and the frequency of hyperthyroidism in patients with low (<5000 IU/l), intermediate (≥5000 but <50 000 IU/l) and high (≥50 000 IU/l) serum HCG was assessed.

Results: For 144 of 148 eligible patients, thyroid function tests were available. Five patients with hyperthyroidism (3.5%) were identified, who all had high-serum HCG (mean 1 325 147 IU/l). Fifty percent of the patients with high HCG levels had hyperthyroidism versus 0% of the patients with HCG <50 000 IU/l (P < 0.001). Free thyroxin levels normalized within 26 days after starting chemotherapy in all patients.

Conclusions: Hyperthyroidism frequently accompanies NSGCT with highly elevated HCG. Since its symptoms overlap with those of extensive metastatic disease, it may not be recognized. Thyroid function should be assessed in patients with high HCG levels and symptomatic hyperthyroidism should be treated temporarily with beta-blockade or antithyroidal medication.

Key words: human chorionic gonadotrophin, hyperthyroidism, testicular cancer

original article

introduction

Non-seminomatous germ-cell tumors (NSGCT) can comprise several different histological components. One of these components is choriocarcinoma, which produces human chorionic gonadotrophin (HCG). In patients with NSGCT and high-serum HCG levels, hyperthyroidism has been recognized and is considered to be a paraneoplastic phenomenon. The prevalence of hyperthyroidism in patients presenting with metastatic NSGCT is not known. In one small series, Giralt et al. [1] reported elevated thyroxine levels in 7 of 17 NSGCT patients with HCG levels in excess of 50 000 mIU/ml. The aim of our study was to establish the prevalence of hyperthyroidism and accompanying symptoms in a large cohort of patients with disseminated NSGCT.

patients and methods

This is a planned prospective analysis of thyroid function in all consecutive patients treated with chemotherapy for disseminated NSGCT at our institution from April 2001 to April 2007. Thyroid function is routinely assessed at our institution at start or within 1 week after start of chemotherapy for NSGCT by measuring thyroid-stimulating hormone (TSH) and free thyroxin (FT4) levels with fluoroimmunometric assays (AutoDELFIA, Wallac Oy, Turku, Finland). Hyperthyroidism was diagnosed when the combination of decreased TSH (<0.40 mU/l) with an elevated FT4 (>18.2 pmol/l) was found. Subclinical hyperthyroidism is defined as a suppressed TSH (<0.40 mU/l) with normal FT4. Information on disease symptoms and clinical outcome was recorded.

Because paraneoplastic hyperthyroidism is thought to depend on elevated HCG levels, we studied the relation between HCG levels and thyroid function. The HCG cut-off levels for the different risk groups according to the International Germ Cell Consensus Classification were used, with levels <5000 IU/l defined as low, levels ≥5000 but <50 000 IU/l defined as intermediate and levels ≥50 000 IU defined as high [2]. HCG levels were measured with a chemiluminescence immunoassay (Architect, Abbott, Abbott Park, IL).

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results

From April 2001 to April 2007, 148 patients with disseminated NSGCT were treated with chemotherapy at our institution and were eligible for this study. Thyroid function tests were available for 144 patients (see Table 1 for baseline characteristics). Low HCG levels were documented in 122 patients (85%), 12 patients (8%) had intermediate and 10 patients (7%) had high HCG levels.

Five patients with hyperthyroidism (3.5%) were identified. All five patients had high HCG levels on presentation. In the group of patients with high HCG levels, 5 of 10 were diagnosed with hyperthyroidism whereas none of the 134 patients with low or intermediate HCG levels had hyperthyroidism ($P < 0.001$).

Thyroid function tests consistent with subclinical hyperthyroidism were found in three patients (2%).

A correlation between HCG and thyroid function was found neither for the entire patient cohort nor for the group of patients with high HCG levels. Characteristics of the patients with high HCG levels are outlined in Table 2.

The five patients with hyperthyroidism had TSH levels ranging from 0.002 to 0.021 mU/l and FT4 levels ranging from 21.3 to >75 pmol/l. The HCG levels in these patients at start of chemotherapy ranged from 414 735 to 2 918 600 IU/l. None of them had a previous history of thyroidal disease. Potential manifestations of thyreotoxicosis in these patients were weight loss ($n = 5$), tachycardia ($n = 4$), perspiration ($n = 3$), irregular pulse ($n = 2$) and restlessness ($n = 1$). Weight loss, however, was also a presenting symptom in the five patients with a high HCG level without hyperthyroidism (see Table 2).

One of the patients with hyperthyroidism (patient 5) was temporarily treated with propranolol for tachycardia, restlessness and anxiety. FT4 normalized within 26 days after start of chemotherapy in all patients (range 6–26 days). As an example, Figure 1 shows the course of HCG, FT4 and TSH in patient 3. During the first 6 months after start of chemotherapy, a significant correlation between HCG and FT4 for this individual patient was found ($P = 0.019$).

The three patients with subclinical hyperthyroidism had TSH levels ranging from 0.22 to 0.39 mE/l. One of these patients had a high HCG level (1 040 000 IU/l) whereas the other two patients had a low HCG level (<1.2 and 58 IU/l, respectively).

All patients received bleomycin, etoposide and cisplatin (BEP) chemotherapy. Within the group of patients with high HCG levels, two patients with hyperthyroidism and two patients without hyperthyroidism died of refractory disease. The remaining six patients are alive and free of disease 2.7–5.5 years after start of chemotherapy.

discussion

Since the first description of hyperthyroidism in a patient with testicular cancer, several cases have been published [1, 3–19]. The prevalence of this paraneoplastic phenomenon, however, is unknown. In our large patient cohort, we found hyperthyroidism to be present in 3.5% of the patients with disseminated NSGCT. In patients with high-serum HCG levels (>50 000 IU/l), we found a prevalence of hyperthyroidism of 50%.

These data are in accordance with Giralt et al. who reported hyperthyroidism based on an elevated T4 in 7 out 17 selected patients (41%) with HCG >50 000 mIU/ml. Three of these seven patients had symptoms that could be attributed to hyperthyroidism [1]. According to the currently accepted definition, however, hyperthyroidism is diagnosed when an elevated FT4 is accompanied by a suppressed TSH level. Thyroxin levels are not reported in combination with TSH.

Table 1. Baseline characteristics of patients with NSGCT at start of chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>No (subclinical) hyperthyroidism, $n = 135$</th>
<th>Hyperthyroidism, $n = 5$</th>
<th>Subclinical hyperthyroidism, $n = 3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>29.8 (16–60)</td>
<td>23.8 (17–34)</td>
<td>29.6 (20–47)</td>
</tr>
<tr>
<td>HCG level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>120 (88)</td>
<td>0</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>12 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High</td>
<td>4 (3)</td>
<td>5 (100)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Tumor markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCG (IU/l) mean</td>
<td>13 503</td>
<td>1 325 147</td>
<td>346 868</td>
</tr>
<tr>
<td>HCG (IU/l) range</td>
<td>&lt;1.2–635 177</td>
<td>414 735–2 918 600</td>
<td>&lt;1.2–1 040 000</td>
</tr>
<tr>
<td>LDH (U/l) mean</td>
<td>443</td>
<td>1118</td>
<td>693</td>
</tr>
<tr>
<td>LDH (U/l) range</td>
<td>99–2159</td>
<td>568–1324</td>
<td>192–1265</td>
</tr>
<tr>
<td>AFP (µg/l) mean</td>
<td>2385</td>
<td>81</td>
<td>1956</td>
</tr>
<tr>
<td>AFP (µg/l) range</td>
<td>&lt;1.2–109 339</td>
<td>&lt;1.2–155</td>
<td>5–5398</td>
</tr>
</tbody>
</table>

NSGCT, non-seminomatous germ-cell tumors; HCG, human chorionic gonadotrophin, AFP, alpha-fetoprotein, LDH, lactate dehydrogenase.

Statistics

Spearman correlation coefficient was used to examine a correlation between HCG levels and thyroid function tests. Fisher’s exact test was used to compare the prevalence of hyperthyroidism in patients with low, intermediate and high-serum HCG levels. Statistical tests were two sided and $P$ values $<0.05$ were considered statistically significant.
levels by Giralt et al., so these data cannot be fully compared with our series.

The pathophysiological mechanism behind paraneoplastic hyperthyroidism is probably the ability of HCG to activate the TSH receptor. HCG consists of two subunits, the α subunit that is identical to the α subunit of the pituitary gonadotrophins and TSH, and the β subunit which is unique to HCG but strongly resembles the β subunit of luteinizing hormone (LH). Studies in animals as well as in men as well as in women have shown that HCG can activate the TSH receptor [20]. Several clinical observations support the theory that high levels of HCG are capable of inducing hyperthyroidism by stimulating the TSH receptor. In the first place, during normal pregnancy, peak levels of HCG in weeks 9–11 are accompanied by a drop in TSH levels [20]. Secondly, in women with hydatidiform moles, trophoblastic tumors and choriocarcinoma, which are conditions with strongly elevated HCG levels, hyperthyroidism is a well-known phenomenon [20]. Furthermore, evacuation of a mole resulted in a fast parallel decline in serum levels of thyroid hormones and HCG [21].

In our study, we have demonstrated a significant correlation between HCG and FT4 levels in one of the patients, like Voigt et al. [19] described in their report of a patient with testicular cancer accompanied by paraneoplastic hyperthyroidism. The slow decline of HCG and the rapid normalization of FT4 demonstrate that HCG is a weak TSH receptor agonist and that only very high HCG levels can stimulate the TSH receptor.

The observation that high HCG levels are not accompanied by hyperthyroidism in all patients may be explained by the existence of HCG variants. HCG exists in different isoforms due to variation in sialic acid amount and glycosylation.

Thyroid-stimulating activity is increased several fold in desialylated and deglycosylated HCG variants. HCG molecules with a nicked loop in the β subunit and truncated molecules that lack the C-terminal tail from the β subunit are also more potent stimulators of the TSH receptor [20, 22]. Differences in concentrations of these HCG variants may explain why some patients with high HCG levels develop hyperthyroidism while others do not. Another explanation for this observation might be presence of polymorphisms of the TSH receptor gene, resulting in increased sensitivity of the TSH receptor to HCG. Rodien et al. [23] described a missense mutation in the extracellular domain of the TSH receptor causing gestational hyperthyroidism in a woman and her mother. Engineered TSH receptor mutants were also shown to have increased sensitivity to HCG [24]. Alternatively, development of hyperthyroidism may be related to the duration of exposition to high HCG levels.

In our study, we found subclinical hyperthyroidism in three patients (2%). One of these patients had a high HCG level whereas the other two patients had HCG levels <1.2 and 58 IU/l, respectively. Subclinical hyperthyroidism can precede overt hyperthyroidism. For the patient with strongly elevated HCG, exposure to high HCG levels may have been too short to develop overt hyperthyroidism. Another explanation for subclinical hyperthyroidism in this patient is the presence of HCG isoforms that have intermediate capacity to stimulate the TSH receptor or a TSH receptor polymorphism with intermediate sensitivity to HCG.

Patients with paraneoplastic hyperthyroidism in our study as well as individual patients reported in the literature are characterized by a highly elevated HCG and a high load of
metastatic disease. Recognition of thyreotoxicosis may be difficult in these patients, as its symptoms like fatigue and weight loss overlap with those of metastatic disease. For example, in our study, weight loss was not a discriminating symptom for the presence of hyperthyroidism since in all patients with high HCG levels, weight loss was one of the presenting symptoms. Start of chemotherapy in patients with hyperthyroidism results in a fast decline of HCG and FT4. HCG has a half-life of 18–36 h, but starting chemotherapy can initially result in a tumor marker surge [25]. Theoretically, this surge can aggravate hyperthyroidism and may result in thyroid storm. Thyroid storm is an acute, life-threatening, hypermetabolic state characterized by fever, tachycardia, hypertension and neurological and gastrointestinal abnormalities. In our series, none of the patients with hyperthyroidism developed a thyroid storm while two of five had a HCG surge. In the literature, a case of thyroid storm has been reported and Tilbrook et al. reported a patient who, according to the description, may have had fatal thyroid storm [4, 18]. Thyroxin has a half-life of 6–7 days but in case of hyperthyroidism this may be reduced to 3–4 days, which is in accordance with the fast normalization we observed after starting treatment.

One of our patients was temporarily treated with propranolol for tachycardia, restlessness and anxiety with good result. Beta-blockage has been used by others for symptomatic treatment of paraneoplastic hyperthyroidism [3, 6, 9, 11, 18]. Thionamides, drugs that decrease thyroid hormone synthesis, have also been administered for treatment of hyperthyroidism in patients with NSGCT [5, 6, 10, 11, 18]. Some patients received combination treatment with beta-blockage and thionamide [6, 11, 18]. It is not known whether treatment with thionamides or beta-blockers can prevent patients from developing thyroid storm due to HCG surge, but treatment of hyperthyroidism should not delay the start of chemotherapy.

This study shows that hyperthyroidism frequently accompanies NSGCT with high-serum HCG levels. Thyreotoxicosis can be difficult to recognize since its symptoms overlap with those of extensive metastatic disease. Thyroid function should be measured in all patients with serum HCG levels >50 000 IU/l and hyperthyroidism should be treated temporarily in symptomatic patients to improve well-being and performance, which may result in better tolerability of chemotherapy.

Figure 1. Course of HCG and thyroid function in patient 3; cycle 1 is day 1 of first cycle of chemotherapy and cycle 2 is day 1 of the second cycle of chemotherapy, etc. (A) HCG, human chorionic gonadotrophin, (B) FT4, free thyroxin and (C) TSH, thyroid-stimulating hormone.

**references**