Clinical case

Sexual precocity and recurrent β-human chorionic gonadotropin upsurges preceding the diagnosis of a malignant mediastinal germ-cell tumor in a 9-year-old boy

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Numerous disorders are known to cause sexual precocity. β-human chorionic gonadotropin (β-HCG)-secreting germ-cell tumors are one of the sources that have to be considered in the differential diagnosis of processes inducing a peripheral precocious puberty. Germ-cell tumors might be located in the ovaries or testes, retroperitoneum, mediastinum or the cranium.

We present the case of a 9-year-old boy with sexual precocity and a recurrent transient β-HCG elevation. After an interval of 2 years with repeated radiological examinations including the mediastinum, a mediastinal tumor was identified by magnetic resonance imaging. To our knowledge, this is the first case of a diagnosis of a mediastinal choriocarcinoma with a recurrent serum β-HCG elevation. So far, factors that might be responsible for the repeated spontaneous β-HCG decline are unknown.

Key words: β-human chorionic gonadotropin elevation, mediastinal choriocarcinoma, sexual precocity

Introduction

Sexual precocity can be classified into central and peripheral precocious puberty; the latter is luteinizing hormone releasing hormone (LHRH) independent. A β-human chorionic gonadotropin (β-HCG)-secreting germ-cell tumor is a rare cause of peripheral precocious puberty in boys, inducing a secretion of testosterone from Leydig cells. Characteristically, in choriocarcinomas β-HCG is distinctly elevated and therefore serves as a specific tumor marker. In fact, in cases of elevated β-HCG in combination with neoplasia in children, germ-cell tumors are most likely. Benign disorders are rarely associated with β-HCG elevation.

In this report, we describe the case of a 9-year-old boy with an elevated β-HCG and precocious puberty. Because of the undulating and recurrent β-HCG elevation over a period of 2 years this case is of special interest. In addition we will give a short review of the differential diagnoses of sexual precocity.

Case report

In January 1998, a 9-year-old boy, who had previously been healthy, presented with signs of sexual precocity. Within three months he had developed a deep voice, slight acne, with a stage of puberty, according to Tanner [1], of PH 4, G 4 and no gynecomastia. The testes had a prepubertal volume of 2.5 ml and were normal on palpation. His height was 144.0 cm (75–90 percentile) and weight 42.2 kg (97 percentile); otherwise, the clinical examination and the family history were normal. Hormone analyses revealed elevated serum levels of testosterone >1000 ng/dl (normal <20 ng/dl), estradiol 80 pg/ml (normal <10 pg/ml) and a markedly elevated β-HCG at 1425 IU/l (normal <5 IU/l). The skeletal age was slightly accelerated (10.5 years). The sonographic examination of the abdomen and the magnetic resonance imaging (MRI) of the brain and abdomen, including the adrenal gland, were normal. One month later, testosterone and β-HCG decreased spontaneously to 480 ng/ml and 302 IU/l, respectively. The LHRH test revealed a suppression of the gonadotropins with only a minimal LH increase. β-HCG in the cerebrospinal fluid was within normal limits as were the serum levels of adrenal gland hormones. The spiral computed tomography (CT) scan of the chest showed a thymus size in the upper normal range;
otherwise it was normal as was the MRI of the pituitary gland. An open biopsy of both testes in combination with measuring the β-HCG concentration in both spermatic venes did not reveal any abnormalities. Supposing that an early exposure to β-HCG had mediated inappropriately high testosterone concentrations and induced a central precocious puberty, a therapy with LHRH agonists was started.

In the following months, the β-HCG showed a highly variable course with peaks of 2353 mg/dl and repeated spontaneous regressions to normal values (Figure 1). Radiological examinations, including repeated chest MRI and CT scans did not show any correlation to the β-HCG elevation. The structure in the anterior mediastinum had no clear progression, although a tumor could not be excluded. In April 2000, β-HCG surged up to 286000 IU/l. At this time the CT scan examination and an MRI of the chest showed a tumor mass in the anterior mediastinum measuring 8.5 × 6 cm. Beside signs of sexual precocity the clinical examination of the boy was always normal.

In view of the extremely elevated β-HCG levels in combination with a mediastinal mass, the clinical diagnosis of a secreting germ-cell tumor was definite and treatment was started with chemotherapy according to the German MAKEI 96 protocol for malignant germ-cell tumors in children, including cisplatin, etoposide and ifosfamide. After one course, β-HCG dropped down to 6021 IU/l and the tumor showed a reduction of nearly 30%. The resection of persisting tumor tissue was performed, followed by three consolidating chemotherapy courses. Histology revealed necrosis of the choriocarcinoma immature teratoma cells with some vital tumor cells.

Now, 5 months after the end of chemotherapy, β-HCG levels are normal and the boy is in good health without any signs of relapse.

**Discussion**

One cause of sexual precocity might be the autonomous secretion of β-HCG, which induces a testosterone secretion from Leydig cells [1, 2]. In children, markedly elevated serum levels of β-HCG are highly suggestive for a malignant secreting germ-cell tumor. In several reports it has been demonstrated that children with either intra- or extracranial germ-cell tumors may develop sexual precocity [3–5]. The β-HCG secretion results in a Leydig cell hyperplasia only, and does not stimulate Sertoli cells. For this reason the testes might be found to be small, as in our patient. In girls, elevated β-HCG secretion alone does not induce sexual precocity because follicle-stimulating hormone is needed for ovarian estradiol production [1].

Germinomas/seminomas might also be capable of producing, predominantly β-chains of, β-HCG at low levels (<200 IU/ml) [6]. The clinical diagnosis of a secreting germ-cell tumor includes, in addition to clinical symptoms, markedly elevated tumor markers and a radiological proof of a tumor at characteristic tumor sites, such as mediastinum, abdomen, testes and cranium. In order to avoid an operation with a thoracotomy, histology is not mandatory in order to start treatment in cases of markedly elevated tumor markers and definitive radiological findings. Thus, β-HCG helps to establish the clinical diagnosis of a germ-cell tumor and, on the other hand, gives the possibility of evaluating the tumor response in patients treated with primary chemotherapy.

Other non-malignant disorders such as renal insufficiency are rarely associated with a slightly elevated β-HCG [7]. In adults, β-HCG may be elevated in patients with a non-trophoblastic neoplasm such as cancer of the stomach (23%), liver (17%), lung (19–33%), urinary bladder (30%), pancreas (69%) as well as in some non-trophoblastic gynecological cancers (10–18%) [8].

![Figure 1. Variable course of β-HCG with spontaneous regressions to normal values.](image-url)
Despite the assumption of the existence of a tumor in our patient from the day of the first presentation, this could not be confirmed sufficiently by radiology. For this reason, CT or MRI scans were repeated in cooperation with our endocrinologists to exclude a tumor. However, the radiological findings did not indicate the need to perform a thoracotomy. In addition, in our experience needle biopsies of mediastinal tumors in children are often of minor diagnostic value. Repeated non-diagnostic biopsies may also affect compliance in pediatric patients.

For germ-cell tumors it has been demonstrated that in the case of bulky disease, neoadjuvant chemotherapy is more favourable, in view of complete tumor resection by a delayed operation, especially in mediastinal germ-cell tumors [9, 10]. Because of the tumor size, the primary treatment in our patient consisted of chemotherapy, which was started immediately, with cisplatin, etoposide and ifosfamide, according to the German treatment protocol of malignant non-testicular germ-cell tumors of children and adolescents (MAKEI 96).

During the last 4 years, 376 patients with extracranial non-testicular germ-cell tumors were registered in the MAKEI 96 trial [9]. Among these choriocarcinomas are rare tumor entities. Only 33 patients had a choriocarcinoma with a β-HCG elevation between ~7 and 1600000 IU/ml. The localization was distributed among ovary (21 patients), retroperitoneum (four patients), mediastinum (four patients), intrathoracal site (one patient), urogenital site (one patient), liver and lung (one patient) and soft tissue (one patient). The reported patient is the only one who presented with sexual precocity. During the last 17 years, there have been no other cases registered in the MAKEI trial with an undulating β-HCG level comparable to this patient. To our knowledge, no similar case of a transient β-HCG elevation preceding a choriocarcinoma is reported in the literature. The phenomenon of the spontaneous decline of β-HCG and its recurring sudden upsurges over a period of 2 years might lead to the hypothesis that a specific immunological response was responsible for the undulating β-HCG.

We want to emphasize that in patients with sexual precocity in combination with an elevated β-HCG, secreting germ-cell tumors should be high on the list of differential diagnoses. To exclude a malignant germ-cell tumor the diagnostic check up should include imaging of chest, abdomen, testes and cranium. Even if β-HCG is decreasing spontaneously a germ-cell tumor cannot be excluded and further biochemical and radiological controls should be performed.

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References