CASE REPORT

First report of ectopic ACTH syndrome and PTHrP-induced hypercalcemia due to a hepatoblastoma in a child

Thomas G P Grunewald1,2, Irene von Luettichau1, Ulrich Welsch3, Helmuth-Günther Dörr4, Frank Höpner5, Kalman Kovacs6, Stefan Burdach1,2 and Wolfgang Rabl1

1Department of Pediatrics, Klinikum rechts der Isar, Technische Universität München, Kölner Platz 1, D-80804 Munich, Germany, 2Laboratory of Functional Genomics and Transplantation Biology, Children's Cancer Research Center, Pediatric Oncology and Roman Herzog Comprehensive Cancer Center, Klinikum rechts der Isar, Technische Universität München, Kölner Platz 1, D-80804 Munich, Germany, 3Anatomical Institute, Ludwig Maximilians University Munich, Pettenkoferstrasse 11, D-80336 Munich, Germany, 4University Hospital for Children and Adolescents, Friedrich-Alexander-University of Erlangen, Loschgestraße 15, D-91054 Erlangen, Germany, 5Department of Pediatric Surgery, Klinikum Schwabing, Kölner Platz 1, D-80804 Munich, Germany and 6Division of Pathology, Department of Laboratory Medicine, St Michael’s Hospital, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8

(Correspondence should be addressed to W Rabl; Email: wolfgang.rabl@lrz.tum.de)

Abstract

Context: Only occasionally, endocrine-active tumors develop directly from hepatic tissue, and may lead to paraneoplastic syndromes (PNS). PNS mostly accompany malignancy of adulthood and are exceedingly rare in children.

Patient: A girl aged 6 years and 9 months presented with a 2-month history of rapidly progressive weight gain, abdominal distension, and polyuria/pollakiuria accompanied by short episodes of abdominal pain. She showed the typical clinical features of Cushing’s syndrome and a huge hepatic mass. An abdominal computed tomography (CT) scan revealed a large liver tumor. Blood glucose and serum calcium were greatly elevated.

Design and objective: Case report describing the causative relationship of the clinical findings.

Methods: Physical examination; ultrasound of the abdomen; CT scan of the abdomen and the chest; conventional X-rays; routine hematology; blood chemistry and multiple parameters of calcium and phosphorus metabolism; multisteroid analysis in serum and urine; adrenocortical stimulation and suppression tests; histopathological assessment of the resected tumor; immunohistochemistry for ACTH, -endorphin, corticotrophin-releasing hormone (CRH), and PTH-related peptide (PTHrP); electron microscopy of tumor cells; ACTH and CRH extraction from the tumor tissue; and clinical follow-up for more than 20 years.

Results: Giant hepatoblastoma (HB; ~1000 ml volume) of the right lobe of the liver with combined ectopic ACTH syndrome and PTHrP-induced tumor-associated hypercalcemia. Wide local excision and polychemotherapy led to complete reversal of the paraneoplastic phenotype.

Conclusions: This is the first report of an endocrine-active HB causing both Cushing’s syndrome and PTHrP-related ‘humoral hypercalcemia of malignancy’. This information should be added to the well-known β-human chorionic gonadotropin-related paraneoplastic effects of HB in children.

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Case report

The case

A girl aged 6 years and 9 months (height: 115.5 cm (z-score -0.87); weight: 23.8 kg (z-score 0.42); body mass index (BMI): 18.1 kg/m² (z-score 1.24); breast and pubic hair development Tanner stage 1) of healthy Caucasian parents was referred to our endocrine clinic because of polyuria/pollakiuria and episodes of mild abdominal pain. Within the last 2 months, she had experienced a remarkable change in her facial features, weight gain, and abdominal distension. Otherwise, her own as well as her family history was essentially negative. On physical examination, she presented with the typical signs of Cushing’s syndrome including a ‘moon face’, a buffalo hump, central obesity, and hirsutism most prominent at the lower back. She also had a protruding abdomen due to a huge abdominal mass (Fig. 1).

Her blood pressure was elevated at 160/120 mmHg, and blood glucose amounted to 365 mg/dl. A computed tomography (CT) scan and an ultrasound of the abdomen revealed a giant liver tumor of the right lobe of the liver with a volume of ~1000 ml (Fig. 2A) and bilateral nephrocalcinosis (Fig. 2B). Excretion of serum calcium and urinary calcium was markedly elevated.
Plasma ACTH was elevated ranging from 184 to 819 pg/ml (normal 15–50), and was unresponsive to either CRH stimulation or dexamethasone suppression (2 and 8 mg), suggesting ectopic ACTH production. Serum corticotropin-releasing hormone (CRH) was undetectable. All urinary steroids, except for tetrahydroaldosterone, were greatly elevated. By contrast, serum multisteroid analysis revealed high levels of cortisol, cortisone, corticosterone, and DHEAS, whereas progestins (progesterone and 17β-OH-progesterone) and mineralocorticoids (11-deoxycorticosterone and aldosterone) were normal (Table 1).

Figure 1 Representative images of the patient. (A) Two months before admission to hospital; (B) one month before admission; (C and D) on admission to hospital: the patient shows the classical phenotype of Cushing’s syndrome; (E) hirsutism of the back and neck; (F) 12 months after surgical resection of the tumor. Authors have obtained informed written consent for use of patient’s images.

Figure 2 CT scan and ultrasound of the abdomen and conventional X-rays of the spinal column. (A) Abdominal CT scan revealed a large tumor in the right lobe of the liver. (B) Ultrasound of the kidneys showed bilateral nephrocalcinosis (the right kidney is depicted). (C) Conventional X-rays demonstrated severe demineralization leading to deformation of the vertebra.
Urine allotetrahydrocortisol; aTHB, allotetrahydrocorticosterone; THF, tetrahydrocortisol; aTHF, THA, tetrahydro-11-dehydrocorticosterone; THB, tetrahydrocorticosterone; and a-hCG. Serum values are given in ng/ml, and urine values in g/24 h. Analyses were performed as described previously (30). Aet, aetiocholanolone; PT, pregnanetriol; P5T, pregnenetriol; THE, tetrahydrocortisone; 11-OH-AN, 11-hydroxyandrosterone; 11-OH-Aet, 11-hydroxyetiocholanolone; aCL, a-clotol; aCL, a-clotolone; bCL, b-cortol; bCL, b-cortolone; b, CRH, resulting in paraneoplastic pseudoprecocious puberty mainly in boys (‘virilizing HB’) (3).

### Discussion of diagnosis

Paraneoplastic syndromes (PNS) are commonly associated with certain tumor entities. Virtually any cancer may result in PNS, but in some tumors such as small cell lung cancer, gynecologic cancers (breast and ovarian), thymoma, and plasma cell tumors, PNS are more frequently encountered. PNS can arise either from hormone-producing tumors or from auto-reactive antibodies induced by antigenic mimicry of tumor-associated antigens (1). Only rarely do endocrine-active tumors develop directly from hepatic tissue (2). However, the most common ectopic hormone produced in HB is β-hCG, resulting in paraneoplastic pseudo-precocious puberty mainly in boys (‘virilizing HB’) (3).
and very rarely in a forme fruste in girls (4). In our case, β-hCG production could not be demonstrated. Often, symptoms of PNS are the first signs of an otherwise occult tumor, prompting the patients to seek medical attention. Cushing’s syndrome results from prolonged exposure to excessive amounts of glucocorticoids. Non-iatrogenic Cushing’s syndrome can be related to excessive ACTH production from the pituitary gland, ectopic ACTH secretion by a non-pituitary tumor, or excessive autonomous secretion of cortisol from a hyperfunctioning adrenocortical tumor. Ectopic ACTH production by a non-pituitary tumor is the cause of non-iatrogenic Cushing’s syndrome in ~10% of all cases in adults (5), but it is exceedingly rare in children (6). To our knowledge, a ‘liver tumor’ has been reported only once as a cause of ectopic ACTH production in children (7). In another single case, ‘humoral hypercalcemia of malignancy’ (HHM) due to a HB has been observed. However, definitive pathological diagnosis and/or identification of the hormones are not available (8). Our case report is the first of combined ectopic ACTH syndrome and PTHrP-induced tumor-associated hypercalcemia in a child with HB.

Hypercalcemia complicating malignancy is a serious and frequent occurrence in adults, but it is extremely rare in children (9). The polypeptide PTHrP was discovered 1 year after admission of the patient to our hospital (10). Kemp et al. showed PTHrP to have a much stronger activity than PTH in 1987 (11). In the same year, PTHrP was found to be the cause of HHM (10, 12).

Surprisingly, serum calcitriol was elevated in our patient (Table 2), whereas PTHrP generally suppresses calcitriol synthesis in HHM. However, rarely PTHrP-induced HHM is associated with increased calcitriol levels, and recent work has shown that short-term exposure to very high doses of PTHrP can also induce renal calcitriol synthesis, which may only decline after long-lasting exposure to PTHrP (13). Thus, we assume that either PTHrP levels were unusually excessive in our patient and/or time of exposure was insufficient to suppress calcitriol production.

Histologically, the HB of our case was partially composed of typical HB cells and mesenchymal cells of an embryonic hepatoma (also known as infantile sarcoma) as assessed by local and reference pathologists. This biphenotypic tumor was subsequently classified as HB of the mixed type. HBs are the most common liver cancers of childhood with ~90% occurring within the first 5 years of life (14). In particular, HBs with low expression of α-fetoprotein, like in this case, belong to a more undifferentiated subtype with a worse prognosis (15).

Morphologically, HB is classified into different patterns, including the frequent fetal pattern that evokes the prenatal fetal liver with sheets of uniform, cuboidal cells showing low mitotic activity; the more immature embryonic type characterized by higher cell density, enlarged nuclei, and frequent mitosis; macrotrabecular patterns evoking hepatocellular carcinoma (HCC); and small cell undifferentiated pattern, suggesting that HB may arise from a primitive, uncommitted progenitor cell (16). Accordingly, HB is divided into molecular subclasses by liver differentiation stages that rely entirely on tumor transcriptional profiling (17).

HBs are embryo- or fetal-like liver cancers displaying a stem cell-like phenotype, which is often observed in a wide variety of liver cancers (17, 18). A salient feature of immature HB is the characteristic interplay of stemness and high proliferation found in aggressive tumors (19). To date, it is not definitively clear if HB is directly derived from infant hepatic stem cells.
(the hepatoblasts) through arrest of maturation or from mature hepatic cells, which resemble a hepatoblast-like phenotype upon reactivation of a conserved transcriptional stemness program, through the process of de-differentiation (18, 20). Indeed, liver cancer stem cells have been isolated from human hepatoma cell lines, primary HCC, and blood of HCC patients, supporting the notion that some HCC subtypes are derived from hepatic progenitors (17, 21, 22). Blockage of tumor stemness may allow differentiation into a large cohort of differentiated tissues as seen in other solid pediatric malignancies (23, 24). Moreover, infant hepatic stem cells (also called hepatoblasts) physiologically divide asymmetrically and give rise to both a differentiated and a stem cell-like daughter cell (18). Thus, it is tempting to speculate that in the biphenotypic HB reported in this case study, some tumor (stem) cells aberrantly differentiated in hormone-producing cells upon yet unknown stimuli through asymmetric cell division (25).

Ontologically, hepatoblasts and endocrine-active pancreatic progenitor cells descend from the same stem cells of the ventral endoderm, and specific evolutionarily conserved inductive signals promote differentiation into liver cells or pancreatic cells (extensively reviewed by Zaret et al. 2008 (26)). The plasticity of differentiation into endocrine cells may be conserved also in tumors derived from hepatoblasts – the infant hepatic stem cells.

Consistent with this hypothesis, sporadic childhood pancreatic islet cell tumors rarely produce ACTH (27).

Since recent evidence suggests that stemness is rather a state than a fate (23, 24, 28), our case could suggest a clinical correlate for tumors partially phenocopying differentiated cells upon inductive micro-environmental imprinting. In accordance, the well-defined multiple histopathological and molecular stages of HB differentiation, which reflect genetically and/or epigenetically programmed loss of stemness signature, may be intimately contextualized in developmental stages of the embryonic, fetal, or infant liver harboring the hepatic cancer stem cell (16, 17, 21, 22, 29).

**Treatment and management**

Due to the severe symptoms of hypercortisolism, the marked hypercalcemia, which was unresponsive to a short treatment trial with calcitonin, and the uncertain response to chemotherapy, the local expert panel decided on the primary resection of the tumor. Accordingly, the giant liver tumor was completely removed through resection of the whole right lobe of the liver. The tumor had a weight of 1.5 kg, and histologically proved to be a HB. Surgery turned out to be very challenging and lasted for 9 h. Intra-operatively, the patient needed resuscitation due to breakdown of circulation and cardiac arrest. The critical episode lasted for 3 min. Perioperatively, pharmacological doses of hydrocortisone were administered to avoid relative hypocortisolism after removal of the ACTH-producing HB. Postoperatively, the patient needed artificial ventilation, but could be extubated successfully after 5 days. In the following 3 months, we treated the patient with a combined adjuvant chemotherapy based on cisplatin, etoposide, adriblastina, and ifosfamide, which was tolerated without severe complications. One year after surgery, the girl developed symptomatic complex-partial seizures, clonal stutter, prominent deficiencies of coordination, and a more left-sided hemiparesis. A brain CT scan revealed mild brain atrophy probably as a result of brain hypoxia during resuscitation. On several follow-up electroencephalography (EEG) examinations, dysrhythmic groups and diffuse sharp waves were detected, especially while the patient was asleep, which were absent in routine EEG before surgery. Seizures could be controlled and prevented partially through therapy with carbamazepine and valproic acid, but the girl experienced severe learning difficulties in adolescence due to residual mental handicap. To date, the patient is 29 years old (height: 156 cm (z-score = -1.13); weight: 70 kg (z-score 0.96); BMI: 28.8 kg/m² (z-score 1.41); breast and pubic hair development Tanner stage 5; regular menses) and physically well, and has regularly attended our outpatient clinic for follow-up for more than two decades. Presently, there is no evidence of relapse and/or metastasis, and laboratory parameters are normal.

**Conclusion**

To our knowledge, this is the first report of an endocrine-active HB leading to combined PNS of Cushing’s syndrome and PTHrP-related HHM. This information should be added to the well-known β-hCG-related PNS effects of HB in children.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Author contribution statement**

T Grunewald drafted and wrote the paper, designed the figures and the tables. I von Luettichau and S Burdach provided oncological guidance and corrected the paper. U Welsch performed ultrastructural analysis of the tumor by electron microscopy. H-G Dörr performed serum steroid analyses. F Höppner performed the surgery, and K Kovacs delivered the immunohistochemistry and the histology slides. W Rabl was responsible for the initial diagnostic work-up, provided endocrinologic guidance throughout the patient’s care, and helped with the final draft of the paper. All authors approved the final manuscript.

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