CASE REPORT

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

Thomas G P Grunewald^{1,2}, Irene von Luettichau¹, Ulrich Welsch³, Helmuth-Günther Dörr⁴, Frank Höpner⁵, Kalman Kovacs⁶, Stefan Burdach^{1,2} 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; multiteroid analysis in serum and urine; adrenocortical stimulation and suppression tests; histopathological assessment of the resected tumor; immunohistochemistry for ACTH, β -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.

European Journal of Endocrinology 162 813–818

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/m^2 (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.

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.

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 multiteroid analysis revealed high levels of cortisol, cortisone, corticosterone, and DHEAS, whereas progestins (progesterone and 17α -OH-progesterone) and mineralocorticoids (11-deoxycorticosterone and aldosterone) were normal (Table 1).

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 vertebrae.

Table 1 Serum and urinary steroid hormones before surgery.

	Value	Reference
Serum		
Aldosterone	0.064	0.18–0.69
Progesterone	0.069	0.08–0.89
11-Deoxycorticosterone	0.25	<0.03–0.37
17 α -OH-progesterone	0.61	<0.03–0.84
11-Deoxycortisol	1.33	0.16–1.70
Corticosterone	12.9	<0.05–6.45
Cortisone	28.9	7.0–27.0
Cortisol	673.5	39.8–136.0
DHEAS	1150	<500
Urine		
Aet	1016	0–71
11-OH-AN	2643	25–223
11-OH-Aet	3253	0–119
PT	5286	34–278
P⁵T	1016	0–142
THE	25 416	138–1559
THA	406	22–489
THB	1016	0–216
a-THB	1016	38–568
THF	39 039	17–715
a-THF	5896	47–1416
α-CL	3253	91–390
β-CL, β-C	7929	26–380
α-C	4473	22–168
THS	3049	0–427
a-THS	609	0–229
Cortisol	1829	<100
6β-OH-cortisol	4879	<100
20α-OH-cortisol	1016	<100
6α-OH-β-CL	1016	<100
1β-OH-β-CL	2236	0–158
THE/THF	0.65	1.5–7.0
THF/α-THF	6.62	0.5–3.5

Reference values are age adjusted, and elevated values are marked in bold font. Serum values are given in ng/ml, and urine values in μ g/24 h. Analyses were performed as described previously (30). Aet, aetiocholanolone; 11-OH-AN, 11-hydroxyandrosterone; 11-OH-Aet, 11-hydroxyetiocholanolone; PT, pregnanetriol; P⁵T, pregnenetriol; THE, tetrahydrocortisone; THA, tetrahydro-11-dehydrocorticosterone; THB, tetrahydrocorticosterone; aTHB, allotetrahydrocorticosterone; THF, tetrahydrocortisol; aTHF, allotetrahydrocortisol; α -C, α -cortol; α -CL, α -cortolone; β -CL, β -cortolone; β -C, β -cortol; THS, tetrahydro-11-deoxycortisol; aTHS, allotetrahydro-11-deoxycortisol.

Corrected serum calcium was 14.2 mg/dl (normal: 8.4–10.6) and phosphate was 2.2 mg/dl (normal: 4.0–7.0). Calcitriol (1,25-(OH)₂D₃) was slightly elevated and urinary cAMP was massively elevated, whereas phosphate reabsorption was decreased. Serum parathyroid hormone (PTH 44–68), calcidiol (25-(OH)D₃), alkaline phosphatase, osteocalcin, and urinary hydroxyproline (Pro-OH) were normal, and intact PTH was suppressed, suggesting the presence of a PTH-like factor distinct from PTH (Table 2). Conventional X-rays of the spinal column demonstrated significant demineralization of the skeleton (Fig. 2C). There was no evidence of metastases on routine staging. α -fetoprotein and β -human chorionic gonadotropin (β -hCG) levels in serum were normal. The tumor was surgically removed, and was proven to be a hepatoblastoma (HB) by histology. Hormone extraction from the tumor mass

yielded 8.3 ng/ml ACTH and 0.04 ng/ml CRH. Initial immunohistochemical staining was positive for ACTH, β -endorphin, and traces of CRH, but negative for α -fetoprotein. Retrospectively, after successful cloning of PTH-related peptide (PTHrP) in 1987, PTHrP could also be detected by secondary immunohistochemical analysis in preserved tissue of the tumor. Multiple hormone granules were observed in individual tumor cells by electron microscopy (Fig. 3). Postoperatively, serum ACTH, calcium, blood glucose, and blood pressure rapidly reverted to normal. In addition to surgery, the girl also received adjuvant polychemotherapy. Four months later, basal as well as CRH- and insulin tolerance test-stimulated ACTH and cortisol levels were normal. Accordingly, the signs of Cushing's syndrome disappeared, and the bilateral nephrocalcinosis dissolved within several months. We have followed the girl for more than two decades. The patient is doing physically well and shows no signs of relapse or metastasis.

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)

Table 2 Serum and urinary calcium/phosphate parameters before surgery.

	Value	Reference
Serum		
Ca (mg/dl)	14.2	8.4–10.6
P (mg/dl)	2.2	4–7
AP (U/l)	319	200–600
Osteocalcin (ng/ml)	6.4	7–15
PTH (44–68) (pmol/l)	51	30–90
PTH (intact) (pg/ml)	<12	12–55
bioPTH (ng/ml)	30	1–19
Calcidiol (ng/ml)	14.7	10–50
Calcitriol (pg/ml)	61	20–40
Urine		
Ca/Cr (μg/mg)	760	6–174
cAMP (nmol/dlGF)	6.7	1.6–4.9
TRP (%)	71.4	80–95
TmPO₄/GFR (mg/dl)	1.6	4.5–6.8
Pro-OH/Cr (μg/mg)	107	60–160

Reference values are age adjusted, and abnormal values are marked in bold font. TRP, tubular reabsorption of phosphate; TmPO₄/GFR, renal threshold phosphate concentration; Pro-OH/Cr, hydroxyproline.

Figure 3 Surgical specimen and light and electron microscopy of tumor cells. (A) *In situ* image of the giant tumor. The tumor mass had a volume of ~1000 ml and a weight of 1.5 kg. (B) Macroscopic section of the large tumor (arrow). (C) H&E staining of the HB (magnification 100 $\times$). (D) Strong immunohistochemical staining positivity of ACTH (brown) of many tumor cells (magnification 100 $\times$). (E) Strong staining positivity of PTHrP (brown) in some restiform like tumor cells by immunohistochemistry (magnification 100 $\times$). (F) Low-power electron micrograph of HB epithelial cells, forming irregular strands separated by a loose connective tissue matrix. Note irregularly shaped nuclei with highly uncondensed chromatin, and well-developed rough endoplasmic reticulum typical for increased protein synthesis (magnification 1100 $\times$). (G and H) Small groups of roundish, oval and rod-shaped dense core granules are noted in some of the cytoplasmic processes of the HB cells, which are likely to be hormone-containing granules (arrows; magnification 2300 $\times$ and 10 000 $\times$ respectively).

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, adriablastina, 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/m^2 (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.

Funding

This research did not receive any specific grant from any agency in the public, commercial, or not-for-profit sector.

Author contribution statement

T Grunewald drafted and wrote the paper, designed the figures and the tables. I von Luetichau 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 Höpner 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.

Acknowledgements

We are very grateful to Dr Klaus Kruse for analysis of serum and urinary calcium/phosphate parameters, to Dr Otto-Albrecht Müller for ACTH and CRH extraction from the tumor tissue, to Dr Janos Homoki for the urinary steroid analysis, to Dr Franz Prantl for the histological diagnosis, Dr Helmut Hahn for the X-ray, ultrasound and CT images, and to Dr Stephan Müller-Wehrich for the initial oncological care of the patient.

References

- Thirkill CE. Immune-mediated paraneoplasia. *British Journal of Biomedical Science* 2006 **63** 185–195.
- DeLellis RA & Xia L. Paraneoplastic endocrine syndromes: a review. *Endocrine Pathology* 2003 **14** 303–317.
- Beach R, Betts P, Radford M & Millward-Sadler H. Production of human chorionic gonadotrophin by a hepatoblastoma resulting in precocious puberty. *Journal of Clinical Pathology* 1984 **37** 734–737.
- Perilongo G, Rigon F & Murgia A. Oncologic causes of precocious puberty. *Pediatric Hematology and Oncology* 1989 **6** 331–340.
- Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA & Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4955–4962.
- Newell-Price J, Trainer P, Besser M & Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocrine Reviews* 1998 **19** 647–672.
- Kracht J. Adrenal pathology of Cushing's syndrome in children and juveniles (author's transl). *Verhandlungen der Deutschen Gesellschaft für Pathologie* 1971 **55** 142–146.
- Omenn GS. Ectopic hormone syndromes associated with tumors in childhood. *Pediatrics* 1971 **47** 613–622.
- McKay C & Furman WL. Hypercalcemia complicating childhood malignancies. *Cancer* 1993 **72** 256–260.
- Suva LJ, Winslow GA, Wettenhall RE, Hammonds RG, Moseley JM, Diefenbach-Jagger H, Rodda CP, Kemp BE, Rodriguez H & Chen EY. A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. *Science* 1987 **237** 893–896.
- Kemp BE, Moseley JM, Rodda CP, Ebeling PR, Wettenhall RE, Stapleton D, Diefenbach-Jagger H, Ure F, Michelangeli VP & Simmons HA. Parathyroid hormone-related protein of malignancy: active synthetic fragments. *Science* 1987 **238** 1568–1570.
- Ralston SH. The pathogenesis of humoral hypercalcaemia of malignancy. *Lancet* 1987 **2** 1443–1446.
- Horwitz MJ, Tedesco MB, Sereika SM, Syed MA, Garcia-Ocana A, Bisello A, Hollis BW, Rosen CJ, Wysolmerski JJ, Dann P, Gundberg C & Stewart AF. Continuous PTH and PTHrP infusion causes suppression of bone formation and discordant effects on 1,25(OH)₂ vitamin D. *Journal of Bone and Mineral Research* 2005 **20** 1792–1803.
- Schmidt D, Harms D & Lang W. Primary malignant hepatic tumours in childhood. *Virchows Archiv. A, Pathological Anatomy and Histopathology* 1985 **407** 387–405.
- De Ioris M, Brugieres L, Zimmermann A, Keeling J, Brock P, Maibach R, Pritchard J, Shafford L, Zsiros J, Czauderna P & Perilongo G. Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: the SIOPEL group experience. *European Journal of Cancer* 2008 **44** 545–550.
- Zimmermann A. The emerging family of hepatoblastoma tumours: from ontogenesis to oncogenesis. *European Journal of Cancer* 2005 **41** 1503–1514.
- Cairo S, Armengol C, De Reynies A, Wei Y, Thomas E, Renard CA, Goga A, Balakrishnan A, Semeraro M, Gresh L, Pontoglio M, Strick-Marchand H, Levillayer F, Nouet Y, Rickman D, Gauthier F, Branchereau S, Brugieres L, Laithier V, Bouvier R, Boman F, Basso G, Michiels JF, Hofman P, Arbez-Gindre F, Jouan H, Rousselet-Chapeau MC, Berrebi D, Marcellin L, Plenat F, Zachar D, Joubert M, Selves J, Pasquier D, Bioulac-Sage P, Grotzer M, Childs M, Fabre M & Buendia MA. Hepatic stem-like phenotype and interplay of Wnt/beta-catenin and Myc signaling in aggressive childhood liver cancer. *Cancer Cell* 2008 **14** 471–484.
- Sell S & Leffert HL. Liver cancer stem cells. *Journal of Clinical Oncology* 2008 **26** 2800–2805.
- Ginsky GV. Death-from-cancer signatures and stem cell contribution to metastatic cancer. *Cell Cycle* 2005 **4** 1171–1175.
- Sell S. Cellular origin of cancer: dedifferentiation or stem cell maturation arrest? *Environmental Health Perspectives* 1993 **101** 15–26.
- Lee JS, Heo J, Libbrecht L, Chu IS, Kaposi-Novak P, Calvisi DF, Mikaelyan A, Roberts LR, Demetris AJ, Sun Z, Nevens F, Roskams T & Thorgeirsson SS. A novel prognostic subtype of human hepatocellular carcinoma derived from hepatic progenitor cells. *Nature Medicine* 2006 **12** 410–416.
- Libbrecht L. Hepatic progenitor cells in human liver tumor development. *World Journal of Gastroenterology* 2006 **12** 6261–6265.
- Burdach S, Plehm S, Unland R, Dirksen U, Borkhardt A, Staeger MS, Muller-Tidow C & Richter GH. Epigenetic maintenance of stemness and malignancy in peripheral neuroectodermal tumors by EZH2. *Cell Cycle* 2009 **8** 1991–1996.
- Richter GH, Plehm S, Fasan A, Rossler S, Unland R, Bennani-Baiti IM, Hotfilder M, Lowel D, von Luetichau I, Mossbrugger I, Quintanilla-Martinez L, Kovar H, Staeger MS, Muller-Tidow C & Burdach S. EZH2 is a mediator of EWS/FLI1 driven tumor growth and metastasis blocking endothelial and neuro-ectodermal differentiation. *PNAS* 2009 **106** 5324–5329.
- Morrison SJ & Kimble J. Asymmetric and symmetric stem-cell divisions in development and cancer. *Nature* 2006 **441** 1068–1074.
- Zaret KS & Grompe M. Generation and regeneration of cells of the liver and pancreas. *Science* 2008 **322** 1490–1494.
- Styne DM, Isaac R, Miller WL, Leisti S, Connors M, Conte FA & Grumbach MM. Endocrine, histological, and biochemical studies of adrenocorticotropin-producing islet cell carcinoma of the pancreas in childhood with characterization of proopiomelanocortin. *Journal of Clinical Endocrinology and Metabolism* 1983 **57** 723–731.
- Kagalwala MN, Singh SK & Majumder S. Stemness is only a state of the cell. *Cold Spring Harbor Symposia on Quantitative Biology* 2008 **73** 227–234.
- Burdach S. *Epigenetic Maintenance of Stemness in Pediatric Malignancy*. Société Internationale d'Oncologie Pédiatrique (SIOPEL) Educational Booklet, 2009.
- Homoki J, Holl R & Teller WM. Urinary steroid profile in Cushing syndrome and in tumors of the adrenal cortex. *Klinische Wochenschrift* 1987 **65** 719–726.

Received 21 December 2009

Accepted 3 February 2010