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Extra-adrenal composite phaeochromocytoma/neuroblastoma in a 15-month-old child

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ABSTRACT

A 15-month-old boy was diagnosed with malignant hypertension caused by a catecholamine excreting retroperitoneal paraganglioma consisting of a composite phaeochromocytoma/differentiating neuroblastoma. After alpha-blockade the tumor was excised. No adjuvant treatment was given, and he is doing well eight years after the diagnosis. The patient is the first child known to have an extra-adrenal retroperitoneal composite tumor, and also the youngest child with a composite phaeochromocytoma/neuroblastoma reported in the English literature.

Composite phaeochromocytoma (CP) in children is so rare that every new case ought to be reported. In adults CP accounts for three percent of phaeochromocytomas [1]. In children about 30% of phaeochromocytomas are extra-adrenal (paragangliomas) [2]. CP occurs almost exclusively in adult patients; pediatric CP is so infrequent that meaningful estimates of incidence are precluded [3–11]. Herein we report the patient history and outcome of a 15 m-old boy with malignant hypertension and a lumbar, retroperitoneal paraganglioma consisting of a phaeochromocytoma combined with a differentiating neuroblastoma.

1. Case presentation

At 15 months of age a boy who had suffered from profuse sweating and increased thirst since birth was diagnosed with malignant hypertension. He had heart failure with dilated left atrium, hypertrophied left ventricle and a blood pressure of 180/130. Pro Brain Natriuretic Peptide (ProBNP) was 2420 pmol/l (reference value <35).

The first four days in Oslo University Hospital he was sedated on ventilator and the blood pressure was monitored invasively. He was medicated with nitroprusside and labetalol via a central venous line. However, troublesome, spiky hypertension and spells with hypotension persisted, and after a week amlodipin was added and nitroprusside tapered.

A CT study disclosed a 7 × 6 × 4 cm retroperitoneal tumor located at the lower pole of the right kidney (Fig. 1).

Urinary catecholamine excretions were: VMA/HVA: 133/252 μmol/mmol creatinine (reference values <10/<18), dopamine: 3489 nmol/24 h (146–2014), norepinephrine: 2726 nmol/24 h (60–400) and epinephrine: 9 nmol/24 h (0–70).

During an MRI study in general anesthesia two days after admission bradycardia suddenly occurred and blood pressure became immeasurable. He was resuscitated and after about 8 min adequate blood pressure was restored. After weaning off the ventilator two days after the MRI-incident he was conscious but without adequate eye contact and had rigid upper extremities. EEG was normal but cerebral MRI revealed pronounced, diffuse cortical hypoxic injuries.

Abbreviations: CP, composite phaeochromocytoma; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; ProBNP, pro brain natriuretic peptide; VMA, vanillylmandelic acid.

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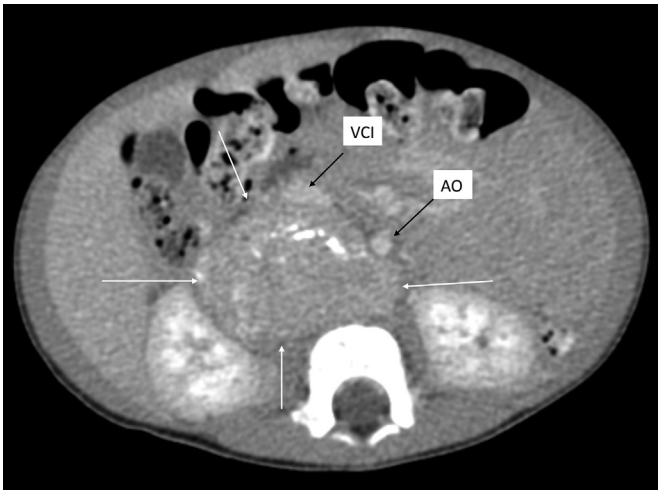

Fig. 1. Axial CT taken the day after admission, showing a right-sided calcified, paraspinal tumor (white arrows) displacing the vena cava inferior (VCI) and the aorta (AO) anteriorly (black arrows).

The tumor did not show any isotope uptake in a ^{123}I-MIBG scan taken two weeks after admission. Even normal background activity was absent. At the time of the MIBG scan he received labetalol 15 mg/kg/day and amlodipin 0.5 mg/kg/day.

The work-up revealed no evidence of metastatic disease. A clinical diagnosis of phaeochromocytoma was made, but Tru-Cut biopsies taken three days after admission revealed a differentiating neuroblastoma. The negative MIBG scan was interpreted as caused by blocked uptake of MIBG by labetalol, an effect that has been reported [12].

The boy received preoperative medication as if he had phaechromocytoma. In addition to labetalol and amlodipin he was given terazosin 0.4 mg/kg/day to ensure effective alpha-blockade (phenoxybenzamine was not available).

Twenty-five days after admission and after two weeks with normalized blood pressure he was operated with complete excision of a 75 g firm, encapsulated retroperitoneal tumor located posterior to the lumbar vena cava and aorta. One week after the operation urinary excretion of VMA and HVA were normal, respectively 7 and 12 μmol/mmol creatinine.

Histology showed a composite paraganglioma with elements of phaeochromocytoma and differentiating neuroblastoma with low mitosis-karyorrhexis index (Fig. 2). Details of the pathology findings are given in the figure legend.

The prognosis of the neuroblastoma component was favorable according to the International Neuroblastoma Pathology Classification [13]. Tumor margins were free. One of six adherent lymph nodes contained neuroblastoma tissue. There were no indications of *MYCN* amplification, gain of 17q or loss of 1p/11q by fluorescence in situ hybridization. Array comparative genomic hybridization (Affymetrix SNP array 6.0) did not reveal segmental, only numerical chromosomal aberrations.

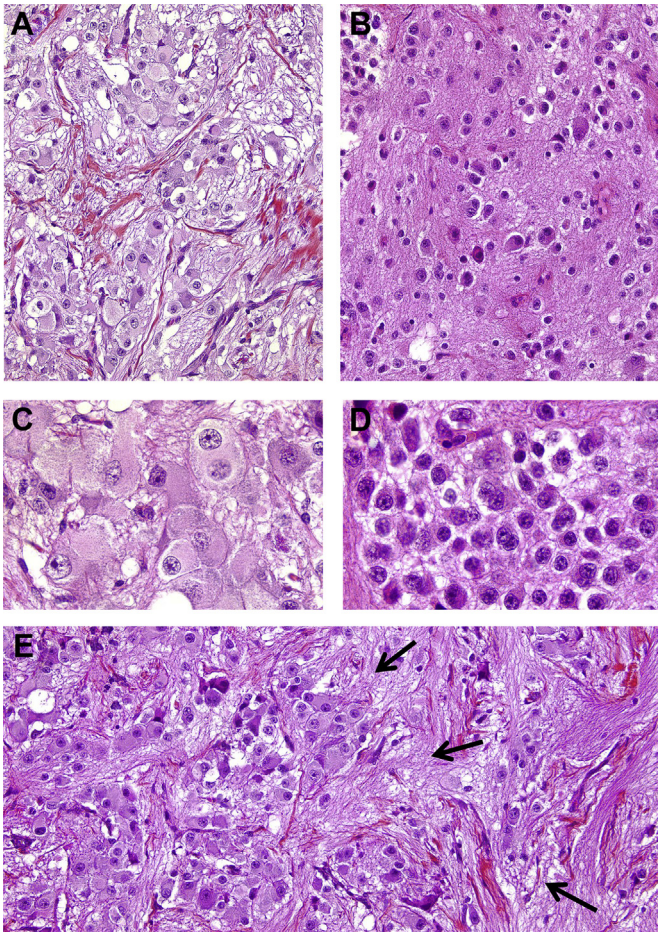

Fig. 2. (A–E) H&E stained histological sections from different areas of the excised tumor showing (A) a lobular growth pattern of phaeochromocytoma, while the neuroblastoma component (B) is characterized by diffuse distribution of differentiating neuroblasts on a background of abundant neuropile. Cytologically the phaeochromocytoma (C) is composed of more uniformly looking, tightly packed large cells with abundant light eosinophilic cytoplasm whereas the neuroblasts (D) are generally smaller, display a darker eosinophilic cytoplasm and comprise a spectrum of poorly differentiated to differentiating neuroblasts. There is no sharp border between the tumors, but a transitional zone (arrows in E) where the lobular phaeochromocytoma-like architecture (left part of the image) is gradually broken up by an increasing amount of neuropile surrounding small groups or single neuroblasts (right part of the image) (A, B and E: objective ×20 and identical final magnification; C and D: objective ×40 and identical final magnification).

Table 1
Composite phaeochromocytoma/paraganglioma in children under 15 year of age.

Author	Year	Reference	Age/Sex	Location	Histology	Follow-up	Outcome
Wahl et al.	1943	[3]	4 year/M	Mediastinum	PH/NB	8 m	Died
Nakagawara et al.	1985	[4]	14 year/F	Adrenal	PH/GNB	6 m	Died
Tatekawa et al.	2006	[8]	5 year/M	Adrenal	PH/NB	Unknown[b]	Alive[b]
Ch'ng et al.	2007	[9]	9 year/F	Adrenal	PH/MPNST	28 years	Died
Thiel et al.	2010	[10]	9 year/F	Adrenal	PH/GNB	18 m	Alive
Kikuchi et al.	2012	[11]	12 year/F	Adrenal	PH/GN[a]	14 years	Died
Current case	2015		1 year/M	Retro-peritoneum	PH/NB	8 y	Alive

PH; phaeochromocytoma, NB; neuroblastoma, GNB; ganglioneuroblastoma, GN; ganglioneuroma, MPNST; malignant peripheral nerve sheath tumor.
[a] With WDHA: watery diarrhea hypokalaemia achlorhydria.
[b] Cited from Ref. [8]: "After operation, the patient is doing well and is free from the symptoms of hypertension."

No adjuvant chemotherapy or radiation was given. One month after the tumor excision all neurological symptoms had subsided and his vision was normal. The blood pressure and the function of the heart were normalized but antihypertensive medication was continued. One month after the operation, during which no labetalol was given, a repeated ^{123}I-MIBG scan showed normal background activity but no tumor suspect areas. Also an octreotide scintigraphy was normal. Both studies were done in order to detect metastases. He received tapering doses of antihypertensive medication for one year. Ten months after the ischemic brain insult cerebral MRI was normal.

The patient had a negative history of familial tumors and relevant gene tests (*RET*, *VHL*, *SDHB* and *SDHD*) did not disclose mutations.

Eight years after treatment the patient is doing well without evidence of disease. However, after starting school, he has been diagnosed with attention deficit hyperactivity disorder (ADHD), which is successfully treated with psychostimulants.

Both parents have given informed consent to publication.

2. Discussion

Only six children with CP are reported in the English literature; five tumors were adrenal and one mediastinal [3,4,8–11] (Table 1).

The youngest patient with CP was 4 years old [3]. Our patient was diagnosed at 15 m of age, but had symptoms since birth and had heart findings compatible with longstanding hypertension. It is therefore likely that his catecholamine-producing tumor was present at birth. Accordingly our patient is both the first child reported to have an extra-adrenal retroperitoneal CP, and also the youngest patient with a CP.

During the first week in hospital the patient was unstable, posing great challenges for the treating physicians. We were confused by the negative preoperative MIBG scan, but assume in retrospect that it was caused by a blocking effect of the large dose of labetalol [12]. If possible it may be wise to postpone medication with labetalol until after diagnostic MIBG studies.

Patients with untreated phaeochromocytoma are at high risk for circulatory collapse, and it is strongly recommended to avoid operations and procedures in anesthesia until effective alpha-blockade has been established [2,14,15]. It seems reasonable to treat children with labile blood pressure of uncertain etiology likewise. Accordingly, in retrospect we admit that the MRI study in our case should not have been done. If really needed it should have been postponed to a later time.

Many details, especially on medication, could have been elaborated on, but with an eight-year retrospective view we have chosen to focus on the aspects most relevant for the main messages of this report: 1) Extra-adrenal CP can also occur in younger children. 2) In hypertensive patients with suspected phaeochromocytoma operations and procedures in anesthesia should whenever possible be postponed until effective alpha-blockade has been established. 3) In absence of unfavorable features, patients with CP can be cured with surgical treatment alone.

Conflicts of interests

None of the authors has any conflicts of interest to declare.

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