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Disseminated choriocarcinoma in infancy is curable by chemotherapy and delayed tumour resection

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Abstract

Infantile choriocarcinoma has a poor prognosis with only 2 surviving children reported in the literature. 2 additional successfully treated children are presented. 2 infants (age 3 and 4 months at diagnosis) suffering from rapidly progressive choriocarcinoma with widespread haematogenous metastases involving the liver were treated according to the cooperative germ cell tumour treatment protocol (MAKEI 96) of the German Society of Pediatric Oncology and Hematology (GPOH). PEI-chemotherapy (cisplatin, etoposide, ifosfamide; no ifosfamide before the age of 4 months) was combined with delayed tumour resection. Treatment resulted in sustained remission in both children (event-free survival 42 and 40 months). Interphase fluorescent *in situ* hybridisation (FISH) analysis of the paraffin-embedded tumour sample from case one revealed four to eight copies of chromosomes X, 1 and 17 and two Y chromosomes. Hybridisation with sub-telomere and centromere specific probes for chromosome 1 displayed an imbalance between the short and long arms of chromosome 1. In the tumour cells from case 2, only a polysomy of chromosome X could be proven, other aberrations were not analysed in this case for technical reasons.

Keywords: Choriocarcinoma; Chemotherapy; Germ cell tumour; Infant; Neonatal; Prognosis; Tumour marker; Tumour genetics

1. Introduction

Germ cell tumours are responsible for 4.6% of all neoplastic diseases in children aged less than 16 years in the German paediatric cancer registry [1] and in more than 60% they occur during the first year of life [2,3]. During infancy, the leading germ cell tumour diagnoses are mature and immature teratoma followed by yolk sac tumour, whereas germinoma (seminoma/dysgerminoma) are not described [4] and choriocarcinoma only in case reports during this period [5–30]. Therefore, it is not surprising that between 1980 and July 2000 only 2 of 1015 children with germ cell tumours registered into the German paediatric tumour registry suffered from pure infantile choriocarcinoma. These two infantile choriocarcinoma patients were both treated in accordance with the protocol guidelines of the cooperative protocol MAKEI 96 for malignant non-testicular germ cell tumours [3,31].

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2. Patients and methods

The reported cases of infantile choriocarcinoma were treated according to the arm for metastatic disease of the presently open cooperative treatment protocol for extracranial non-testicular germ cell tumours of the German Society of Pediatric Hematology and Oncology (MAKEI 96). This study collects germ cell tumour cases and stratifies treatment according to tumour histology, localisation, tumour stage and completeness of resection. In cases with localised completely resectable tumours, primary resection should be performed. In metastatic disease or in cases in whom — based on preoperative assessment — a primary complete resection seems impossible, neoadjuvant chemotherapy followed by a delayed tumour resection is recommended. Central review of the histology of all cases registered into the study is mandatory. Informed consent of the parents to data collection and treatment stratification was obtained, as well as ethical approval of the appropriate committees.

Fluorescence *in situ* hybridisation (FISH) was performed on cytospin slides containing cell nuclei from paraffin-embedded tumour samples as described by Stock and colleagues [32]. Satellite DNA probes, specific for chromosomes 1, 17, X and Y were used to determine the copy number of the different chromosomes in the interphase nuclei. To analyse the integrity of the short arm of chromosome 1, DNA probe p1.79 hybridising to 1p36.33 (D1Z2) was applied simultaneously with the probe pUC 1.77 specific to the paracentromeric region of chromosome 1. All slides were analysed with a Zeiss fluorescence microscope. Images were taken with the ISIS software from MetaSystems, Altlussheim, Germany.

2.1. Case reports

2.1.1. Case 1

A 4-month-old boy born after an uneventful pregnancy and without previous medical problems presented with a soft tissue mass dorsal to the scapula. On ultrasound scan the solid, but inhomogeneous tumour measured 6.3×6.3×4.3 cm showing no bony invasion and spanning the back muscles. The tumour extended to the lateral chest wall and into the shoulder joint. T2-magnetic resonance imaging (MRI) demonstrated large oedematous zones and multiple small cysts. Axillary lymph nodes were enlarged. Despite an elevated serum lactate dehydrogenase (410 U/l), the immediate biopsy was judged to be representative of a benign process upon light microscopy — possibly villo-nodular synovitis. While awaiting the results of immune histochemistry, the local tumour enlarged to 9×8×7 cm protruding mushroom-like through the then dehiscent surgical scar. Positivity for cytokeratin and human

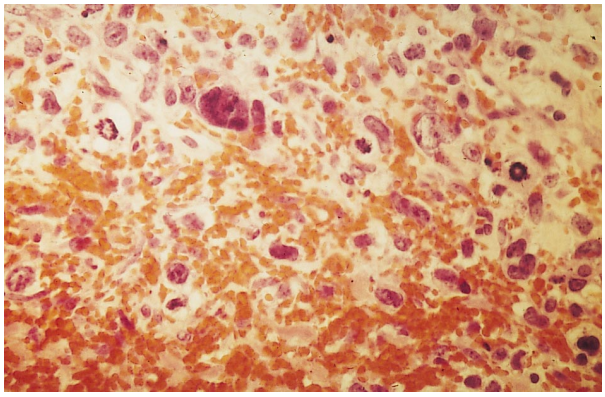

Fig. 1. Case 1. Biopsy from the scapula showing atypical cells with mitotic activity. Haematoxylin-eosin (HE) 100×.

chorionic gonadotrophin (HCG) resulted in a histological diagnosis of choriocarcinoma (Figs. 1 and 2). In the meantime, the boy had deteriorated dramatically, developing ascites and tumour masses within the liver, as well as multiple lung metastases. At this point, the tumour marker β-HCG was grossly elevated to 790 000 IU/l, serum alpha fetoprotein (AFP) was not elevated and the serum testosterone was 45.1 nmol/l. Life-threatening bleeding from the liver metastases into the abdominal cavity with haemorrhagic shock was only reversed after instituting cytostatic therapy. The boy received PEI-chemotherapy consisting of cisplatin (0.66 mg/kg/day on days 1–5), etoposide (3.3 mg/kg/day) and ifosfamide (50 mg/kg/day on days 1–5) every 3 weeks. After four courses of chemotherapy, the serum β-HCG level had dropped to 9.5 IU/l. At this point, the two liver metastases could be resected, the histological specimens showed complete tumour necrosis.

The shoulder tumour had only partially responded, thus far, and the β-HCG serum level again rose to 150 IU/l, indicating viable tumour. A fifth course of PEI chemotherapy was administered prior to resection, after which histology showed complete tumour necrosis and

Fig. 2. Case 1. The tumour cells are intensively positive for β-human chorionic gonadotrophin (HCG). Immunohistochemistry, alkaline phosphatase-anti-alkaline phosphatase (APAAP) method, β-HCG, 100×.

negative lymph nodes. Nevertheless, a final course of PEI chemotherapy was given, since only a macroscopic clearance could be achieved and the lungs still contained visible changes.

β-HCG remained above normal values for almost 5 months maintaining the increased serum testosterone levels with a peak level of 48.5 nmol/l after 1 month of therapy. Signs of precocious puberty developed with penile enlargement to 6–7 cm, an increasing testicular volume up to 3 ml 2 months after initial presentation and scrotal pigmentation. Linear growth well above the 97th percentile was paralleled by bone age acceleration.

Presently, at 40 months follow-up from diagnosis, the patient is in sustained complete remission without evidence of disease: β-HCG, chest X-ray, and abdominal ultrasound scan are negative. There is no clinical or laboratory (normal serum phosphate, creatinine) evidence of nephrotoxicity following cisplatin and ifosfamide chemotherapy. The signs of precocious puberty have regressed, but owing to the long-lasting elevation of serum testosterone, bone age is still accelerated, currently by 21 months. No primary tumour has been found in the patient. The mother did not show any evidence of gestational trophoblastic disease, maternal β-HCG serum levels remained negative, but the placenta had not been examined.

Interphase FISH analyses were performed on isolated nuclei from the paraffinised tumour specimen. The tumour cells showed on average 4–8 centromeric signals specific for chromosome X, pentasomy of chromosome 1, and more than four copies of chromosome 17. Two Y chromosomes were observed. Co-hybridisation of centromeric and telomeric DNA sequences revealed, on average, five centromeric signals, whereas only three copies of the telomeric sequences were observed. This hybridisation pattern either indicates a loss of genetic material at the short arm of chromosome 1 or, less likely, a gain of the long arm and is designated as chromosomal imbalance.

2.1.2. Case 2

At the age of 4 weeks this girl (a non-identical first twin, born in the 38th gestational week, birth weight 2550 g, birth length 46 cm) gradually started to have recurrent episodes of flatulence, abdominal pain and later vomiting. At the age of 3 months, she presented with marked anaemia (Haemoglobin 70 g/l) and failure to thrive (weight and length below the 3rd percentile). There were no clinical signs of precocious puberty. Serum lactate dehydrogenase was elevated to 2906 U/l. Ultrasound scan revealed a large cystic liver tumour (6.7×6.2×5.5 cm) without ascites. There was a haemodynamically relevant shunt through the highly vascularised tumour. The patient received digoxin for congestive cardiac failure. She was anaemic and thrombocytopenic requiring repeated packed red cell transfusions. In order to stabilise the patient, a ligation of the right branch of the hepatic artery supplying the tumour was performed at the age of 4 months. Tumour biopsy was diagnostic, immunohistochemical staining was strongly positive for β-HCG and pan-cytokeratin and negative for AFP leading to the diagnosis of a choriocarcinoma (Figs. 3 and 4). Serum β-HCG was grossly elevated to 1 300 000 IU/l, serum AFP was within the age-related normal range. Serum oestradiol and progesterone were both grossly elevated. Intraoperatively large ovarian cysts were noted and marsupialised. The ovarian tissue contained benign theca lutein cysts. After the first course of cisplatin, etoposide (PE)-chemotherapy, which was commenced at the age of 3 months (cisplatin and etoposide in dosages as in case 1, no ifosfamide due to the age below 4 months), on the chest X-ray a round shadow in the left lower lobe measuring 1.5 cm in diameter interpreted as lung metastasis was noted. Therefore, two further courses of PEI chemotherapy (including ifosfamide) were administered. There was a partial response to chemotherapy with the pulmonary lesion disappearing after the second course of chemotherapy, the liver tumour shrinking to 3.4×4×4 cm and serum

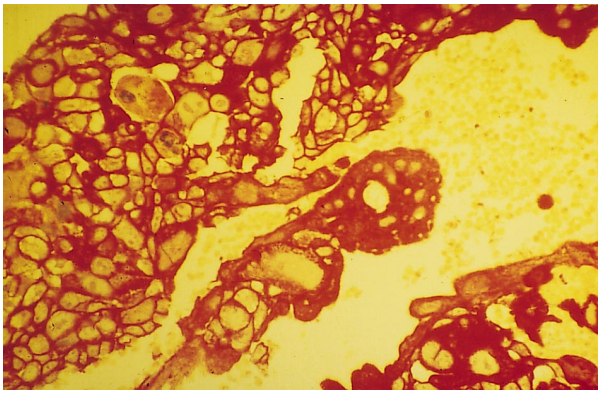

Fig. 3. Case 2. Biopsy from the liver presenting with cytokeratin-positive cytotrophoblast cells and multinucleated syncytiotrophoblast cells. Immunohistochemistry, alkaline phosphatase-anti-alkaline phosphatase (APAAP) method, antibody KL 1, 80×.

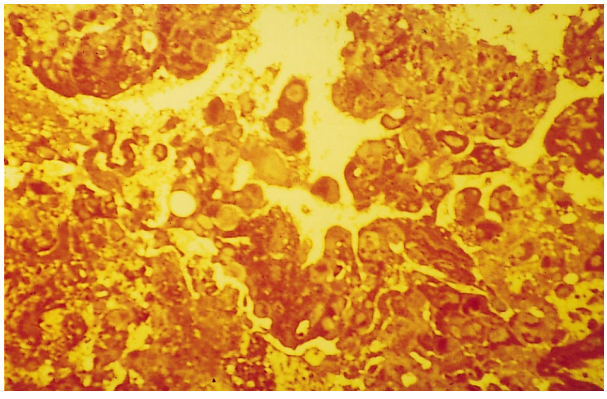

Fig. 4. Case 2. The tumour cells are intensively positive for human chorionic gonadotrophin β-(HCG). Immunohistochemistry, alkaline phosphatase-anti-alkaline phosphatase (APAAP) method, β-HCG, 40×.

β-HCG declining to 10.4 IU/l. The delayed liver tumour resection after the third course of chemotherapy with an extended right hemihepatectomy including the segments 4 to 8 at the age of $6\frac{1}{2}$ months revealed only necrotic tumour. Postoperatively β-HCG declined to <5 U/l. A fourth course of PEI chemotherapy was administered.

The patient is now at 42 months follow-up from diagnosis, thriving and without evidence of disease. Tumour marker and chest X-ray remain negative. The serum creatinine, phosphate and alkaline phosphatase are within normal ranges. At the age of 2 years, weight and height had dropped 1.5 kg and 5 cm below the 3rd percentile. Presently, at the age of 3 years 9 months, the weight has reached the 3rd percentile, there is catch-up growth, but the height has not yet reached the 3rd percentile. Histological work-up of the placenta was negative, both the mother and the other twin had persistently negative serum β-HCG levels. The second twin was healthy.

FISH analysis with centromere-specific DNA probes showed a polysomy of chromosome X on the isolated tumour nuclei. No further FISH data or data on the DNA content could be obtained due to the poor condition of the paraffinised tumour sample.

3. Discussion

Choriocarcinoma is a subentity of highly malignant germ cell tumours. According to the holistic concept by Teilum and colleagues [33], germ cell tumours originate from pluripotent germ cells that may differentiate along different lines into (highly) malignant tumours (such as yolk sac tumour, embryonal carcinoma, choriocarcinoma, seminoma/dysgerminoma) or histologically benign forms (such as teratoma) [4].

The present concept is that infantile choriocarcinoma becoming clinically manifest at or soon after birth, after an apparently normal pregnancy, originates from focal trophoblastic disease in the placenta. This concept is supported by the finding of Y chromosomes in the tumour from case 1.

A placental choriocarcinoma may lead to haematogenous metastases in mother and/or offspring [34]. Maternal gestational trophoblastic disease was present in 16 (i.e. 62%) of the 26 previously reported neonatal/infantile choriocarcinoma cases [7–10,12–17,19,24,27–30]. Only in two of these 26 cases [12,15] was the placenta histologically examined, a placental choriocarcinoma could, however, not be detected. A placental choriocarcinoma co-existent with an apparently normal fetus has been described [35], as well as cases with co-existent molar and healthy non-molar pregnancy [36,37]. There is genetic evidence by chromosome-specific locus-specific minisatellite probes, that choriocarcinoma can originate from a normal conceptus as well as from a hydatidiform mole [38].

Both cases showed polysomy of the X chromosome by interphase FISH analyses of the isolated tumour cells. In addition, in case 1, other chromosomes were found to be tetrasomic or up to octosomic. The FISH results support the assumption that these tumours are aneuploid which is a common finding in paediatric and adult germ cell tumours [32,39–46]. Germ cell tumours from adult patients frequently display isochromosome 12i(12q) or gain of the short arm of chromosome 12 generated by another mechanism [41]. In choriocarcinoma of women, chromosome 12 aberrations were found only in approximately one-third of the tumours [42]. In paediatric germ cell tumours chromosome 12 aberrations are also found infrequently [32,43], whereas other genetic aberrations, i.e. numerical and structural changes, are frequently found in these tumours [32,43–45]. Deletions at 1p36 or imbalances of the short and long arm of chromosome 1 were found in the majority of paediatric embryonal carcinomas and yolk sac tumours [32,43,44,47]. No deletion at 1p36 or imbalance of the short and long arm of chromosome 1 was found either in pure mature or mixed teratomas [32,44]. The 1p36.33 deletion/imbalance in paediatric choriocarcinoma has not previously been described. This finding may help to understand the genetic pathways of germ cell tumour differentiation or dedifferentiation. The diagnostic and prognostic importance of the other chromosomal abnormalities found in the male patient's tumour are not yet clear. The gender of both tumours was identical to the gender of the reported children. Whether the X-chromosomes in case 2 are of paternal or maternal origin is not known.

As choriocarcinoma is secreting β-HCG, treatment response can be estimated by the decline in serial serum β-HCG levels [48]. Serum β-HCG or the historic frog pregnancy test were invariably positive in all tested infantile choriocarcinoma cases. Thus, serum β-HCG provides a very useful non-hazardous diagnostic tool helping to avoid delay in diagnosis and initiation of treatment in infantile, as well as in maternal choriocarcinoma. The endocrinological effects of elevated serum β-HCG may lead to precocious puberty and accelerated bone age in the affected infants. These effects were marked in case 1. The elevated testosterone levels took several months to resolve, the accelerated bone age persisted. This persistent endocrinological effect after tumour remission has not been described previously in infantile choriocarcinoma.

As neonatal/infantile choriocarcinoma — according to the above described concept — is of placental origin, the stillborn [12,15], neonatal (11 children) [11,16–18,21,23,26–30] and infantile (13 children) [5–10,13,14,19,20,22,24,25] choriocarcinoma cases reported in the literature (see Table 1) are discussed together. In 19 (73%) of the 26 previously reported neonatal/infantile choriocarcinoma cases, the liver was involved [5,7,9–11,

Table 1
Neonatal and infantile choriocarcinoma, treatment and outcome

[Ref.]	Age at presentation	Age reached	Antitumour treatment	Outcome
[5]	36 days	48 days	None	DOD
[6]	7 months	7 months	S	DOC[a]
[7]	7 weeks	7 weeks	None	DOD
[8]	1 month	7 months	S	DOD
[9]	5 months	7 months	None	DOD
[10]	5 weeks	5 weeks	S	DOC[a]
[11]	At birth and 6 weeks	3 months	None	DOD
[12]	Term	–	None	IUFD
[13]	2 months	3 months	L+S	DOC[a]
[14]	2 months	6 weeks	None	DOD
[15]	Term	–	None	IUFD
[16]	Birth	24 days	C	DOD
[17]	1 day	20 days	None	DOD
[18]	4 weeks	4 weeks	None	DOD
[19]	8 weeks	1 year+	C+S	CR
[20]	5 months	42 months	S+C+Rx+ABMT	DOD
[21]	12 days	2 years+	S+C	CR
[22]	4 months	10 months	S+C+Rx	DOD/DOC[b]
[23]	2 weeks/7 weeks	8 weeks	None	DOD
[24]	7 weeks	3 months	None	DOD
[25]	3 months	3 months	None	DOD
[26]	2 weeks	3 weeks	None	DOD
[27]	Birth/3 weeks	4 weeks	None	DOD
[28]	Birth	38 days	None	DOD
[29]	Birth	38 days	C	DOD
[30]	Birth	38 days	C	DOD
Case 1	4 months	44 months+	C+S	CR
Case 2	3 months	45 months+	L+C+S	CR

ABMT, autologous bone marrow transplantation; C, chemotherapy; DOC, dead of complication; DOD, dead of disease; IUFD, intrauterine fetal demise; Rx, radiotherapy; S, surgery; CR, complete response; L, ligation of tumour-supplying artery.

[a] Intra-/perioperative death.

[b] Pneumonia.

13–15,17,19–21,23,25–30], a lung involvement was reported in 17/26 (65%) of the children [5,6,8,10,11,13–16,19,22–26,29,30]. 2 patients required red cell transfusions in the neonatal period, were discharged and presented again later [23,27]. Both liver and lung tumours might be considered as haematogenous metastases of a placental primary tumour.

The prognosis for paediatric metastatic choriocarcinoma has been very poor. Surgery is technically very difficult due to the highly vascularised friable tumours and not curative in a disseminated metastatic situation. Historic intra- and perioperative mortality was high. In 8 (31%) reported cases, a (partial) resection was performed [6,8,10,13,19–22], 1/8 children died during the operation [10], 2/8 children within 24 h of surgery [6,13].

Chemotherapy was given to 7/26 (27%) of the patients reported in the reviewed literature [16,19–22, 29,30]. Under the presumptive diagnosis of a hepatic angiosarcoma, 2 patients were unsuccessfully treated with steroids and doxorubicin [29,30]. One non-responding patient received methotrexate monotherapy [16]. 4 patients received multi-agent chemotherapy [19–22]. Only 3 of these 4 cases responded to chemotherapy. One of them, however, died after the third relapse and extensive treatment including radiotherapy, multi-agent chemotherapy and repeated autologous bone marrow transplantations [20]. One of the two responding and surviving babies in the literature was treated with primary liver tumour resection and four courses of BEP chemotherapy (bleomycin, etoposide, cisplatin) [21]. In the case of the other surviving child with a choriocarcinoma, the tumour occurred simultaneously in mother and infant. Treatment of this infant consisted of BEP chemotherapy and delayed tumour resection [19].

Radiotherapy was employed in 2 cases [20,22], both patients had advanced disease and died.

In 12/26 (46%) of the previously reported cases, the diagnosis could only be established on post-mortem examination [5,7,11,12,15,17,18,25,26,28–30].

The reported 2 additional cases from the MAKEI series are comparable to the cases cured by surgery and BEP chemotherapy [19,21], as a modern cisplatin-containing chemotherapy regimen was employed. In our cases, chemotherapy was given prior to a delayed tumour resection. This makes resection of the highly vascularised and very friable choriocarcinoma technically easier, reduces the risk of a possibly fatal haemorrhage and avoids unnecessary mutilation. Resection of the lung metastases was not required [49], as they responded well to chemotherapy. In case 2, a ligation of the tumour-supplying branch of the hepatic artery was performed to stabilise the patient initially. This was previously described by Aozosa and colleagues [13]. However, in that case, the child died due to bleeding 4 days after the initial ligation of the right hepatic artery on the day of a secondary partial liver resection. Considering the life-threatening nature of the disease, it seems justified to treat paediatric non-resectable choriocarcinoma patients aggressively with platinum-containing regimens as platinum has proven efficient in women with advanced choriocarcinoma [50,51], as well as in paediatric testicular choriocarcinoma [52].

Interestingly, in our cases, neither of the mothers were affected nor the other non-identical twin sibling in case two.

4. Conclusions

In infantile choriocarcinoma:

- Diagnostic delay can be avoided by early measurement of the serum tumour marker β-HCG in suspected cases. Biopsy of the highly vascularised

partially necrotic tumours can be non-diagostic unless HCG staining is used.

- BEP or PEI combination chemotherapy was curative in two cases each reported in the literature and observed in the cooperative MAKEI germ cell tumour study. In three of the cases, chemotherapy was administered prior to a delayed resection.
- The endocrinological effects induced by β-HCG in affected infants may persist longer than the tumour itself.
- The genetic alterations in one case resemble those found in infantile embryonal carcinoma and yolk sac tumour.

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