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BRIEF REPORT

Choriocarcinoma in neonates and infants: A severe but curable disease

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Abstract

Choriocarcinoma in neonates and infants (N-CC) is an extremely rare, but aggressive cancer, frequently observed with concomitant maternal disease. A retrospective, bi-national study of patients treated in France and Poland for infantile choriocarcinoma analysed eight cases of N-CC, median age of 6 weeks. All tumours were diffuse. Six patients received a platinum-based regimen, and five had delayed surgery on residual distant tumour sites. At the end of follow-up, four patients were in complete remission and four had died of the disease. In all but two cases, mothers had simultaneous metastatic choriocarcinoma. Even if the outcome remains poor, patients could be cured with multimodal therapy.

KEYWORDS

chemotherapy, choriocarcinoma, maternofetal transmission, neonatal tumour

Abbreviations: hCG, human chorionic gonadotropin; N-CC, neonatal choriocarcinoma.

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1 | INTRODUCTION

Choriocarcinoma in neonates and infants (N-CC) is a rare and poorly known malignant trophoblastic tumour arising from a gestational event. It is commonly recognised as the result of metastatic progression of a placental choriocarcinoma, and occurs in around one of 160,000 pregnancies.¹ N-CC onset usually occurs between 0 and 6 months of age, and its outcome remains frequently fatal. Histologically, malignant cells proliferate from abnormal maturation of the trophoblast during embryonic development or following malignant transformation of a hydatidiform mole.² Initially developing from trophoblastic cells, it corresponds to a tumour placental allograft in the mother, and can lead, through hematogenous dissemination, to metastatic involvement in both the mother and foetus.^{3,4} First symptoms in infants are usually of sudden onset pallor, anaemia, hepatomegaly and digestive, pulmonary or urinary bleeding due to the diffuse tumour spread. The outcome is rapidly fatal, most of the time due to haemorrhagic complications. The diagnosis is sometimes suspected in infants when the tumour has been previously detected in the placenta, or when the mother is found to have choriocarcinoma metastases before the birth.³ High serum human chorionic gonadotropin (hCG) hormone level confirms the diagnosis. Due to its rarity, no specific therapeutic recommendations are available

2 | RESULTS

To better analyse this rare tumour, we performed a retrospective binational study. We selected patients aged 0–6 months, with N-CC confirmed by pathology and/or by significant elevation in serum hCG level, and treated in France or in Poland from January 2000 to December 2022 (<https://rnce.inserm.fr/>). Institutional review board approval was obtained. Clinical characteristics were directly extracted from medical records.

Eight cases, four males and four females, with N-CC were selected (Table 1). In all but two cases, the mothers had simultaneous metastatic choriocarcinoma. During pregnancy, one mother had neurologic symptoms due to a cerebral stroke and another COVID-19 infection. All deliveries were uneventful with normal immediate adaptation to extrauterine life for all babies. None of them presented with immediate neonatal anaemia, except the newborn whose mother had COVID-19. For all infants, diagnosis was suspected after the first clinical symptoms appeared, even for the two patients whose mothers were receiving therapy for choriocarcinoma. Main telling signs were digestive (five cases) and haemorrhagic (four cases) with frequent hepatomegaly (five cases). Median age at N-CC diagnosis was 6 weeks (range: 4–22). All patients had anaemia (median haemoglobin 6.8 g/dL; range: 5.4–11.4) and high serum hCG (median 72,000 IU/L; range: 5952–272,759). In addition, the disease was confirmed by pathology findings in six of eight cases. All tumours were diffuse, and metastatic sites mainly affected the lungs (seven cases), liver (six cases), brain (three cases), pelvis (one case) and/or intestine (two cases; multiple possible).

One patient, initially diagnosed with cystic, diffuse, unresectable lymphangioma, initially received vincristine and interferon therapy, which was ineffective. After correction of the diagnosis, due to poor general condition, only supportive care was delivered. One patient underwent autopsy and postmortem diagnosis following sudden death. Six patients received a dose-adapted platinum-based chemotherapy regimen (Table 1). First-line chemotherapy regimen included mainly a dose-adapted etoposide–carboplatin regimen (four cases), exclusively in three cases (range: five to seven courses), associated with three subsequent lines of therapy (Patient 7). One included etoposide. Finally, a 5-month-old patient (Patient 4) initially received a VIP regimen (etoposide–ifosfamide–cisplatin), followed by several lines of therapy due to tumour resistance. Overall, five patients had wide residual distant site tumour resection after neoadjuvant chemotherapy: liver (two cases, associated with hepatic thermal ablation in one child), brain, pelvis and thorax (one case each). Residual viable cells were present in three cases.

At the end of follow-up, four patients remained in complete remission, including one after three lines of therapy due to a refractory tumour, and four died of the disease. No toxic deaths occurred. The median follow-up for patients still alive is 5 years (range: 2–11). All affected mothers are alive after chemotherapy (four French cases + two Polish cases) and surgery (one case).

3 | DISCUSSION

This study confirmed that N-CC is rare. There were only eight cases over a 22-year period in two countries, and it is frequently associated with a maternofoetal transmission. Since the first case of “chorioepithelioma” published by J. L. Emery in 1952, only 44 case reports were published up until 2023 (Table 2: complete list of references available under request to corresponding author).³ Our study of the literature confirmed that this disease affects very young children. Due to the rarity of the disease, no therapeutic consensus is available. However, recent experience has confirmed that patients might be cured through multidisciplinary care with platinum-based chemotherapy, with dose adapted to the patient’s young age, and removal of all residual tumour sites. Despite this, the outcome can remain dismal mainly related to the rapidly aggressive nature of the disease, the infants’ poor general condition at diagnosis and the difficulties of delivering efficient poly-chemotherapy regimens in very young infants due to the relative immaturity of their organs.^{5,6}

Even if N-CC is a very rare tumour, this diagnosis should be evoked when faced with serious, unexplained symptoms occurring in an infant with severe anaemia, or with healthy newborns in the case of maternal placental choriocarcinoma, for whom systematic screening must be performed.⁷ The French register of trophoblastic diseases recommends that all newborns whose mothers have placental choriocarcinoma should have a plasma hCG test. If this is normal, no further test is required. Conversely, if the hCG level is high, a tumour workup and a paediatric oncology opinion should be sought. In particular, initial N-CC symptoms can be unspecified, with digestive disorders

TABLE 1 Clinical characteristic of infants with choriocarcinoma.

Year of diagnosis	Maternal age (years)	Sex	Affected mother	Gestational age (weeks)	Weight at birth (kg)	1st symptoms date (weeks)	Symptoms	Age at diagnosis (weeks)	Time to first symptoms and diagnosis (weeks)	Hb level at diagnosis (g/dL)	Plasma hCG level (IU/L) at diagnosis	Affected organs	Treatment	Outcome	Age at death or last FU (months)
Case no. 1 France	31	F	Yes	36	2400	4	Hepatomegaly; mother history	4 weeks	1	11.4	27,000	Brain, liver	Chemotherapy (7 VP16-carboplatin), abdominal surgery	First CR	60
Case no. 2 France	25	M	Yes	40	3540	2	Feeding difficulties; hematemeses	5 weeks	21	5.4	72,000	Brain, liver, intestine, lungs	No dedicated therapy (vincristine-interferon for initial wrong diagnosis)	Died from the disease	1
Case no. 3 France	ND	F	No	40	3400	1	Vomiting, haemorrhagic shock, sudden death	6 weeks	1	5.8	5952	Autopsy: Lungs, liver (brain not evaluated)	-	Died from the disease	1.5
Case no. 4 France	30	M	Yes	40	3430	5	Lower intestine haemorrhage	5 weeks	2	7.4	19,422	Liver, lungs, intestine	Chemotherapy (5 VP16-carboplatin)	First CR	132
Case no. 5 France	35	M	Yes	39	2270	21	Abdominal pain; early puberty	22 weeks	6	7.3	27,860	Liver, lungs, nodes	Chemotherapy (3 VIP then other lines*), abdominal surgery	Died from the disease	10
Case no. 6 France	32	F	No	41	4090	8	Vomiting hypotonia	8 weeks	1	6.0	1,286,495	Mesosalpinx, lung	Surgery, chemotherapy (6 VP16-carboplatin), pelvic surgery	First CR	121
Case no. 7 Poland	27	M	Yes	37	3095	27 days	Digestive haemorrhage; pallor	4.5 weeks	0.5	6.8	2,813,000	Liver, lungs	Chemotherapy (VP16)	Died from the disease	1
Case no. 8 Poland	28	F	Yes	37	2900	28 days	Feeding difficulties; anemia; activity reduction	32 days	0.5	6.4	2,710,759	Brain, liver, lungs	Chemotherapy (6 VP16-carboplatin, 4 VIP then other lines*), Omentum and liver surgery with hepatic thermal ablation	Fourth CR	24

Note: Other lines included: *, methotrexate, vinblastine, bleomycin, cisplatin, doxorubicin; °, methotrexate, D-actinomycin, cyclophosphamide, cisplatin, doxorubicin, bleomycin. Abbreviations: CR, complete remission; F, female; FU, follow-up; M, male; ND, not detailed; VIP, etoposide, ifosfamide, cisplatin.

TABLE 2 Literature data on choriocarcinoma in neonates (44 published cases).

Clinical characteristics	Results	Median	Range	Missing data	Total number of patients analysed
Age at first symptoms (weeks)		5.6	0–20	8	36
Male/female ratio	21/17			6	38
Affected mother	23			8	36
Initial symptoms in the infant ^a :					
Digestive	19				
Cutaneous pallor	17				
Hepatomegaly	10				
Neurologic	9				
Tumour lump	9				
Respiratory	6				
Absence (maternal history)	5				
Haemorrhage	5				
Cardiac dysfunction	4				
Time to diagnosis (weeks)		3	0–21	7	37
Affected organs ^a :					
Liver	37				
Lung	31				
Brain	10				
Skin	9				
Intestine	5				
Bone	2				
Ovaries	1				
Haemoglobin level at diagnosis (g/dL)		5.8	1.4–9.7	22	22
hCG level at diagnosis (IU/L)		1,018,763	131–2,813,000	22	22
Therapy:					
Exclusive chemotherapy	9			19	25
Exclusive surgery	3				
Surgery + chemotherapy	13				
Surgery + chemotherapy + radiotherapy	1				
No therapy (palliative)	20				
Outcome:					
Death before diagnosis	20				
Death from disease	11				
Toxic death	–				
Remission	13				

^aMultiple possible.

such as vomiting or feeding difficulties. This was the case for 87% of patients in our study and 43% in the literature. Even if initial diagnosis may be misleading, serum hCG analysis is a helpful tool for making an early diagnosis. The clinically leading symptom of severe bleeding is explained by tumour characteristics, as choriocarcinoma cells have a high tendency of vascular invasion and destruction, reflecting the physiology of syncytiotrophoblasts during placental development. This may well explain the occurrence of multifocal haemorrhage and

the risk of distant hematogenous spread. Imaging can show single or multiple lesions with variable aspects, but highly vascularised images are evocative of diagnosis. Main differential diagnoses, at this age, in light of rapidly growing highly vascularised masses are infantile fibrosarcoma, immature haemangiomas (non regressive or regressive immature congenital hemangiomas) or other sarcomas such as rhabdoid tumour or infantile rhabdomyosarcoma.^{8–10} Biopsy should take account of the potential haemorrhagic risk.

Overall, due to histologic similarities with choriocarcinoma in older children, and despite a different embryological origin, regimens are mainly platinum compound based and inspired by malignant germ cell tumour protocols adapted to the patient's age and weight. In addition, chemotherapy regimen dosages are frequently adapted from protocols used in other neonatal paediatric cancers (neuroblastoma, retinoblastoma, infantile sarcoma).¹¹ Drug metabolism is primarily managed by the liver. Hepatic enzymes involved in phase I and II reactions are still in maturation in newborns and infants. At birth, CYP450 enzymes (phase I) have low activity, which increases during childhood, reaching adult level during puberty. Conjugation (phase II) reactions like glucuronidation are reduced at birth before reaching adult levels by 6–12 months.¹² Glomerular filtration rate is low at birth and increases to adult value at 6–12 months, which explains why the plasma half-life of certain cytotoxic drugs can be prolonged. In addition, tubular function and biliary excretion are also low at birth and reach adult values, respectively, at 1–2 years and 6 months. For these reasons, the authors suggest etoposide–carboplatin as first-line treatment in infants with N-CC and suggest avoiding cisplatin administration that maybe too highly toxic. Overall drug dosages are prescribed in mg/kg, with additional further reduction according to patient weight and age for the first courses before adapting them to overall tolerance.^{12,13} Carboplatin serum dosages help to adapt chemotherapy.¹⁴ Notably, in mothers with high-risk gestational trophoblastic neoplasia, the EMA regimen (etoposide, methotrexate, D-actinomycin) alternating every week with CO (vincristine, cyclophosphamide) is a standard of care.¹⁵ As the biology of infants' tumours is similar, an option could be to use this type of regimen in children too. No real comparison exists, and various regimens have been used in the past.¹⁶

In conclusion, this study confirms that N-CC, even though it is a constantly diffuse disease, could be curable, thanks to adapted platinum-based poly-chemotherapy combined with the removal of all residual tumour lesions.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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