

Case Report

Chorangiocarcinoma in a term placenta with postpartum pulmonary metastasis: a case report and review of the literature

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Abstract: Chorangiocarcinoma is an extremely rare primary placental neoplasm, with only five cases reported in the literature (Table 1). Some researchers considered it as a bona fide chorangiocarcinoma, but most cases described a chorangioma with abnormal trophoblastic proliferation. In spite of atypia in cytology, marked mitosis and tumor necrosis, chorangiocarcinoma was always reported benign. No metastasis or invasion has been described yet. Here, we report the first case of chorangiocarcinoma with postpartum pulmonary metastasis, combined with markedly elevated maternal β hCG level. Microscopically, the tumor is characterized by large caliber stem villus-like structures, composed of chorangioma in the stroma and surrounding malignant trophoblasts. These neoplastic trophoblasts are pleomorphic and represents striking necrosis, increased mitotic figures and high Ki-67 labeling index. Immunostaining shows these neoplastic trophoblasts are cytotrophoblasts and few intermediate trophoblasts. Overall, chorangiocarcinoma may be a chorangioma with variable trophoblastic proliferation, consisting of atypical trophoblastic hyperplasia, carcinoma in situ or even metastatic carcinoma.

Keywords: Chorangiocarcinoma, metastasis, chorangioma, choriocarcinoma, trophoblastic lesions

Introduction

In this article we present the first case of chorangiocarcinoma in a term placenta with pulmonary metastasis has occurred during the postpartum period, combined with markedly elevated maternal serum β hCG level and a review of the literature.

Case history

A 27-year-old woman had an emergency Lower Segment Caesarean Section on demand at 39+1 weeks of gestation on May 9, 2012. During the surgery, amniotic fluid was clear and its amount was approximately 500 ml. One female infant in cephalic presentation was born weighing 3950 g with Apgar 9/10. The baby cried loudly after cleaning off fluids from nose and mouth. The placenta was expelled spontaneously and completely.

Pathologic findings

Grossly, the placenta is 19 cm×17 cm×3.5 cm in size. The fetal surface is yellowish and the

maternal surface is intact. Cut surface shows a yellow-gray nodule located 3 cm away from the base of the umbilical cord. The nodule is well-demarcated, measuring 5 cm×4.5 cm×3.5 cm, bulging from the fetal surface by the size of 2.5 cm×1.5 cm×1.0 cm. The cut surface is heterogeneous with some regions appear micropapillary, while others have a yellow-gray caseous appearance. The cord is attached eccentrically, having 3 vessels and is 20 cm in length and 1.2 cm in the greatest diameter.

Microscopically, the nodule in the placenta is mostly composed of abnormal stem villus-like structures and papillary terminal-like villi. Stem villus-like structures are filled with aggregates of proliferative, expanded and hyperemic tiny blood vessels, along with small amounts of irregular trophoblast masses (**Figure 1B**). Canalis haemalis infiltration is not seen. There are large amounts of tiny capillaries in irregular terminal-like villi. Villi are covered by proliferative trophoblasts in an irregular layer structure. The trophoblasts have marked cytologic atypia and

Chorangiocarcinoma and metastasis

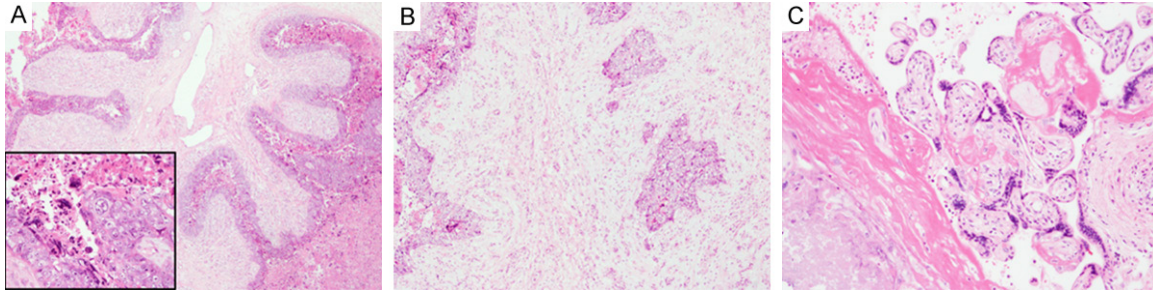


Figure 1. H&E stain. A. (20×) Chorangiocarcinoma is characterized by aggregates of closely packed capillaries in the villus stroma resembling chorangioma, which is covered by multilayers of pleomorphic polygonal cells with prominent nuclei (inset, 200×). There is striking necrosis in the center of these tumor cells, and some of the necrotic cells are apparently multinucleated. B. (40×) Small amounts of irregular neoplastic trophoblasts represents as masses in the chorionic villi. C. (100×) Trophoblastic layers are replaced by fibrinoid deposits in large areas at the junction between tumor and adjacent placenta.

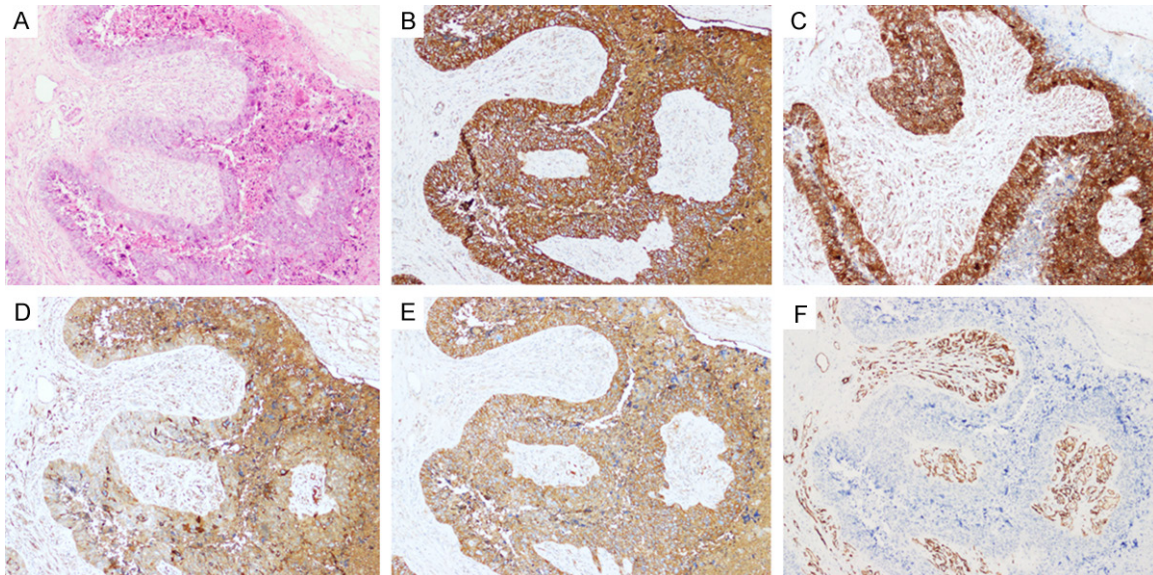


Figure 2. Immunohistochemical profiles of chorangiocarcinoma (40×). A. H&E stain. B. Strong CK expression in neoplastic epithelial cells. C. β -Catenin strongly positive expression in cytotrophoblasts. D. Immunostaining for β hCG is positive for trophoblasts with scattered or focal strong reactivity. E. E-Cadherin is diffusely positive in trophoblastic cells. F. CD31 immunostaining demonstrates capillary vasculatures within large caliber chorionic villus stroma.

prominent mitotic activity (**Figure 1A**). Basal lamina has an irregular surface with edema and liquefaction. Tumor necrosis is considerable within intervillus spaces. Tumor tissue far away from villus vessels is almost completely necrotic, but tumor cells near the vessels still have residual nuclear outline. Tumor nodule is well-circumscribed from the surrounding placental parenchyma. At the junction a thin line of fibrin is deposited and little villus necrosis left, the inner side of the junction is thoroughly necrotic and the outer side is deposited with diffuse perivillous fibrin including scattered cal-

cification, without obvious tumor invasion (**Figure 1C**). Fetal membranes and the umbilical cord are unremarkable.

Immunostaining for trophoblasts are as follows: CK, β -Catenin and E-Cadherin, strongly positive; hCG, positive, with scattered or focal strong reactivity; P63, weakly positive signal is found in the partial cell nucleus; Ki-67, proliferation index is approximately 80%; Endothelium in the placental villi is immunoreactive for CD31; Basal lamina is weakly reactive for Collagen IV; hPL, PLAP, S-100, HNK-1 (CD57) and Inhibin- α , negative (**Figure 2**).

Chorangiocarcinoma and metastasis

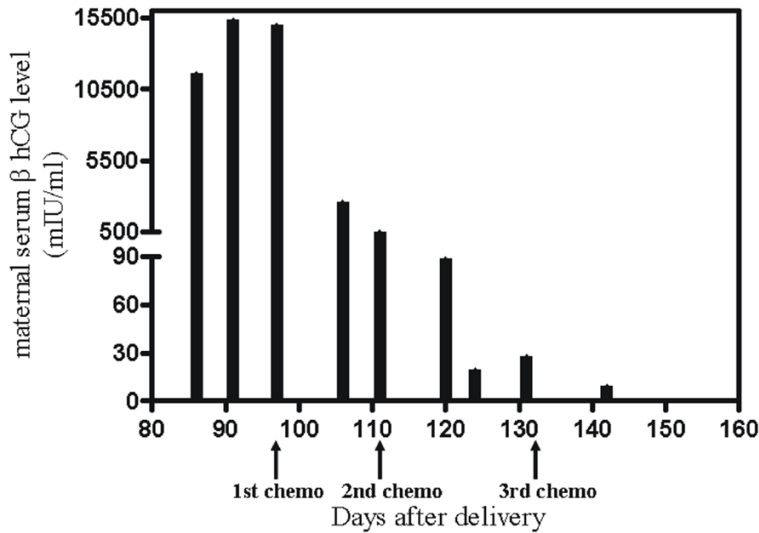


Figure 3. Serum measurement of maternal β hCG titre showed metastatic chorangiocarcinoma had great respond to EMA-EP chemotherapy.

Treatment and follow-up

Three months after birth, the infant was in good health on physical examination. However, the maternal serum β hCG level was elevated to 11705.49 mIU/ml and continued to rise to 15409.14 mIU/ml five days later. Pelvic Magnetic Resonance (MR) image for the mother showed asymmetric endometrium thickening, an appearance suggesting placental site trophoblastic tumor. Chest CT scan showed a 3 cm \times 2.6 cm spherical-like mass, which was homogenous and sharply circumscribed, located in the middle lobe of right lung (**Figure 4A**). Enhanced CT demonstrated an enhanced nodular margin. Pelvic ultrasound revealed a normal sized uterus and flaky heterogenous echogenic areas measuring 7 mm \times 20 mm with indistinct border within the endometrial cavity. Ultrasound also noted a 14 mm \times 10 mm hypoechoic, well-circumscribed mass in the region of left ovary. Anechoic area in recto-uterine pouch is 13 mm in anteroposterior diameter. The radiologic sign on chest CT and pelvic ultrasound, together with clinical exams were interpreted with chorangiocarcinoma of the placenta metastasized to lung.

The patient underwent EMA-EP chemotherapy against the carcinoma. The level of serum β hCG began to decrease during the treatment continually. After three courses of chemotherapy, as expected, serum β hCG was dropped to

10.60 mIU/ml (**Figure 3**). Chest CT scan also revealed the mass in the middle lobe of right lung was shrunk to 2.6 cm \times 2.4 cm (**Figure 4B**), with homogenous density and distinct border. Enhanced CT showed a bit enhanced margin, which was suspicious with encapsulated effusion. 6, 9, 12, 24 and 48 months follow-up of maternal serum β hCG showed a normal level, the mass in the lung was almost the same as before and the infant had no evidence of disease.

Discussion

Chorangiocarcinoma is an extremely rare primary neoplasm of the placenta. There have been only a few cases noted worldwide, and bona fide invasion or metastasis in mother or neonates has never been reported so far (**Table 1**). Chorangiocarcinoma was first proposed by E. Jauniaux in 1988 as a combined lesion of chorangioma and choriocarcinoma, showing vascularity together with atypical trophoblast proliferation [1]. The authors drew the conclusion that chorangiocarcinoma is a true tumor rather than hamartoma. The second case was reported by C. Trask and colleagues, as choriocarcinoma in situ with atypical proliferation of fetal capillaries. The lesion presented histologically as vascularity and malignant trophoblasts [2]. Two similar cases were also described, with one patient accompanied with hydatidiform mole [3, 4].

From pure morphologic grounds, another two cases showed that chorangiocarcinoma is more malignant for chorangioma combined with large amounts of atypical hyperplastic trophoblasts, with the characteristics of striking necrosis, focal multinucleated and pleomorphic cells with high mitoses [5, 6]. However, compared with classical choriocarcinoma, there is once again neither stromal invasion nor metastasis in these reported chorangiocarcinoma. The author thought chorangioma is like a frame which surround and support these trophoblasts.

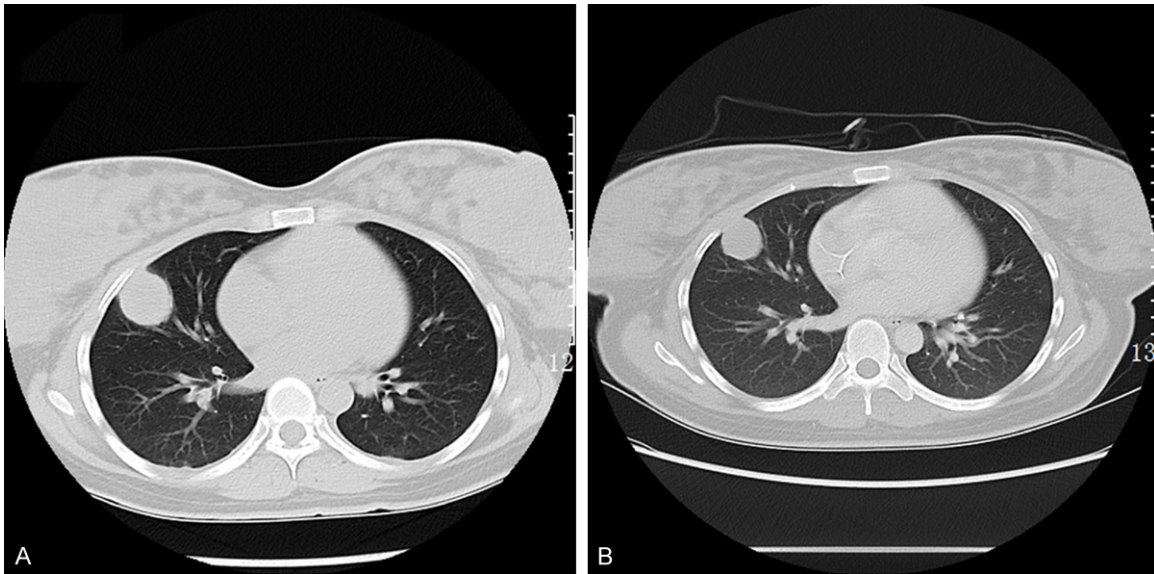


Figure 4. Contrast of metastatic chorangiocarcinoma in chest CT image before (A) and after (B) chemotherapy. Chest CT image showed a well-circumscribed round nodule decreasing from 3 cm×2.6 cm to 2.6 cm×2.4 cm after using chemotherapeutic agents.

Nevertheless, probably more common than scattered reports of chorangiocarcinoma would imply, for two different groups Khong and Ogino both found that chorangioma are often together with increased proliferation of trophoblasts [7, 8]. Khong et al. reviewed 23 cases of chorangioma and found that 15 in 23 cases fit the “chorangiocarcinoma” histological criteria, for abundant vascularity and atypical trophoblastic proliferation [7]. Therefore, most cases of chorangiocarcinoma might be a misnomer and actually variants of chorangioma [7-9].

Chorangioma (placental hemangioma) is a common benign non-trophoblastic disease of placenta, while intraplacental choriocarcinoma, or choriocarcinoma in situ is a rarely and malignant trophoblastic disease. Choriocarcinoma in situ usually occurs in a term or near term placenta, and tumor size is mostly tiny. Maternal metastases were frequently found, combined with markedly elevated serum β hCG titre [10-13]. Two patients presented with intraplacental choriocarcinoma developed metastatic diseases in both mother and her infant [11, 14]. A collision neoplasm of these two diseases might occur at a very low rate. Aonahata et al. described a specific case of choriocarcinoma adjacent to hemangioma in the same placenta, also with no metastasis. The transition of these two diseases were not seen as the interface was full of necrosis [15].

To summarize the reported instances, in the placenta, chorangiocarcinoma presents as a single discrete solid lesion commonly resembling an infarct or tan/yellow-gray nodule. Tumor size varies from 1.5 cm to 8 cm in diameter. Most tumors are located under the chorionic plate or at the margin. On histological examination, chorangiocarcinoma is composed of chorangioma within the villous stroma and surrounding atypical trophoblasts, and in some cases there is marked necrosis and high mitotic figure strongly indicating malignant nature.

Present case of chorangiocarcinoma is unique for malignant behavior and high sensitivity to chemotherapy, supporting this is a true case of malignant chorangiocarcinoma. Immunostaining confirmed the tumor cells are arising from trophoblastic cells. However, the patient refused to take lung biopsy, so we still lack direct confirmation of the histology of the lung mass. According to the clinical course, the patient was healthy before pregnancy and diagnosed chorangiocarcinoma postpartum prior to the suspicious pulmonary metastasis and elevated β hCG was found. We thought lung lesion is metastasized from the placental chorangiocarcinoma.

Compared with gestational choriocarcinoma, our case has similarities and differences. It shows elevated maternal β hCG level after baby

Chorangiocarcinoma and metastasis

Table 1. Cases of reported chorangiocarcinoma

Case	Age	G/P	Duration of gestation	Presentation	Gross features	Maternal β hCG	Metastasis	Follow-up period
Jauniaux et al. (1988)	35	G4P3	35 wk	CS for shoulder presentation and vaginal bleeding	A well circumscribed round nodule, 1.5×1.5 cm	Negative	None	9 mo pp
Trask et al. (1994)	36	G3P1	36 wk	NSVD (a twin gestation)	Infarct, 3×2.5×1.2 cm	Negative	None	3 mo pp
Guschmann et al. (2003)	31	G1P0	34 wk	Terminated for fetal distress and IUGR	Infarct, 3 cm	Negative	None	Unknown*
Ariel et al. (2009)	23	G1P0	37 wk	CS for severe perineal condylomata	Infarct, 8×8×5 cm	Negative	None	Not stated
Faes et al. (2012)	36	G3P2	at term	At term in labor	A well circumscribed mass, 8×7×6 cm	Negative	None	3 mo pp
Present case	27	G1P0	39 wk	CS	A well circumscribed yellow-gray nodule, 5×4.5×3.5 cm	Elevated	Yes	48 mo pp

Abbreviations: G, gravidity; P, parity; CS, Cesarean section; NSVD, normal spontaneous vaginal delivery; IUGR, intrauterin growth restriction; mo, month; pp, postpartum; *, unknown for a non-English paper.

Chorangiocarcinoma and metastasis

birth, metastasis to the lung and sensitivity to chemotherapy. For histological features, both lesions have pleomorphic nuclei and high mitotic activity. However, this case differs from choriocarcinoma for absence of admixed trophoblast types and vessel invasion.

From pure morphologic view, it's still difficult to totally rule out metastatic anaplastic carcinoma which originated from the mother. Thus it would be good to perform microsatellite profile of the carcinoma, to demonstrate that it is identical to that of the fetus and not the mother. However, the patient refused. A poorly differentiated carcinoma may contain minor foci of trophoblastic differentiation, but there are usually normal trophoblast layers between the villus and the intervillous tumor mass. In this study, tumorous epithelial cells are almost uniformly in the tumor region without interface normal layers.

It's still an open question for the origin and pathogenesis for chorangiocarcinoma. Traditionally, choriocarcinoma are characterized by biphasic pattern of syncytiotrophoblast and cytotrophoblast. Mao et al. observed that the majority of these mononucleate cells in choriocarcinoma were intermediate trophoblasts (IT), along with cytotrophoblasts at 5% (in 31% cases). These ITs, which were positive for MUC-4, HLA-G, and Mel-CAM, might arise from the small portion of trophoblastic stem cells-transformed cytotrophoblasts. The cytotrophoblasts were positive for nuclear β -Catenin, a cytotrophoblast-associated marker [16]. In our work, based on microscopic and immunohistological findings, it seems that these neoplastic trophoblasts of chorangiocarcinoma developed from stem cells and differentiated into cytotrophoblasts and few ITs.

For the pathogenesis of hemangioma in placenta, there are controversial hypotheses. Some thought it was due to abnormal angiogenesis as villous formation in early trimester [17]. Others thought adverse gestation stimulates including hypoxia and ischemia play the major role in vascular proliferation. It is supported by the fact that placental hemangioma is closely related to pre-eclampsia [8, 18, 19]. In addition, according to epidemiology study, pregnancies at high altitude bear elevated incidence of chorangioma [20]. In this study, we speculate that prominent and diffuse prolifera-

tion of vessels inside villous stroma may be reactive response to bad perfusion of maternal circulation due to surrounding neoplastic trophoblasts. This is also supported by the fact that chorangiocarcinoma is never found in early trimester cases, as the reactive form can not built in a short time.

For investigation of prognostic factors in choriocarcinoma, studies indicate that ABO blood group is highly related to the incidence and prognosis of choriocarcinoma. Women of group A face the highest risk when having group O husband [21]. Interestingly, the mother in the present instance is also A type with a O-type husband.

In summary, chorangiocarcinoma is an extremely rare tumor usually found in a term or near-term placenta. Chorangiocarcinoma may have uneventful sequelae or result in maternal lung metastasis at the time of diagnosis. Associated metastatic disease may have full response to chemotherapy. Thorough examination of uterine, and distant metastatic sites including lung, liver, brain, breast, combined with serial follow-up of β hCG level when diagnosed is indispensable.

Disclosure of conflict of interest

None.

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Chorangiocarcinoma and metastasis

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