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Case Report

Multiple metastatic gestational trophoblastic disease after a twin pregnancy with complete hydatidiform mole and coexisting fetus, following assisted reproductive technology: Case report and literature review

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ABSTRACT

Objective: Twin pregnancy with complete hydatidiform mole and coexisting fetus (CHMCF) is rare and associated with severe complications during pregnancy and subsequent gestational trophoblastic disease (GTD). We encountered a case of multiple metastatic GTD after a twin pregnancy with CHMCF, following conventional in vitro fertilization (IVF). Only one case of metastatic GTD after CHMCF due to assisted reproductive technology (ART) has been reported. Here, we present the clinical course and reveal the clinical features of CHMCF after ART through a literature review.

Case report: A 42-year-old primigravida woman had an abnormal pregnancy (i.e., CHMCF) by IVF. She had persisting severe vaginal bleeding, which led to termination of her pregnancy at 10 weeks of gestation. Pathohistological examination revealed that this was a case of CHMCF. Five weeks after the termination, the serum β-human chorionic gonadotropin level was still extremely high, and systemic contrast-enhanced computed tomography revealed a tumor in the uterine corpus and more than 30 lung nodules. After 11 cycles of combination chemotherapy with etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine (EMA/CO) to treat high-risk GTD, hysterectomy was needed as radical therapy.

Conclusion: Cases of CHMCF following ART may also have higher malignant potential and higher risk of GTD development and become more aggressive biologically. The clinical course of CHMCF after ART seems to be almost the same as that without ART based on the results of literature review.

Introduction

Twin pregnancy with complete hydatidiform mole and coexisting fetus (CHMCF) is rare, with the incidence ranging from 1 per 20,000 to 100,000 pregnancies [1]. These pregnancies are difficult to manage because they can be associated with severe complications (e.g., massive vaginal bleeding, hyperthyroidism, preterm delivery, preeclampsia, and/or fetal death) and subsequent gestational trophoblastic disease (GTD). Only a dozen cases of CHMCF after assisted reproductive technologies (ART) have been reported to date (Table 1) [2–16]. We encountered a case of multiple metastatic GTD after a twin pregnancy with CHMCF, following conventional in vitro fertilization (IVF) and embryo transfer (ET). Eleven cycles of combination chemotherapy, with etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine (EMA/CO), and hysterectomy were needed for radical therapy. To the best of our knowledge, only one case of metastatic GTD following CHMCF from ART has been reported [2]. Here, we present the patient's clinical course and reveal the clinical features of CHMCF after ART through literature review.

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Table 1
Literatures reported cases of complete hydatidiform mole coexisting with a fetus after assisted reproductive technologies.

Type of ART	Published Year	Authors [reference number]	Maternal age	Gravida/Para	Number of ET	Maximum serum β hCG (mIU/mL)	Delivery or termination (weeks)	Complications during pregnancy	Live neonate (birth weight)	GTD	Metastases	Chemotherapy (number of cycles)	Hysterectomy
IVF	1994	Jinno et al. [2]	35	0/0	2	1,024,000	31	hyperthyroidism, lung metastasis	yes (1,729g) but died #1	yes	lung	MA (6)	no
	1995	Cheng et al. [3]	29	0/0	3	501,808	29	preterm delivery	yes (986g)	no	no	no	no
	1999	Montes-de-Oca-Valero et al. [4]	41	1/0	3	840,000	27	preeclampsia, massive vaginal bleeding	yes (980g)	no	no	no	no
	2002	Kwon et al. [5]	35	5/2	NM	174 ng/mL	21	chorioamnionitis	no	yes	no	MTX (1)	no
	2005	Lin et al. [6]	39	NM	4	2,861	36	massive vaginal bleeding	yes (1960g) #2	yes	no	MTX (1)	no
	2005	Wu et al. [7]	36	1/0	4	685,000	24	massive vaginal bleeding, fetal death	no	no	no	no	no
	2008	Hsu et al. [8]	31	NM	1	NM	14	fetal death	no	no	no	no	no
		Present case	42	0/0	2	647,472	9	massive vaginal bleeding	no	yes	lung	EMA/CO (11)	yes
ICSI	2001	Petignat et al. [9]	29	NM	2 #3	191,437	15	preeclampsia (lung edema), massive vaginal bleeding	no	yes #4	no	no	no
	2006	Hamanoue et al. [10]	40	2/0	3	NM	33	preterm delivery	yes (1544g)	no #5	no	no	yes #5
	2008	Dodes st al. [11]	32	0/0	4	870,000	26	hyperthyroidism, preterm delivery	yes (720g) but died #6	no	no	no	no
	2008	Yamada et al. [12]	33	0/0	3 #7	774,840	15	preeclampsia (massive pleural effusion)	no	yes	no	MTX (2) → EMA/CO (8)	yes
	2008	Vandenhove et al. [13]	31	0/0	2	1,638,200	18	hyperthyroidism, massive vaginal bleeding	no	yes	no	MTX	no
	2009	Dolapcioglu et al. [14]	34	0/0	NM	198,000	29	pregnancy induced hypertension, massive vaginal bleeding	yes (1180g) #2	no	no	no	no
	2009	Kashani et al. [15]	29	1/0	NM	73,000	19	preeclampsia, fetal death	no	no	no	MTX #8	yes
	2012	Ferraz et al. [16]	39	2/0	2	1,402,565	13	none	no	yes	no	NM	NM

ART: assisted reproductive technologies, ET: embryo transfer, GTD: gestational trophoblastic disease, NM: not mentioned.
IVF: in−vitro fertilization, ICSI: intracytoplasmic sperm injection.
MA: methotrexate and actinomycin-D, MTX: methotrexate, EMA/CO: etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine.
#1: The infant was born with asphyxia and died 4 hours post partum, secondary to severe respiratory distress syndrome.
#2: Small for gestational age.
#3: One cleavage-stage embryo was obtained from a single pronucleus (1 PN). This 1 PN was at the origin of the hydatidiform mole.
#4: Repeat curettage was performed for the high concentration of β -humman chorionic gonadotropin, revealing decidual change without evidence of trophoblastic tissue on histopathology.
#5: Hysterectomy was performed at the time of cesarean section for the prevention of GTD.
#6: The infant died of extreme prematurity.
#7: Triplet pregnancy of complete hydatidiform mole with two coexsisting fetuses.
#8: Chemotheraphy was performed for the prevention of GTD.

Case report

A 42-year-old primigravida woman became pregnant by IVF at a private infertility clinic. In all embryos, two pronuclei (PN) and two polar bodies were confirmed the day after IVF, before they were frozen. Two early embryos (grade 2) were thawed and transferred into the uterus after assisted hatching in a cycle, in which she took drugs to suppress her own hormones. Then, she took hormone replacement therapy to prepare her uterus. Forty-five days after the transfer, she was referred to our hospital with vaginal bleeding suspected as threatened abortion complicated with large subchorionic hematoma. Upon examination, there was persistent vaginal bleeding from the external os of the uterus, and an enlarged, well-movable, goose egg-sized uterus was palpable in her pelvis. On ultrasound examination, one gestational sac (GS) with fetal cardiac activity was detected, and the fetus with a crown-rump length of 18.9 mm was visualized (Fig. 1). In addition, the region of low echogenicity, which had been suspected as a large subchorionic hematoma around the GS, was multivesicular and considered a hydatidiform mole. Serum β-human chorionic gonadotropin (β-hCG) level was 450×10^3 mIU/mL. Chest roentgenography did not reveal metastases. These results were suggestive of (a) CHMCF, (b) partial hydatidiform mole, or (c) threatened abortion complicated with large subchorionic hematoma. CHMCF or partial hydatidiform mole is associated with the severe complications during pregnancy and subsequent GTD. However, the patient and her family elected to continue the pregnancy. She was admitted to our hospital immediately and rested in bed. She had continuous bleeding, which caused her hemoglobin to decrease rapidly by approximately 2.0 g/dL in a week, to 7.5 g/dL, and her serum β-hCG level increased to 647×10^3 mIU/mL. Consequently, the patient and her family decided to terminate the pregnancy. Aspiration curettage was performed on the 10th day of hospitalization. On macroscopic examination, products of conception could be easily distinguished, with abundant fragments of marked cystic swollen villi, from fragments of grossly normal chorionic villi. Pathohistological examination revealed numerous edematous villi with frequent cistern formations and circumferential areas of hyperplastic trophoblast, which were typical of a complete hydatidiform mole. Moreover, these extravillous cytotrophoblasts and villous stromal cells were not immunoreactive to p57kip2. Other chorionic villi fragments corresponded to normal parenchyma composed of immature intermediate and mesenchymal villi, which were adequate for 8 weeks of gestation. We concluded that this case was a twin pregnancy with CHMCF. Recurrent aspiration curettages were added on the 10th and 18th day after the first aspiration curettage. However, after 5 weeks of initial aspiration curettage, the serum β-hCG level was still 310×10^3 mIU/mL (>1000). We diagnosed the patient with persistent GTD. Systemic contrast-enhanced computed tomography (CT) was performed immediately. The primary GTD tumor, which measured 23 mm, was detected in the uterine corpus, and more than 30 lung nodules, which were considered metastases, were also detected. The maximum size of the lung nodules is 13 mm in various scales. The uterine tumor exhibited a hyperintense signal on T2-weighted images (T2WI) and prominently enhanced on contrast-enhanced T1-weighted images (T1WI) with flow void on magnetic resonance images (MRI) (Fig. 2a,b). The patient was at FIGO stage III (i.e., GTD extends to the lungs with or without known genital tract involvement), and her World Health Organization prognostic score was 9, that is, (1) 42 years old (1 point), (2) molar pregnancy is antecedent (0 point), (3) within 4 month from the index pregnancy (0 point), (4) pretreatment β-hCG level ($\geqq 10^5$ mIU/mL; 4 points), (5) largest tumor size (<3 cm; 0 point), (6) lung metastases (0 point), (7) more than eight metastases (4 points), and (8) before chemotherapy (0 point). Hence, combination chemotherapy with EMA/CO for management of high-risk GTD (clinical choriocarcinoma) was administrated every 2 weeks. After seven cycles of chemotherapy, her serum β-hCG level returned to normal. Four additional cycles of adjuvant chemotherapy with the same protocol were administered. After the chemotherapy, multiple metastatic pulmonary lesions disappeared completely on CT. However, the uterine tumor, which measured approximately 1 cm, could be detected as a hypointense signal on T2WI and could still be enhanced on contrast-enhanced T1WI on MRI (Fig. 2c,d). We could not completely ignore that the viable malignant tumor cells might still be present at a region in the uterus. The patient ultimately chose hysterectomy for radical therapy (Fig. 3a). Pathohistological examination revealed that histiocyte and spindle-shaped granulation tissue formed a hyperplasia with remarkable necrosis. No viable cancer cells remained (Fig. 3b,c). Additional treatment was not given, and the patient remains healthy five years after the surgery.

Discussion

Managing CHMCF is difficult because it is associated with various severe complications such as fetal death, vaginal bleeding, preeclampsia, and subsequent GTD [1]. Therefore, early termination of pregnancy had traditionally been advised. However, in 2002, Sebire et al. suggested that women with CHMCF have a chance of a livebirth, and continuation of their pregnancies has been considered through other treatment alternatives. They concluded that approximately 40% of CHMCF resulted in livebirths without

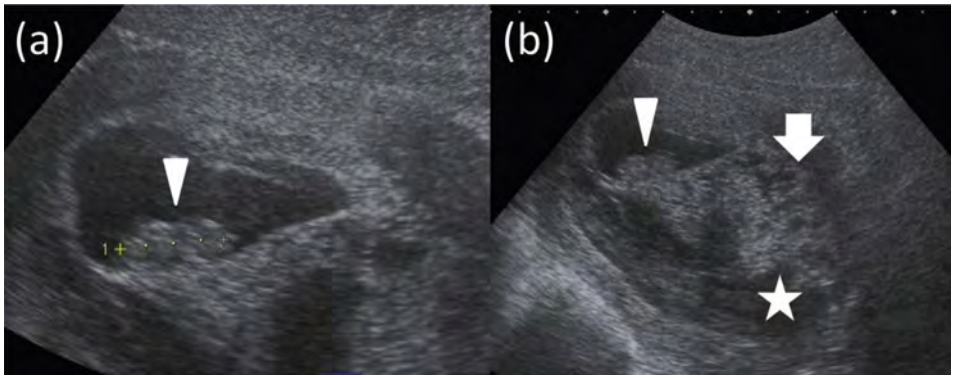

Fig. 1. (a) On transabdominal ultrasound examination, one gestational sac (GS) with fetal cardiac activity was detected and the crown-rump length (18.9 mm) of the fetus (triangle) was appropriate for gestation (8 weeks and 6 days). (b) The region of low echogenicity (asterisk), which had been suspected as a large subchorionic hematoma around GS, was multivesicular (arrow) and then considered as hydatidiform mole. The viable fetus (triangle) was also detected.

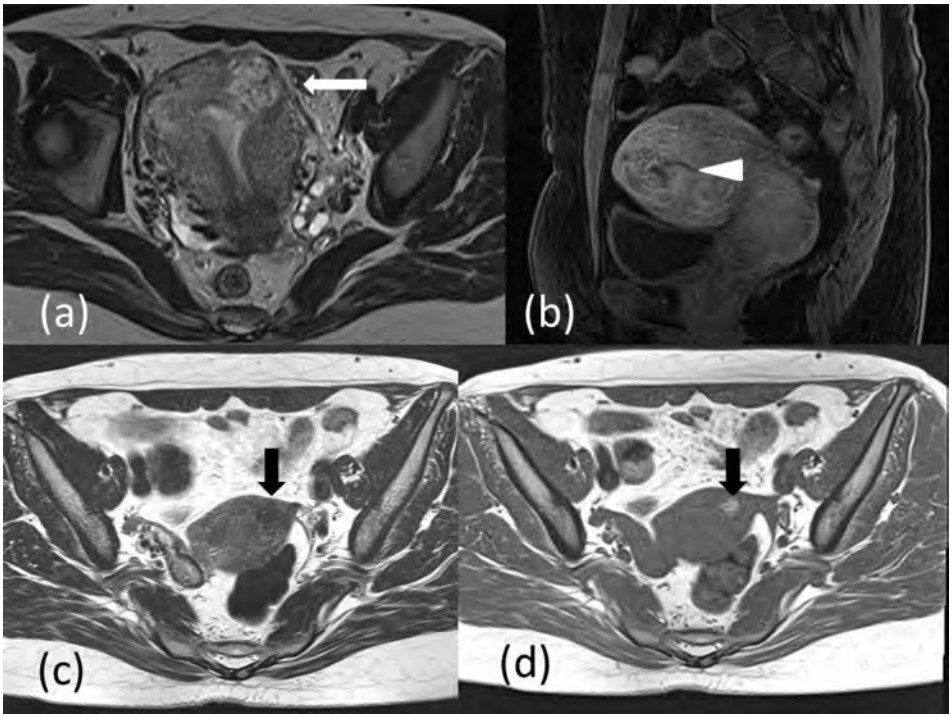

Fig. 2. Magnetic resonance images. (a) The uterine tumor (arrow) exhibited a hyperintense signal on axial T2-weighted image at the time of diagnosis as metastatic gestational trophoblastic disease. (b) The prominent tumor with flow void (triangle) on sagittal contrast-enhanced T1-weighted image. (c) The uterine mass (arrow) reduces in size, approximately 1 cm, and could be detected as a hypointense signal on T2-weighted images after 11 cycles of combination chemotherapy. (d) The enhanced region (arrow) on contrast-enhanced T1-weighted image.

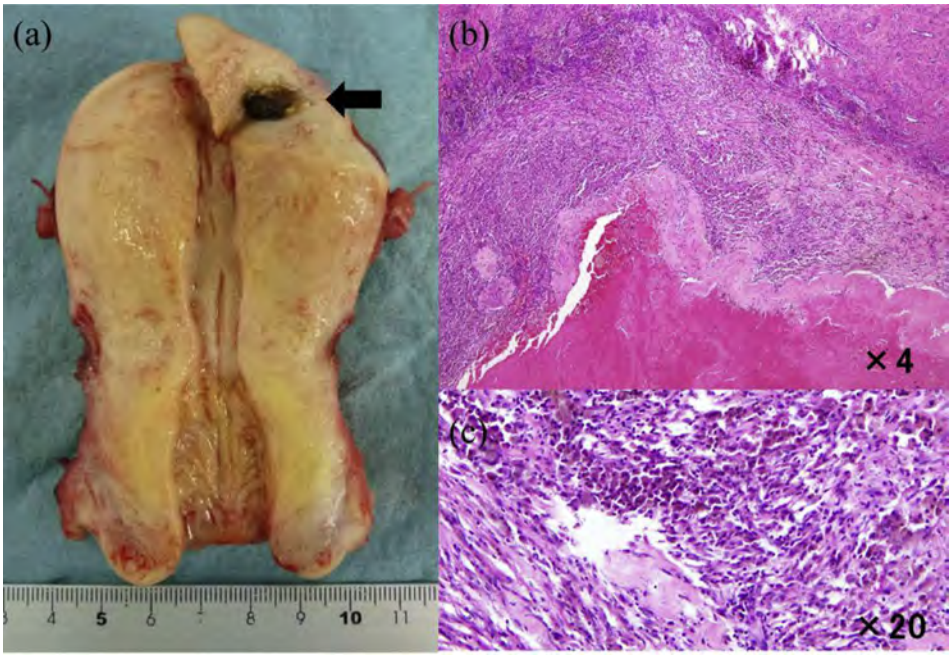

Fig. 3. (a) Macroscopic findings. The necrotic region that measured approximately 1 cm was observed in the fundal region of the uterus (arrow). (b, c) Histological examination revealed histiocyte and spindle-shaped granulation tissue that formed a hyperplasia with remarkable necrosis. No viable cancer cells remained (hematoxylin and eosin stain, objective magnification × 4 × 20).

significantly increasing the risk of subsequent GTD, and they reported that the overall incidence of GTD was 19.5% [1]. However, they diagnosed CHMCF using histological records, without genetic analysis; hence, partial hydatidiform mole would be included in the study. Therefore, it is now thought that the incidence of GTD after CHMCF is more than 50% [17,18]. This incidence rate is also much higher than that of GTD after simple complete hydatidiform mole (12.5%) [19].

There are several reports of CHMCF that occurred after ART (Table 1) [2–16]. The induced superovulation is one of the reasons

of an enucleated egg, given that a complete hydatidiform mole comes from a chromosomally "empty" ovum by multi-sperm fertilization. Petignat et al. warned that an embryo with one PN would develop into a complete hydatidiform mole [9]. However, in most cases after IVF or intracytoplasmic sperm injection, two PNs and two polar bodies have been confirmed in the oocytes. Jinno et al. discussed that observation of pronuclear and embryonic development under stereomicroscopy might not be able to identify and prevent a sporadic complete hydatidiform mole [2]. At present, identifying and preventing a complete molar gestation before the ET stage by microscopic examination of the pre-transferred embryo is impossible [3]. Hsu et al. reported a case of CHMCF following IVF, in which only one embryo was transferred, and speculated that there are two possible mechanisms of fertilization: by a diploid sperm or two haploid sperms [8]. The mechanisms of inducing CHMCF after ART will induce the disruption of the meiotic spindle and the loss of maternal chromosomes because of oocyte handling or due to fragmentation or degeneration of the oocyte [21].

When a pregnant woman is suspected of having CHMCF, the fetal karyotype should be identify by sampling the amniotic fluid or the chorionic villi to rule out partial hydatidiform mole [14]. Furthermore, in case of CHMCF, most patients and their physicians will have a clinical dilemma whether to provide immediate intervention or expectant management, especially in case of highly desired pregnancies, such as in patients after ART [5]. In the present case, fetal karyotyping could not be done because the patient had severe vaginal bleeding. Thus, her condition could not help in terminating the pregnancy in a week.

The clinical courses of our case and the 15 previously reported cases, which were twin pregnancies with CHMCF after ART, are shown in Table 1 [2–16]. Most cases were primigravida, and more than two embryos were transferred. Most cases had complications during pregnancy, and the pregnancy was terminated for these complications. The maximum gestational age at delivery was 36 weeks, and live deliveries occurred in 5 (31.3%) of the 16 cases. The chances of a live-birth for patients with CHMCF were the same as those reported previously [14]. These reports indicate that the extent of complications decide the pregnant period and the possibility of having a live neonate. Molar trophoblastic cells will be more benign; thus, and the patients very occasionally develop maternal complications including GTD. Cases (including our case) that have to be terminated early were biologically more aggressive and had a higher risk for development of GTD [14].

Some investigators reported that fetal survival rate was accompanied by signs of a less exuberant molar growth such as uterine volumes and lower hCG values. They also indicated that uterine enlargement and very high hCG were more aggressive trophoblasts [13]. However, some pregnancies of CHMCF develop malignancy irrespective of the time the pregnancy was interrupted, and even when intervention was given in early pregnancy, the risk of malignancy persists [20]. Serum hCG level, quantity of molar tissue, and gestation at the time of diagnosis are not reliable indicators of the malignant potential of a mole [4]. Moreover, hCG level is not valuable in predicting subsequent GTD cases that may require chemotherapy [22].

The incidence of GTD in the listed cases was 53.3% (8/15; excluding #5 in Table 1) and the risk of GTD was also the same as those in previous literatures [17,18]. Previous cases that developed lung metastases required multi-drug combination chemotherapy [2]. The present case had also more than 30 metastatic lung nodules of various sizes, and we thought the patient needed EMA/CO. Three patients underwent hysterectomy for radical therapy or for the prevention of GTD previously. In the present case, after the multi-cycle combination chemotherapy, the tumor, approximately 1 cm, could be detected still as a hypointense signal on T2WI and enhanced on contrast-enhanced T1WI on MRI, but pathohistological examination revealed that no viable cancer cells were present in the uterus. Consequently, hysterectomy might not be needed for radical therapy, but the patient ultimately chose hysterectomy. Besides, she had been given many cycles of EMA/CO which is strongly toxic to an ovum; thus, future pregnancy will be almost impossible.

In conclusion, case of CHMCF after IVF may also have higher malignant potential with higher risk for development of GTD and become more aggressive biologically. We revealed that the incidences of a live-birth and GTD for patients with CHMCF following ART were 31.3% and 53.3%, respectively, found through literature review. These fetal survival rate and risk rate of GTD were the same as those in previous literatures [14,17,18]. Therefore, the clinical course of CHMCF with ART seems to be almost the same as that without ART.

Conflict of interests

All authors declare that there is no conflict of interests regarding the publication of this paper.

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