

Case report

High-risk gestational choriocarcinoma with an unusual presentation and the treatment course of refractory or quiescent/minimally invasive disease

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1. Introduction

Approximately 20% of patients with high-risk gestational trophoblastic neoplasia (GTN) experience progression during or after primary chemotherapy, but 75%–80% of these individuals are still salvaged (Alifrangis et al., 2013). In a previous study, patients who failed to enter remission and had refractory disease had a poor prognosis with 5-year survival rates of 43% (95% confidence interval, 12%–73%) compared with those with relapsed disease (Powles et al., 2007). A proportion of patients with GTN have persistently low human chorionic gonadotropin (hCG) levels without clinical or radiological evidence of disease; this is called quiescent GTN (Ngan et al., 2012). Although representing a small proportion of all GTN cases, the management of patients with chemorefractory and quiescent/minimally invasive disease is often challenging.

We present a case of a patient with high-risk choriocarcinoma who entered remission once with primary chemotherapy but had refractory or quiescent/minimally invasive disease thereafter.

2. Case report

A 44-year-old Japanese woman, para 1-0-5-1, had her last menstruation in October 2002 and underwent dilatation and curettage (D&C) because of incomplete abortion at the end of November. She had experienced normal vaginal delivery at 22 years of age and induced abortion and spontaneous abortion twice each between 28 and 43 years of age. On May 31, 2004, she had atypical vaginal bleeding and underwent D&C, with a diagnosis of suspicious choriocarcinoma. On June

9, 2004, she was referred to our hospital. On admission, her serum hCG level was 155,926 mIU/ml and chest x-ray revealed multiple lung shadows in both lung fields. On June 10, 2004, during a computed tomography (CT) examination, she had sudden severe abdominal pain and shock, presumably hemorrhagic shock due to uterine perforation by choriocarcinoma. Emergency laparotomy was performed and uterine perforation was observed at the right side of the uterine fundus with a total of 2600 ml of intra-abdominal hemorrhage. Total abdominal hysterectomy was performed. The patient was ultimately diagnosed with high-risk choriocarcinoma, International Federation of Gynecology and Obstetrics (FIGO) stage III: 12 (Fig. 1).

EMA-CO was commenced as the initial chemotherapy regimen [Day 1: actinomycin D, 0.5 mg; etoposide, 100 mg/m²; and methotrexate, 100 mg/m²; followed by 200 mg/m² over a period of 12 h; Day 2: actinomycin D, 0.5 mg; etoposide, 100 mg/m²; and leucovorin, 15 mg every 6 h (4 doses, 24 h after the first methotrexate dose); and Day 8: vincristine, 1 mg and cyclophosphamide, 600 mg/m²]. After completing seven cycles, the patient's serum hCG reduced to the cutoff level. Three additional cycles of EMA-CO were administered, and the patient achieved remission (Fig. 2).

However, 4 weeks after the completion of EMA-CO, her serum hCG level increased to approximately 100 mIU/ml. No lesion was observed on CT scan and magnetic resonance imaging (MRI). Furthermore, chemotherapy was reinstated with 100 mg/m² of etoposide on days 1 and 2, 0.5 mg of actinomycin D on days 1 and 2, and 1000 mg/m² of methotrexate over a period of 24 h on day 1, followed by folinic acid rescue; on day 8, she was administered 150 mg/m² of etoposide and 75 mg/m² of cis-platinum (EP-EMA). The regimen was repeated every

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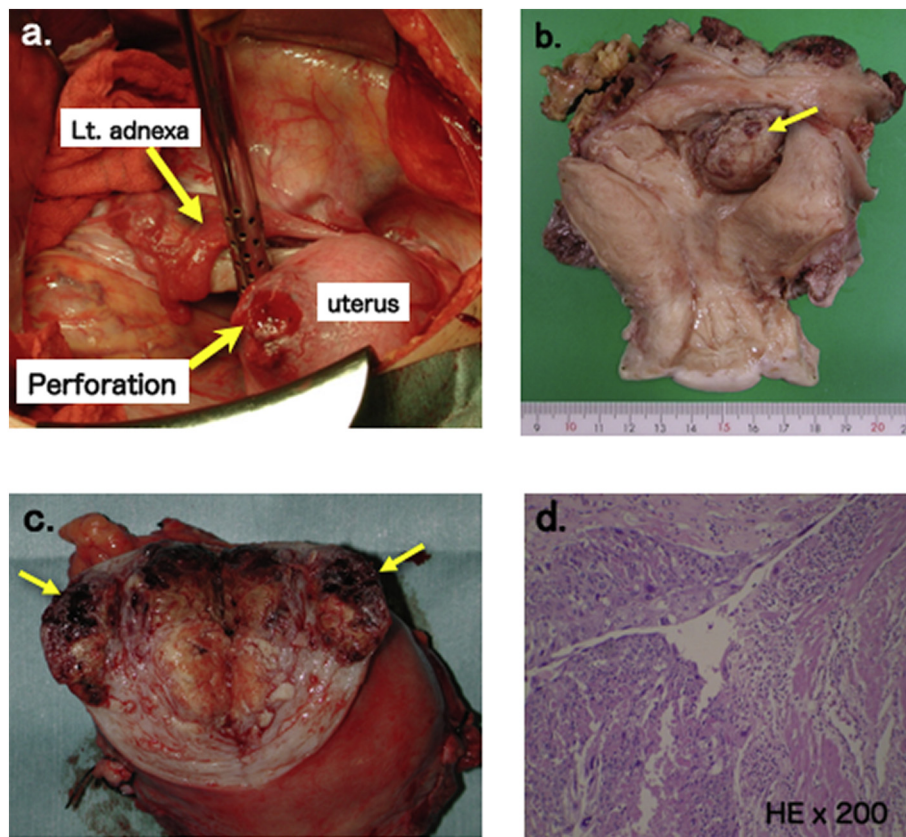


Fig. 1. a. Uterine perforation is observed on the right side of the uterine fundus. b. Choriocarcinoma protruding into the uterine cavity (arrow). c. Cut surface on the perforation site (arrows). d. Choriocarcinoma on the perforation site (hematoxylin and eosin, x200).

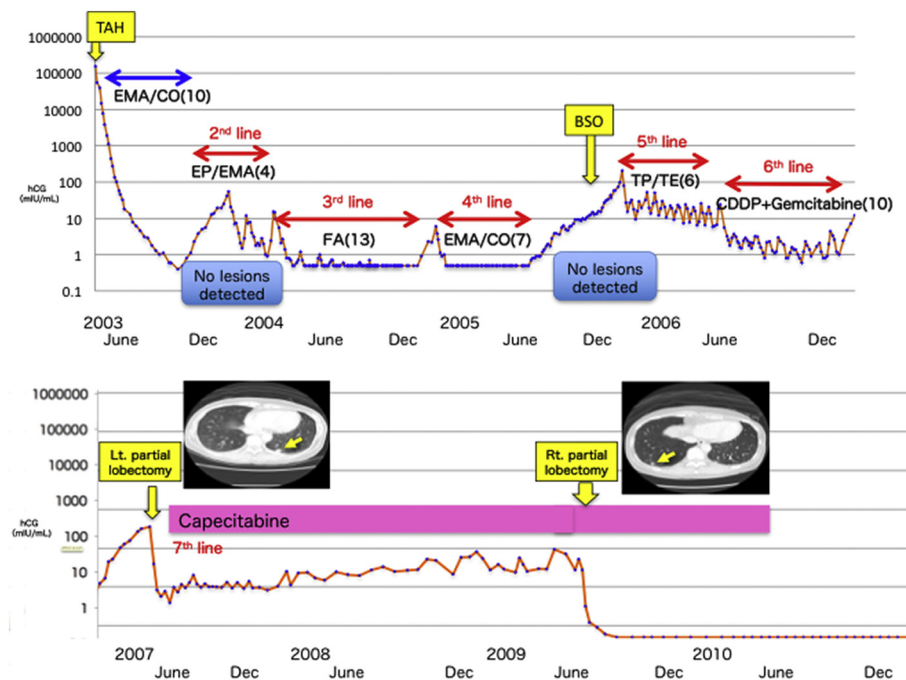


Fig. 2. Clinical treatment course.

14 days. Even after completing four cycles, her serum hCG failed to reduce to the cutoff level. She received a third-line regimen comprising 1500 mg/m² of 5-fluorouracil infusion over 8 h and 0.5 mg of actinomycin D on days 1–5 (FA) (Matsui et al., 2002). After completing 13 cycles with the FA regimen, her serum hCG level decreased to the

cutoff level. Two months after the completion of the FA regimen, her serum hCG level elevated once again to approximately 100 mIU/ml, and no lesion was observed on CT and MRI. During the course, she experienced grade IV thrombocytopenia and anemia. She again underwent seven cycles of EMA-CO and achieved remission. However, her

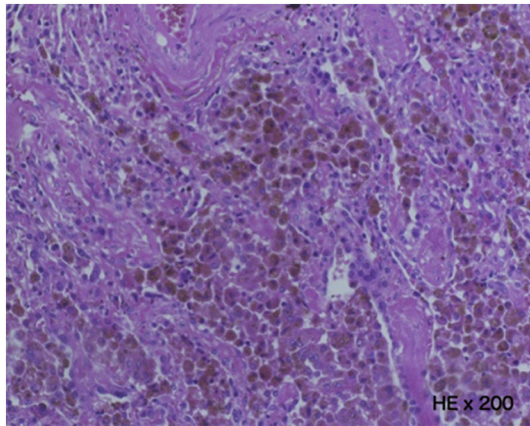


Fig. 3. Choriocarcinoma is confirmed pathologically in the removed left lung tumor (hematoxylin and eosin, x200).

serum hCG level elevated to approximately 100 mIU/ml again 3 months after completion of EMA-CO, and the patient underwent bilateral salpingo-oophorectomy, resulting in failure to demonstrate a choriocarcinoma pathologically.

Her serum hCG level remained constant at approximately 100 mIU/ml. A regimen comprising six cycles of paclitaxel (135 mg/m²)/cisplatin (60 mg/m²) alternating with paclitaxel (135 mg/m²)/etoposide (150 mg/m²) (TP/TE) regimen was administered. TP alternating every 2 weeks with TE formed one cycle of therapy (Wang et al., 2008). After completing six cycles of TP/TE, her serum hCG failed to reduce to the cutoff level and remained between constant at 20–80 mIU/ml. Additionally, she experienced grade IV thrombocytopenia with platelet infusion several times and had antiplatelet antibodies. We administered 1250 mg/m² of gemcitabine on days 1 and 8 combined with 75 mg/m² of cisplatin on day 1 (GC) (Pandian et al., 2004). Her hCG level decreased from 10 to 1 mIU/ml. After completing 10 cycles of GC, her serum hCG level elevated to 500 mIU/ml. Finally, CT revealed a solitary tumor in the left lung. Partial lobectomy of the left lung was performed, and pathological examination of the excised tumor confirmed choriocarcinoma (Fig. 3).

Postoperatively, her serum hCG level decreased to approximately 10 mIU/ml and was maintained at that level. We tried a less toxic drug, capecitabine, as the seventh-line chemotherapy at 2500 mg/m² for 2 weeks followed by 1 week of rest (Bianconi et al., 2007). The patient continued to receive capecitabine without severe adverse effect. During this period, her serum hCG level varied between 10 and 100 mIU/ml. Two years after left partial lobectomy, CT monitoring demonstrated a solitary mass in the right lung. In June 2010, partial lobectomy of the right lung was performed, and choriocarcinoma was confirmed pathologically (Fig. 4). Her serum hCG level decreased to the cutoff level. She received capecitabine for an additional 6 months after the second lung surgery without elevation of serum hCG. Eventually, the patient displayed no evidence of disease for 15 years after initial treatment and 9 years from the second lung resection.

3. Discussion

Our patient with high risk choriocarcinoma temporarily entered remission with hysterectomy and primary chemotherapy, but thereafter had refractory or quiescent/minimally invasive disease treated with seven lines of chemotherapy and salvage surgeries. During the treatment course, the patient had persistently low hCG levels, occasionally below the cutoff level, without clinical or radiologic evidence of disease for 4 years.

Drug resistance and relapse reportedly occur in approximately 7%–10% of high-risk GTN cases (Newlands, 2003). A proportion of patients with GTN have persistently low hCG levels without clinical or

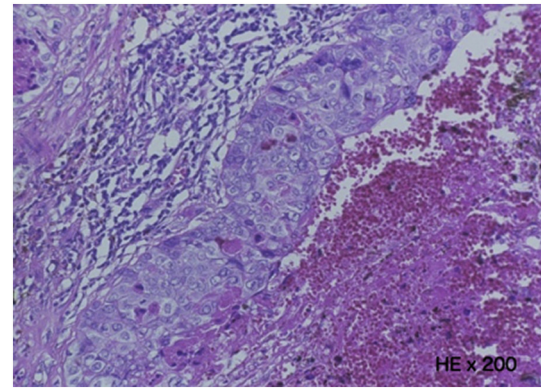


Fig. 4. Choriocarcinoma is confirmed pathologically in the removed right lung tumor (hematoxylin and eosin, x200).

radiologic evidence of disease; this is known as quiescent GTN (Ngan et al., 2012; Khanlian et al., 2003). Quiescent GTN is an inactive or benign phase of trophoblastic disease and arises from highly differentiated trophoblast cells. Cole et al. (Cole and Muller, 2010) demonstrated that quiescent GTN is 100% chemoresistant and proposed the definition of minimally invasive GTN. Minimally invasive GTN can be identified by a slow increase in total hCG with a doubling time of 2–6 weeks, < 40% hyperglycosylated hCG (hCG-H) of total hCG, and resistance to chemotherapy regimens. The measurement of hCG-H has been proposed for the diagnosis and management of quiescent and minimally invasive GTN, because hCG-H is a glycoprotein secreted by cytotrophoblast cells and is related to trophoblast invasion, cell growth, and promotion of placental implantation (Cole, 2010) and is the main form of hCG produced in active choriocarcinoma (Cole, 2012).

During the treatment course, our patient had persistently low hCG levels (< 200 mIU/ml), occasionally below the cutoff level, without clinical or radiologic evidence of disease for 4 years. Notably, her serum hCG level was persistently low, and the doubling time of hCG was 31 days after seven cycles of the second EMA-CO. Although the hCG-H assay is not feasible at our institute, it is possible that our patient was in the state of quiescent or minimally invasive GTN. Cole et al. (Khanlian et al., 2003) cautiously recommended halting the treatment until the trophoblastic disease meets biochemical criteria of growth and invasion, allowing patients to advance to a total hCG level of > 3000 mIU/ml before treatment with chemotherapy. However, the management of patients with chemoresistant or quiescent/minimally invasive GTN is often challenging. We tried seven lines of chemotherapy to overcome chemorefractory choriocarcinoma.

Four years after the initial relapse, radiological evidence of pulmonary metastasis was finally achieved, and the patient was salvaged by surgery. At that time, quiescent/minimally invasive GTN may have progressed to active GTN. Surgery alone can effectively salvage some patients with isolated foci of chemoresistant disease identified at the site of active disease to facilitate surgical resection and cure. Metastatic lung lesions related to drug resistance is amenable to surgery, and thoracotomy and lung resection, with a reported remission rate of up to 90%, should be considered (Alifrangis et al., 2012), particularly in a case of a solitary pulmonary nodule, no evidence of other metastatic sites or uterine disease, and an hCG level < 1000 mIU/ml. Again 2 years after salvage lung surgery was performed on the patient, pulmonary metastasis on the opposite side was salvaged by surgery. Finally, she displayed no evidence of disease 15 years after the primary treatment. Therefore, it is crucial to identify the site of active disease to facilitate surgical resection and cure.

Author contribution

The work presented here was carried out in collaboration among all

authors. YN, and YA designed methods, analyzed the data, interpreted the results, and wrote the manuscript. All authors (YN, TN, TN, YT, and YA) are chief doctors and treated the patients.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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