

Case report

Spontaneous regression of gestational trophoblastic neoplasia



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1. Introduction

Gestational trophoblastic neoplasia (GTN) includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor (Lurain, 2011). In Japan, when the serum hCG values after evacuation of a hydatidiform mole are above the regression curve and histological diagnosis is not possible, GTN is diagnosed as ‘clinical invasive mole’ or ‘clinical choriocarcinoma’. This diagnosis is made according to the Japan Society of Obstetrics and Gynecology (JSOG) classification using imaging tests including ultrasonography, chest X-ray, and computed tomography (CT) (Japan Society of Obstetrics and Gynecology, 2011). The hCG regression curve is drawn by connecting the points where the serum hCG titers are 1000 mIU/ml at 5 weeks, 100 mIU/ml at 8 weeks, and non-detectable at 24 weeks. The accuracy of histologic diagnosis using this classification has over 90% sensitivity (Sasaki, 2003). Clinical invasive moles diagnosed by the JSOG criteria are considered the equivalent of low-risk postmolar GTNs according to the FIGO criteria, and generally only need single agent chemotherapy.

Invasive moles occur after hydatidiform moles in 10–20% of cases. Chemotherapy is needed for treatment of invasive moles because 15–40% cases show lung metastasis (Lurain, 2010). Although almost all invasive moles, including clinical invasive moles or low-risk postmolar low-risk GTNs, may achieve primary remission after treatment, 1–3% of those show recurrence and develop into choriocarcinoma (Goto et al., 2004; Khan et al., 2003). This indicates that invasive mole or postmolar GTN requires prompt and adequate treatment.

Spontaneous regression of cancer is rare. The rate of spontaneous regression is estimated to be 1/60,000–1/100,000 (Cole, 1981). Several

mechanisms have been described to explain the spontaneous regression of cancer. These include stimulation of the immune process, endocrine influence, complete surgical removal, fever and acute infection, allergic reaction, the elimination of carcinogens, angiogenesis inhibition, enhanced apoptosis, and epigenetic mechanisms.

In this case report, we present two female cases with a diagnosis of low-risk GTN with lung metastases after hydatidiform mole who showed spontaneous regression without treatment.

2. Case reports

[Case 1] A 29-year-old woman (nulligravida) underwent abortion evacuation. A tissue sample taken at the time contained hydatidiform moles as determined by pathological examination. Because her hCG levels remained high (153.6 mIU/ml) 14 weeks after the evacuation, she was referred to our hospital. We monitored her hCG levels over time. At 26th week, the hCG levels remained high (29.8 mIU/ml) and CT showed two discrete lung metastases. One lung metastasis measured 5 mm in the right lower lobe and the other measured 8 mm in the left lower lobe. She was diagnosed with clinical invasive mole according to the JSOG classification. She was also diagnosed with postmolar GTN with FIGO stage III and a diagnostic score of 2 because her hCG levels had remained elevated for 6 months. While we were preparing for chemotherapy, her hCG levels declined little by little and she preferred to be followed up without any treatment. Finally, her hCG levels decreased spontaneously to the cut-off value at 43rd week (Fig. 1A). The CT showed disappearance of the lung metastases 75 weeks after the evacuation (Fig. 1B–E). She gave birth one year later. There has not been any clinical evidence of recurrence for over five years.

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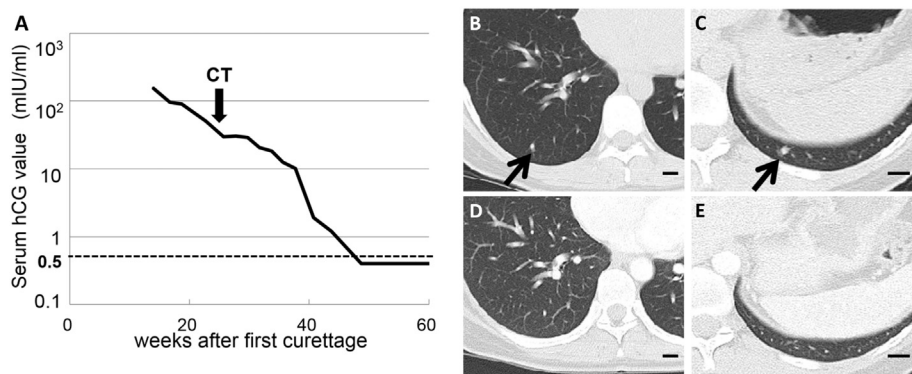


Fig. 1. (A) The clinical course of case 1. (B), (C) A chest CT scan shows two nodules (arrows) in the right lower lobe and the left lower lobe 26 weeks after evacuation. (D), (E) A chest CT scan shows regression of the tumors 75 weeks after evacuation. The slice diameter of the CT scan is 5 mm. Scale bar = 10 mm.

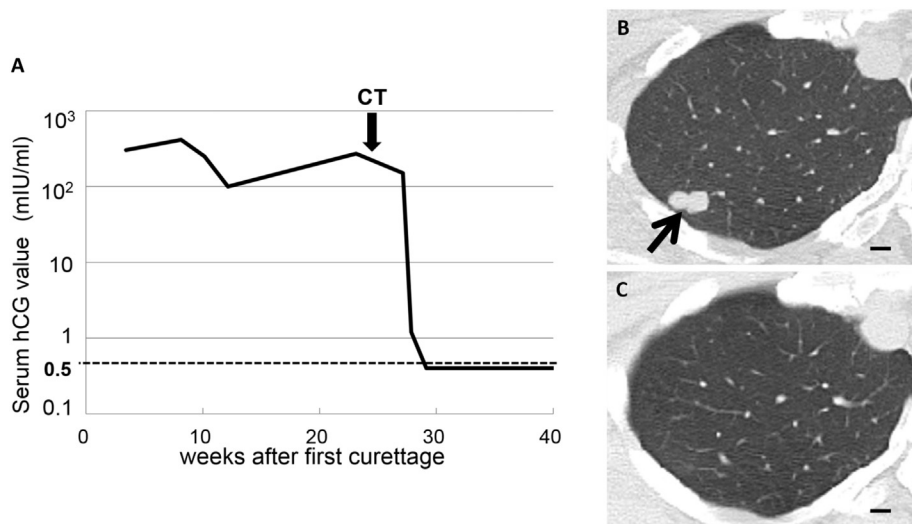


Fig. 2. (A) The clinical course of case 2. (B) A chest CT scan shows two adjacent nodules (arrow) in the right upper lobe 27 weeks after evacuation. (C) A chest CT scan shows regression of the tumor 87 weeks after evacuation. The slice diameter of the CT scan is 5 mm. Scale bar = 10 mm.

[Case 2] A 41-year-old woman (gravida 1, para 1) visited our hospital because she had undergone an evacuation at another clinic and the pathological diagnosis was hydatidiform mole. It was 12 weeks after the evacuation and her hCG level was 100.4 mIU/ml. She was followed up by another clinic from 13th to 23rd weeks. When she visited our hospital at 27th week, her hCG levels remained high (151.0 mIU/ml). Then, CT showed two adjacent lung metastases of 10 mm in the right upper lobe. These nodules were well-defined with rounded density. She was diagnosed with clinical invasive mole according to the JSOG classification and postmolar GTN with FIGO stage III and a diagnostic score of 3 because the hCG levels had remained elevated for 6 months. However, her hCG levels in 28th week decreased to cut-off and CT showed no evidence of lung metastases 87 weeks after the evacuation (Fig. 2).

3. Discussion

Our cases were diagnosed as postmolar GTNs and clinical invasive moles according to the JSOG classification. Most GTN cases need appropriate chemotherapy using methotrexate, etoposide, and/or actinomycin D. However, our cases showed spontaneous regression before the start of treatment.

Cole et al. studied 176 cases with complete or partial disappearance of malignancies in the absence of treatment and investigated these cases based on the type and location of the cancer. Of the 176 cancer cases, choriocarcinoma accounted for 19 cases (10.8%) and was the fourth leading cause behind leukemia, squamous cell cancer, and lymphomas (Cole, 1976). It has been suggested that gestational trophoblast neoplasia has a tendency towards spontaneous regression because the trophoblast is seen as a foreign material. There is a theory that rejection

of trophoblasts occurs via the combined effect of maternal immune factors and the invasiveness of the fetal tissue (Hertz, 1976). The trophoblasts in GTN, including choriocarcinoma, in combination with a normal pregnancy might induce high expression of human leukocyte antigen-G (HLA-G), a non-classical HLA class Ib molecule. HLA-G molecules have been shown to participate in immune responses such as maternofetal tolerance during pregnancy. In choriocarcinoma cells, HLA-G might inhibit natural killer activity through increasing HLA-E cell surface expression (Sala et al., 2004). Cases of regression of metastases after surgery of the primitive tumor, in particular in renal carcinoma, have been reported. The reason for regression in these cases has been attributed to the immune system increasing its activity against the cancer cells when the primary tumor has undergone surgery (Ricci and Cerchiari, 2010). The factors associated with spontaneous regression in our two cases might be related to the immune system after elimination of the primary lesion in the uterus.

On thin-section CT, small pulmonary nodules are difficult to differentiate from metastases and other tumors. Hamamiya et al. evaluated 308 patients with extrapulmonary carcinomas or sarcomas and detected nodules on CT in 75% of patients. The characteristics of the nodules were defined based on diagnostic biopsy or nodule growth. The results showed that 95% of nodules smaller than 10 mm were benign; for example, lymph nodes or old granulomas (Hanamiya et al., 2012). The pulmonary nodules in our two cases were multiple, and showed discrete rounded nodular densities that are usually seen in metastases from any primary malignancy. Furthermore, these nodules disappeared as hCG levels decreased. Therefore, we considered the lung nodules to be metastases of GTN. As for GTN, pulmonary lesions are considered trophoblastic embolisms or true metastases. However, some researchers have proposed that although embolic cells have growth and metastatic

potential, they might be inhibited by the activation of local thrombotic and inflammatory cascades (Roberts et al., 2003). Many reports have shown that fluorine-18 fluoro-2-deoxyglucose positron emission tomography ([18F]-FDG PET) is helpful in identifying metastatic GTN, but it cannot detect small lung metastases less than 5 mm (Mapelli et al., 2013).

The clinicopathological significance of pulmonary micrometastasis detected on CT of the thorax, but not on chest X-ray, in GTN remains controversial. Although the FIGO 2000 criteria and Japanese Diagnostic Scores both agree that CT can be used in the diagnosis of pulmonary metastases, both scoring systems are based on chest X-ray. In previous reports, the clinical outcome of time to remission was not significantly different in low-risk GTN patients with micro-lung metastases. However, these patients are more likely to need second line chemotherapy than the patients without metastases (Darby et al., 2009). In contrast, among 434 low-risk GTN patients, the recurrence rate was significantly higher in patients with lung metastases compared with patients without metastases, after eliminating factors of antecedent pregnancy and interval (Vree et al., 2016). In clinical practice, we often use a CT scan to detect lung metastases, so we need further investigation to evaluate whether pulmonary metastases are an independent risk factor. Based on that result, we may need a modified FIGO or Japanese diagnostic scoring system adjusted for risk evaluation using CT scan.

This report documents the spontaneous regression of postmolar GTN with lung metastases. The mechanism behind this phenomenon remains unclear. Further research on this mechanism may suggest that aggressive chemotherapy is not required for patients with postmolar GTN when hCG values decline, even if only slightly, six months after evacuation. We should carefully consider the appropriate treatment for patients with postmolar GTN and these results.

Conflict of interest statement

None declared.

Disclosure statement

The authors have nothing to disclose.

Consent

Written informed consent was obtained from the patients for

publication of this case report and accompanying images.

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