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Successful management of nongestational ovarian choriocarcinoma complicated with choriocarcinoma syndrome: A case report and a literature review

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ABSTRACT

Nongestational ovarian choriocarcinoma (NGOC) accounts for <1% of ovarian germ cell tumors and may develop into the rare and fatal complication of choriocarcinoma syndrome. We reported a case of a 12-year-old girl with NGOC that metastasized to the lungs, retroperitoneal lymph nodes and brain. On day 2 of chemotherapy with actinomycin D and etoposide, choriocarcinoma syndrome developed due to a massive pulmonary hemorrhage, presenting as acute respiratory distress syndrome. The patient received mechanical ventilation and multimodal support and completed two cycles of an actinomycin D and etoposide regimen with intubation. After the patient's acute respiratory distress syndrome was under control, she received 9 cycles of more intensive chemotherapy regimens and achieved complete remission. An exploratory laparotomy with salpingo-oophorectomy confirmed ovarian choriocarcinoma. The patient remained disease-free at a 3-month follow-up visit. In conclusion, appropriate management consisting of multimodal support and timely, sequential and intensive chemotherapy is effective for NGOC complicated with choriocarcinoma

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syndrome. Stating with mild regimens would probably reduce the risk of choriocarcinoma syndrome, or at least lessen its severity. To our knowledge, we presented the first report of NGOC-related choriocarcinoma syndrome.

ARTICLE INFO

Keywords: Nongestational ovarian choriocarcinoma; Choriocarcinoma syndrome; Acute respiratory distress syndrome; Chemotherapy

Introduction

Nongestational ovarian choriocarcinoma (NGOC) accounts for <1% of ovarian germ cell tumors, which occur most frequently in adolescents and young females and occasionally in postmenopausal women.[1-3] Pure NGOC is rarer than a mixed subtype,[4] and is probably the most aggressive type of germ cell tumor, with rapid progression and distant metastasis. Patients with advanced NGOC may develop a rare but life-threatening complication defined as choriocarcinoma syndrome, which was first described in 1982.[5] Choriocarcinoma syndrome consists of hemorrhagic manifestations of metastases in advanced germ cell cancer and contains large elements of choriocarcinoma. It should be suspected in patients with a high tumor mass, multiple metastases, elevated tumor markers, and other characteristic of germ cell tumors.[6] Choriocarcinoma syndrome occurs in 2 different clinical settings, either within a few hours after the initiation of combined chemotherapy, which is more common, or spontaneously in advanced disease without any relation to the treatment, which is much less common.[7] The pathogenesis may be related to tumor invasion of the small blood vessels.[8] This syndrome is known to have a poor prognosis, particularly in patients with β-human chorionic gonadotropin (β-hCG) values above 50,000 IU/L.[9]

Here, we report a case of NGOC in a 12-year-old female suffering from severe acute respiratory failure due to pulmonary hemorrhage that developed on day 2 after the initiation of combination chemotherapy with actinomycin D and etoposide (AE). Aggressive management consisting of multimodal support and intensive chemotherapy achieved a complete response.

Case presentation

The patient is a 12-year-old girl. Her parents, as her guardians in this report, provided consent for publication. The patient first experienced an episode of sudden dyspnea and frequent coughing after routine physical activity. A chest computed tomography (CT) scan showed multiple, round, multilobed, heterogeneous hypodense lesions. Abdominal and pelvic CT scans revealed a pelvic mass measuring $15 \times 9 \times 6.5$ cm. A brain magnetic resonance imaging showed multiple patchy equal-length T1 signals and long-length T2 signals in the brain. A transthoracic core biopsy suggested glandular cancer. Her chromosome karyotype was “46, XX”. The patient soon developed a severe cough, dyspnea, headache, and persistent fever and was transferred to our hospital.

The patient had no menophania. She denied any sexual experiences or a personal or family history of cancer. Her body height and weight were 160 cm and 60 kg, with a body mass index of 23.4 kg/m^2. Upon physical examination, the patient could not lie in a supine position. Her vital signs showed tachycardia (heart rate 130/min), tachypnea (26/min), and normal blood pressure (100/70 mm Hg). Abdominal and anal examination revealed a large mass up to the

level of the umbilicus, with no guarding or rebound tenderness. The serum biomarker levels were measured as follows: β-hCG 120,420 IU/L, alpha fetoprotein 1.56 ng/mL, CA125 261.3U/mL, neuron-specific enolase 24.0 ng/mL, and lactate dehydrogenase 514 IU/L.

Considering the elevated β-hCG and alpha fetoprotein levels, the patient was suspected to have a malignant mixed germ cell tumor, International Federation of Gynecology and Obstetrics (FIGO) stage IV. In view of the heavy tumor burden and poor physical performance, a mild chemotherapy regimen of AE (actinomycin D 500 μg and etoposide 100 mg/m^2 on day 1-3) was started after her parents participated in the decision-making process and provided informed consent. On day 1 of AE (October 26, 2018), several hours after the completion of the chemotherapy regimen, the patient complained of severe dyspnea, headache, and coughing with a small amount of hemoptysis. She was transferred immediately to the intensive care unit. Her conditions soon deteriorated, and her consciousness decreased the next day. A sudden decrease in blood pressure and hemoglobin levels suggested intrathoracic hemorrhage. A bronchoscopic examination revealed massive bleeding from both upper bronchi. She soon received mechanical ventilation as the lowest oxygen partial pressure was 50 mm Hg with an oxygen mask. Under the conditions of 80% fraction inspired oxygen (FIO_2) and 5 cm H_2O positive end-expiratory pressure, arterial blood gas analysis showed that the pressure of arterial O_2 (PaO_2) was 105 mmHg and the pressure of arterial CO_2 ($PaCO_2$) was 49.9 mm Hg with a PaO_2/FIO_2 ratio of 131. Combined with the CT scan (Fig 1), these findings suggested acute respiratory distress syndrome (ARDS). Massive transfusion with a vasopressor and an intensive antibiotic regimen were given to salvage the hemorrhagic shock and potential infection. The subsequent regimens of the first cycle of AE (etoposide 100 mg/m^2 on day 2 to 3) continued. Recombinant granulocyte colony-stimulating factor (G-CSF) was initiated to manage grade 3 neutropenia following chemotherapy. The patient responded well to all treatments. Thirteen days after the initiation of first-cycle chemotherapy, on November 8, 2018, a second cycle of full-dose AE was given with in situ intubation. As her respiratory function gradually improved, extubation was performed 18 days after first-cycle chemotherapy, and the patient was discharged from the intensive care unit. Later, the patient received 3 cycles of EMA/CO chemotherapy (100 mg/m^2 etoposide on days 1-2, 300 mg/m^2 methotrexate [MTX] on day 1, 0.5 mg/kg actinomycin D on day 1-2; then, 12 hours after the last dose of MTX, four doses of 15 mg methyltetrahydrofolate were given to rescue the MTX; this treatment was followed by 600 mg/m^2 cyclophosphamide on day 8 and 2 mg vincristine on day 8) at 14-day intervals and intrathecal MTX (12.5 mg weekly). After 5 cycles of chemotherapy, the β-HGG levels decreased from 120,420 IU/l (October, 25, 2018) to 12.8 IU/l (December 23, 2018), and an imaging evaluation showed that most of the lung metastases and peritoneal disseminations had decreased, but the lesions in her left pelvis remained (Fig 1).

On December 27, 2018, four days after the last chemotherapy, an exploratory laparotomy was performed with right unilateral salpingo-oophorectomy. During the operation, a dark red, fleshy, hemorrhagic and necrotic mass measuring $8 \times 5 \times 4$ cm in diameter was found attached to the right fallopian tube and the rectum. No other residual lesions were found in the abdominal and pelvic cavity. A histopathological examination showed that the tumor was composed of clusters and sheets of neoplastic mononuclear cytotrophoblastic and multinucleated syncytiotrophoblastic cells in a highly necrotic background (Fig 2). Immunohistochemical staining revealed a strongly positive cytoplastic immunoactivity for hCG in the syncytiotrophoblastic cells. Other immunohistochemical staining tests included EMA (+), CD146 (+), P63 (-), HpL (-), PLAP (-), and Ki-67 (index 5%). A diagnosis of Non-gestational ovarian choriocarcinoma with FIGO stage IV was confirmed. Three days after the surgery (December 30, 2018), β-hCG decreased to 5.49 IU/L. Seven days after the surgery, the patient received another 5 cycles of EMA/CO, and 4 cycles were performed after the β-hCG level normalized. As the concentration of β-hCG remained normal and the intracranial loci disappeared after the first 2 cycles of EMA/CO, no intrathecal MTX was given during these cycles. The treatment duration and changes in the β-hCG level are summarized in Figure 3. The severe adverse events related to chemotherapy were grade 3 neutropenia and alopecia.

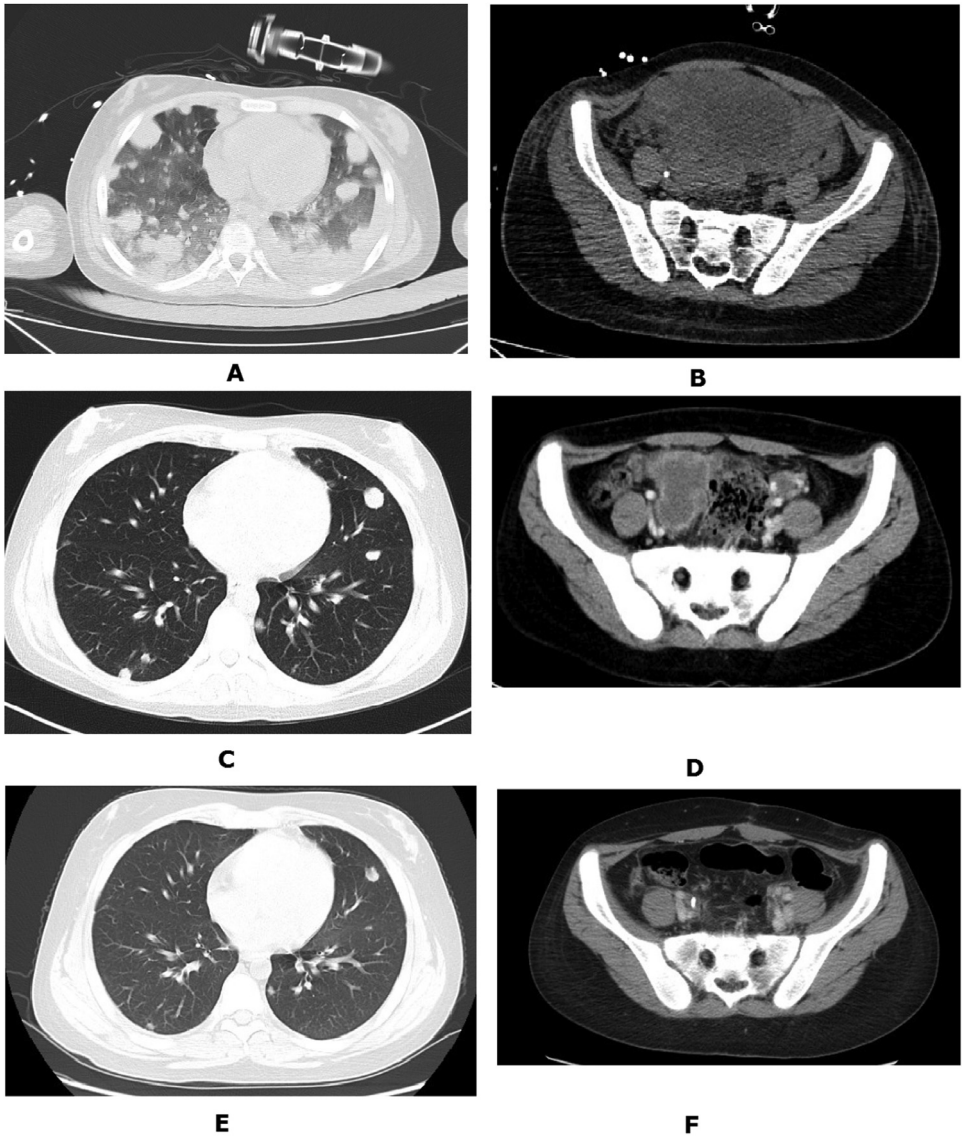

Fig. 1. Imaging changes in the thoracic and pelvic cavities via computed tomography (CT) during the treatment period. (A and B) were taken on the second day (October 27, 2018) of first cycle of actinomycin D and etoposide (AE). (C and D) were taken on December 17, 2018, after 2 cycles of AE and 2 cycles of chemotherapy with transvenous etoposide, methotrexate and actinomycin D/cyclophosphamide and vincristine (EMA/CO) and intrathecal methotrexate (MTX). (E and F) were taken on February 6, 2019, 1 month after the unilateral salpingo-oophorectomy surgery. (A) Chest CT scan showed multiple nodules surrounded by areas of ground-glass opacity, bulky lymphadenopathy in the hilum and mediastinum, multiple fibrous stripes and bilateral pleural effusion and atelectasis. (B) Pelvic CT scan showed an irregular bulky mass with a 10 cm diameter. (C and E) Chest CT scan showed persistent shrunken thoracic nodules and bulky lymphadenopathy compared with (A). Bilateral pleural effusion and atelectasis disappeared. (D) Pelvic CT scan showed a significantly shrunken mass compared with (B). (F) Pelvic CT showed the disappearance of the bulky mass in (B) and (D).

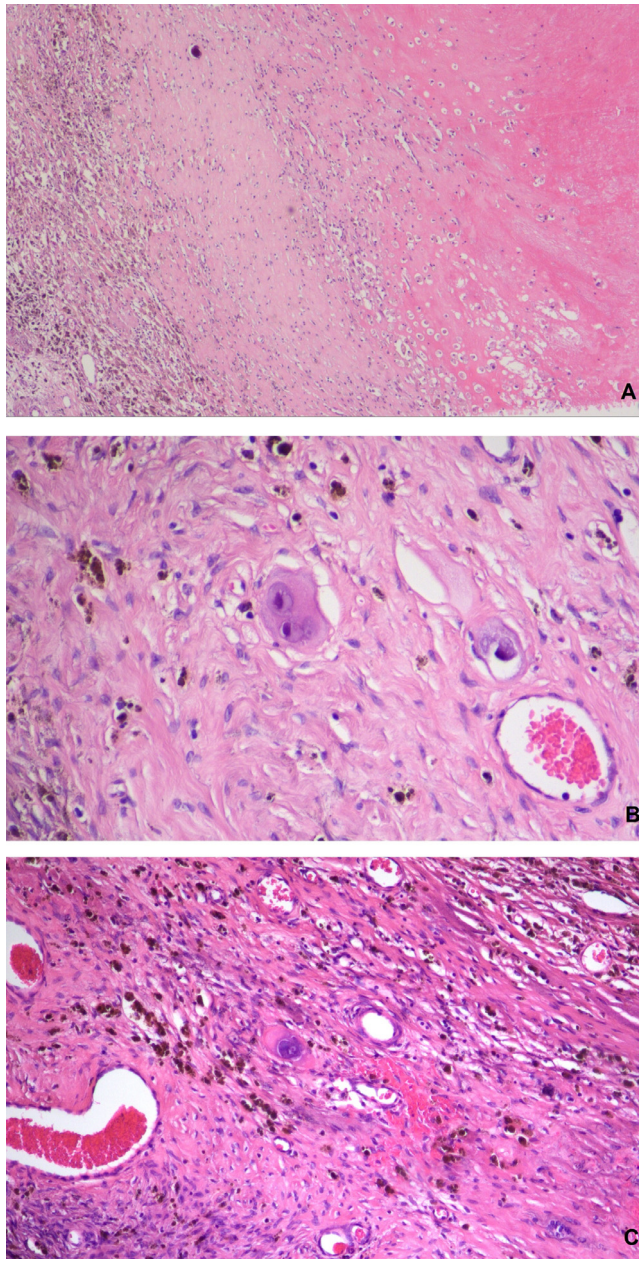

Fig. 2. The postoperative pathological examination of the right ovarian tumor revealed a hemorrhagic necrotic nodule, with a few degenerative atypical cells in the peripheral area (hematoxylin and eosin staining, 50 × in A, 100 × in B and C).

Discussion

Choriocarcinoma is categorized as either gestational or nongestational. It is necessary to distinguish these 2 modalities of the ovary since NGOC has a poorer prognosis than gestational cases and requires more aggressive therapy with multiple chemotherapeutic agents.[10] The

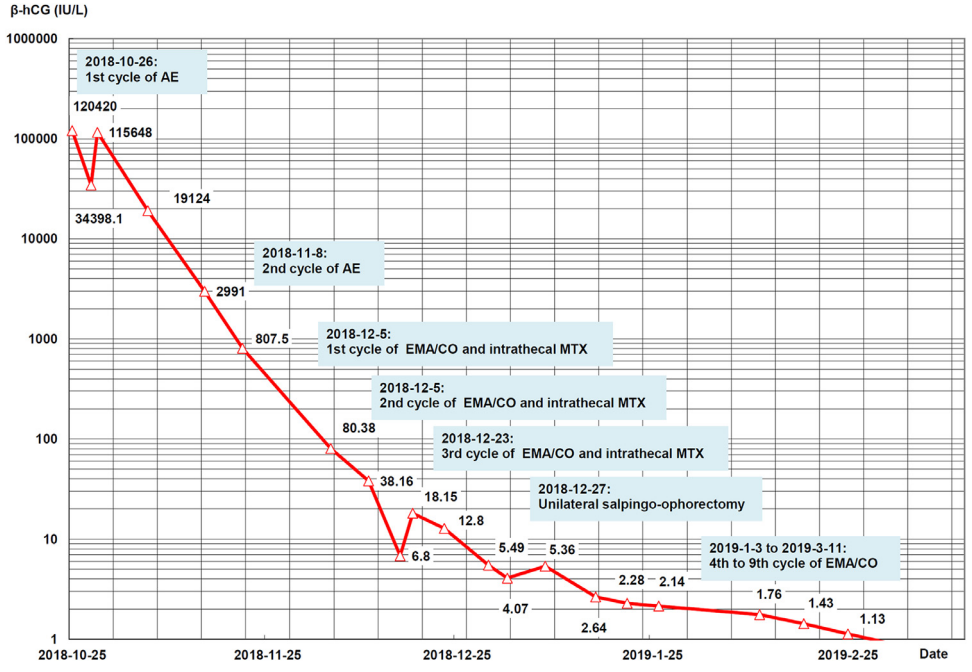

Fig. 3. The changes in β-human chorionic gonadotropin (β-hCG) before diagnosis to the end of all treatments. Figures denote the measured β-hCG. Date and notes denote the major treatment (chemotherapy or surgery) and its beginning date. AE, chemotherapy with actinomycin D and etoposide; EMA/CO, chemotherapy with etoposide, methotrexate and actinomycin D/cyclophosphamide and vincristine; MTX, methotrexate.

clinical manifestations of NGOC include vaginal bleeding, abdominal pain and pelvic masses, tumoral secretion of hCG and, in certain cases, precocious puberty and endocrine abnormalities.[11] Distant metastasis to the lungs, liver, and brain is common.[12] These characteristics are very similar to those of epithelial ovarian cancer. Most NGOC cases are misdiagnosed, and patients are initially treated for ovarian tumor torsion or other ovarian cancer subtypes before surgeries, especially in emergency situations.[13,14] DNA polymorphism analysis may aid the diagnosis.[3,15-18] Fisher et al.[15] first used site-specific microsatellite probes to analyze DNA restriction fragment length polymorphisms of tumor tissue by comparing blood samples obtained from patients and their spouses. In our report, the patient had typical clinical presentations of germ cell tumors, and the histology results, clinical history without prior pregnancies are supportive of the diagnosis. But the diagnosis of NGOC was confirmed only after surgery. She had a normal chromosome karyotype, and the DNA polymorphism analysis was not completed due to the limited tumor tissue and the degraded nature of the biopsy material.

Early detection, diagnosis, and treatment of NGOC are important factors for patient prognosis.[19] Jiao et al.[2] reported 21 cases of NGOC with a mean follow-up period of 71.4 months and an overall 5-year survival rate of 79.4%. Due to its malignant prognosis, NGOC requires a more aggressive therapy with multiple standard chemotherapeutic agents.[2] A total of 75% of FIGO stage IV NGOC patients are expected to achieve complete or prolonged remission when treated with multiagent chemotherapy regimens.[20] EMA/CO was reported to be an efficient regimen for NGOC.[21,22] Surgical treatment is probably essential for the improved prognosis. In a study by Goswami et al.,[23] the 2-year survival rate was 81% in patients who underwent surgery combined with chemotherapy and 28% in patients who underwent surgery alone.[23] The presence of the residual tumor after surgery appears to be the single most important factor for a poor prognosis.[24-28] Fertility-sparing surgery is the main surgical pattern for NGOC.[29] For patients with an advanced-stage disease, maximum cytoreductive surgery appears to be beneficial.[25]

In this case, we did want to avoid choriocarcinoma syndrome by starting with AE rather than EMA/CO. Although the complications occurred, the patient survived and completed subsequent more extensive treatment uneventfully. For patients with advanced stage diseases, starting with nonfull dose chemotherapy as reported in our case would probably avoid the risk of choriocarcinoma syndrome, or at least lessen the severity. The mild regimens would produce less adverse events than the extensive ones, while still keeping favorable treatment effects. These opinions have been documented in the consensus about male choriocarcinoma [30] and in the treatment of female gestational choriocarcinoma.[31]

Similar to the case in our report, choriocarcinoma syndrome usually occurs in choriocarcinoma patients with high-volume disease, which is associated with very high β-hCG levels. Most reports have shown that choriocarcinoma syndrome typically occurs on day 2 or 3 after the beginning of chemotherapy.[32-36] However, these reports are all about male germ cell tumors. Hemorrhaging can occur at any site of metastasis, which could be a sudden onset dyspnea, hemoptysis, chest pain, and/or abdominal pain.[3] Acute hemorrhage in the pulmonary metastasis with respiratory compromise is the most common presentation of choriocarcinoma syndrome, which is always fatal and associated with ARDS.[37,38] To prevent this fatal syndrome, modified BEP (bleomycin, etoposide, and cisplatin) regimes have been reported.[39] In a report by Massard et al.,[40] the prevalence of ARDS secondary to choriocarcinoma syndrome decreased from 13/15 (86.7%) patients to 3/10 (30.0%) patients, and the mortality decreased from 10/15 (66.7%) patients to 2/10 (20.0%) patients after modified BEP (bleomycin, etoposide, and cisplatin) treatment. However, there is no report on NGOC-related choriocarcinoma syndrome to our knowledge.

Choriocarcinoma syndrome needs early recognition and urgent multimodal treatment to save patients' lives.[35] There is no consensus about the management of choriocarcinoma syndrome. This urgent situation raises the dilemma of clinical disposition. The critical status of patients requires extensive support, which seldom permits intensive chemotherapy. However, as with other highly malignant germ cell tumors, delaying chemotherapy would worsen the disease. When the hemodynamics of a patient are unstable, any radical treatment to save their lives would risk disputes and even a lawsuit. Our experiences provided in this report were established with close communication and a physician-patient (or their attorney) relationship. In our opinion, once the patient's condition is mostly under control, a mild but full-dose chemotherapy regimen should be initiated immediately, followed by intensive regimens. As NGOC is highly sensitive to the appropriate chemotherapy, such efforts would result in a fair prognosis. An exploratory laparotomy is probably appropriate since it would provide opportunities for reducing the tumor burden and performing a pathological evaluation. As NGOC-related choriocarcinoma syndrome has not been reported before, more cases are needed to accumulate experiences for the prediction, prevention, and management of choriocarcinoma syndrome.

Conclusions

Choriocarcinoma syndrome is a fatal complication of advanced NGOC. Multimodal support and timely, sequential and intensive chemotherapy are key components of the successful management of choriocarcinoma syndrome because of its rarity. However, in such situation, stating with mild regimens would probably reduce the risk of choriocarcinoma syndrome, or at least lessen its severity. To our knowledge, this is the first report on NGOC-related choriocarcinoma syndrome.

Ethical approval and consent to participate

The patient in this report provided consent for participation in this study. The Institutional Review Board of Peking Union Medical College Hospital approved this study.

Consent to publish

The patient in this report provided consent for the anonymous publication of her experiences. All authors of this report agree with and are greatly obliged to the Editorial Board for the publication of this report.

Disclosures

All authors declare that they have no conflicts of interest to disclose.

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