Case Report

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Ultra-high-risk choriocarcinoma with atraumatic splenic rupture: a rare case report

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Abstract

Choriocarcinoma is a malignant tumor associated with early vascular invasion and a high mortality. Ultra-high-risk choriocarcinoma, which was proposed in the International Federation of Gynecology and Obstetrics cancer report of 2018, has a higher risk of treatment failure and a worse prognosis than choriocarcinoma. We report a rare case of a 39-year-old female patient with ultra-high-risk choriocarcinoma (stage IV:20) with hemorrhage secondary to atraumatic splenic rupture as the initial sign. A satisfactory outcome was achieved through comprehensive treatment with surgery, chemotherapy, immunotherapy, and targeted therapy.

Keywords

Choriocarcinoma, ultra-high risk, splenic rupture, pathology examination, management strategy, beta-human chorionic gonadotropin, hemorrhage

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Introduction

Choriocarcinoma is a malignant tumor derived from cells of villous trophoblasts. Choriocarcinoma may occur following a diagnosis of hydatidiform mole, abortion,

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or delivery of a term pregnancy. This condition is associated with early vascular invasion and a high mortality rate. Choriocarcinoma mostly metastasizes to the lungs (80% of cases) and the vagina (30% of cases),[1] and splenic metastases are uncommon. Although most cases of gestational trophoblastic neoplasia (GTN) can be cured by chemotherapy, approximately 25% of high-risk patients are chemotherapy-resistant and require remedial treatment. Indeed, ultra-high-risk choriocarcinoma has a higher risk of treatment failure and a poorer prognosis than choriocarcinoma.[2]

In this study, we describe a rare case of a 39-year-old female patient with ultra-high-risk choriocarcinoma who presented with hemorrhage secondary to atraumatic splenic rupture as the initial sign. After an emergency splenectomy, the patient was diagnosed with choriocarcinoma (stage IV:20). The initial chemotherapy had failed, and as a relapsed drug-resistant case, the patient underwent comprehensive treatment with chemotherapy, surgery, immunotherapy, and targeted therapy. At the time of writing this report, serum beta-human chorionic gonadotropin (β-HCG) levels were <1 mIU/mL, there were no residual lesions, and the treatment effect was satisfactory. This case report conforms to the CARE guidelines (for CAse REports).[3]

Case presentation

A 39-year-old woman (G10P2) whose last delivery was by cesarean section at full term in August 2016 was admitted to our emergency room complaining of sudden abdominal pain and irregular vaginal spotting in November 2018. In 2014, this patient presented with an invasive molar pregnancy (stage I: risk score of 5) and was treated with two cycles of 5-day single-agent methotrexate. The HCG level was decreased to 16 mIU/mL after which the patient was lost to follow-up.

Her abnormal uterine bleeding had lasted for almost 3 months. She occasionally had lower abdominal pain for 7 days before admission and was urgently hospitalized in November 2018 with severe left abdominal pain, nausea, and transient syncope without a history of trauma. She was not using any effective contraception. On a physical examination, her vital signs were normal, except for a heart rate of 108 beats/minute. She was pale and had generalized tenderness of her abdomen with guarding. The tenderness was so severe that the uterus and adnexa were not clearly felt on a pelvic examination. Blood tests showed anemia. Her β-HCG level was $>15{,}000$ mIU/mL, which was the upper limit of the assay used in the emergency laboratory. Ultrasonography revealed a large amount of free fluid in the abdomen and rupture of a 6.75×7.27-cm mass on the surface of the spleen was suspected Several smaller solid masses in the liver, and a normal adnexa and uterus were observed (Figure 1). An emergency computed tomography (CT) scan showed the same findings. Culdocentesis was performed immediately and yielded nonclotted blood. The differential diagnoses were considered as rupture of splenic metastases secondary to choriocarcinoma and rupture of an ectopic pregnancy.

In view of the life-threatening intraperitoneal hemorrhage, laparoscopic exploration was performed in the Emergency Department. There had been spontaneous rupture of the upper splenic mass with active bleeding and approximately 3000 mL of free blood was aspirated from the peritoneum. Conversion to open splenectomy was performed to control the bleeding more quickly.

A 5-cm-long split covered by the omentum was found on the surface of the upper pole of the spleen. Scattered tumor metastases were observed on the omentum. Soft lesions with sizes of 1 and 2 cm were palpated in the right lobe of the liver. No

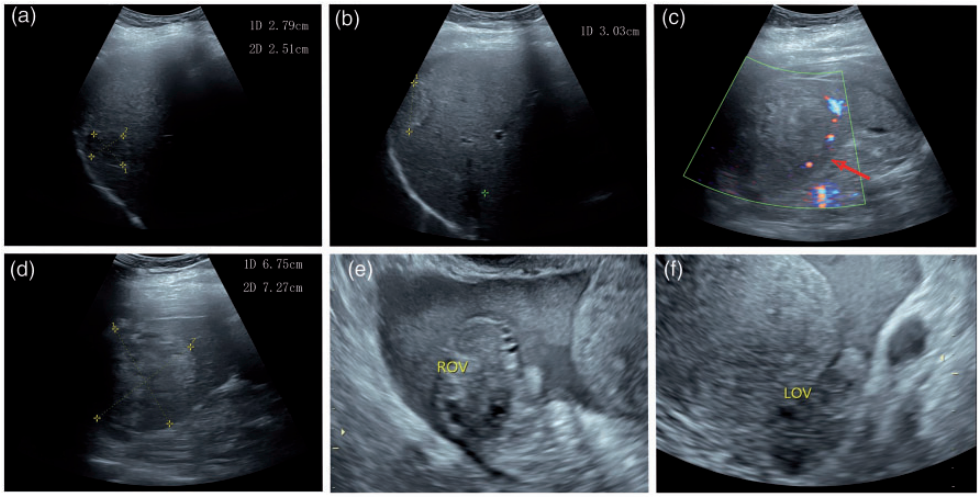

Figure 1. (a, b) Ultrasound of the liver showing liver lesions before emergency surgery. (c, d) Ultrasound of the spleen showing a spleen lesion before emergency surgery (arrow). (e, f) Ultrasound of the ovary showing no abnormalities before emergency surgery.

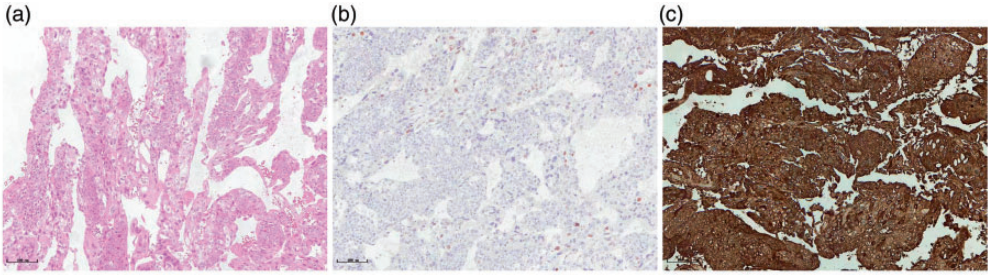

Figure 2. Histological features. (a) Hematoxylin and eosin staining of the spleen shows a choriocarcinomatous component consisting of cytotrophoblastic and syncytiotrophoblastic cells (magnification, ×200). (b) Immunohistochemical staining shows that syncytiotrophoblasts are immunoreactive for p57KIP2 (magnification, ×200). (C) Immunohistochemical staining shows that syncytiotrophoblasts are immunoreactive for β-human chorionic gonadotropin (magnification, ×200).

abnormality was found in the uterus or adnexae. We decided to perform splenectomy and resection of omental metastases. A histological examination showed metastasis of the spleen and omentum secondary to choriocarcinoma (Figure 2).

On the 3rd, 6th, and 10th days after surgery, β-HCG levels were 177,400 mIU/mL, 231,000 mIU/mL, and 1,210,630 mIU/mL, respectively. The patient had an uneventful recovery, and her lung CT and brain magnetic resonance imaging findings were normal (Figure 3).

According to the International Federation of Obstetrics and Gynecology (FIGO) 2000 scoring system,[4] her condition was diagnosed as stage IV:20 choriocarcinoma, which predicted an ultra-high–risk for mortality and chemoresistance. She received two lines of multi-agent chemotherapy.

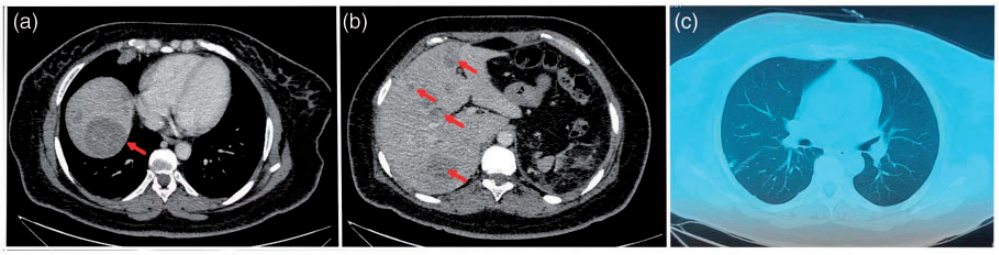

Figure 3. (a, b) Computed tomographic image shows multiple low-density areas, suggesting liver metastases before chemotherapy (arrow). (c) Computed tomographic image shows no significant metastasis in the lungs before chemotherapy.

The first regimen was floxuridine, actinomycin D, etoposide, and vincristine (FAEV). The patient received seven cycles with a rise in β-HCG levels. Second-line multi-agent chemotherapy was then provided with five cycles of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA/CO) therapy.

Partial liver resection was performed after two cycles of EMA/CO chemotherapy because follow-up CT showed no significant reduction in the size of the tumor in the right lobe of the liver. EMA/CO chemotherapy was continued for three more cycles and then stopped owing to the patient's rejection at which time β-HCG levels had dropped to <5 mIU/mL three times. However, 2 months after completion of EMA/CO therapy, β-HCG levels began to rise again. With a subsequent rise in β-hCG levels, the patient received immunotherapy (programmed cell death protein 1 inhibitor, camrelizumab) and targeted therapy (apatinib). In the 20th month of follow-up, a laparoscopic partial lung resection was performed for new lung metastases. The serum β-HCG level at this time was 250 mIU/mL. The pathology of the liver and lung lesions was consistent with metastasis of choriocarcinoma. The patient received two lines of multi-agent chemotherapy, underwent surgery of the liver and lungs, and received immunotherapy and targeted therapy. Up to the time of writing this report, the patient had been receiving HCG administration of approximately 1 mIU/mL for 9 months (Figure 4).

Discussion

Choriocarcinoma is a highly malignant tumor belonging to the spectrum of GTN. The incidence of choriocarcinoma is 5 to 202/100,000 pregnancies in China,[5] 3.3 and 9.2/40,000 pregnancies in Japan and Southeast Asia, respectively, and 1/40,000 in Europe and North America.[6] The most common metastases of choriocarcinoma are the lungs, vagina, brain, liver, kidneys, and gastrointestinal tract.[1] Atraumatic rupture caused by splenic metastasis of choriocarcinoma is rare, and only six cases have been reported.[7–12]

Choriocarcinoma is characterized by secretion of high HCG levels. Blood β-HCG levels in our patient were $>15{,}000$ mIU/mL, and she had multiple liver and spleen lesions, a suspicious ruptured spleen, and massive hemoperitoneum. Therefore, we were able to diagnose choriocarcinoma before laparoscopy. To reduce fatal bleeding, we converted to open splenectomy in this patient. A histological examination showed metastasis of the spleen and omentum secondary to choriocarcinoma.

According to the FIGO 2000 staging and classification,[4] our patient was diagnosed with stage IV:20 choriocarcinoma.

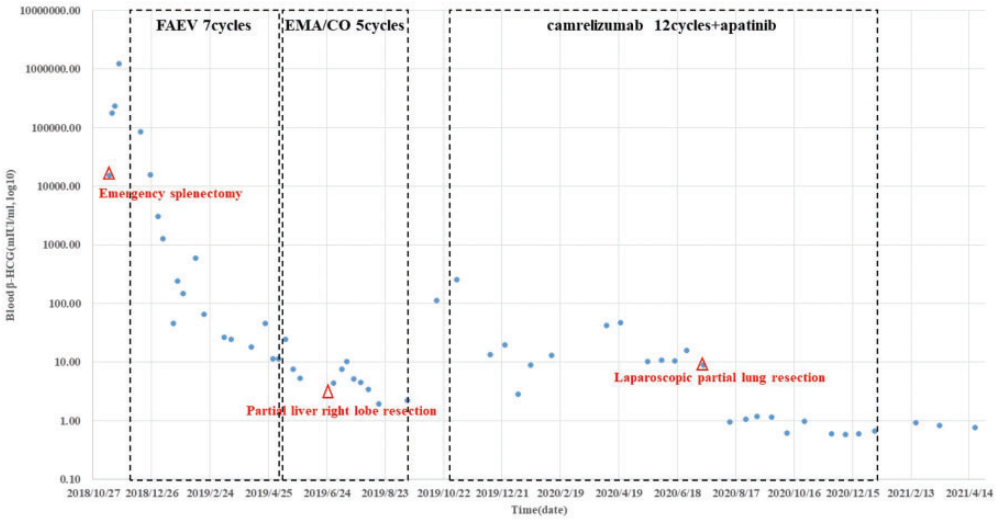

Figure 4. Timeline showing the time course, β-HCG levels, and interventions received (chemotherapy, surgery, and immunotherapy). The blue dots indicate blood β-HCG levels (log10), the red triangle indicates surgery, and the black dashed box indicates received interventions.
β-HCG, beta-human chorionic gonadotropin.

The new concept of an ultra-high-risk choriocarcinoma group was proposed in the FIGO cancer report of 2018.[6] The ultra-high-risk choriocarcinoma group with a risk score $\geq$13 for the liver, brain, or extensive metastases, has a higher treatment failure rate, and thus a poorer prognosis, compared with just choriocarcinoma.[13] According to previous reports, the 5-year mortality rate of patients with ultra-high-risk choriocarcinoma was 38.4%, while that of patients at a high risk was 12%.[14] Improvements in the understanding and treatment of refractory choriocarcinoma have led to more salvage treatment options.[15] Findings from a large number of these cases have shown that these patients can be treated at a highly specialized gestational trophoblastic disease center.

Generally, GTN is treated by chemotherapy. Combined chemotherapy based on 5-Fu or fluorouracil is commonly used in China and chemotherapy based on the EMA/CO regimen is commonly used elsewhere. Li et al. reported that patients with ultra-high-risk choriocarcinoma had similar complete response rates with EMA/CO (55.2%) and FAEV (63.1%) in first-line treatment.[16] In patients with initial treatment failure, several effective salvage regimens were recommended in the FIGO cancer report of 2018.[6] Immunotherapy with pembrolizumab, as a salvage treatment method for chemotherapy-resistant relapsed GTN, has a high efficiency and few adverse effects.[6,17] Recently, Traboulsi et al. provided theoretical support for endocrine gland-derived-vascular endothelial growth factor receptor-targeted therapy of choriocarcinoma.[18] However, targeted therapy for choriocarcinoma is still being explored as an option.

Surgery plays an important role in managing uncontrolled lesion bleeding and isolated drug-resistant tumors to improve survival.[19] Notably, the timing of surgery for new lesions and larger lesions that cannot be reduced by previous treatment is critical and satisfactory results can be

obtained only when blood HCG levels are normal or close to normal.[20] The initial FAEV chemotherapy regimen was not successful in our patient and it was changed to the EMA/CO regimen. The liver lesion was removed when the blood HCG level was low, but the patient relapsed soon after chemotherapy ended. Our patient was initially resistant to chemotherapy and successively underwent liver and lung resection. After receiving immunotherapy and targeted therapy in chemotherapy, a new lung lesion was removed when the blood β-HCG level was low. Subsequently, her blood β-HCG levels returned to normal with no residual lesions. The combined therapeutic effect was satisfactory. Immunotherapy and targeted therapy are new treatment options for ultra-high-risk choriocarcinoma, but their efficacy needs further monitoring.

Conclusion

Ultra-high-risk choriocarcinoma is a serious condition that is difficult to manage. These patients should be identified as soon as possible and referred to a trophoblastic disease diagnosis and treatment center that is capable of diagnosing and treating them efficiently. The treatment of patients with drug resistance and relapse should focus on the development of individualized treatment plans according to the degree of disease and previous treatments. At the same time, the importance of surgical treatment should be emphasized and a comprehensive assessment should be made. In addition to active chemotherapy, surgery should be used to remove drug-resistant or recurrent lesions as much as possible. For chemotherapy-resistant patients, research trials on immunotherapy and targeted therapy still need to be performed

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Ethics statement

We obtained a signed consent form from the patient for publication and explained to this patient that all identity information would be de-identified. The Medical Ethics Committee of Tianjin Third Central Hospital provided approval for publication of this case report.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Stevens FT, Katzorke N, Tempfer C, et al. Gestational Trophoblastic Disorders: An Update in 2015. *Geburtshilfe Frauenheilkd* 2015; 75: 1043–1050.
2. Kong YJ, Yang JJ, Jiang F, et al. Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: A retrospective cohort study. *Gynecol Oncol* 2017; 146: 81–86.
3. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547.
4. Ngan HY, Bender H, Benedet JL, et al. FIGO Committee on Gynecologic Oncology. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *Int J Gynaecol Obstet* 2003; 83 Suppl 1: 175–177.
5. Cheng HY, Yang JJ, Zhao J, et al. Preliminary study of PD-1 inhibitor in the treatment of drug-resistant recurrent gestational trophoblastic neoplasia. *Zhonghua Fu Chan Ke Za Zhi* 2020; 55: 390–394.
6. Ngan HYS, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of

gestational trophoblastic disease. *Int J Gynaecol Obstet* 2018; 143 Suppl 2: 79–85.
7. Yürüyen M, Yildiz O, Papila C, et al. Gestational choriocarcinoma diagnosed with spontaneous splenic rupture after pregnancy induced by in vitro fertilization: a case report. *Cases J* 2009; 2: 7518.
8. Galazi M, Tait P, Seckl M, et al. Successful embolization of a life threatening bleeding splenic metastasis in a patient with gestational choriocarcinoma. *Clin Obstet Gynecol Reprod Med* 2015; 1: 16–18.
9. Challis DE, Rew KJ and Steigrad SJ. Choriocarcinoma complicated by splenic rupture: an unusual presentation. *J Obstet Gynaecol Res* 1996; 22: 395–400.
10. Nethra S, Hawe J and Elder J. Splenic rupture: a rare presentation of metastatic choriocarcinoma. *Gynecol Surg* 2011; 8: 435–437.
11. Ghinescu C, Sallami Z and Jackson D. Choriocarcinoma of the spleen–a rare cause of atraumatic rupture. *Ann R Coll Surg Engl* 2008; 90: W12–W14.
12. Aloysius TMN and Shelat VG. Laparoscopic splenectomy for splenic rupture secondary to metastatic choriocarcinoma. *Ann Hepatobiliary Pancreat Surg* 2018; 22: 79–82.
13. Yang J, Xiang Y, Wan X, et al. Analysis of the prognosis and related factors for patients with stage IV gestational trophoblastic neoplasia. *Int J Gynecol Cancer* 2014; 24: 594–599.
14. Bolze PA, Riedl C, Massardier J, et al. Mortality rate of gestational trophoblastic neoplasia with a FIGO score of $\geq$13. *Am J Obstet Gynecol* 2016; 214: 390.e1–8.
15. Brown J, Naumann RW, Seckl MJ, et al. 15 years of progress in gestational trophoblastic disease: Scoring, standardization, and salvage. *Gynecol Oncol* 2017; 144: 200–207.
16. Li J, Yue H, Wang X, et al. Chemotherapy for gestational trophoblastic neoplasia patients with a FIGO score of 12 or greater: A multistudy analysis. *Eur J Obstet Gynecol Reprod Biol* 2019; 238: 164–169.
17. Ghorani E, Kaur B, Fisher RA, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. *Lancet* 2017; 390: 2343–2345.
18. Traboulsi W, Sergent F, Boufettal H, et al. Antagonism of EG-VEGF Receptors as Targeted Therapy for Choriocarcinoma Progression In Vitro and In Vivo. *Clin Cancer Res* 2017; 23: 7130–7140.
19. Ngan HY, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynecol Obstet* 2015; 131 Suppl 2: S123–S126.
20. Feng F, Xiang Y, Li L, et al. Clinical parameters predicting therapeutic response to surgical management in patients with chemotherapy-resistant gestational trophoblastic neoplasia. *Gynecol Oncol* 2009; 113: 312–315.